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 2016-2017

The National Immunisation Programme in the Netherlands

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

Authors:
R. van Alebeek, K. Benschop, B. van Benthem, G.A.M. Berbers, R. van Binnendijk, J.A. Bogaards, H.J. Bootsma, I. Brinkman, P. Bruijning-Verhagen, A. Buisman, J. Cremer, R. Donken, E. Duizer, C.A.C.M. van Els, A. van der Ende, M. Ensink, I.H.M. Friesema, M. van Gent, B. de Gier, S. Gouma, F. van Heiningen, W. van der Hoek, S. Hofstraat, M. Hooiveld, K. Hulshof, A. Janga-Jansen, P. Jochemsen, P. Kaaijk, J. van de Kassteele, P.B. van Kasteren, J.M. Kemmeren, H. van den Kerkhof, A.J. King, F.R.M. van der Klis, M.J. Knol, H. Korthals Altes, B. Lehmann, E.A. van Lier, M. Luinstra-Passchier, W. Luytjes, N.A.T. van der Maas, M.J.J. Mangen, S. McDonald, A. Meijer, H.E. de Melker, L. Mollema, S. Monge, M. Nielen, D.W. Notermans, H. Pasmans, E. Pinelli, R. Prettner, V. Qendri, F.A.G. Reubsaet, K. Romijnders, N.Y. Rots, W.L.M. Ruijs, T.M. Schurink-van 't Klooster, J. van Slobbe, A.W.M. Suijkerbuijk, A.C. Teirlinck, I.K. Veldhuijzen, H. Vennema, J.D.M. Verberk, R.A. Vos, P. van der Weele, P.J. Woestenberg en T. Woudenberg

Contact:
H.E. de Melker
Centre for Epidemiology and Surveillance of Infectious Diseases
hester.de.melker@rivm.nl

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Contents

Synopsis

The National Immunisation Programme in the Netherlands

Surveillance and developments in 2016-2017

In 2016, about 760,000 children aged 0 to 19 years received a total of 2,140,000 vaccinations within the National Immunisation Programme (NIP). Participation in the NIP was high (more than 90% depending on the vaccine), but dropped by around 0.5% for newborns for the third consecutive year. The participation in vaccinations against human papillomavirus (HPV) declined from 61 to 53 per cent. The number of reports (1,483) of adverse events following immunisation (in total 3,665) in 2016 was comparable to the number of reports in 2015.

NIP target diseases

The number of reported cases of most NIP target diseases was again low. However, the number of cases of *Haemophilus influenzae* type b (Hib) disease in 2016 (n=44) was considerably higher than in the previous five years (22-34 cases), with the highest incidence occurring among children under five years of age. Pertussis incidence in 2016 fits within the usual fluctuations. However, six people died from pertussis in 2016.
The incidence of cervical cancer cases increased in 2016 (9.3 per 100,000 compared with 7.7 per 100,000 in 2015). In 2017, two fully vaccinated employees were exposed to a wild poliovirus type 2 (WPV2). Due to strict isolation, no transmission was detected.

Potential NIP target diseases

An increase in the number of meningococcal (Men) disease was observed after more than two decades of decrease. An ongoing increase in the number of cases of MenW disease has been observed (9, 50 and 34, respectively, in 2015, 2016 and the first five months of 2017).

Dutch Health Council recommendations

The RIVM facilitate the Dutch Health Council with their recommendations on vaccinations and therefore has collected and structured relevant national and international information in background documents concerning rotavirus, meningococcal disease and HPV.

The Health Council has advised earlier that maternal pertussis vaccination should be provided. The Ministry of Health, Welfare and Sport (VWS) has expressed a positive attitude towards the advice but still has to make a decision. In 2017, the Health Council also advised that all employees who are in close contact with young infants during work should be offered vaccination against pertussis. In addition, the Dutch Health Council advised in September 2017 positive on vaccination against rotavirus and the minister decided to vaccinate against MenACWY in 2018.

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 2016–2017

In 2016 kregen ongeveer 760.000 kinderen van 0 tot 19 jaar samen 2.140.000 vaccinaties vanuit het Rijksvaccinatieprogramma (RVP). De deelname aan het RVP is hoog (afhankelijk van het vaccin meer dan 90 procent), maar is voor het derde achtereenvolgende jaar met ongeveer 0,5 procent gedaald onder pasgeborenen. Het aantal meisjes dat zich tegen het humaan papillomavirus (HPV) heeft laten vaccineren, is gedaald van 61 naar 53 procent. Het aantal meldingen (1483) van mogelijke bijwerkingen (in totaal 3665) van vaccins in 2016 is vergelijkbaar met het aantal meldingen in 2015.

RVP-ziekten

Wederom waren er weinig meldingen van mensen die een ziekte kregen waartegen via het RVP wordt ingeënt. Wel was het aantal zieken door *Haemophilus influenzae* type b (Hib) in 2016 hoger (44) dan in de afgelopen 5 jaar (22-34), vooral onder kinderen jonger dan 5 jaar. Het aantal mensen met kinkhoest in 2016 paste in het normale patroon. Toch overleden dat jaar 6 mensen aan deze ziekte. Het aantal mensen met baarmoederhalskanker is gestegen in 2016 (9,3 per 100.000 vergeleken met 7,7 per 100.000 in 2015). In 2017 zijn twee volledig gevaccineerde werknemers blootgesteld aan wild poliovirus type 2 (WPV2). Door hen strikt te isoleren heeft de ziekte heeft zich niet verder verspreid.

Ziekten voor potentiele RVP-vaccins

Het aantal mensen met Meningokokkenziekte (Men) neemt toe nadat het meer dan twee decennia is gedaald. Een aanhoudende sterke stijging wordt gezien in Meningokokken serogroep W-ziekte (9, 50 en 34 patiënten in respectievelijk 2015, 2016 en de eerste 5 maanden van 2017).

Adviezen Gezondheidsraad

Het RIVM faciliteert de Gezondheidsraad voor hun adviezen over vaccinatie en verzamelt daarvoor nationale en internationale informatie over rotavirus, meningokokkenziekte en HPV.

De Gezondheidsraad heeft eerder geadviseerd om alle zwangere vrouwen tijdens de zwangerschap een kinkhoestvaccinatie aan te bieden. De minister van VWS staat hier positief tegenover maar moet nog een besluit nemen. Aanvullend heeft de Gezondheidsraad in 2017 geadviseerd om alle werknemers die tijdens hun werk in contact staan met pasgeborenen vaccinatie aan te bieden tegen kinkhoest. Verder adviseerde de Gezondheidsraad in september 2017 positief over vaccinatie tegen rotavirus en besloot de minister diezelfde maand om in 2018 te gaan vaccineren tegen Meningokokkenziekte veroorzaakt door typen A, C, W en Y.

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

Dutch National Immunisation Programme (NIP)
Highlights Surveillance 2016 – 2017

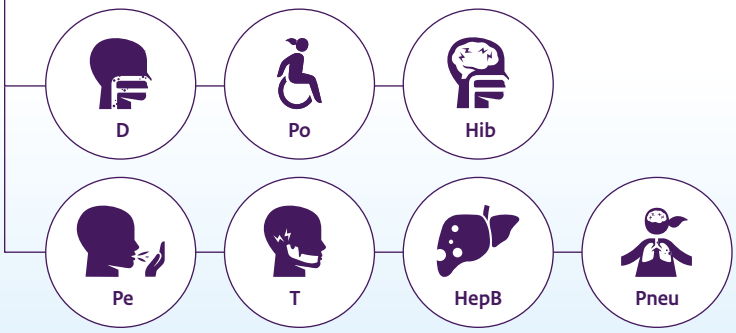
RIVM continuously monitors the effectiveness and safety of the NIP

Surveillance of vaccine uptake

National vaccination coverage data

For the third consecutive year vaccination coverage for new-borns is **decreasing** by about **0.5 percent**.

HPV vaccination coverage declined from **61 percent** in 2016 to **53 percent** in 2017.



Disease surveillance

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

A **resurgence** of measles in Europe occurred, with most cases observed in Romania, Italy and Germany. Cases in the Netherlands in 2016/first half of 2017 (n=16) were mostly imported or import-related.

The number of cases of *Haemophilus influenzae* type b (Hib) disease was **higher** (44 in 2016) than in the previous five years (22-34), especially among children under five.

An **ongoing increase** in the number of cases with meningococcal serogroup W (MenW) disease was observed. Therefore, the Dutch minister of Health decided to introduce MenACWY vaccination in 2018.

Pathogen surveillance

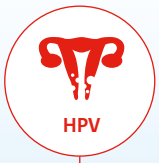
Laboratory data

In 2017, two fully vaccinated **employees were exposed** to a wild poliovirus type 2 (WPV2) spill. In stool and sewage samples of one employee WPV2 was found. Strict isolation was implemented. No transmission was detected.

Immunosurveillance

Seroprevalence data from a representative sample

The HPV16/18 two-dose schedule induces high **antibody levels** and avidity against vaccine-types up to at least 24 months of follow-up.



Surveillance of adverse events

Enhanced spontaneous reporting of adverse events following immunisation

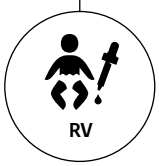
There was considerable **media attention** for vaccination coverage at the end of 2016. Vaccination was a topic of frequent discussion on social media on alleged side effect chronic fatigue syndrome after HPV vaccination.

Health Council recommendations

The Ministry of Health, Welfare and Sport stated to have a positive attitude towards the Health Council advice offering **maternal pertussis vaccination**.

The Dutch Health Council has recommended to the Ministry of Health, Welfare and Sport to vaccinate children with high risk for rotavirus infection. The council is positive towards mass vaccination incorporated in the NIP, however, this will not be cost-effective seen the current vaccine prices.

The Health Council advised in 2017 that all **employees** with infants during work should be vaccinated against pertussis.



This infographic is part of the RIVM report The National Immunisation Programme in the Netherlands: Surveillance and developments in 2016 – 2017.

Preface

This report presents an overview of surveillance and developments in the 2016-2017 period that are relevant for the Netherlands with respect to the diseases included in the current National Immunisation Programme (NIP): diphtheria, *Haemophilus influenzae* serotype b (Hib) disease, hepatitis B, human papillomavirus (HPV) infection, measles, meningococcal disease, mumps, pertussis, pneumococcal disease, poliomyelitis, rubella and tetanus. It also describes surveillance data concerning potential target diseases: hepatitis A infection, respiratory syncytial virus (RSV) infection, rotavirus infection and varicella zoster virus (VZV) infection. In addition, an overview of vaccines for infectious diseases that are undergoing clinical trials and are relevant for the Netherlands is included in this report.

The report has the following structure:
Chapter 1 gives a short introduction of the organization of the NIP. Recent results on vaccination coverage are discussed in Chapter 2. Public acceptance of vaccination and the communication of the NIP are described in Chapter 3. Chapter 4 focuses on the burden of diseases included in the NIP, while information on adverse events following immunisation (AEFI) is provided in Chapter 5. In Chapter 6, various research topics that address the evaluation of the NIP in a broader sense are presented. These include the progress made with data collection in the third seroepidemiological study in the Netherlands, the results of a seroepidemiological study conducted among refugees, as well as the results of research of non-specific effects and age differences with respect to vaccination. Chapter 7 focuses on the current target diseases of the NIP. For each disease, key points at the start of the section give the most prominent findings, followed by figures and tables; thereafter an update of information on epidemiology, the pathogen, the results of current and ongoing studies and international developments are given. For the first time, developments in the current target diseases of the NIP on the BES islands are also presented (Chapter 8). Chapter 9 describes potential new target diseases that are under consideration for (future) vaccination implementation. Finally, in Chapter 10, an overview is given of vaccines for infectious diseases that are undergoing clinical trials and are potentially relevant for the Netherlands.

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

Comprehensive summary

This report presents an overview of surveillance data and scientific developments in the Netherlands for vaccine-preventable diseases (VPDs) which are included in the National Immunisation Programme (NIP), i.e. diphtheria, pertussis, tetanus, poliomyelitis, *Haemophilus influenzae* disease, measles, mumps, rubella, meningococcal disease, hepatitis B, pneumococcal disease and human papillomavirus (HPV) infection (Figure 1). Surveillance data and scientific developments are also presented with regard to potential 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

Phase 1	Injection 1	Injection 2
6-9 weeks	DTaP-IPV Hib HBV	PCV
3 months	DTaP-IPV Hib HBV	
4 months	DTaP-IPV Hib HBV	PCV
11 months	DTaP-IPV Hib HBV	PCV
14 months	MMR	MenC

Phase 2	Injection 1	Injection 2
4 years	DTaP-IPV	

Phase 3	Injection 1	Injection 2
9 years	DT-IPV	MMR

Phase 4	Injection 1	Injection 2
12 years	HPV*	HPV* (6 months later)

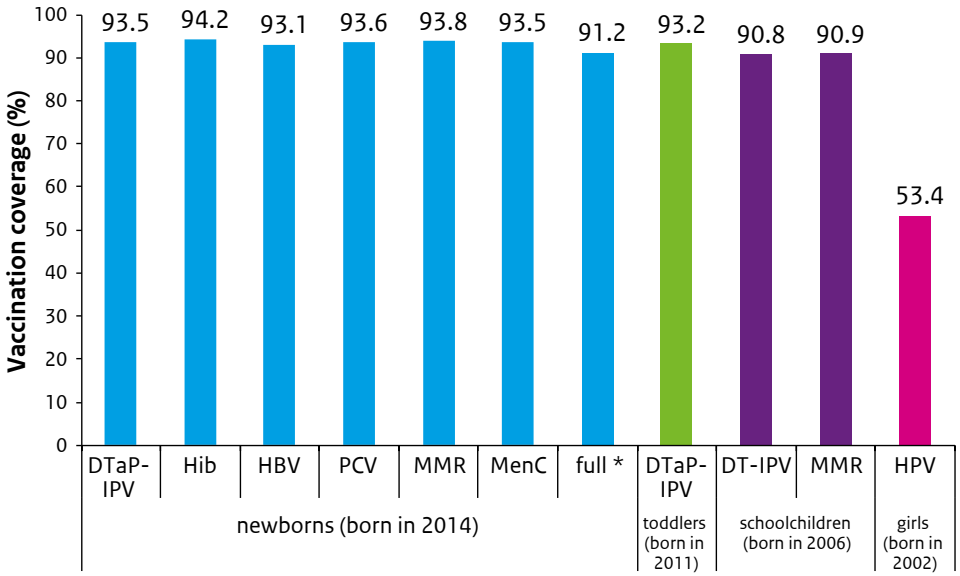
Meaning of the abbreviations

D	Diphtheria	HBV	Hepatitis B	MenC	Meningococcal C disease
aP	Pertussis (whooping cough)	PCV	Pneumoccal disease	HPV	Human papillomavirus
T	Tetanus	M	Mumps		
IPV	Poliomyelitis	M	Measles	*	Only for girls
Hib	*Haemophilus influenzae* type b	R	Rubella		

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

Vaccination coverage

Vaccination coverage in the Netherlands is high. Nevertheless, for newborns, participation in most vaccinations declined by approximatley 0.5% for the third consecutive year. In 2017, participation in HPV vaccination declined to 53%, after an earlier rise from 56% (2012) to 61% (2015-16).



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

Figure 2 Vaccination coverage per vaccine for newborns, toddlers, schoolchildren and adolescent girls in report year 2017
Source: Præventis

Acceptance of vaccination

In June 2017, E-learning about the NIP for child vaccine providers (CVPs) became available. A new NIP website for both the public and professionals is currently being developed. From 2018 onwards, more time will be available for discussions of vaccination between CVPs and parents.

The vaccination coverage among orthodox Protestants increased among subsequent generations. Pregnant women prefer to be counselled by a midwife or gynaecologist and to be vaccinated either by a general practitioner (GP) or their midwife.

Burden of disease

The estimated disease burden caused by (partly) vaccine preventable diseases expressed in Disability Adjusted Life Years (DALY) for the year 2016 was highest for invasive pneumococcal disease (9,827 DALY/year), pertussis (1,502 DALY/year), invasive meningococcal disease (875 DALY/year), invasive *Haemophilus influenzae* disease (857 DALY/year) and rotavirus infection (673 DALY/year). The average annual disease burden for HPV in the period 2011-2014 was estimated at 13,795 DALY (76% among women), higher than any of the diseases mentioned above. Compared with the estimated burden in 2015, the burden in 2016 was relatively low for pertussis and rotavirus infection and relatively high for meningococcal disease because of the rise in the number of patients with meningococcal serogroup W disease (not included in the NIP).

Adverse events

In 2016, Lareb received 1,482 reports with a total of 3,366 adverse events following immunisation (AEFI), which is in line with the numbers received in previous years. No signals emerged to indicate that vaccines used in the NIP were unsafe.

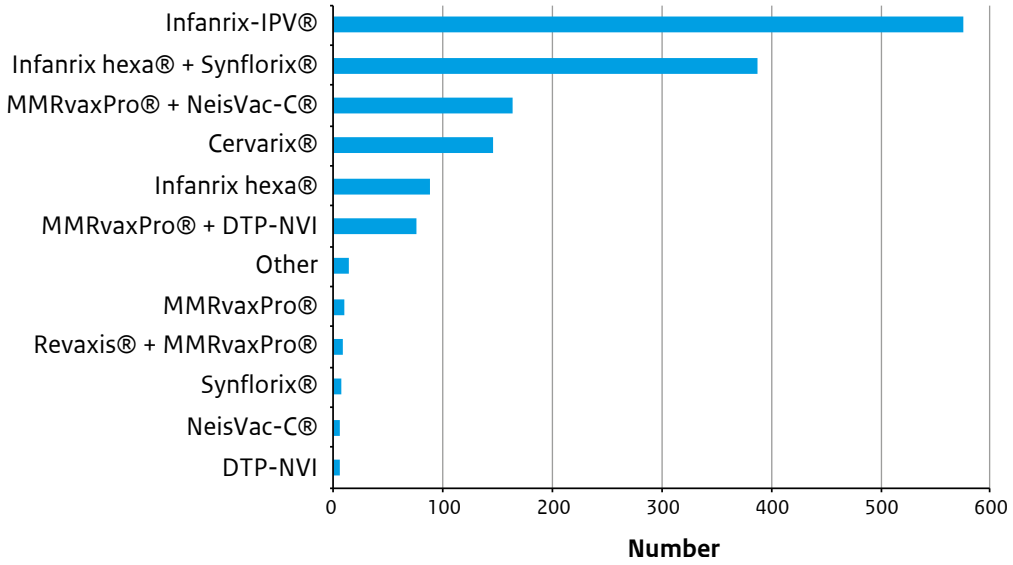


Figure 3 Number of reports of adverse events per suspected vaccine(s) in 2016
Source: Lareb

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

In February 2016, the third national seroepidemiological study started (PIENTER-3). Interim reports show that, after visiting 38 of the 40 municipalities, 4,995 persons were included in the study (response rate 16.8%). Inclusion of participants will continue until the end of October 2017. Results of a seroprevalence study conducted among more than 600 adult refugees indicated that the overall seroprevalence of protective antibodies against mumps, rubella, varicella, diphtheria, tetanus, polio and hepatitis A is generally high. But for measles, the seroprevalence was below the threshold of 95% required for herd immunity.

Using data from the PIENTER2 study (2006/2007), no indications were found to lead to the assumption that there are substantial differences between boys and girls in IgG levels/titres after vaccination against measles, mumps, rubella, MenC, and polio that would warrant a differential vaccination schedule for boys and girls.

Current NIP

Diphtheria

In 2016, two diphtheria notifications were received. These concerned a 52-year-old female and a 32-year-old male, both vaccinated. Furthermore, in 2017 up to July 1st, one notification was received about a 64-year-old male with unknown vaccination status.

Haemophilus influenzae disease

The number of cases of *Haemophilus influenzae* type b (Hib) disease in 2016 (n=44) was 52% higher than in the previous five years (22-34 cases). Up to May 2017, 18 cases were reported. In 2016, the incidence of Hib disease was highest among children under the age of five (2.4 per 100,000) and significantly increased compared with the previous five years (0.5-1.5 per 100,000). There were 12 Hib cases with vaccine failure in 2016 (50% of all 24 vaccine eligible Hib cases), resulting in a Hib vaccine effectiveness estimate of 95%, which was similar to the previous years. The number of cases caused by nontypeable Hi (NTHi) strains did not increase further in 2016 (n=124) compared with 2015 (n=127).

Hepatitis B

The incidence of acute hepatitis B virus (HBV) infection notifications remained stable in 2016 at 0.6 per 100,000 people. Among both men and women, heterosexual contact was the most frequently reported risk factor for acute HBV infection. In 2016, genotype A continues to be the dominant genotype among acute HBV cases. However, almost 90% of the total number of the 1,100 reported hepatitis B cases involved a chronic infection and, of those, 85% were in people born abroad.

Human papillomavirus (HPV) infection

The incidence of cervical cancer increased in 2016 (9.3 per 100,000 compared with 7.7 per 100,000 in 2015), while the number of deaths only slightly increased (2.7 per 100,000 in 2016 compared with 2.4 per 100,000 in 2015).

In a prospective cohort study (HAVANA), high vaccine effectiveness (VE) against vaccine types HPV16/18 was found for 12-month persistent infections up to six years post-vaccination (98%; 95%CI 82-100%). In addition, significant cross-protection against incident HPV infections by HPV31/35/45 and against 12-month persistent infections caused by HPV31 was found. In incident infections, vaccinated study participants show significant lower viral loads compared with non-vaccinated study participants. Among 16- to 24-year-old STI clinic visitors (PASSYON study), the VE against HPV16/18 positivity was high (90%). In addition, significant cross-protection against types 31, 35, 45 and 52 was found (91%, 57%, 50% and 37%, respectively).

Measles

In 2016, with only six reported cases, the number of reported cases remained low and comparable to 2015. In 2017 up to July, 10 cases were reported.
In Europe, a resurgence of measles was observed in 2016 (n=3,767), which continued in 2017 (n=2,480 up to March). Most cases were reported in Romania, Italy and Germany.

Meningococcal disease

The number of cases involving meningococcal serogroup C (MenC) disease is still very low (incidence 2016: 0.04/100,000); there was one vaccine failure in 2017. However, after more than two decades of decrease, the incidence of meningococcal serogroup B (MenB) disease seems to increasing again, especially among < five-year-olds (incidence 2016: 3.0/100,000).

Furthermore, in 2016 and 2017, an ongoing increase in the number of cases involving meningococcal serogroup W (MenW) disease was observed, from nine cases in 2015 to 50 cases in 2016 and 34 up to May 2017. The current incidence of MenW disease is highest among persons aged 65 or older (0.60 per 100,000), followed by 15- to 24-year-olds (0.55 per 100,000) and < five-year-olds (0.41 per 100,000). The increase in MenW disease is due to an increase in finetype P1.5,2:F1-1, which is associated with the hypervirulent clonal complex 11. Because of the increasing incidence of MenW disease, the Dutch minister of Health decided to replace MenC vaccination at 14 months of age by MenACWY vaccination, and to introduce a MenACWY vaccination at 12-14 years of age. These changes will be actualized in 2018.

The number of cases involving meningococcal serogroup Y (MenY) disease in 2016 was somewhat higher than in the previous five years, mainly in persons aged 65 or older (incidence: 0.29/100,000).

Mumps

The incidence of mumps in 2016 was low (0.4 per 100,000) and comparable to the previous two years. Molecular typing indicated that mumps endemic transmission was present in 2016 and 2017. Most of the mumps cases in the Netherlands were caused by genotype G.

Pertussis

The 2016 pertussis epidemiology fits within the long-term epidemiology. Incidence amounted to 32.6 per 100,000, compared with 38.8 in 2015. Yet six people, i.e. three infants and three adults, died from pertussis. The prevalence of pertactin-deficient (i.e. a component of acellular vaccines) strains was 12% in 2016, compared with 16% in 2010-2015.

Data from a maternal pertussis vaccination trial showed that pertussis- specific antibody titres are higher at birth and at two and three months of age in infants of mothers that were vaccinated during pregnancy, compared with control infants of mothers that were vaccinated immediately after delivery. This means that, in combination with maternal pertussis vaccination, antibody titres are sufficient to postpone the start of the infant vaccination until the age of three months. The Ministry of Health, Welfare and Sport has a positive attitude towards the Dutch Health Council advice to offer maternal pertussis vaccination. In addition, the Health Council recommended that all employees who are in close contact with young infants during work should be offered vaccination against pertussis.

Pneumococcal disease

The introduction of pneumococcal conjugate vaccination (PCV) led to a significant decrease in overall invasive pneumococcal disease (IPD) in children under five, five- to 49-year-olds and in the elderly aged 65 and older. The incidence of PCV7 type invasive pneumococcal disease (IPD) remained very low in 2016/2017, with an incidence of 0.6 per 100,000. There were no cases of IPD caused by the additional serotypes in PCV10 (PCV10-7: serotype 1, 5 and 7F) in children younger than five in 2016/2017. In other age groups, the incidence of PCV10-7 type IPD further decreased in 2016/2017, due to herd protection. The increasing trend in the incidence of non-PCV10 type IPD continued in the 2016/2017 period. The vaccine effectiveness (VE) of at least two doses of PCV10 was 85% (95%CI 41-96%) against vaccine type IPD and 91% (95%CI 33-99%) against serotype 7F.

The incidence of PCV13-10 type IPD (3.2/100,000), including serotype 19A, was significantly higher in 2016/2017 than before the introduction of PCV7 (76% increase) and PCV10 (29% increase). It was similar to the incidence in 2015/2016 (3.2/100,000). The incidence of PPV23-PCV13 type IPD in 65+ year-olds has increased steadily over the last few years, from 10.6 per 100,000 in 2004/2005 to 25.8 per 100,000 in 2016/2017.

Poliomyelitis

In 2016 and in 2017 up to July 1st, no cases of poliomyelitis were reported. In April 2017, two fully vaccinated employees were exposed to a wild poliovirus type 2 (WPV2) spill in a Dutch vaccine manufacturing plant. Four days later, WPV2 was found in the stool of one of them and later on in sewage samples. Strict isolation was implemented. Shedding stopped 29 days later. No transmission was detected.

Rubella
In the year 2016 and in the first six months of 2017, no cases of rubella were reported.

Tetanus
In 2016, one case of tetanus was reported. It concerned an unvaccinated 72-year-old male who was hospitalised with signs of tetanus. No cases were reported in 2017 up to July 1st.

The immunisation programme on Bonaire, St. Eustatius and Saba

Since 2016, the national immunisationtion programme on Bonaire, St. Eustatius and Saba contained the same target diseases as the NIP in the European Netherlands.

On Bonaire during the past five years, one Hib case and in 2016 several pertussis cases were reported. Saba recently experienced a large varicella outbreak, with approximately 200-250 inhabitants affected. For the first time, the PIENTER survey, as part of the so-called Health Study, was conducted on Bonaire, St. Eustatius and Saba from May to August 2017 in order to assess how well the islands are protected against infectious diseases, among other things.

Potential NIP target diseases

Hepatitis A
In 2016, the number of reported hepatitis A patients (81 cases) remained low (2015: 80 cases) compared with previous years (2011 2014: 105-125 cases). Fifty-six per cent of the patients were aged 20 or older, hospitalisation in this group was higher (42%) than in cases involving persons younger than 20 (8%). Fifty-eight percent of the Dutch cases were reported to be travel-related, with Morocco reported most frequently.

An international outbreak of hepatitis A among MSM, ongoing since July 2016, also affects the Netherlands (~100 Dutch cases in one year).

Respiratory syncytial virus (RSV) infection
In the Netherlands, RSV mainly causes hospitalisation in infants, but is also estimated to cause considerable morbidity and mortality in the elderly. In the 2016/2017 season, RS-viruses were detected in 12% (n=123/1060) of nose and throat swabs taken from ILI and other ARI patients and collected by sentinel GPs.

Currently, 14 vaccine candidates are at least in phase 1 clinical trials, but only one has reached phase 3 trials. This vaccine candidate in phase 3 trials aims to vaccinate pregnant women to protect the newborn. The same vaccine was tested in the elderly, but showed no effectiveness.

Rotavirus infection

In 2016, a second low-endemic rotavirus season was observed (n=679), similar to 2014, while 2015 and 2017 showed average rotavirus epidemics, comparable to the years prior to 2014. Together, these observations suggest a possible transition from an annual to a biennual rotavirus epidemic pattern in the Netherlands. G9P[8] was the most prevalent genotype in 2016. The Dutch Health Council has published in September 2017 a recommendation on rotavirus vaccination to the Ministry of Health, Welfare and Sport. They recommend vaccinating high-risk group children (premature children, children with low birth weight or congenital pathology). In addition, they state that the Health Council is positive towards mass vaccination incorporated in the NIP, however, they mention that this will not be cost-effective seen the current vaccine prices.

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

The VZV epidemiology (incidence of GP consultations, hospitalisations and deaths) is comparable to previous years; in 2015 GPs recorded 250 varicella and 530 herpes zoster episodes per 100,000 population. For the prevention of herpes zoster (HZ), HZ/su might be a promising alternative to the already available herpes zoster vaccine, due to the higher sustained vaccine efficacy. It is now being submitted for regulatory approval in the USA, Canada, Japan and Europe.

Uitgebreide samenvatting

In dit rapport worden surveillancedata en wetenschappelijke ontwikkelingen in Nederland gepresenteerd voor ziekten waartegen binnen het Rijksvaccinatieprogramma (RVP) gevaccineerd wordt (difterie, kinkhoest, tetanus, polio, *Haemophilus influenzae* ziekte, mazelen, bof, rodehond, meningokokkenziekte, hepatitis B, pneumokokkenziekte en infectie met humaan papillomavirus (HPV; Figuur 1). Ook worden surveillancedata en wetenschappelijke ontwikkelingen beschreven voor ziekten waarvoor een vaccin (nog) niet in het RVP is opgenomen (rotavirusinfectie, infectie met varicella zoster-virus (VZV; waterpokken en gordelroos), hepatitis A en infectie met respiratoir syncytieel virus (RSV)).

Huidig vaccinatieschema

Fase 1	Inenting 1	Inenting 2
6-9 weken	DKTP Hib HepB	Pneu
3 maanden	DKTP Hib HepB	
4 maanden	DKTP Hib HepB	Pneu
11 maanden	DKTP Hib HepB	Pneu
14 maanden	BMR	MenC

Fase 2	Inenting 1	Inenting 2
4 jaar	DKTP	

Fase 3	Inenting 1	Inenting 2
9 jaar	DTP	BMR

Fase 4	Inenting 1	Inenting 2
12 jaar	HPV*	HPV* (6 maanden later)

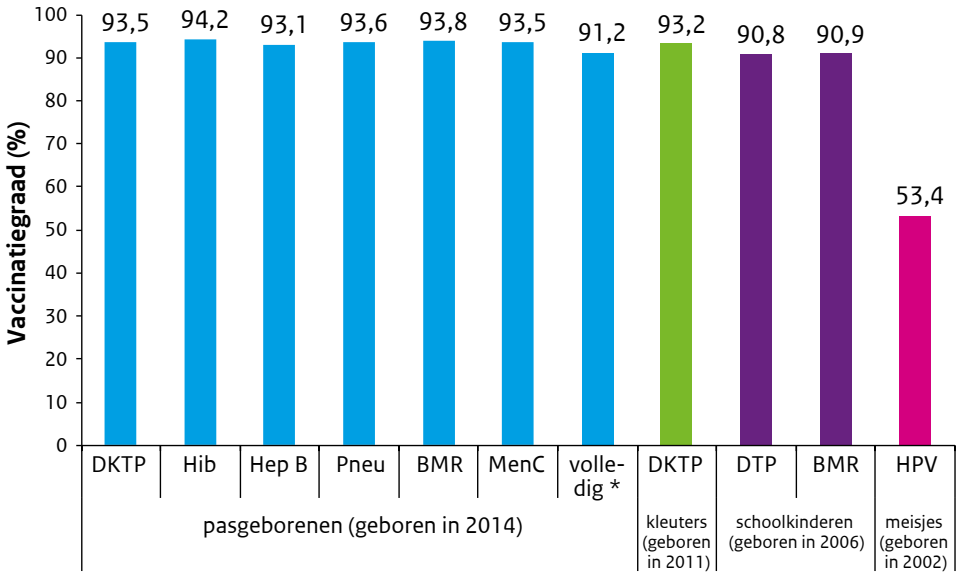
Betekenis afkortingen

D	Difterie	HepB	Hepatitis B	MenC	Meningokokken C
K	Kinkhoest	Pneu	Pneumokokken	HPV	Humaan Papillomavirus
T	Tetanus	B	Bof		
P	Polio	M	Mazelen	*	Alleen voor meisjes
Hib	*Haemophilus influenzae* type b	R	Rodehond		

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

Vaccinatiegraad

De vaccinatiegraad in Nederland is hoog. Toch daalde de participatie van pasgeborenen voor het derde achtereenvolgende jaar.voor de meeste vaccinaties met ongeveer 0,5%. Ook is in 2017 de vaccinatiegraad voor HPV-vaccinatie gedaald naar 53%, dit na een eerdere stijging van 56% (2012) naar 61% (2015-16).



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

Figuur 2 Vaccinatiegraad per vaccine voor pasgeborenen, kleuters, schoolkinderen en adolescente meisjes in verslagjaar 2017
Bron: Præventis

Acceptatie van vaccinatie

In juni 2017 is er een e-learning beschikbaar gekomen voor professionals die betrokken zijn bij de uitvoering van het RVP. Een nieuwe website voor het publiek en professionals is nog in ontwikkeling. Vanaf 2018 zal er voor professionals meer tijd beschikbaar zijn om de vaccinaties te bespreken met ouders.

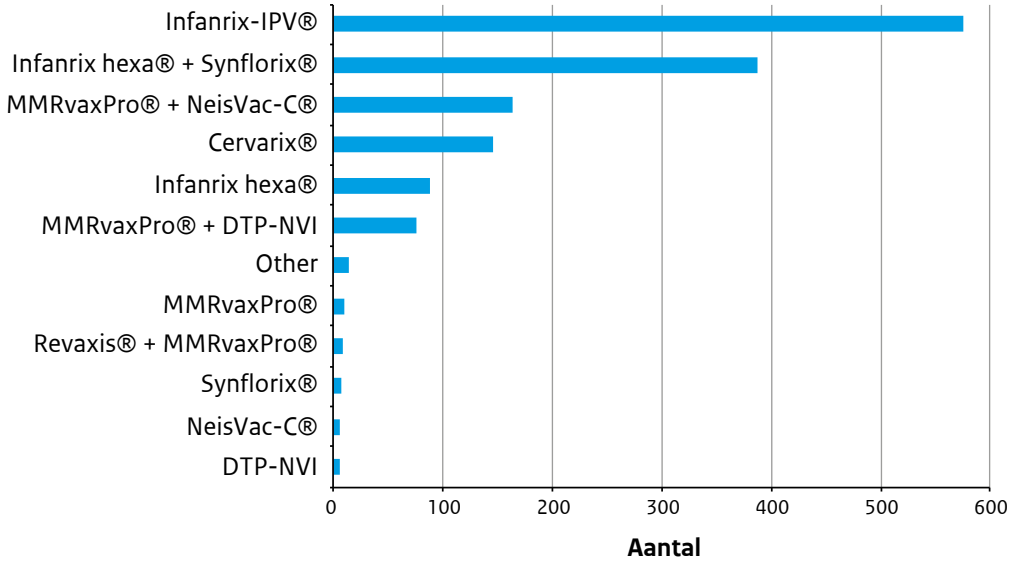
De vaccinatiegraad onder orthodox-protestanten is over langere termijn gestegen. Zwangere vrouwen worden het liefst geadviseerd door een verloskundige of gynaecoloog en gevaccineerd door de huisarts of hun verloskundige.

Ziektelast

De geschatte ziektelast veroorzaakt door ziekten die (deels) door vaccinatie te voorkomen zijn, uitgedrukt in Disability Adjusted Life Years (DALY), was in 2016 het hoogst voor: invasieve pneumokokkenziekte (9.827 DALY/jaar), kinkhoest (1.502 DALY/jaar), invasieve meningokokkenziekte (875 DALY/jaar), invasieve *Haemophilus influenzae*-ziekte (857 DALY/jaar) en rotavirusinfectie (673 DALY/jaar). De gemiddelde jaarlijkse geschatte ziektelast voor HPV in de periode 2011-2014 was 13.795 DALY (76% voor vrouwen); hoger dan voor alle bovengenoemde ziekten. De geschatte ziektelast in 2016 was relatief laag voor kinkhoest en rotavirusinfectie en relatief hoog voor meningokokkenziekte, vergeleken met de geschatte ziektelast in 2015, door de stijging in aantal patiënten met meningokokken serogroep W-ziekte (niet opgenomen in het RVP).

Bijwerkingen

In 2016 ontving Bijwerkingencentrum Lareb 1.482 meldingen van in totaal 3.366 mogelijke bijwerkingen van vaccins. Deze aantallen zijn vergelijkbaar met het aantal ontvangen meldingen in voorgaande jaren. De meldingen van vermoede bijwerkingen in 2016 hebben geen nieuwe signalen aan het licht gebracht.



Figuur 3 Aantal meldingen van bijwerkingen per vaccin(s) in 2016
Bron: Lareb

Verschillende onderzoeksonderwerpen over de evaluatie van het RVP in bredere zin

In februari 2016 is de derde nationale sero-epidemiologische studie gestart (PIENTER3). Tussentijdse rapportage na bezoek van 38 van de 40 gemeenten laat een deelname van 4.995 personen zien (16,8%). Inclusie van deelnemers zal tot eind oktober 2017 plaatsvinden. Resultaten van een seroprevalentiestudie onder ruim 600 volwassen asielzoekers laten zien dat de seroprevalentie van antistoffen tegen bof, rodehond, varicella (waterpokken en gordelroos), difterie, tetanus, polio en hepatitis A over het algemeen hoog is. De seroprevalentie van antistoffen tegen mazelen was echter lager dan de WHO-drempel van 95%.

In de data van de PIENTER2-studie (2006-2007) werden geen indicaties gevonden voor wezenlijke verschillen in IgG-antistoftiters tussen jongens en meisjes na vaccinatie tegen mazelen, bof, rodehond, meningokokken C en polio, die een verschillend vaccinatieschema naar geslacht zouden rechtvaardigen.

Huidig RVP

Difterie

In 2016 waren er twee meldingen van difterie, een 52-jarige vrouw en een 32-jarige man die beiden gevaccineerd waren. In de eerste maanden van 2017, tot 1 juli, werd één geval gemeld, een 64-jarige man met een onbekende vaccinatiesatatus.

Haemophilus influenzae ziekte

Het aantal gevallen van invasieve ziekte veroorzaakt door *Haemophilus influenzae* type b (Hib) in 2016 (n=44) was 52% hoger dan het aantal in de afgelopen 5 jaar (22-34 gevallen). Tot en met mei 2017 werden er 18 gevallen van Hib gemeld. In 2016 werd de hoogste incidentie gevonden onder kinderen jonger dan 5 jaar (2,4 per 10.000), dit was significant hoger dan in de vijf voorgaande jaren (0,5-1,5 per 100.000). Er waren 12 Hib-vaccinfalens in 2016 (50% van alle 24 cases die in aanmerking kwamen voor vaccinatie), wat resulteerde in een schatting van de vaccineffectiviteit (95%) vergelijkbaar met voorgaande jaren.
Het aantal gevallen veroorzaakt door een niet-typeerbare Hi-stam steeg in 2016 niet verder (n=124) vergeleken met 2015 (n=127).

Hepatitis B

De incidentie van meldingen van acute hepatitis B-infecties bleef in 2016 met 0,6 per 100.000 inwoners stabiel. Voor zowel mannen als vrouwen was heteroseksueel contact de meest gerapporteerde risicofactor voor een acute hepatitis B-infectie. In 2016 was genotype A nog steeds het dominante genotype onder acute hepatitis B-gevallen. Bijna 90% van de in totaal 1100 gerapporteerde hepatitis B-patiënten had een chronische infectie; van hen is 85% in het buitenland is geboren.

Human papillomavirus (HPV) infectie
Alhoewel de incidentie van baarmoederhalskanker is gestegen in 2016 (9,3 per 100.000 vergeleken met 7,7 per 100.000 in 2015), steeg het aantal sterfgevallen maar licht (2,7 per 100.000 in 2016 vergeleken met 2,4 per 100.000 in 2015).

In een prospectieve cohortstudie (HAVANA) werd een hoge vaccineffectiviteit gevonden tegen 12-maanden persistente infecties met de HPV-vaccin-typen 16/18; tot in ieder geval 6 jaar na de vaccinatie (98%; 95%BI 82-100%). Ook werd significantie kruisbescherming gevonden tegen incidente infecties met HPV31/25/45 en tegen 12 maanden persistente infecties met HPV31. Voor incidente infecties werden onder gevaccineerde deelneemsters significant lagere virale loads gevonden vergeleken met niet-gevaccineerde deelneemsters. Ook onder 16- tot 24-jarige bezoekers van SOA-klinieken (PASSYON-studie) was de vaccineffectiviteit tegen HPV16/18 positiviteit hoog (90%). Tevens werd significante kruisbescherming gevonden tegen HPV-typen 31, 35, 45 en 52 (respectievelijk 91%, 57%, 50% en 37%).

Mazelen
In 2016 was het aantal meldingen met 6 gevallen laag en vergelijkbaar met 2015. In 2017 zijn er tot en met juli 10 gevallen gerapporteerd.
In Europa is in 2016 een opleving van mazelen waargenomen (3.767 patiënten) die doorging in 2017 (2.480 in de eerste drie maanden). De meeste patiënten zijn gerapporteerd in Roemenië, Italië en Duitsland.

Meningokokkenziekte
Het aantal gevallen van meningokokken serogroep C (MenC)-ziekte is nog steeds erg laag (incidentie 2016: 0,04 per 100.000). Er was één vaccinfalen in 2017. Het aantal gevallen van meningokokken B is stijgende na meer dan twee decennia daling, voornamelijk in kinderen jonger dan 5 jaar (incidentie 2016: 3,0 per 100.000).

In 2016 en 2017 was een aanhoudende stijging van het aantal gevallen van MenW-ziekte met 50 gevallen in 2016 en 34 in 2017 tot en met mei. De huidige incidentie van MenW-ziekte is het hoogst onder personen van 65 jaar of ouder (0,60 per 100.000), gevolgd door 15- tot 24-jarigen (0,55 per 100.000) en kinderen jonger dan 5 jaar (0,41 per 100.000). De stijging in MenW-ziekte is te wijten aan een stijging in finetype P1.5,2:F1-1 die geassocieerd is met hypervirulent klonaal complex 11. Vanwege de toename in meningokokkenziekte serogroep W heeft de minister van VWS besloten om de huidige MenC vaccinatie op 14 maanden te vervangen door een MenACWY vaccinatie, en om MenACWY vaccinatie aan te bieden aan 12-14 jarigen. Deze aanpassingen zullen in 2018 geëffectueerd worden.

Het aantal gevallen van meningokokken serogroep Y (MenY)-ziekte was in 2016 iets hoger dan in de voorgaande vijf jaar, voornamelijk in personen van 65 jaar of ouder (incidentie: 0,29 per 100.000).

Bof
De incidentie van bof was in 2016 laag (0,4 per 100.000) en vergelijkbaar met de voorgaande twee jaar. Moleculaire typering toont endemische transmissie van bof in 2016 en 2017.
De meeste gevallen van bof worden veroorzaakt door genotype G.

Kinkhoest
De kinkhoestepidemiologie van 2016 past in het epidemiogisch beeld over een langere periode. De incidentie was 32,6 per 100.000, vergeleken met 38,8 per 100.000 in 2015.
Er overleden wel 6 mensen aan kinkhoest; drie zuigelingen en drie volwassenen.
De prevalentie van pertactine-deficiënte stammen (een component van acellulaire vaccins) was 16% in 2010-2015, vergeleken met 12% in 2016.

Data van een maternale kinkhoestvaccinatie-trial laten zien dat kinkhoestspecifieke antistoffen bij kinderen van moeders die gevaccineerd zijn tijdens de zwangerschap bij de geboorte en na 2 en 3 maanden hoger zijn dan bij kinderen van vrouwen die direct na de bevalling zijn gevaccineerd (de controlegroep). Dit betekent dat in combinatie met maternale kinkhoestvaccinatie de antistoffen hoog genoeg zijn als vaccinatie wordt gegeven aan baby's van 3 maanden oud. De minister van Volksgezondheid, Welzijn en Sport is positief over het advies van de Gezondheidsraad om alle zwangere vrouwen tijdens de zwangerschap een kinkhoestvaccinatie aan te bieden. In aanvulling hierop heeft de Gezondheidsraad geadviseerd om alle werknemers die tijdens hun werk met pasgeborenen in contact komen een kinkhoestvaccinatie aan te bieden.

Pneumokokkenziekte
Introductie van pneumokokkenvaccinatie (PCV) heeft geleid tot een significante daling in invasieve pneumokokkenziekte onder kinderen jonger dan 5 jaar, onder 5- tot 49-jarigen en onder ouderen van 65 jaar of ouder. De incidentie van PCV7-typen pneumokokkenziekte bleef met 0,6 per 100.000 erg laag in 2016-2017. Er waren in deze periode geen gevallen van pneumokokkenziekte veroorzaakt door de additionele typen in PCV10 (serotype 1, 5 en 7F) onder kinderen jonger dan 5 jaar. In andere leeftijdsgroepen daalde de incidentie van niet-PCV10-typen nog verder. De vaccineffectiviteit van minimaal twee doses PCV10 was 85% (95%BI 41-96%) tegen pneumokokkenziekte veroorzaakt door vaccintype IPD en 91% (95%BI 33-99%) tegen serotype 7F.

De incidentie van pneumokokkenziekte veroorzaakt door additionele typen in PCV13 (3,2 per 100.000), inclusief serotype 19A, was significant hoger in 2016-2017 dan vóór introductie van PCV7 (76% stijging) en PCV10 (29% stijging). De incidentie was vergelijkbaar met de incidentie in 2015-2016 (3,2 per 100.000). De incidentie van pneumokokkenziekte veroorzaakt door additionele typen in PPV23 in personen van 65 jaar en ouder steeg gestaagd over de laatste jaren; van 10,6 per 100.000 in 2004-2005 naar 25,8 per 100.000 in 2016-2017.

Polio
In 2016 en 2017, tot 1 juli, werden geen gevallen van polio gerapporteerd. In april 2017 werden twee volledig gevaccineerde werknemers blootgesteld aan wild poliovirus type 2 (WPV2) tijdens het productieproces van het poliovaccin. Vier dagen later werd WPV2 gevonden in de ontlasting van één van hen en later in rioolwatermonsters. Strikte isolatie werd geïmplementeerd. De uitscheiding stopte 29 dagen later. Er is geen transmissie gedetecteerd.

Rodehond
In 2016 en de eerste zes maanden van 2017 werden geen gevallen van rodehond gerapporteerd.

Tetanus
In 2016 werd één melding gedaan van tetanus. Het ging om een 72-jarige ongevaccineerde man die in het ziekenhuis was opgenomen met symptomen van tetanus. In 2017, tot 1 juli, werden geen meldingen van tetanus gedaan.

Het vaccinatie programma op Bonaire, St. Eustatius and Saba

Sinds 2016 is het RVP op Bonaire, St. Eustatius and Saba qua vaccinatieaanbod gelijk aan het RVP in Europees Nederland. Op Bonaire zijn er in de afgelopen vijf jaar één geval van Hib en begin 2016 een aantal gevallen van kinkhoest gemeld. Saba heeft recent een grote varicella-uitbraak gehad waarbij ongeveer 200 tot 250 inwoners waterpokken hebben gekregen.

Tussen mei en augustus 2017 vindt er voor het eerst een PIENTER-studie, als onderdeel van de zogenoemde Health Study, plaats op Bonaire, St. Eustatius and Saba. Het doel is onder andere om de bescherming van de inwoners tegen infectieziekten te bepalen.

Potentiële RVP-kandidaten

Hepatitis A
In 2016 bleef het aantal gevallen van hepatitis A laag (n=81) vergeleken met voorgaande jaren (2015: 80 gevallen; 2011-2014: 105 125 gevallen). Van de gevallen was 56% ouder dan 20 jaar. Ook het aantal ziekenhuisopnames was hoger in deze groep (42%) dan in patiënten jonger dan 20 jaar (8%). 58% van de Nederlandse gevallen was reis-gerelateerd, voornamelijk met reizen naar Marokko.

Sinds juli 2016 is er een internationale uitbraak van hepatitis A gaande onder mannen die seks hebben met mannen die ook in Nederland voor gevallen heeft gezorgd (ongeveer 100 gevallen in een jaar).

Respiratoir syncytieel virus (RSV)-infectie
In Nederland veroorzaakt RSV met name ziekenhuisopname onder pasgeborenen, maar waarschijnlijk is RSV ook de oorzaak van veel morbiditeit en sterfte onder ouderen. In het seizoen 2016-2017 werd in 12% (n=123/1060) van de neus- en keelswabs van ILI- en ARI-patiënten, verzameld door peilstationhuisartsen, RSV aangetoond.

Op dit moment lopen er 14 vaccinkandidaten in tenminste fase 1-trials; nog maar één daarvan heeft fase 3 bereikt. Dit vaccin is voor zwangere vrouwen en gericht op bescherming van hun pasgeborene. Hetzelfde vaccin is ook getest in ouderen, maar daar is geen effectiviteit aangetoond.

Rotavirusinfectie

In 2016 werd, vergelijkbaar met 2014, opnieuw een laag-endemisch seizoen geobserveerd (n=679), terwijl 2015 en 2017 normale endemische jaren waren, vergelijkbaar met de jaren 2009-2013. De rotavirusseizoenen zoals geobserveerd vanaf 2014 suggereren een mogelijke overgang van een jaarlijks naar een tweejaarlijks epidemisch patroon. G9P[8] was het meest voorkomende genotype in 2016. De Gezondheidsraad heeft in september 2017 een advies uitgebracht voor het Ministerie van Volksgezondheid, Welzijn en Sport betreffende rotavirus vaccinatie. Ze adviseren kinderen te vaccineren die een hoog risico lopen op een rotavirus infectie (dit zijn te vroeg geboren kinderen, kinderen met een laag geboortegewicht of aangeboren afwijkingen). Daarnaast staat de commissie ook positief tegenover vaccinatie van alle kinderen en dit op te nemen in het RVP. Echter, ze laten weten dat met de huidige vraagprijzen van de vaccins de kosteneffectiviteit ongunstig is wanneer alle kinderen worden gevaccineerd.

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

De epidemiologie van VZV (huisartsenbezoeken, ziekenhuisopnames en sterfgevallen) is vergelijkbaar met voorgaande jaren; in 2015 registreerden huisartsen 250 waterpokken- en 530 gordelroosepisodes per 100.000 inwoners. HZ/su is mogelijk een veelbelovend alternatief voor het al beschikbare herpes zoster-vaccin voor de preventie van herpes zoster (HZ) door de aanhoudende vaccineffectiviteit. Resultaten worden momenteel ingediend voor registratie van het vaccin in USA, Canada, Japan en Europa.

1
Introduction

1.1 Vaccination schedule of the NIP

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

Phase 1	Injection 1	Injection 2
6-9 weeks	DTaP-IPV Hib HBV	PCV
3 months	DTaP-IPV Hib HBV	
4 months	DTaP-IPV Hib HBV	PCV
11 months	DTaP-IPV Hib HBV	PCV
14 months	MMR	MenC

Phase 2	Injection 1	Injection 2
4 years	DTaP-IPV	

Phase 3	Injection 1	Injection 2
9 years	DT-IPV	MMR

Phase 4	Injection 1	Injection 2
12 years	HPV*	HPV* (6 months later)

Meaning of the abbreviations

D	Diphtheria	HBV	Hepatitis B	MenC	Meningococcal C disease
aP	Pertussis (whooping cough)	PCV	Pneumoccal disease	HPV	Human papillomavirus
T	Tetanus	M	Mumps		
IPV	Poliomyelitis	M	Measles	*	Only girls
Hib	*Haemophilus influenzae* type b	R	Rubella		

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

1.1.1 Changes in vaccination schedule

In 2016 and 2017 up to August, no changes in the vaccination schedule of the NIP were made.

1.1.2 Number of vaccinated children

In 2016, approximately 760,000 children aged 0 to 19 years were immunised in the context of the Dutch NIP. They received a total of 2,140,000 vaccine doses. In 2016, the vaccination schedule consisted of 12 (boys) or 14 (girls) vaccine doses per child. Seven of those were given between 0 and 11 months of age.

1.2 (Maternal) pertussis vaccination

The Ministry of Health, Welfare and Sport (VWS) has expressed a positive attitude towards the advice of the Dutch Health Council to offer all pregnant women in the Netherlands a pertussis vaccination to protect newborns against pertussis.
In June 2017, the Dutch Health Council recommended that all employees who are in close contact with young infants during work should be offered vaccination against pertussis.

1.3 Vaccination of risk groups

In addition to diseases included in the NIP, influenza vaccination is offered through the National Influenza Prevention Programme (NPG) to people aged 60 years and over and to those with an increased risk of morbidity and mortality following influenza. Vaccination against tuberculosis is offered to children of immigrants from high-prevalence countries.
For developments with regard to influenza and tuberculosis, we refer readers to the reports of the Centre for Infectious Disease Control (CIb), the Health Council and the KNCV Tuberculosis Foundation [1-4].

Besides the vaccination against HBV included in the NIP, an additional vaccination programme that targets groups particularly at risk of HBV due to sexual behaviour or profession is in place in the Netherlands [5].

Information on vaccination of travalers and employees who are at risk for infections during their work can be found on the website *www.rivm.nl/vaccinaties*.

1.4 Vaccination outside of public vaccination programmes

There are a number of registered vaccines in the Netherlands that are available to the public outside of public programmes at the person's own expense. On the website *www.rivm.nl/vaccinaties* information on these vaccines can be found. Vaccinations registered for infants are those against gastro-enteritis caused by rotavirus infection, varicella, meningococcal B disease (MenB) and meningococcal ACWY disease (MenACWY). In September 2017 the Dutch Health Council has published a recommendation on rotavirus and the Dutch minister of Health decided to introduce MenACWY vaccination in 2018. For older children and adults, influenza and pertussis vaccinations are available. In September 2017 the Dutch Health Council has published a recommendation on rotavirus and the Dutch minister of Health decided to introduce MenACWY vaccination in the beginning of 2018. For older people, vaccinations against herpes zoster, pneumococcal disease and pertussis are available. In addition, HPV vaccination for boys, hepatitis A vaccination for children with one or both parents coming from a country with high hepatitis A prevalence, as well as hepatitis B vaccination for first and second generation migrants from countries where Hepatitis B is endemic are available. Professional guidelines are also available on herpes zoster, maternal pertussis vaccination, pertussis vaccination for adults, HPV vaccination outside the NIP, meningococcal ACWY vaccination, meningococcal B vaccination, rotavirus vaccination and varicella zoster vaccination.

Others are currently under development, such as guidelines for pneumococcal vaccination for the elderly, and hepatitis A vaccination and hepatitis B vaccination outside the NIP.
In 2015, the Dutch Health Council expanded the evaluation of these vaccines and provided advice on them [6] to the Minister of Health, Welfare and Sport, who will decide how vaccines will be made available. Some vaccines will be included in a public vaccination programme.
It has been advised that vaccination against herpes should not be offered within a national programme, but should remain available at the person's own expense [7].

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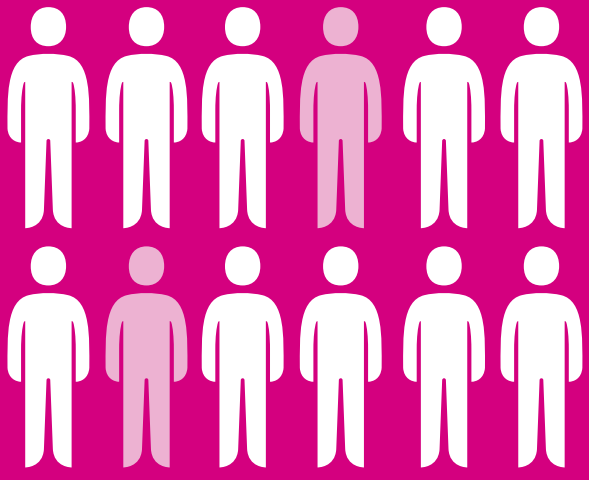
2
Vaccination coverage



E.A. van Lier

2.1 Key points

- Vaccination coverage in the Netherlands is high.
- Participation for most vaccinations declined by around 0.5% among newborns for the third consecutive year.
- In 2017, the participation for HPV vaccination declined to 53%, after an earlier rise from 56% (2012) to 61% (2015-16).

2.2 Tables and figures

Table 2.1 Vaccination coverage (%) per vaccine for age cohorts of newborns, toddlers, schoolchildren and adolescent girls in 2006-2017

	Newborns*							
Report Year	cohort	DTaP -IPV	Hib	HBV [a]	PCV **	MMR	MenC	Full ***
2006	2003	94.3	95.4	15.2	-	95.4	94.8	
2007	2004	94.0	95.0	17.1	-	95.9	95.6	
2008	2005	94.5	95.1	17.9	-	96.0	95.9	
2009	2006	95.2	95.9	18.6	94.4	96.2	96.0	
2010	2007	95.0	95.6	19.3	94.4	96.2	96.1	
2011	2008	95.4	96.0	19.4	94.8	95.9	95.9	
2012	2009	95.4	96.0	19.5	94.8	95.9	95.9	
2013	2010	95.5	96.1	19.7	95.1	96.1	96.0	
2014	2011	95.4	95.9	51.4	95.0	96.0	95.8	
2015	2012	94.8	95.4	94.5	94.4	95.5	95.3	
2016	2013	94.2	94.9	93.8	93.8	94.8	94.6	
2017	**2014**	**93.5**	**94.2**	**93.1**	**93.6**	**93.8**	**93.5**	**91.2**

	Toddlers*				Schoolchildren*			Adolescent girls*	
Report Year	cohort	DTaP -IPV [b]	DTaP -IPV [c]	DTaP -IPV [d]	cohort	DT -IPV	MMR ****	cohort	HPV
2006	2000	92.5	1.4	93.9	1995	93.0	92.9		
2007	2001	92.1	1.6	93.7	1996	92.5	92.5		
2008	2002	91.5	1.6	93.1	1997	92.6	92.5		
2009	2003	91.9	2.0	93.9	1998	93.5	93.0		
2010	2004	91.7	2.6	94.3	1999	93.4	93.1		
2011	2005	92.0	2.6	94.7	2000	92.2	92.1		
2012	2006	92.3	2.1	94.4	2001	93.0	92.6	1997	56.0
2013	2007	92.3	2.4	94.7	2002	93.1	92.9	1998	58.1
2014	2008	92.0	2.4	94.4	2003	92.7	92.4	1999	58.9
2015	2009	91.9	2.2	94.1	2004	92.7	92.7	2000	61.0
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**

* Vaccination coverage is assessed at the ages of two years (newborns), five years (toddlers), 10 years (schoolchildren) and 14 years (adolescent girls).
** Only for newborns born on or after 1 April 2006.
*** Key figure full participation newborns: received all NIP vaccinations at two years of age.
**** Two MMR vaccinations (in the past 'at least one MMR vaccination' was reported).
a Percentage of the total cohort. In 2011 universal hepatitis B vaccination was introduced; only risk groups were vaccinated previously.
b Revaccinated toddlers.
c Toddlers that reached basic immunity at age 2-5 years and were therefore not eligible for revaccination at toddler age.
d Sufficiently protected toddlers (sum of b and c).
Source: Præventis

2.3 Vaccination coverage

The immunisation coverage, i.e. the proportion of newborns, toddlers and schoolchildren who receive vaccinations within the NIP, is still high. The immunisation coverage for mumps, measles and rubella (MMR) has declined slightly for a few years. The 95% threshold of the World Health Organization (WHO) needed to eliminate measles is no longer achieved in the Netherlands for the first MMR vaccination. For the second MMR vaccination this has been the case for a longer time. Also, for other NIP vaccinations, there has been a slight decrease in participation. The participation in HPV vaccination against cervical cancer has decreased for the first year, from 61% to 53% [1].
In the European Region as a whole, a decline in vaccination coverage has also been seen [2, 3]. For example, the coverage for DTP3 decreased from 96% to 92% and for the first dose of the measles-containing vaccine from 95% to 93% in the period 2012-2016 [3]. Examples of countries where the decrease in vaccination coverage is relatively small include England [4] and Slovakia [5], whereas in Italy [6] and Romania [7] the vaccination coverage has dropped to ~85%. For HPV, sometimes significant drops are seen; for example, in Denmark the participation decreased from 82% to 55% [8]. In contrast, the rate of vaccination in the Netherlands among orthodox Protestants seems to be rising over time based on the comparison of coverage among different generations [9].

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* RIVM publication

2.4.2 Other recent RIVM publications

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3
Acceptance of vaccination

L. Mollema, K. Romijnders, R. van Alebeek, R. Prettner, W.L.M. Ruijs, B. Lehmann, M. Ensink

3.1 Key points

- In June 2017, E-learning about the NIP for child vaccine providers (CVPs) became available.
- A new NIP website for both the public and professionals is currently being developed.
- From 2018 onwards, more time will be available for discussions about vaccination between CVPs and parents.
- The vaccination coverage among orthodox Protestants increased among subsequent generations.
- Pregnant women would prefer to be counselled by a midwife or gynecologist and to be vaccinated either by a general practitioner (GP) or their midwife.

3.2 Vaccines included in the NIP

In response to the recent decrease in the vaccination coverage that is shown in the Netherlands, committee "Seydel" was installed at the end of June 2017. This committee has been asked to consider possible gaps and priorities in research into vaccine acceptance. Furthermore, possible practical barriers regarding vaccination uptake in the child welfare centres are being explored at present. In addition, the Minister has decided to invest in more time for discussions between child vaccine providers (CVPs) and parents concerning vaccinations at the child welfare centres (CWCs) from January 2018 onwards. In June 2017, the e-learning tool about the national immunisation programme (NIP) for CVPs became available (see *www.rvp.nl*).

3.2.1 Vaccination acceptance and the need for information among parents

In February and March 2017, focus group discussions were held with parents who vaccinate, partly vaccinate (delay or omit vaccinations) or do not vaccinate their children as a part of the RIVM project "RICALTS" about second-best communication. This four-year project aims to answer the question: 'If we also communicate about second-best options such as starting later or leaving out certain vaccinations, would this result in a public health gain or a public health loss?' Preliminary results are described below.

The results show that, in the decision to (partly) vaccinate or not, more factors played a role in making this choice among parents who delay vaccinating their child (delayers), who omit some vaccinations (omitters), or who do not vaccinate at all (refusers) than was the case with parents who fully vaccinate their child (acceptors). Similar factors seemed to play a role among omitting and refusing parents. The decision to delay, omit and refuse vaccinations sometimes seemed to be based on non-scientific information. Socio-psychological factors such as social norm, anticipated regret, trust in the Dutch government, risk perception of both diseases and side effects, and perceived vaccine effectiveness seemed to play a role in their respective decisions. Parents accepting all vaccinations seemed to have more feelings of anticipated

regret related to refusing vaccinations, had more trust in the government, and were more likely to think vaccines were effective than parents who were omitters, delayers or refusers. Omitting and refusing parents seemed to perceive the risk of getting infectious diseases (of the NIP) was lower than did other parents. Moreover, they perceived the risk of experiencing side effects related to vaccination to be higher compared with delayers and accepters. Factors such as lifestyle (e.g. breastfeeding, healthy living (e.g. healthy food), and not visiting day-care), vaccine components, and trusting that their child's immune system can cope with the infectious diseases appeared to play a role in the decision-making of delayers, omitters and refusers. Additionally, a positive attitude towards experiencing childhood diseases (e.g. measles) and having negative experiences with vaccination might influence the decision-making of omitting and refusing parents.

The results also showed that participants wanted to receive more information about side effects and the consequences of refusing the NIP. Furthermore, participants reported that they found the information they received from both RIVM and the CWCs to be compelling and authoritative. Participants reported that they would seek information if their information need could not be fulfilled by the brochure of the RIVM or by the CWCs. In that case, they searched for the information on the Internet and also made use of their social network. The information provided by the government was perceived as unreliable by some. Participants reported that their trust in the information of the RIVM might increase if the brochure contained more balanced information about the benefits and risks of the various vaccination choices. Most participants perceived information as reliable if there was a continuous update of new scientific research and an overview of all scientific research. In addition, participants mentioned that the entities who performed and financially supported the research should be made transparent. Finally, some participants mentioned that more concrete information shown in the form of absolute figures and percentages was perceived as being more reliable.

3.2.2 Acceptance HPV-vaccination among girls

Research was done (GGD Hart voor Brabant) to find out what thoughts played a role in the decision to vaccinate against HPV among girls that had been invited for HPV vaccination. Methods used were the analysis of a blog, a questionnaire and focus group discussions. Results showed that girls perceived a low risk of contracting HPV-infection and cervical cancer. Furthermore, girls perceived there to be a high risk of adverse events, especially in the short term (e.g. muscle pain, rash and acne), and reported that they were afraid of the injection. Girls reported that they did not receive enough reliable information about the rationale for HPV vaccination and its side effects and therefore they searched for information on their own, especially on social media. On social media they found negative stories about HPV vaccination that influenced their attitude negatively [1].

3.2.3 Discussions between childhood vaccine providers and parents

A recent analysis (2016/2017) has been performed of 20 conversations between CVPs and parents at CWCs and one public panel discussion about childhood vaccination (Wageningen University). All conversations were audiotaped without a researcher being present. The data were analysed with the aid of two related theoretical perspectives, Conversation Analysis and

Discursive Psychology. The results are categorized in discursive practices that are used by parents or health professionals. Parents have been found to either display knowledge that supports their decision on vaccination or employ an investigative stance if they were undecided. These actions are oriented to building the identity of a responsible parent that makes informed decisions. This parental stake was disregarded by health professionals when they portrayed vaccination as a beneficial intervention that needed no further elaboration. Furthermore, health professionals employed two other distinct practices that suppressed parents' possibilities to express concern or ask questions: Resorting to an institutional stance and engaging in a debate. For an undistorted conversation between the two parties, it is advised to let the parent set the agenda at the beginning of the talk. Early inquiries about parents' decision on the matter can have the undesired effect of ending the conversation prematurely. The use of health professionals' practices is mainly attributed to an institutional stance that they occupy during vaccine consultations. Stepping outside this role and reexamining health professionals' purpose in vaccine consultations is considered beneficial for both parties and could foster a more trusting relationship. A guideline to assist health professionals with the diverse requirements of these consultations will be forthcoming and can help to enhance visit experience [2, 3].

3.2.4 Increase in vaccination coverage among orthodox Protestants

Spaan and colleagues (2017) estimated vaccination coverage in subsequent generations of orthodox Protestants and the factors influencing the intention to vaccinate their (future) children. Orthodox Protestants (n=981) in the age group of 18-40 years filled out an online questionnaire on their own vaccination status, the vaccination status of their parents and the vaccination status or vaccination intention for their (future) children. Vaccination coverage among the parents of respondents was 40% and among respondents 55%. This represents an increase of 15% in one generation. About 65% of the respondents vaccinated or intended to vaccinate their (future) children. Orthodox Protestants who were vaccinated themselves, who were highly educated or who were member of less conservative churches more often intended to vaccinate their children. As in earlier studies, there were considerable differences in the vaccination coverage between the various orthodox Protestant denominations. A further increase of the vaccination coverage in the orthodox Protestant community is expected given the shift towards less conservative denominations in the orthodox Protestant community [4].

3.3 Vaccins not (yet) included in the NIP

3.3.1 Maternal pertussis vaccination

Women's attitudes towards maternal pertussis vaccination and its determinants, and women's need for information with regard to maternal pertussis vaccination were assessed. Pregnant women (n=202), mothers of children under the age of two (n=205) and women between 20 and 35 years of age without children (n=238) filled in an online questionnaire that assessed demographics, social cognitive determinants and underlying beliefs, their need for information, as well as practical considerations regarding the implementation of maternal pertussis vaccination. Overall, attitudes towards maternal pertussis vaccination were slightly positive, at 4.49 on a 7-point scale. The results of the three groups were analysed together as

no large differences between the groups were observed. Women's attitudes towards maternal pertussis vaccination were mainly predicted by their perception of the effectiveness of the strategy and beliefs about its safety, as well as moral norms and decisional uncertainty. The majority of women would like to receive information concerning the safety and effectiveness of the vaccine, the risk of infants contracting pertussis and its severity. They would prefer counselling by a maternal caregiver and would like to be vaccinated either by their general practitioner or a midwife. Pregnant women need to be educated about the effectiveness and safety of maternal pertussis vaccination to ensure a positive attitude towards maternal pertussis vaccination. Maternal caregivers need to be trained to be able to counsel and support pregnant women in their vaccination decisions.

3.3.2 Interviews with GPs and paediatricians about childhood vaccinations not (yet) included in the NIP

Semi-structured, in-depth interviews have been held with eight paediatricians and five GPs. The aim was to develop adequate information for health care professionals (HCPs) by gaining more insights into the attitudes, information needs and role-perceptions of the paediatricians and GPs about the NIP-candidates that target varicella, meningococcal B/ACWY, rotavirus and HPV in boys as well as in girls. Participating GPs seemed to prioritize the rotavirus vaccine in particular and perceived the meningococcal B/ACWY vaccines as the second most useful. In addition, they showed positive attitudes towards the HPV vaccine for both girls and boys. However, their opinion about the varicella vaccine varied. In the case of the participating paediatricians, the attitudes varied by paediatrician and vaccine but all NIP-candidates were regarded as relatively useful, particularly the meningococcal B/ACWY vaccines. The rotavirus vaccine was considered to be useful and cost-effective by the paediatricians. The varicella vaccine was especially perceived to be beneficial in cases involving risk groups. Both GPs and paediatricians emphasised that cost-effectiveness studies should be decisive to determine whether a candidate should be incorporated in the NIP and that new additions should never be harmful to the current NIP.

Regarding their information needs, the participating GPs would like to receive more information about topics such as the age of administration, how many times it needs to be administered, the possibility to administer it in vaccine-combinations, long-term effects, effectiveness, the duration of the protection, and possible adverse events and safety. In contrast, the majority of the participating paediatricians reported they only need extra information if (one of) the NIP-candidates are officially introduced in the NIP. A minority wanted to know more about topics such as the age of administration, long-term effects and possible side effects.

The majority of both GPs and paediatricians preferred the current way the NIP is being performed. They envisage a small role for themselves now and in the future regarding the actual administration of the NIP-candidates. Among the GPs, this role consisted of circumstances in which someone falls outside the scope of the target group. With respect to paediatricians, this role especially lies in the context of hospital-based children, such as premature children [5].

3.3.3 The intention of Dutch general practitioners to offer vaccination against pneumococcal disease, herpes zoster and pertussis to people aged 60 years and older

Lehmann et al. studied the intention among Dutch GPs to offer vaccination to people aged 60 and older. According to the 723 participating GPs, the pneumococcal vaccine (74.6%) had the highest chance of being included in a vaccination programme, followed by HZ vaccine (10.5%) and pertussis vaccine (4.2%) [6]. Providing GPs with evidence-based information about the severity and prevalence of diseases, and the effectiveness and health benefits of the vaccines could modify their intention.

3.4 Communication

3.4.1 New website for Dutch NIP

By the end of 2017, RIVM will present a new website for the Dutch NIP. This website is meant for parents and professionals. The website will contain both practical and background information about the programme, the different infectious diseases and vaccinations. The website will also present visual and graphic information to reach non-native speakers and low-literates. A responsive webdesign will be used, allowing desktop webpages to be viewed in response to the size of the screen (e.g. smartphones and tablets) or web browser one is viewing with without loss of readability or user interface.

3.5 Literature

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4
Burden of disease

E.A. van Lier, B. de Gier, M.J.J. Mangen, S. McDonald, M.J. Knol, I. Veldhuijzen, N.A.T. van der Maas, J. van de Kassteele, H.E. de Melker

4.1 Key points

- The estimated disease burden caused by (partly) vaccine preventable diseases expressed in Disability Adjusted Life Years (DALY) for the year 2016 was highest for invasive pneumococcal disease (9,827 DALY/year), pertussis (1,502 DALY/year), invasive meningococcal disease (875 DALY/year), invasive *Haemophilus influenzae* disease (857 DALY/year) and rotavirus infection (673 DALY/year).
- In a separate analysis, the average annual disease burden for HPV in the 2011-2014 period was estimated at 13,795 DALY (76% among women), higher than any of the diseases mentioned above.
- Compared with the estimated burden in 2015, the burden in 2016 was relatively low for pertussis and rotavirus infection and relatively high for meningococcal disease because of the rise in the number of patients with meningococcal serogroup W disease (not included in the NIP).

4.2 Tables and figures

Table 4.1 Estimated annual disease burden in DALY (with 95% uncertainty intervals) in the Netherlands 2012-2016, and DALY per 100 infections in 2016 (2015 for hepatitis B) [1, 2]

Disease	DALY (95% uncertainty interval)					DALYs/ 100 infections
	2012	2013	2014	2015	2016	
Diphtheria	1 (1–1)	0 (0–0)	1 (1–2)	4 (3–5)	2 (2–3)	122 (97–147)
Hepatitis A virus infection	65 (40–108)	59 (36–98)	57 (35–94)	43 (27–72)	44 (27–73)	11 (7.8–15)
Hepatitis B virus infection (acute)[a]	663 (621–702)	396 (367–424)	246 (231–261)	101 (94–107)		19 (18–21)
Human papillomavirus infection[b]						
• Females	10,720 (10,050–11,420)	9,976 (9,302–10,680)	10,830 (10,130–11,550)			n.a.
• Males	2,991 (2,366–3,774)	3,698 (3,025–4,506)	3,699 (2,967–4,546)			n.a.
Invasive *H. influenzae* disease	666 (629–704)	615 (580–650)	690 (653–730)	844 (797–890)	857[c] (803–909)	401 (377–424)
Invasive meningococcal disease	761 (610–925)	779 (630–943)	588 (463–731)	560 (437–696)	875[d] (728–1,041)	549 (499–600)
Invasive pneumococcal disease	10,090 (9,447–10,735)	10,791 (10,151–11,448)	9,075 (8,534–9,618)	10,847 (10,195–11,503)	9,827[e] (9,179–10,440)	350 (328–372)
Measles	26 (17–35)	8,597 (6,316–11,060)	396 (312–486)	15 (10–20)	16 (10–22)	23 (14–32)
Mumps	3 (3–3)	2 (1–2)	0 (0–0)	1 (1–1)	1 (1–1)	0.4 (0.4–0.4)
Pertussis	5,744 (5,329–6,186)	1,416 (1,324–1,513)	3,572 (3,307–3,869)	2,726 (2,525–2,951)	1,502 (1,397–1,613)	1.1 (1.1–1.2)
Poliomyelitis	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	n.a.
Rabies	0 (0–0)	35 (35–35)	49 (49–49)	0 (0–0)	0 (0–0)	n.a.
Rotavirus infection	1,237 (516–2,416)	1,432 (590–2,813)	602 (252–1,178)	1,270 (516–2,515)	673 (278–1,329)	0.5 (0.3–0.9)
Rubella	0 (0–0)	4 (3–5)	213 (171–260)	0 (0–0)	0 (0–0)	n.a.
Tetanus	11 (9–12)	6 (5–7)	0 (0–0	9 (7–10)	2 (2–2)	174 (167–181)

DALY = disability-adjusted life years

n.a. = not applicable; no cases occurring in 2016 or unknown number of infections (HPV)

a Annual burden estimates not available for 2016.

b Annual burden estimates not available for 2015 and 2016. To estimate the burden, the numbers of cases with cancer, anogenital warts and high-grade cervical lesions attributable to HPV were used.

c Proportion caused by the vaccine preventable type b in 2016: 38%.

d Proportion caused by the vaccine preventable type C in 2016: 3%; proportion caused by type B in 2016: 64%.

e Proportion caused by the vaccine preventable types 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F in 2016: 17%.

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

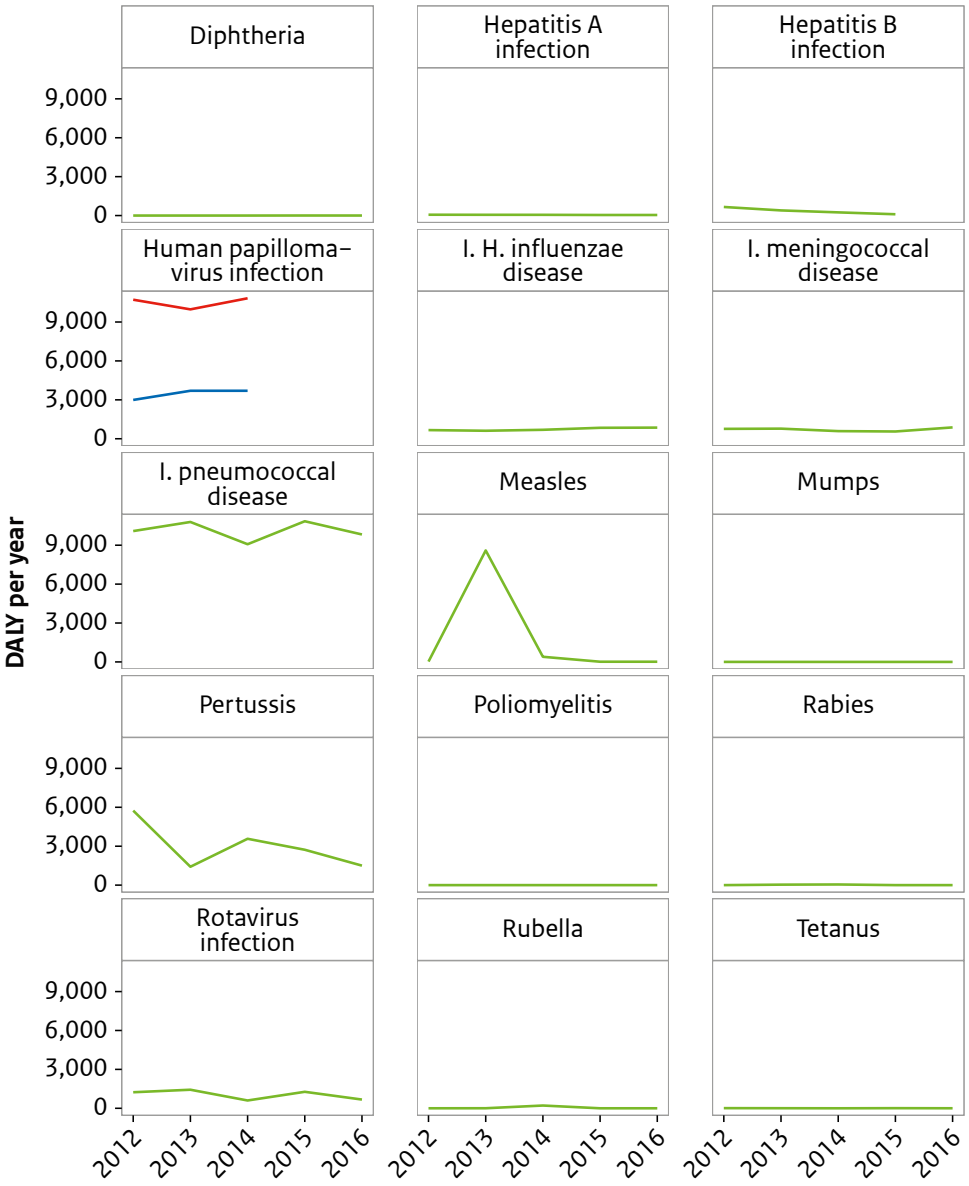

Figure 4.1 Estimated annual disease burden in DALY in the Netherlands 2012-2016 [1, 2]

1. Vaccination against rabies, hepatitis A and rotavirus infection is not included in the NIP.
2. For the three invasive diseases, there was only a vaccine available against certain serotypes: *Haemophilus influenzae* serotype b (Hib), meningococcal C and pneumococcal serotype 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F. For HPV infection, there was only a vaccine 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.

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

4.3 Burden of disease

Here we present an update for the disease burden, expressed in disability-adjusted life years (DALY), of vaccine-preventable diseases in the 2012-2016 period. We present the same estimates as published in the 'State of infectious diseases in the Netherlands, 2016' [1]. In contrast to previous burden estimates [3-6], the newly available European disability weights by Haagsma et al. [7] and the life expectancy as determined for the Global Burden of Disease (GBD) 2010 study [8] were applied. More detailed information on these changes and a full overview of the disability weights and durations that were used in the disease models can be found in the 'State of infectious diseases in the Netherlands, 2016' [1]. Estimates for human papillomavirus (HPV) infection were derived from a previous separate analysis [2]. Note that the calculation method used for HPV is not fully comparable to the other diseases: a different period (2011-2014) and life table (Dutch life expectancy 2014) have been used and, instead of using the number of incident infections (which are unknown), the numbers of cases with cancer, anogenital warts and high-grade cervical lesions attributable to HPV were used.

Table 4.1 shows the estimated DALY per year with 95% uncertainty intervals and the DALY per 100 infections in 2016 (2015 for acute hepatitis B), which is a measure of the disease burden at the individual patient level. With the exception of mumps, years of life lost (YLL) contribute more to the total DALY than years lived with disability (YLD). For poliomyelitis, rabies and rubella, the estimated disease burden in 2016 was zero because there were no cases reported in this year. For mumps, diphtheria, and tetanus, the disease burden in 2016 was estimated to be very low, while the highest burden was estimated for HPV infection (based on the burden in 2012-2014 instead of 2016), followed by invasive pneumococcal disease and pertussis.

The influence of outbreaks on the disease burden is apparent from Table 4.1 and Figure 4.1. The 2013/14 measles outbreak is clearly visible, as is that of rubella in 2014. The incidence of pertussis and rotavirus infection is known to surge every few years, which is also visible from Table 4.1. For both diseases, the incidence in 2016 was relatively low. For acute hepatitis B virus infection, a clear downward trend is visible due to decreasing incidence, but the estimate for 2016 was not yet available. For invasive meningococcal disease, the burden in 2016 was relatively high because the number of patients with serogroup W has increased. Vaccination against meningococcal disease serogroup W is not included in the NIP.

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 2012-2015, which means that the disease burden of (chronic) hepatitis B cases infected prior to this period is not included.

4.4 Literature

4.4.1 References

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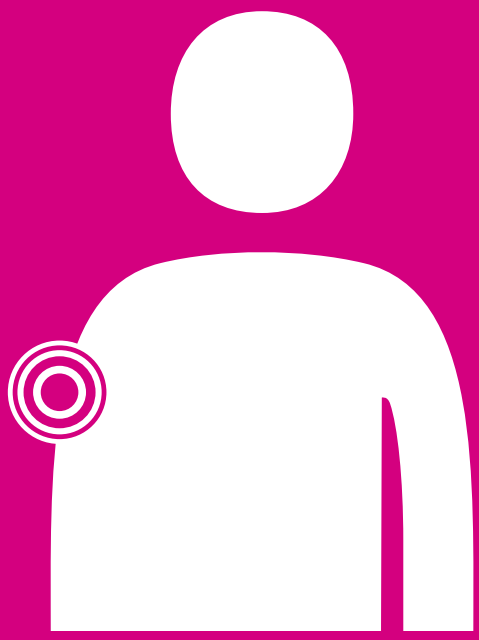
5
Adverse events



J.M. Kemmeren

5.1 Key points

- In 2016, Lareb received 1,482 reports of a total of 3,366 adverse events following immunisation (AEFI), which is in line with the numbers received in previous years.
- No signals emerged to indicate that vaccines used in the NIP were unsafe.

5.2 Tables and figures

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

Vaccines	Total 2015	Total 2016	2m	3m	4m	11m	14m	4yr	9yr	12-13yr	Other/ Unknown
Infanrix hexa® + Synflorix®	387	**387**	167		85	125					10
Infanrix hexa®	84	**88**	5	60	6	1					16
Synflorix®		**7**	2		4						1
MMRvaxPro® + NeisVac-C®	194	**163**					163				
MMRvaxPro®	15	**10**					5		1		4
NeisVac-C®	3	**5**					3				2
Infanrix-IPV®	422	**575**						572			3
MMRvaxPro® + DTP-NVI	80	**75**							72		3
Revaxis® + MMRvaxPro®		**8**							8		
DTP-NVI	6	**5**							3		2
Cervarix®	257	**146**								146	
Other	46	**14**									14
Total	1494	**1483**	174	60	95	126	171	572	84	146	55

Source: Lareb [1]

5.3 Passive surveillance system

5.3.1 Reports

The enhanced passive surveillance system, managed by the National Centre for Pharmacovigilance Lareb, receives reports of AEFI for all vaccines included in the NIP. In 2016, Lareb received 1,483 reports of a total of 3,665 AEFI (Table 5.1) [1]. This is in line with the numbers in 2015 (1,494 reports with 3,366 AEFIs). The most reported AEFIs were crying (n=351), fever (n=543) and injection site reactions (n=474). These numbers are also comparable with the number of reports in 2015. Of the reports, 111 (7.5%) were classified as serious.

In 2016, a higher number of reports (n=575) were received after administration of DTP-IPV at the age of 4 years, compared with 2015 (n= 422) and 2014 (n=274). Starting in 2017, another vaccine with a low-dose antigen content is being introduced for this age group. The RIVM and Lareb will monitor its effect on the number of reported AEFIs. The number of notifications received after administration of the HPV vaccine declined from 257 in 2015 to 146 in 2016. Additional information about the kind of AEFI per vaccination is lacking at present. This information would make it possible to interpret changes in the number of reports. Overall, there is no indication that vaccines used in the NIP are unsafe.

5.3.2 Signals

In 2016, Lareb published an updated report with an overview of reports of long-lasting AEFIs in association with Cervarix that were received between 1 January 2009 and 31 October 2016 [2]. In this period, Lareb received 1,436 reports of possible AEFIs following HPV vaccination, including 346 reports of long-lasting AEFIs with a duration of two months or more. The reported rate of long-lasting AEFIs per birth cohort is constant, about five per 10,000 vaccinated girls. Fatigue was the most frequently reported long-lasting AEFI (n=256). Several combinations of frequently reported AEFIs were found, but there was no consistent combination pattern in all the reports of long-lasting AEFIs received by Netherlands Pharmacovigilance Centre Lareb [2]. One of the most frequently reported combinations of long-lasting AEFIs concerns fatigue combined with headache and musculoskeletal discomfort. This combination of complaints, including the fact that no known medical explanation was found, are partially compatible with the criteria for chronic fatigue syndrome (CFS) used by the Dutch Institute for Healthcare Improvement (CBO) [3]. Although some reports concern symptoms that could be indicative of postural orthostatic tachycardia syndrome (POTS) or complex regional pain syndrome (CRPS), indications for these diagnoses were not found in any of the reports. In order to study whether long-lasting fatigue occurs more often in vaccinated girls than in unvaccinated girls and in order to determine the presence and strength of a causal relationship, Lareb recommended that epidemiological research be conducted. The RIVM had already started a study. See also Section 5.4.1.5 for international developments.

5.4 International developments

5.4.1 Vaccines targeting diseases included in the current NIP

5.4.1.1 MMR

Three studies demonstrated the safety of the MMR vaccine not only in children vaccinated during the regular immunisation programme, but also in children less than nine months of age vaccinated during measles outbreaks [4-6]. Apart from mild vaccine-related infections, MMR vaccines were safe when administered within two years after bone-marrow transplantation [7]. However, a case-control study in Italy provided evidence on the possible role of the MMR vaccine in Henoch-Schölein purpura occurrence [8].
A novel MMR vaccine, containing the Hoshino mumps strain, had a similar tolerability profile comparable to an existing MMR vaccine, containing the L-Zagreb mumps strain [9].

5.4.1.2 Pneumococcal disease

In the past year, several studies were published about the safety of pneumococcal vaccines. One study found an independent risk of febrile seizures after PCV7 vaccination (IRR 1.98; 95%CI 1.00-3.91) [10]. No safety issues were found for PCV10 and PCV13 in infants and children [11-13]. Furthermore, the safety profiles between PCV7 and PCV10, and between PCV7 and PCV13 were similar when both vaccines were co-administered with other routine paediatric vaccines [14-16]. The results from a systematic review showed that PCV failure is rare, irrespective of vaccine or schedule [17]. Preterm infants were shown to have a great tolerance to PCV7, PCV10 and PCV13 [18]. PCV10 was well-tolerated in HIV-infected children and children with sickle cell disease [19, 20], whereas no serious adverse events were found in children with nephrotic syndrome after PCV13 vaccination [21]. Also, in children with systemic inflammatory rheumatic diseases, pneumococcal vaccines were well-tolerated [22]. Comparable safety profiles were found for PCV13 in a multidose vial and PCV13 in a single-dose syringe and suggest PCV13 in a multidose vial can help optimize vaccination in resource-limited settings [23].

In adults and the elderly, no new or unexpected safety concerns were identified for PCV13 or for PPSV23 [24-36], although for PPSV23 revaccination was associated with an increased risk of local and systemic adverse events compared with primary vaccination. However, these increases were usually mild and self-limiting. The risk and severity of AEs appeared to decrease with longer intervals between primary and revaccination [26, 29]. Only in patients with cryopyrin-associated periodic syndromes did pneumococcal vaccines frequently trigger severe local and systemic inflammation. In these patients, PCV13 might be preferable over PPSV23.

5.4.1.3 Meningococcal C disease

The safety profiles for MenACWY-TT, co-administered with childhood vaccines, a co-administration of conjugated MenC with a MMRV vaccine and conjugated MenC with a DTaP-IPC-HepB-PRP-T vaccine were as expected for all these vaccines [37-39]. For the novel combined Hib-MenAC conjugate vaccine, no increase in adverse reaction was found and no serious adverse events were judged to be related to this vaccination [40]. Also, booster vaccination with MenACWY-TT or MenACWY-D had a clinically acceptable safety profile 4-6 years after primary vaccination [41, 42].

5.4.1.4 *DTaP-IPV-HBV-Hib*

Many studies in infants demonstrated the safety of the DTaP-IPV-Hib vaccine, the DTaP-Hib-HepB vaccine, the DTaP-IPV and Hib (PRP~T) vaccines, the DTaP-IPV-HepB-PRP-T vaccine, the Hib PRP-CRM197 vaccine and the DTaP-sIPV vaccine in different settings [14, 39, 43-49]. But it is known that replacement of whole-cell pertussis vaccines with acellular pertussis vaccines conincided with a significant increase in pronounced local adverse events after booster doses. A case-control study in the Netherlands demonstrated that four-year-old children with pronounced local reactions had higher humoral and cellular immune responses than did children with (almost) no local reactions [50]. This needs to be evaluated in further studies.

The safety of two investigational formulations of DTPa-HepB-IPV-Hib was evaluated in a primary and a booster vaccination study. Higher incidence of fever (>38°C) was reported in infants receiving the investigational formulations. For this reason, the developments of these formulations were not further pursued [51].

Four studies examined the safety of a combination vaccine containing a 5-antigen pertussis component [52-55]. All studies demonstrated a well tolerated safety profile, which confirmed the conclusion of a review of the use of the DTaP5-HepB-IPV-Hib vaccine in primary and booster vaccination [56]. The safety of the DTaP5-IPV vaccine in children 4 6 years of age was also shown in a phase III trial [57]. DTaP-IPV-Hib concomitantly given with a dengue vaccine in toddlers [58] and a dTpa booster vaccine in older children [59] were well-tolerated.

Case reports have suggested that vaccines may trigger transverse myelitis (TM) or acute disseminated encephalomyelitis (ADEM). In the Vaccine Safety Datalink population, a possible association of ADEM with Tdap vaccine was found, but the excess risk is not likely to be more than 1.16 cases of ADEM per million vaccines administered. For TM, no association with vaccination was found [60]. Among adolescents and adults, Tdap5 was found to be safe [61]. In a phase I/II trial, an aP vaccine containing recombinant genetically detoxified pertussis toxin showed a similar tolerability and safety profile compared to a licensed TdaP vaccine [62]. Furthermore, no safety issues were found for Tdap when administered before, with or after the PCV13 and MenACWY vaccines [63].

Three studies were published about the safety of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccines during pregnancy. No new or unexpected vaccine AEs were noted among pregnant women who received Tdap. Also, no associations between maternal Tdap vaccination and infant outcomes were observed [64-66].

5.4.1.5 *HPV*

Several studies described the safety of bivalent, quadrivalent and nonavalent HPV vaccination in a three-dose schedule [67-71]. The bivalent vaccine administered in a two-dose schedule was also well-tolerated in young girls [72]. Comparable frequencies for the majority of local and general reactions were found for the bivalent and quadrivalent vaccines in healthy UK adolescent females [73]. Only tenderness at the injection site reached a severe level after at least one of the doses in 24% of the bivalent vaccine group and 7% of the quadrivalent vaccine group (p=0.001).

Despite public and scientific concerns [74, 75], no indication has been found for a possible relationship between HPV vaccination and (auto immune-) diseases such as CFS/myalgic encephalomyelitis (ME), multiple scleroses (MS), Guillain-Barre syndrome (GBS), diabetes type I, autoimmune thyroiditis, idiopathic thrombocytopenic purpura (ITP), systemic lupus erythematosus (SLE) and optic neuritis [76-81]. In a recent study, Mølbak et al showed that 316 cases with reports of suspected severe adverse reactions following HPV vaccination had increased care-seeking in the two years before receiving the first HPV vaccine, compared with 163,910 controls [82]. Therefore, they emphasize that pre-vaccination morbidity should be taken into account in the evaluation of safety signals.
Quadrivalent HPV vaccination during pregnancy was not associated with a significantly higher risk of adverse pregnancy outcomes than no such exposure [83].

5.4.2 Other potential future target diseases

5.4.2.1 Meningococcal B disease

Four studies were published about the safety and reactogenicity of 4CMenB. No safety issues were mentioned concerning this vaccine in infants and children [84, 85], adults [86] and persons with high-risk medical conditions [87]. This confirms the findings of a review that concluded that results from four clinical trials do not suggest any safety concerns associated with 4CMenB vaccination in patients 10-25 years of age [88]. In September 2015, the UK became the first country in the world to introduce 4CMenB into the routine vaccine schedule for infants. Since then, almost a million doses have been given, with no safety concerns identified by the National Health Service [89]. However, Kapur et al. studied the emergency department attendance following 4CMenB vaccination [90]. In general, infants presented with fever have a higher risk of serious bacterial infection, but infants with fever in the post-vaccination period may not have the same risk. Therefore, infants presenting after 4CMenB vaccination pose a diagnostic challenge for paediatricians. The risk of missing an infant with a serious bacterial infection must be weighed against unnecessary medical intervention. National guidelines will need to take this group into consideration.

Concomitant administration of the bivalent rLP2086 MenB vaccine with MenACWY and Tdap does not substantially increase the reactogenicity, compared with the bivalent rLP2086 MenB vaccine alone [91].

5.4.2.2 Varicella

Well-tolerated safety profiles were demonstrated for the varicella vaccine (Oka vaccine strain) and MMRV, even when co-administrated with MenC or administered to Kawasaki disease patients who received infliximab [92-95]. Also, for second-dose varicella vaccination, no new or unexpected safety concerns were identified [96-98]. An investigation varicella vaccine developed in India was also found to be safe in healthy children aged 1-12 years [99]. Unexpected was the finding of left-sided facial herpes zoster caused by vaccine-strain varicella-zoster virus [100]. Shaw et al. illustrated the importance of conducting careful and complete evaluations when determining the most likely cause of an AEFI in a one-year-old child with arm paralysis after varicella vaccination. Molecular studies led to the conclusion that wild-type varicella zoster virus was the probable cause instead of the varicella vaccination [101].

5.4.2.3 *Herpes Zoster*

The safety of the live-attenuated herpes zoster vaccine has been demonstrated in healthy individuals, as well as in people with diabetes [102], adults with a prior physician-documented history of herpes zoster [103], in adults with hematologic malignancies receiving anti-CD20 monoclonal antibodies [104] and in patients vaccinated within two years after a bone-marrow transplant [7]. However, some serious reactions and vaccine-related infections were reported in immunosuppressed immune-mediated inflammatory disease or solid organ transplant patients [7].

Local reactogenicity was greater for subcutaneous administration, compared with intramuscular administration [105]. Transient erythema and induration were more common after intradermal administration, compared with subcutaneous administration (31% erythema for full subcutaneous dose and 77% for intradermal dose) [106].

5.4.2.4 *Hepatitis A*

The safety of the live attenuated hepatitis A vaccine and the inactivated hepatitis A vaccine was demonstrated in a phase IV study conducted among healthy children aged 18 months to 16 years [107]. A review focusing on the safety of the live attenuated hepatitis A vaccine also found minimal or negligible safety issues [108].
Li et al. described the safety of the combined vaccine against hepatitis A and hepatitis B. The safety profile of this vaccine was similar to the monovalent hepatitis A or B vaccines [109].

5.4.2.5 *Hepatitis B*

No safety issues were reported for the monovalent hepatitis B vaccine in pre-adolescents primed with hexavalent vaccines 10 years earlier during infancy [110]. Also, a thimerosal-free vaccine in neonates was well-tolerated [111]. Li et al. described the safety of the combined vaccine against hepatitis A and hepatitis B in toddlers. The safety profile of this vaccine was similar to the monovalent hepatitis A or B vaccines [109].
Safety data obtained from a study into HBsAg-binding protein adjuvant for the hepatitis B vaccine warrant further investigation [112]. No safety concerns associated with a 60 µg hepatitis B vaccine were noted in healthy adults [113] and among drug users [114, 115]. In addition, the conclusion of a review was that the hepatitis B vaccine had a clinically acceptable safety profile in all populations studied, including individuals with underlying co-morbidities and immunosuppression [116].
As in earlier years, Geier et al. reported studies into the effect of thimerosal-containing hepatitis B vaccines. They suggest that thimerosal increases the risk of obesity, disturbance of emotions and atypical autism diagnosis [117-119]. However, over the years the methodology of the studies of these authors has been criticized several times [120, 121]. The reliability of their study results is therefore low. In the Netherlands, thimerosal is not used as a preservative in routinely recommended childhood vaccines.

5.4.2.6 Rotavirus

Three studies demonstrated acceptable safety profiles for RV1 or RV5 [49, 122-124]. In addition, findings of Saleh et al. support the future conduct of large clinical trials in order to confirm the safety of rotavirus vaccination in the neonatal period [125]. Rotavirus vaccination may also be safe in a close contact environment because of limited transmission from rotavirus vaccinated infants to unvaccinated infants [126]. In 2010, porcine circovirus type 1 (PCV1) material was unexpectedly detected in RV1. Upon follow-up, it was concluded that the presence of PCV1 in the human RV vaccine is considered to be a manufacturing quality issue and does not appear to pose a safety risk to vaccinated infants [127].

For post-marketing safety surveillance, background incidences of intussusception were determined in Italy and Canada [128, 129], and ranged from 20-30/100,000 in Canada to 39/100,000 in Italy. These incidences are comparable to the background incidences found in the Netherlands [130]. In Canada, no evidence was found of a change in rate after the implementation of routine rotavirus immunisation programmes [128]. Several reviews concluded that the benefits of vaccination with currently available rotavirus vaccines outweigh the low risk of vaccination-associated intussusception [131-133]. However, further research is needed to better understand the relationship of intussusception with wild-type rotavirus and rotavirus vaccines and to delineate the potential aetiologies and mechanisms of intussusception [131]. Furthermore, healthcare professionals are advised to monitor the occurrence of intussusception carefully [134].

Newly developed vaccines, such as the parenteral P2-VP8-P vaccine, a tetravalent bovine-human reassortant rotavirus vaccine and a modified formulation of RV5, were also well-tolerated [135-137].

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*RIVM publication

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

T.M. Schurink-van 't Klooster, J.D.M. Verberk, L. Mollema, M.J. Knol, F.R.M. van der Klis, H.E. de Melker

6.1 Key points

- In February 2016, the third national seroepidemiological study started (PIENTER-3). Inclusion of participants (n=4,995 after visiting 38 of the 40 municipalties) will continue until the end of October 2017.
- A seroprevalence study conducted among adult refugees indicated that the overall sero-prevalence of protective antibodies against mumps, rubella, varicella, diphtheria, tetanus, polio and hepatitis A is generally high. Yet for measles the seroprevalence was below 95%.
- No indications were found for the assumption that there are substantial differences between boys and girls in IgG levels/titres after vaccination against measles, mumps, rubella, MenC and polio that would warrant a differential vaccination schedule for boys and girls.

6.2 Tables and figures

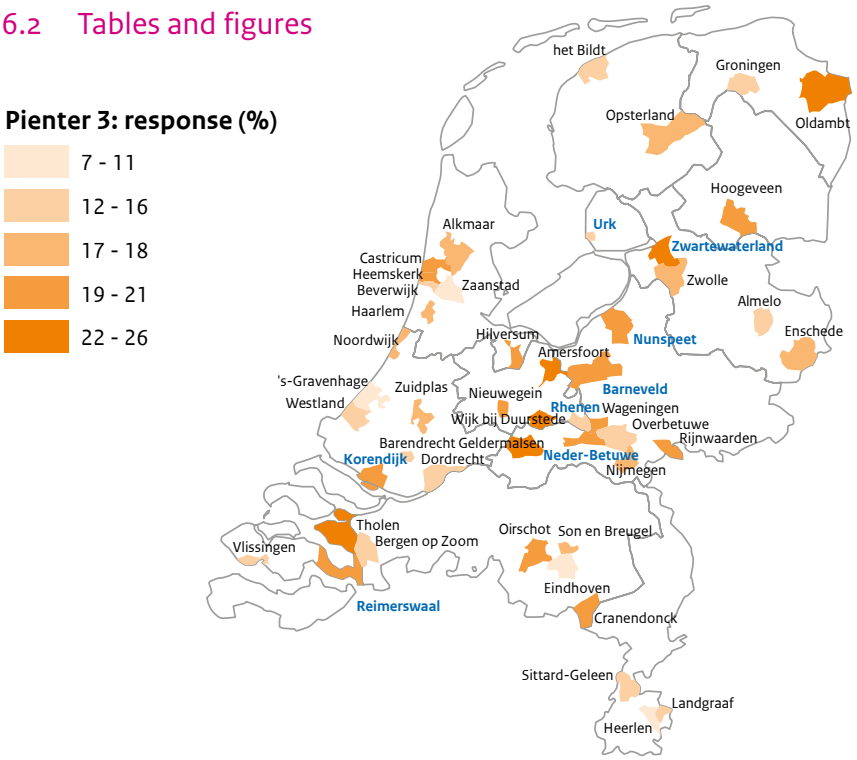

Figure 6.1 Overview of response percentages from the national sample of the included municipalities and low vaccination coverage areas

Blue-coloured names are low vaccination coverage areas. Results are from 38 out of 40 municipalities.

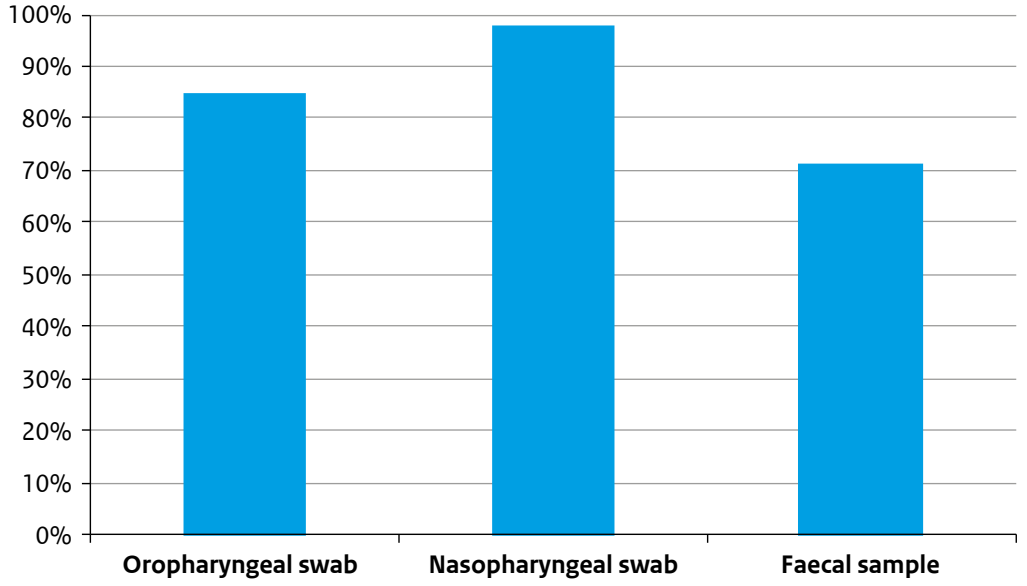

Figure 6.2 Overview of extra materials donated by 3,412 (68.3%) persons from the national sample that participated in the PIENTER-3 study

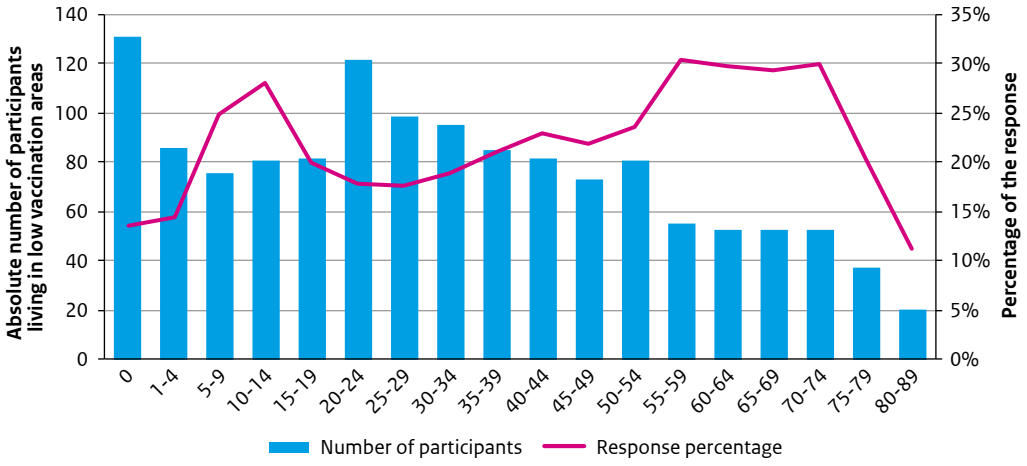

Figure 6.3 Overview of the number of participants and the response rate in low vaccination coverage areas of the PIENTER-3 study

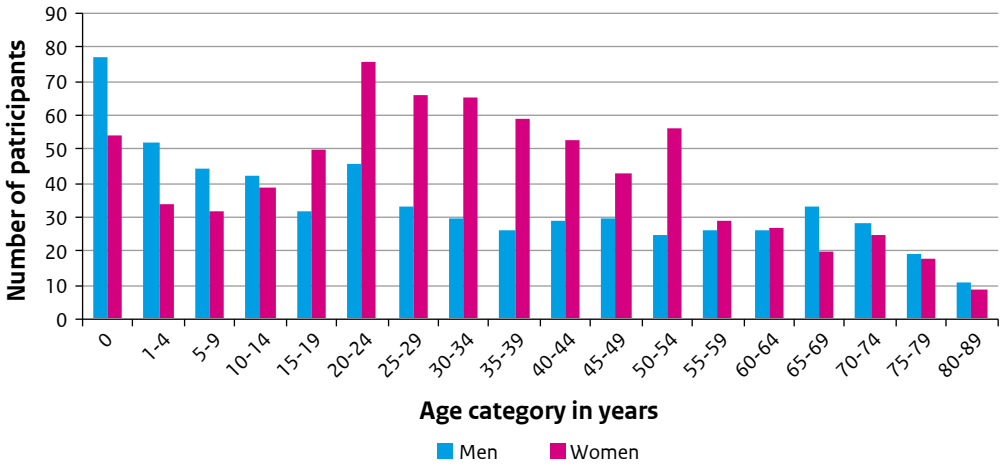

Figure 6.4 Overview of number of participants in low vaccination coverage areas of the PIENTER3-study, stratified by sex

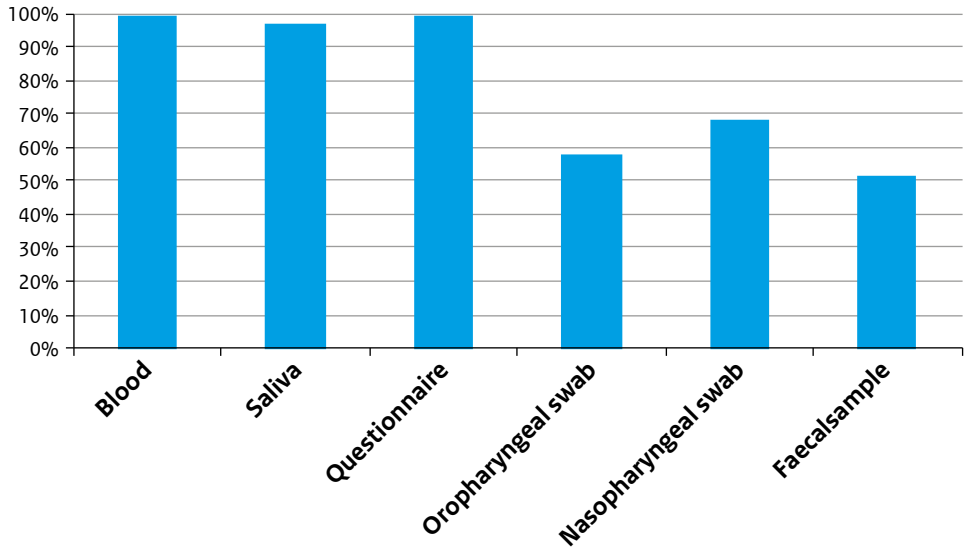

Figure 6.5 Overview of materials collected from participants living in low vaccination coverage areas (N=1,364)

6.3 Immunosurveillance

6.3.1 Seroepidemiological study in the Netherlands

The seroprevalence of NIP-targeted diseases is periodically monitored by national seroepidemiological (PIENTER) studies in order to obtain insight into the age-specific seroprevalence of these diseases in the general population in the Netherlands. The first survey was performed in 1995 1996 (nblood=9,948; 0-79 years) and the second in 2006-2007 (nblood=7,904; 0-79 years) [1, 2]. In February 2016, the third seroepidemiological study started [3]. Materials and data (blood, oral fluid sample and questionnaire) were collected from the general population (national sample, 40 municipalities) and from nine low vaccination coverage (LVC) areas (age strata 0, 1-4, 5-9, ..., 75-79, 80-89 years). In addition to the nationwide sample, non-Western migrants were oversampled in nine of the municipalities to be able to estimate seroprevalences among non-Western migrants as well, as differences in disease epidemiology and vaccination schedules between countries may vary. Furthermore, in the municipalities Amsterdam, Rotterdam and The Hague, an extra sample was taken from persons with a migration background from Suriname, Aruba and the former Dutch Antilles in order to compare them with the results from the health study on the "BES islands" [4].

New in this third serosurvey, compared with the previous studies, is the option for participants to donate nasopharyngeal and oropharyngeal swabs, an oral fluid sample and a faecal sample accompanied by an additional questionnaire. These samples will be used for microbiome investigations and the examination of antibiotic resistance. A small subset of participants will be asked to donate an extra blood sample for cellular immunity analyses and to fill in a diary about contact patterns.
Interim reports show that, after visiting 38 of the 40 municipalities from the national sample, up to 4,995 out of 29,836 persons were included in the study (response rate 16.7% (range 7-24%)) (Figure 6.1). Most of these participants (68.3%) also donated one or more samples for the purpose of additional research (Figure 6.2).
In the nine LVC areas, 609 men (17.3%) and 755 women (22.8%) participated (total response n=1364; 20.0%) (Figure 6.3 and Figure 6.4). Figure 6.5 shows the materials donated by participants living in LVC areas so far. Of the participants from LVC areas, 230 (16.9%) are orthodox Protestant individuals, 51% of which indicated that they did not take part in the NIP. The inclusion of the participants within the PIENTER-3 survey will continue until the end of October 2017. Thereafter the laboratory and epidemiological analyses will start.

6.3.2 Seroepidemiological study among asylum seekers

The number of refugees coming to the Netherlands has increased in recent years. Overall, the risks posed by infectious diseases among asylum seekers seem limited. Yet recent measles outbreaks at asylum seeker centres in Germany and France show that the levels of immunity against measles infection among asylum seekers may not be sufficiently high to ensure herd immunity. While the vaccination status of refugee children up to 18 years of age is assessed and vaccinations are offered according to the NIP, adult refugees are not offered additional vaccinations in the Netherlands. To assess the level of protection against nine vaccine-preventable diseases, we conducted a seroprevalence study among refugees aged 18 to 45

from the top five countries of origin. In July and August 2016, over 600 refugees from Syria, Afghanistan, Iraq, Iran and Eritrea living at three large asylum seeker centres participated in the study [5].
The results indicate that the overall seroprevalence of protective antibodies against mumps, rubella, varicella, diphtheria, tetanus, polio and hepatitis A is generally high among adult refugees in the Netherlands. For measles, the seroprevalence was below the threshold of 95% required for herd immunity in all countries except Eritrea. This was found particularly in the youngest age group (18- to 25-year-olds). The results of this study can provide input for public health policies on the vaccination of refugees, both in general and in the context of outbreaks.

6.4 Non-specific effects of vaccination

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

The first aim of the project focused on non-specific effects was to compare the risk of infectious-disease-related hospital admission posed by having received the DTP-containing vaccine as the most recent vaccine, versus the MMR vaccine as most recent vaccine, in a population-based nationwide cohort study of almost 900,000 Dutch children born between 2005 and 2011 [6]. Data from the national vaccine register was linked to hospital admission data. The DTP-containing vaccine (recommended at 2, 3, 4 and 11 months) consists of vaccinations against diphtheria, tetanus, pertussis, polio and Hib and is administered simultaneously with a vaccination against pneumococcal disease. MMR vaccination (recommended at 14 months) is administered simultaneously with a vaccination against MenC. Cox regression with age as the underlying time scale was used to estimate hazard ratios for infectious-disease-related hospital admissions according to the most recent vaccination (MMR vs. DTaP-IPV-Hib), with the last-received vaccination included as a time-varying variable changing at the age at which the MMR vaccine was received. This effectively means that, at each age (in days), we compared children who had already received the MMR vaccine with children who had not yet received the MMR vaccine, thereby completely adjusting for age. Furthermore, we adjusted for sex, chronic diseases, hospitalisation for any reason at age 8 months, birth weight, gestational age, maternal age and parity, parental country of birth, and postal code. Analyses were repeated with hospitalisation for injuries and poisoning as a negative control outcome. In addition, the rate of infection-related hospitalisation was compared between the fourth DTaP-IPV-Hib vaccination and the third DTaP-IPV-Hib vaccination. Having had the MMR vaccine as most recent vaccination was associated with a hazard ratio (HR) of 0.62 (95%CI 0.57-0.67) for hospitalisation for infection and 0.84 (95%CI 0.73-0.96) for injuries and poisoning, compared with DTaP-IPV-Hib-4 as most recent vaccination. DTaP-IPV-Hib-4 as most recent vaccination was associated with a HR of 0.69

(95%CI 0.63-0.76) for hospitalisation for infection, compared with DTaP-IPV-Hib-3 as most recent vaccination. Our findings suggest that a healthy vaccinee bias at least partly explains the observed lower rate of hospitalisation for infection after MMR vaccination, and that this lower rate is associated with receiving an additional vaccine, and not specifically with MMR.

A systematic review was conducted to evaluate the effects on non-specific and all-cause mortality, in children under five, of Bacillus Calmette-Guérin (BCG), DTP, and standard titre measles-containing vaccines (MCV) [7]. Clinical trials, cohort studies, and case-control studies of the effects on mortality of BCG, whole cell DTP, and standard titre MCV in children under five were included. Results from 34 birth cohorts were identified. Most evidence was taken from observational studies, with some taken from short-term clinical trials. Most studies reported on all-cause (rather than non-specific) mortality. Receipt of the BCG vaccine was associated with a reduction in all-cause mortality: the average relative risks were 0.70 (95%CI 0.49-1.01) from five clinical trials and 0.47 (95%CI 0.32-0.69) from nine observational studies at high risk of bias. Receipt of DTP (usually with an oral polio vaccine) was associated with a possible increase in all-cause mortality on average (RR 1.38; 95%CI 0.92-2.08) from 10 studies at high risk of bias; this effect seemed stronger in girls than in boys. Receipt of standard titre MCV was associated with a reduction in all-cause mortality (RR 0.74; 95%CI 0.51-1.07) from four clinical trials and 0.51 (95%CI 0.42-0.63) from 18 observational studies at high risk of bias); this effect seemed stronger in girls than in boys. Seven observational studies, assessed as being at high risk of bias, have compared sequences of vaccines; results of a subset of these suggest that administering DTP with or after MCV may be associated with higher mortality than administering it before MCV. Evidence suggests that receipt of BCG and MCV reduces overall mortality by more than would be expected through their effects on the diseases they prevent, and receipt of DTP may be associated with an increase in all-cause mortality. Although efforts should be made to ensure that all children are immunised on schedule with BCG, DTP, and MCV, randomised trials are needed to compare the effects of different sequences.

In Denmark, a randomised trial was performed to assess the effect of BCG vaccination at birth on early childhood hospitalisation [8] and parent-reported childhood infections [8]. Newborn children were allocated to BCG or no intervention within 7 days after birth. There was no difference in the risk of hospitalisation up to 15 months of age; 2,129 children, randomised to BCG, experienced 1,047 hospitalisations with a mean of 0.49 hospitalisation per child, compared with 1,003 hospitalisations among 2,133 control children (mean 0.47), resulting in a HR, comparing BCG versus no BCG, of 1.05 (95%CI 0.93 1.18). From 0 to 3 months, there were 291 reported infections in the BCG group vs. 336 infections in the control group, resulting in an IRR of 0.87 (95%CI 0.72-1.05). From 3 to 13 months, there were 7,028 vs. 6,791 reported infections (IRR 1.02; 95%CI 0.97-1.07)). In conclusion, BCG vaccination at birth did not reduce the risk of childhood hospitalisations or parent-reported infections in this high-income setting.

6.5 Sex differences in IgG levels following infant vaccinations

We assessed possible sex differences in immunoglobulin G (IgG) levels after infant and childhood vaccination using data from a national cross-sectional serosurvey conducted in 2006/2007 (PIENTER2 study). Significant differences in IgG were found at specific time points after vaccination against measles, mumps, rubella, MenC, and polio. The geometric mean concentration or titre (GMC/T) ratios ranged between 1.10 for polio type 1, one month to one year after the first childhood booster, to 1.90 for MenC one month to one year after infant vaccination, showing higher IgG levels for girls. There were no significant differences found between boys and girls for diphtheria, tetanus, pertussis, and Hib at any time point. The proportion of protection levels differed significantly between boys and girls at one to three years after infant vaccination against mumps (82.5% boys vs. 91.9% girls, p-value: 0.046), and at one to three years after infant vaccination against MenC (7.0% boys vs. 18.2% girls, p-value: 0.015). In conclusion, we found that, for some infectious disease pathogens, at some time points IgG levels/titres after infant and childhood vaccination were higher among girls. But the differences were generally small and inconsistent. We therefore have no indications to assume that there are substantial differences between boys and girls in IgG levels/titres after vaccination that would warrant a differential vaccination schedule for boys and girls.

6.6 Literature

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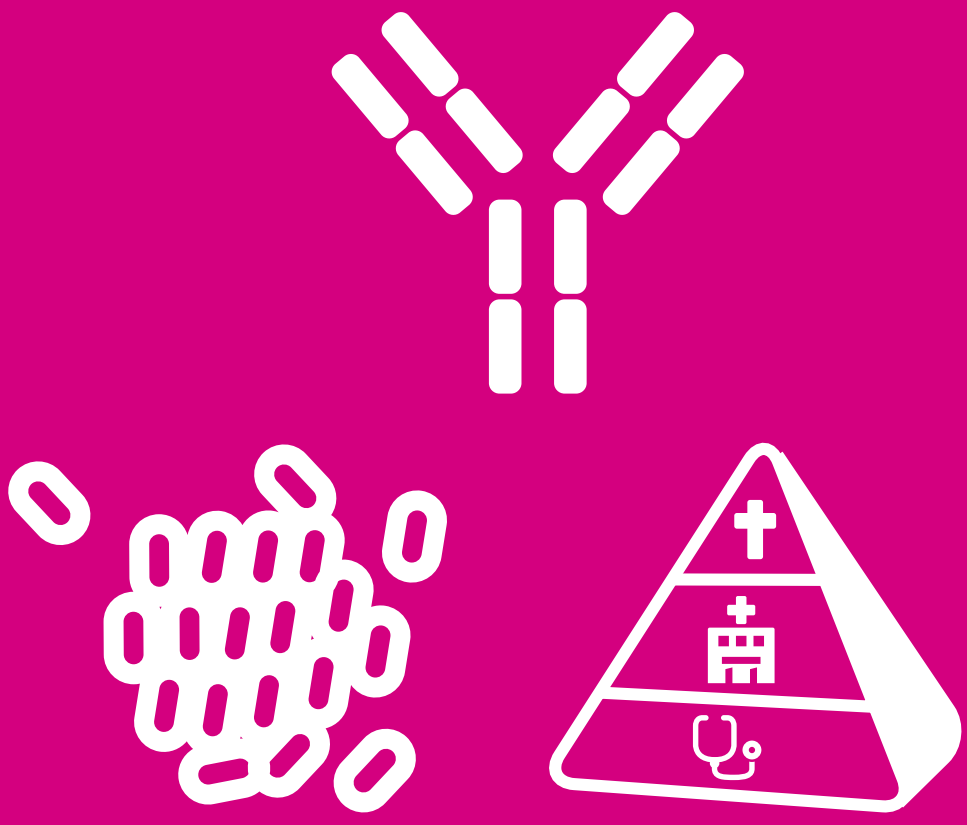
*RIVM publication

7
Current National Immunisation Programme



7.1 Diphtheria

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

7.1.1 Key points

- In 2016, two diphtheria notifications were received.
- In Belgium, a child died of diphtheria after delayed treatment. This accident made it clear that it is important to have a stockpile of Diphtheria antitoxin available in cases of emergency.

7.1.2 Tables and figures

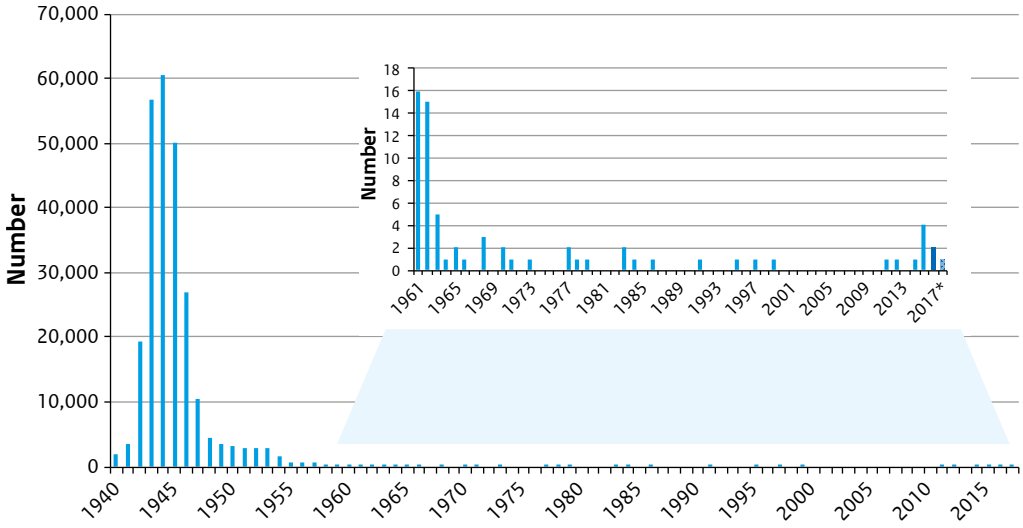


Figure 7.1.1 Diphtheria notifications per year for 1940-2017*

* reports up to July 1st, 2017 are included

Table 7.1.1 Laboratory results of tested Corynebacterium strains for 2015-2017*

	Corynebacterium diphtheriae				Corynebacterium ulcerans			
	PCR negative	PCR positive	Elek positive	Elek non-conclusive	PCR negative	PCR positive	Elek positive	Elek non-conclusive
2015	8	1	1	NA	0	2	1	1
2016	12	1	1	NA	2	1	NA	1
2017*	5	0	0	NA	0	1	NA	1

The sum of PCR negative and PCR positive strains is the number of pathogens, received for diagnostics.
*: Up to July 1st
NA = not applicable

7.1.3 Epidemiology

In 2016, two diphtheria notifications were received (Figure 7.1.1). These concerned a 52-year-old vaccinated female without travel history or known source and a 32-year-old vaccinated male who probably contracted the disease in Indonesia. Furthermore, in 2017 up to July 1st, one notification was received of a 64-year-old male with unknown vaccination status, who developed cutaneous diphtheria, possibly through cats. He had no travel history. None of the reported cases died.

7.1.4 Pathogen

In 2016, the RIVM received 16 Corynebacterium ulcerans or C. diphtheriae strains, 14 of which with the suspicion of cutaneous diphtheria and 2 from respiratory samples.
Likewise, in 2017 up to July 1st, RIVM received six C. ulcerans or C. diphtheriae strains, all with the suspicion of cutaneous diphtheria. See Table 7.1.1 for details on laboratory results for the respective strains.

7.1.5 International developments

In March 2016, an unvaccinated three-year-old Belgian child was hospitalised for diphtheria [1]. Diagnosis was confirmed nine days after the onset of symptoms. Treatment with Diphtheria antitoxin (DAT) was needed, but further delayed since no stockpile of DAT was available in Belgium. The child died 11 days after the onset of symptoms, shortly after treatment was provided using a DAT stockpile of RIVM. Although seldom needed, a stockpile of DAT is required in cases of emergency.

7.1.6 Literature

1. ECDC. RAPID RISK ASSESSMENT: A fatal case of diphtheria in Belgium. 2016; Available from: *https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/RRA-Diphtheria-Belgium.pdf*.

7.2 *Haemophilus influenzae* disease

M.J. Knol, A. van der Ende, S. Monge, H.E. de Melker

7.2.1 Key points

- The number of cases of *Haemophilus influenzae* type b (Hib) disease in 2016 (n=44) was 52% higher than in the previous five years (22-34 cases). Up to May 2017, 18 cases were reported.
- In 2016, the incidence of Hib disease was highest among children under the age of five (2.4 per 100,000) and significantly increased compared with the previous five years (0.5-1.5 per 100,000).
- There were 12 Hib cases with vaccine failure (50% of all 24 vaccine eligible Hib cases) in 2016, resulting in a Hib vaccine effectiveness estimate of 95%, which was similar to previous years.
- The number of cases caused by nontypeable Hi (NTHi) strains did not increase further in 2016 (n=124) compared with 2015 (n=127).

7.2.2 Figures

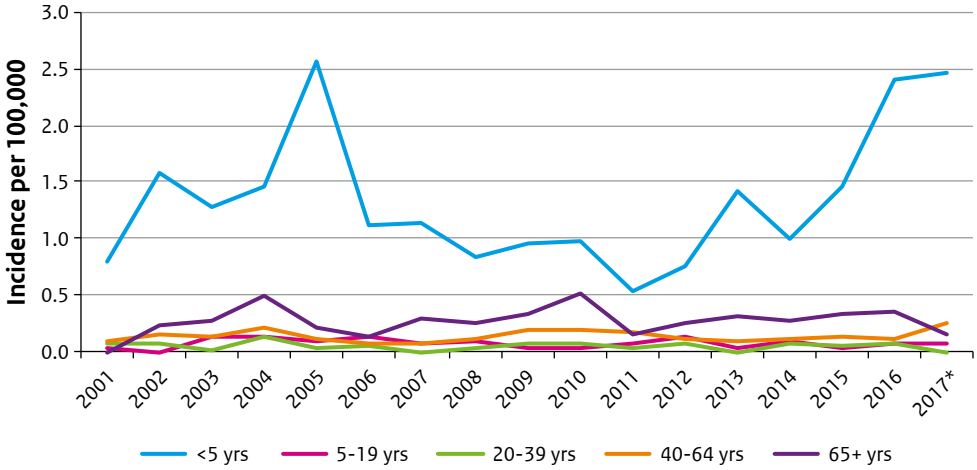


Figure 7.2.1 Age-specific incidence of *Haemophilus influenzae* type b (Hib) disease, 2001-2017* (*up to May)
Source: NRLBM

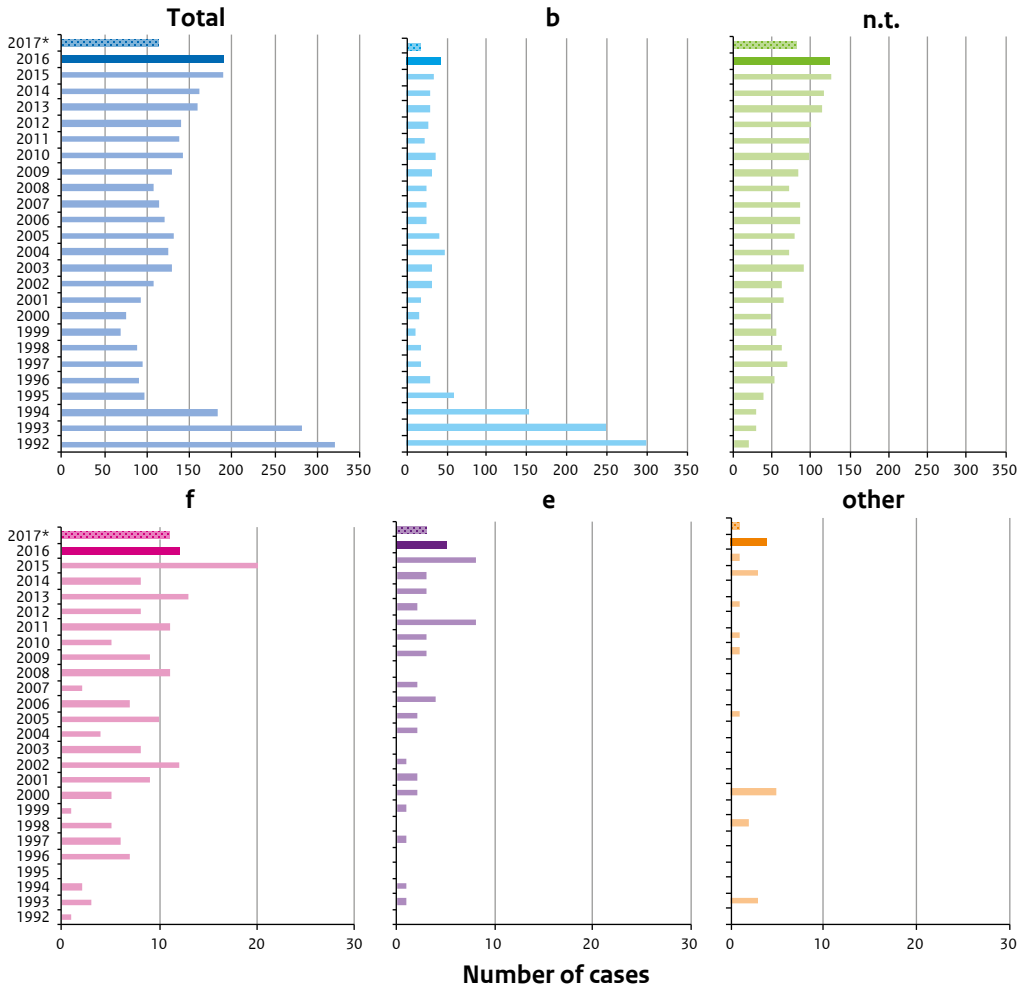


Figure 7.2.2 Absolute number of *Haemophilus influenzae* cases per serotype, 1992-2017* (*up to May)

Note: The scale distribution of the upper figures and lower figures is not equal.

Source: NRLBM

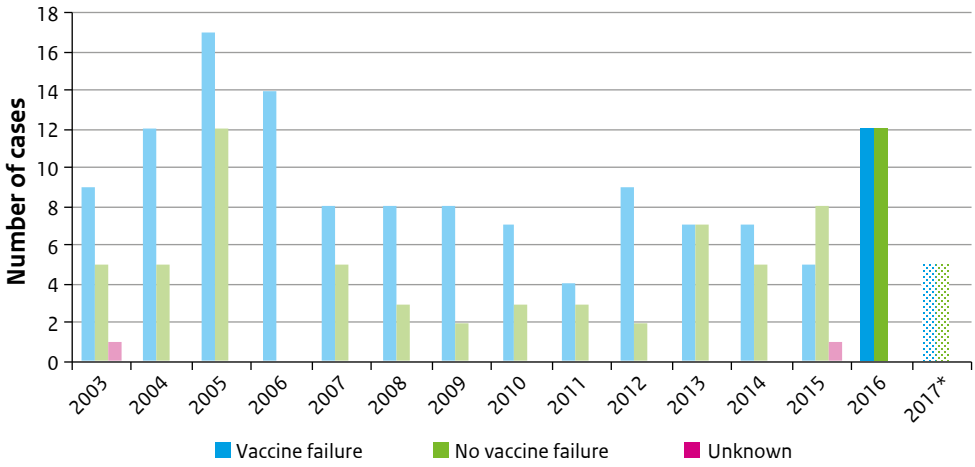


Figure 7.2.3 Absolute number of *Haemophilus influenzae* type b (Hib) cases in cohorts eligible for vaccination (i.e. born after April 1, 1993) by vaccine failure, 2003-2017* (*up to May)
Source: NRLBM, Praeventis, Osiris

7.2.3 Epidemiology

7.2.3.1 *Hib disease*

7.2.3.1.1 *Incidence*

In 2016, the number of Hib cases was 44 (incidence: 0.26 per 100,000), which was 52% higher than in the previous five years (n=22-34; incidence: 0.13-0.20 per 100,000) (Figure 7.2.2). The incidence was highest in children under the age of five (2.4 per 100,000; n=21). This incidence was also significantly higher than in the previous five years (0.5-1.5 per 100,000; n=5-13) (Figure 7.2.1). Up to May 2017, 18 Hib cases were reported, nine of which were below five years of age. The reason for the increase in Hib disease is unknown. There are no indications that Hib vaccination has become less effective (see section 7.2.3.1.3 and 7.2.5). The outcome was known for 26 and 11 cases in 2016 and 2017, respectively. One patient in 2017 died, which was a seven-month-old unvaccinated baby.

7.2.3.1.2 *Vaccine failure*

In 2016 and 2017 (up to May), there were 24 and 10 Hib cases among cohorts eligible for vaccination (Figure 7.2.3). Of these, 12 (50%) and five cases (50%) were vaccine failures (i.e. received at least two vaccinations with at least two weeks between the second vaccination and the date of diagnosis). Thirteen vaccine failure cases were younger than five, four were older than five years. For 12 out of 17 cases with vaccine failure, information on underlying disease was available. Three of these cases (25%) had an underlying disease.

7.2.3.1.3 *Vaccine effectiveness*

The estimated vaccine effectiveness (VE) of Hib vaccination using the 'screening method' was 95% (95%CI 90-98%) for 2016 and 95% (95%CI 84-99%) for 2017 (up to May). The overall VE for 2003-2017 was 92% (95%CI 89-94%).

7.2.3.2 *Non-typeable Hi (NTHi) disease*

In 2016, 124 cases of NTHi were reported, which was comparable with in 2015 (127 cases) (Figure 7.2.2). Up to May 2017, 82 cases have already been reported which was higher than in the same period in 2015 (72 cases) or 2016 (61 cases). In 2016, the incidence was still highest among the elderly aged 65 and older (2.4 per 100,000; n=74) and children under five (1.1 per 100,000; n=10).

7.2.3.3 *Disease due to other Hi serotypes*

In 2016, there were five Hi cases with serotype e (Hie), which was quite similar to the previous years (Figure 7.2.2). Up to May 2017, there were three Hie cases. In 2016, 12 cases of Hif were reported, which was comparable to the previous years (Figure 7.2.2). Up to May 2017, 11 Hif cases were reported. In 2016 and 2017 (up to May), four Hi cases involving serotype a were reported, and one with serotype d (Figure 7.2.2).

7.2.4 Pathogen

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

7.2.5 Research

The hexavalent DTaP-IPV-Hib-HBV vaccine, including the hepatitis B virus (HBV) component, was introduced for high-risk infants in 2006, and universally in 2011. We estimated Hib VE to assess whether the increase in Hib disease in 2016 was explained by decreased VE, and related to the addition of the HBV component. VE was estimated (using the screening method) at 95% for children aged 0 to two years and 68% for children aged three to four years ($p<0.01$), with no time-trend from 2003-2016 ($p=0.16$). VE adjusted for age was similar for cohorts with HBV for risk groups ($p=0.39$), or universal HBV ($p=0.13$), compared to no-HBV cohort. VE for each cohort was, respectively, for children aged 0 to two years: 95%, 92% and 97%; and for children aged three to four years: 65%, 48% and 81%. These results show that Hib VE has not changed over time or by the addition of the HBV component. However, VE declined with age.

The results on Hib VE using the screening method were confirmed by a case control study. The study included 159 Hib cases of children under five years of age diagnosed between 2003 and 2015 and matched to 1,590 controls by age and date of diagnosis. The crude VE was 93% (95%CI 89-95%); adjustment for sex and Western/non-Western origin did not change the result. VE decreased with age ($p<0.001$), but did not differ by year of diagnosis or year of birth. The VE of the hexavalent vaccine (94% (95%CI 89-97%)) was not different from the VE of a pentavalent or other vaccine (92% (95%CI 86-95%); $p=0.36$).

Patient records were retrospectively reviewed from 51 Hib cases eligible for vaccination who were diagnosed between 2005 and 2013. The majority (n=41; 80.4%) of them had been vaccinated. Of the cases, 31.4% were <one year old, 51.0% one to four years old and 17.7% ≥five years old. Clinical presentation included meningitis (64.7%), pneumonia (9.8%), epiglottitis (5.9%) and invasive infection without focus (3.9%). The vaccinated cases presented less frequently with meningitis (58.5% vs. 90.0%, $p=0.08$), but no significant difference was observed regarding predisposing factors (29.3% vs. 20.0%, $p=0.71$), development of

complications (31.7% vs. 30.0%; p=1.00) or sequelae (21.6% vs. 10.0%, p=0.66). Eight of nine cases required intensive care unit (ICU) admission were vaccinated. Four patients died who had all been vaccinated. In both groups, 50% had non-immunocompromising, predisposing factors. In a context of high vaccination coverage, invasive Hib disease still occurs in vaccinated children in the absence of predisposing factors. Although the number of cases in this analysis was small, the severity of disease was comparable, suggesting that vaccinated cases did not experience a milder progression following hospital admission.

7.2.6 International developments

Whittaker et al. described the epidemiology of invasive Hi disease during 2007-2014 in 12 European countries and assessed overall Hi disease trends by serotype and age [1]. The mean annual notification rate was 0.6 cases/100,000 population, with an increasing annual trend of 3.3% (95%CI 2.3-4.3%). The notification rate was highest for patients <one month old (23.4 cases/100,000 population). NTHi caused 78% of all cases and showed increasing trends among persons <one month old and >20 years. Serotype f cases showed an increasing trend among persons >60 years old. Serotype b cases showed decreasing trends among persons one to five months old, one to four years old, and >40 years old.

7.2.7 Literature

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7.3 Hepatitis B

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

7.3.1 Key points

- The incidence of acute HBV notifications remained stable in 2016 at 0.6 per 100,000.
- Among both men and women, heterosexual contact was the most frequently reported risk factor for acute HBV infection.
- In 2016, genotype A continues to be the dominant genotype among acute HBV cases.
- Almost 90% of the total number of reported hepatitis B patients have a chronic infection, and of those, 85% were born abroad.

7.3.2 Tables and figures

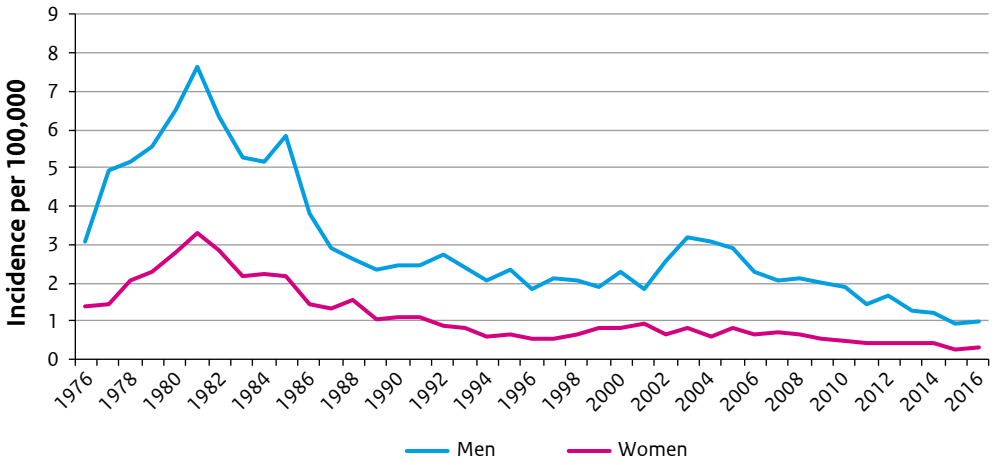

Figure 7.3.1 Incidence of acute HBV infections in men and women in the Netherlands between 1976 and 2016
Source: Osiris

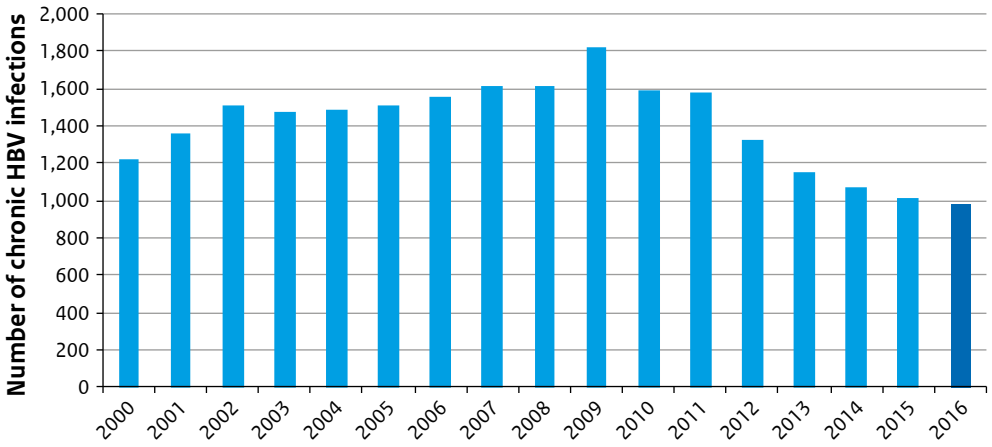

Figure 7.3.2 Number of notified chronic HBV infections in the Netherlands between 2000 and 2016

Source: Osiris

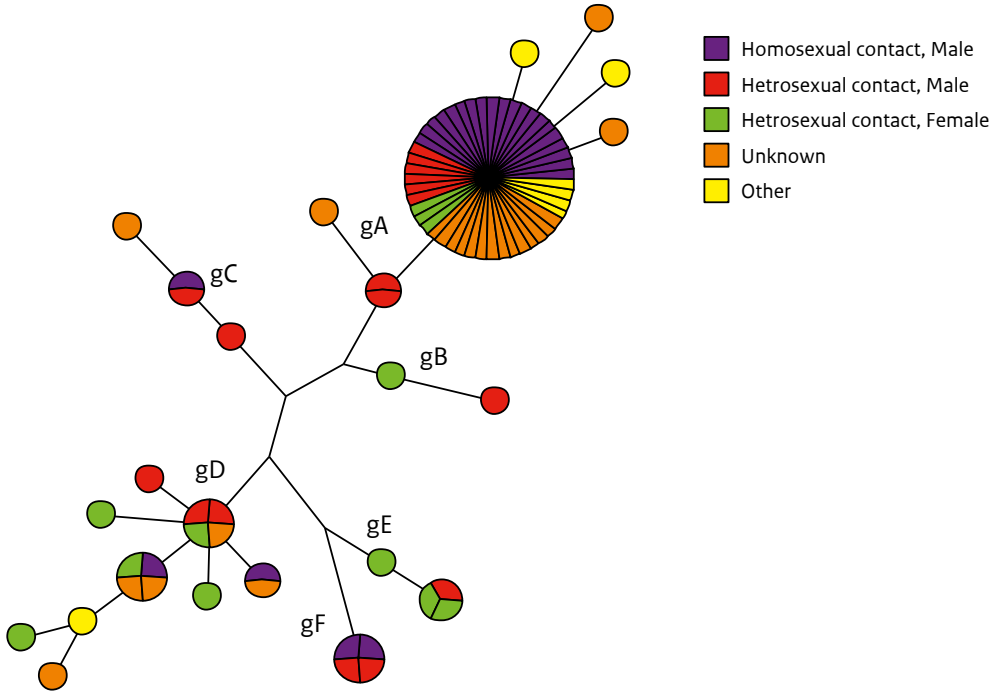

Figure 7.3.3 Basic maximum parsimony tree based on the S-region sequence of acute HBV cases in the Netherlands in 2016 by reported risk factor (n=84)

7.3.3 Epidemiology

In 2016, 1,100 cases of hepatitis B virus (HBV) infection were notified. Of these, 980 (89%) were chronic infections and 110 (10%) acute infections (10 cases unknown status).

7.3.3.1 Acute HBV epidemiology

Compared with 2015 (105 cases), the number of notified acute HBV infections increased slightly. The incidence of acute HBV notifications in 2016 was 0.6 per 100,000, 1.0/100,000 among men and 0.3/100,000 among women. The HBV incidence seems to have stabilised after it has been decreasing for men and women since 2004 (Figure 7.3.1). In the first half of 2017, 61 cases of acute HBV were reported. Over the past ten years, the age at infection has been increasing for acute HBV cases. The mean age was 38 years in 2007 and 46 years in 2016. The mean age at infection is higher in men (48 in 2016) than in women (36 in 2016).

In 2016, most cases of acute HBV infection (64%) were acquired through sexual contact. For 27% of reports of acute HBV infection, the most likely route of transmission remained unknown, despite source tracing. Among men (84 cases), sexual contacts between MSM accounted for 31% of acute infections and heterosexual transmission for 26%. Among women (26 cases), heterosexual contact accounted for 73% of the cases.

7.3.3.2 Chronic HBV epidemiology

Since 2009, the number of chronic HBV notifications has decreased by 46% (n=1820 in 2009 and n=980 in 2015) (Figure 7.3.2). This might reflect a decrease in the prevalence of chronic HBV infection globally and among migrants, but since chronic hepatitis B is largely asymptomatic, the number of new diagnoses is also highly influenced by testing practices. It is unknown how many people are tested for HBV infection annually.

In 2016, 53% of the cases acquired chronic HBV infection through vertical transmission. Six per cent of these cases were infected by sexual contact. For 32% of reports of chronic HBV infection, the most likely route of transmission was unknown. For the remaining 9%, transmission occurred via injecting drug use (IDU), needle stick injuries or via other routes. Ninety per cent of the chronic HBV patients were born abroad (with China, Turkey and Syria as the three most frequently reported countries of birth).

7.3.3.3 HBV infection in children

Vaccination against HBV was introduced in the NIP in 2011 for all children and was offered to children born between 2003 and 2010 with at least one parent born in an endemic country. If vaccine failure would occur, it is unlikely to be identified because HBV infection in children is usually asymptomatic and serological evaluation after vaccination is only advised for children born to mothers with a chronic HBV infection. In the period 2004-2016, four acute HBV infections have been reported in children born in the Netherlands after 2003, all of whom were unvaccinated and most likely did not qualify for vaccination as their mothers were born in the Netherlands.

An evaluation of the perinatal HBV transmission prevention programme showed vaccine failures or breakthrough infections occur in 0.6% of vaccinated infants born to HBsAg positive

mothers [1]. With over 500 children born to HBV-infected mothers each year, around three breakthrough infections are expected annually. Out of 25 children notified with a chronic HBV infection who were born in the Netherlands since 2003, 20 (80%) had been vaccinated, mainly due to the fact that they were born to mothers with chronic HBV infection. Eighteen of the 20 infections in vaccinated children (90%) were identified before the age of 3 years in the period that serological evaluation of children born from HBsAg positive mothers was coordinated by the RIVM (children born from 2003 to May 2011). In this period, an average of two breakthrough infections were identified per year. Since 2011, the serological evaluation has been coordinated by child health care and the general practioner. An evaluation showed that the implementation of this process needs to be improved [2]. Only one child born after May 2011 was notified as having a chronic infection after vaccination up to 2016. This supports the finding that the implementation of the serological evaluation of vaccinated children born to HBV-infected mothers is not optimal. However, this could also be related to increased antiviral treatment during pregnancy, which is an effective way to prevent breakthrough infections [3].

7.3.3.4 HBV-related mortality

Most of the HBV-related mortality is due to chronic hepatitis-B-related liver diseases such as cirrhosis and hepatocellular carcinoma. By combining the cause of death figures taken from Statistics Netherlands with population-attributable fractions for HBV infection as a risk factor, Hofman et al. have estimated chronic HBV-related mortality for the Netherlands. The total mortality of chronic hepatitis B is estimated to have been around 200 per year in the period 2008-2012 [4]. The chronic hepatitis-B-related and hepatitis-C-related mortality does not differ between four regions in Netherlands and the absolute mortality is highest among 50-79 year olds [5].

7.3.4 Pathogen

The molecular sequencing and typing of 87 acute HBV cases (71%) and 14 chronic HBV cases was done in 2016. PCR amplification and sequencing produced results for 84 (97%) samples for the S-region. A basic maximum spanning tree based on S-region sequences of acute HBV cases is shown in Figure 7.3.3. In the Netherlands, six different genotypes were found. The largest cluster of cases continues to be among genotype A cases, the most common genotype for acute HBV in the Netherlands.

7.3.5 Research

7.3.5.1 Prevalence of chronic viral hepatitis and screening policy

An update of the prevalence estimate for chronic HBV infection has been calculated for the Netherlands overall and per risk group. This was done by combining data on the size of different population groups and estimates for the prevalence in these groups. The prevalence of chronic HBV infection is estimated to be 0.34%, corresponding to around 49,000 infected individuals. Of these, 39,000 (81%) are migrants that were born in intermediate to high endemic countries (chronic HBV prevalence ≥2%). The estimated prevalence in the general population at low risk of infection (i.e. born in the Netherlands or another low endemic country, non-MSM, non-injecting drug user) is 0.06%.

In November 2016, the Health Council of the Netherlands published the advisory report 'Screening risk groups for hepatitis B and C' [6]. As the prevalence of chronic hepatitis B and C in the general population is low, the Committee recommends screening for the following risk groups: first generation migrants from endemic countries (including asylum seekers), (ever) injecting drug users and MSM. Certain groups of health care workers should also be screened for chronic HCV infection. Besides case finding via general practitioners and other health services, the organisation of local or regional screening programmes in areas with a large migrant population is recommended.

Together with stakeholders involved in the prevention and treatment of viral hepatitis, the RIVM has supported the development of a National Hepatitis Plan [7]. The plan focuses on five pillars: awareness and vaccination, identification of infected individuals, diagnostics and treatment, organisation of hepatitis care, and surveillance. In 2017, a pilot project focused on a patient registration database started in several hospitals.

7.3.5.2 Cost-effectiveness of the hepatitis B risk group vaccination programme

The vaccination programme for behavioural risk groups started in 2002 and currently targets commercial sex workers (CSW) and MSM. Until the end of 2016, a cumulative number of 54,372 MSM and 21,263 CSW have entered the programme. In 2016, around 4,000 MSM and around 1,000 CSW received at least one vaccination.

The cost-effectiveness of the targeted hepatitis B vaccination programme has been assessed by comparing two time-periods: 2002 2006 and 2007-2012 [8]. The programme is a reasonable cost-effective intervention, but the results show that the programme was more cost-effective during the first period, at less than €21,000/QALY for both MSM and CWS, than in the second period, at €25,800/QALY for CSW and €47,700/QALY for MSM. Saturation within the risk-groups, the participation of individuals with less risky behaviour, and increased recruitment investments in the second period made the programme less cost-effective over time.

7.3.6 International developments

A recent global analysis of prevalence data from 50 countries since the year 2000 shows that the prevalence of chronic HBV infection is declining in most countries, but increasing in some African countries. Europe showed a mixed pattern with higher and stable prevalence in Eastern Europe, and constantly low prevalence in Western Europe [9]. In contrast, the global burden of chronic viral hepatitis infections in terms of absolute mortality and morbidity increased between 1990 and 2013, primarily driven by population growth [10]. The total number of deaths from cirrhosis or liver cancer that was attributable to chronic HBV or HCV infection in Western Europe was estimated to be 77,000 in 2013.

In 2016, a review indicated that antiviral therapy given to pregnant women can reduce mother to child transmission of HBV, but the quality of the majority of the included studies was considered low [11]. Recently, the effectiveness of the antiviral treatment of pregnant women aimed at preventing perinatal transmission has been demonstrated in a randomised, controlled clinical trial in HBeAg positive women with a high viral load (HBV DNA >200,000 IU/ml) [12].

All infants received immunoglobulin and vaccination at birth, and subsequent vaccinations at one and six months of age. None of the 92 infants from mothers who received antiviral treatment (tenofovir) got infected with HBV versus six of the 88 (6.8%) infants in the control group. This finding stresses the importance of adherence to guidelines for health professionals that recommend the referral of pregnant women with chronic HBV infection to specialist care.

7.3.7 Literature

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* RIVM publication

7.4 Human papillomavirus (HPV) infection

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

7.4.1 Key points

- The incidence of cervical cancer increased in 2016, while the number of deaths only slightly increased.
- In a prospective cohort study (HAVANA), a high vaccine effectiveness (VE) against vaccine types HPV16/18 was found for 12-month persistent infections up to six years post-vaccination (98%; 95%CI 82-100%). In addition, significant cross-protection against incident HPV infections by HPV31/35/45 and against 12-month persistent infections caused by HPV31 was found.
- In incident infections, vaccinated study participants show significantly lower viral loads than non-vaccinated study participants.
- Among 16- to 24-year-old STI clinic visitors (PASSYON study), the VE against HPV16/18 positivity was high (90%). In addition, significant cross-protection against types 31, 35, 45 and 52 was found (91%, 57%, 50% and 37%, respectively).

7.4.2 Tables and figures

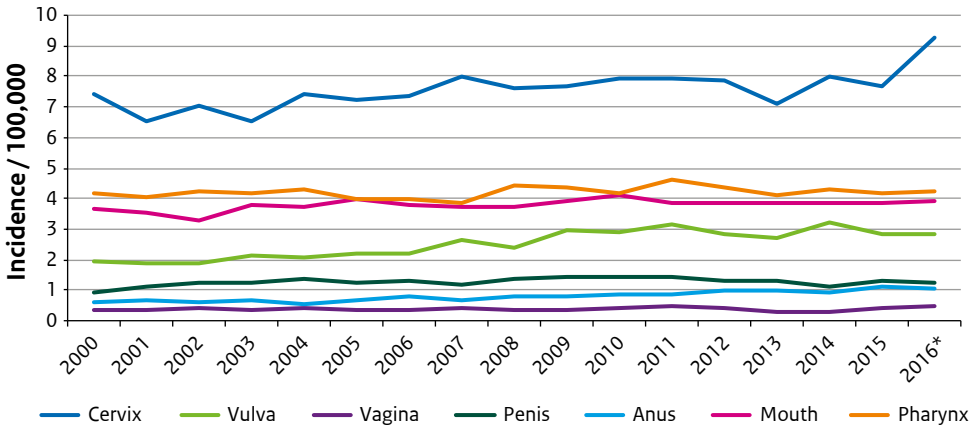

Figure 7.4.1 Incidence / 100,000 (standardised by the European standardised rate) of new cervical, anogenital, mouth/oral and pharynx/pharyngeal cancer cases in the Netherlands in the 2000-2016 period, by cancer type

* Preliminary figures

Source: the Netherlands Cancer Registry (NKR)

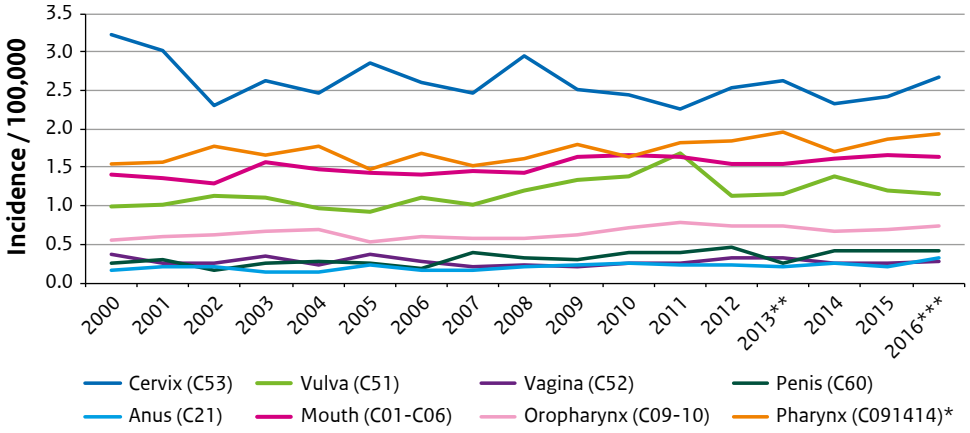

Figure 7.4.2 Incidence / 100,000 of deaths related to cervical, anogenital, mouth, oropharynx and pharynx cancer cases in the Netherlands in the 2000-2016 period, by cancer type

* 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

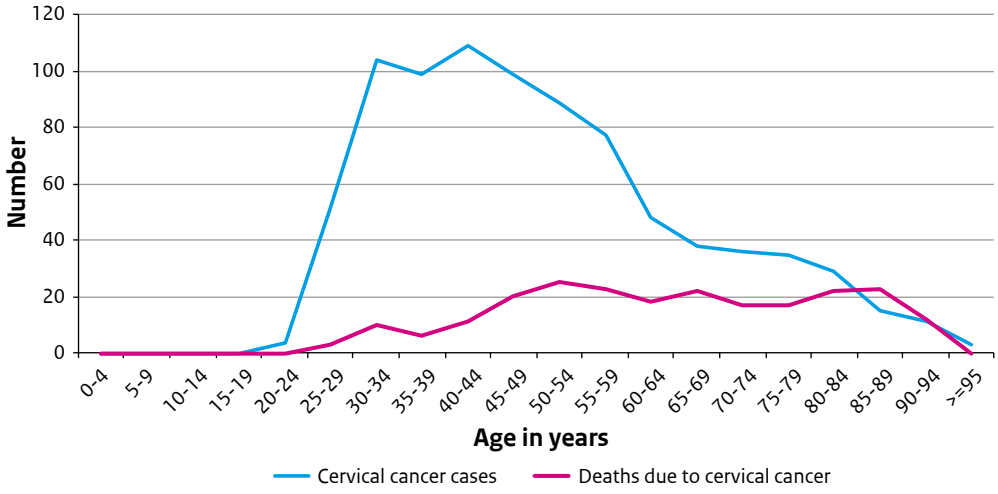

Figure 7.4.3 Age-specific number of cervical cancer cases and deaths due to cervical cancer in the Netherlands in 2016*

* Preliminary data

Table 7.4.1 Attributable fraction to all HPV types of HPV associated cancers in Europe [1]

Cancer site	Attributable fraction % (95%CI)
Cervix	100
Vulva	15.9 (13.5-18.4)
Vagina	70.2 (62.2-77.4)
Anus	87.1 (81.0-91.8)
Penis	29.0 (24.7-33.7)
Oral cavity	3.7 (2.4-5.6)
Nasopharynx	10.8 (3.0-25.4)
Oropharynx	19.9 (17.2-22.8)
Hypopharynx	2.4 (0.3-8.4)
Pharynx	25.0 (10.7-44.9)
Larynx	2.4 (1.2-4.1)

Table 7.4.2 Vaccine effectiveness* against incident and persistent HPV infections in young women in the HAVANA study up to six years post-vaccination

Persistent infections (12 months)	Adjusted* VE (95%CI)
Vaccine types (HPV16/18)	97.6% (82.2-99.7%)
Cross-protective types (HPV31/45)	70.3% (18.3-89.2%)
hrHPV (HPV16/18/31/33/45)	17.9% (-7.7-37.4%)
Types 9valent vaccine (HPV6/11/16/18/31/33/45/52/58)	48.2% (26.1-63.7%)
Incident infections	**Adjusted* VE (95%CI)**
Vaccine types (HPV16/18)	76.7% (63.2-85.2%)
Cross-protective types (HPV31/45)	72.8% (52.2-84.6%
hrHPV (HPV16/18/31/33/45)	10.9% (-4.2-23.9%)
Types 9valent vaccine (HPV6/11/16/18/31/33/45/52/58)	30.6% (15.7-42.8%)

* Adjusted for age, degree of urbanization, smoking, anticonception use, ever had sexual intercourse and currently has a partner.

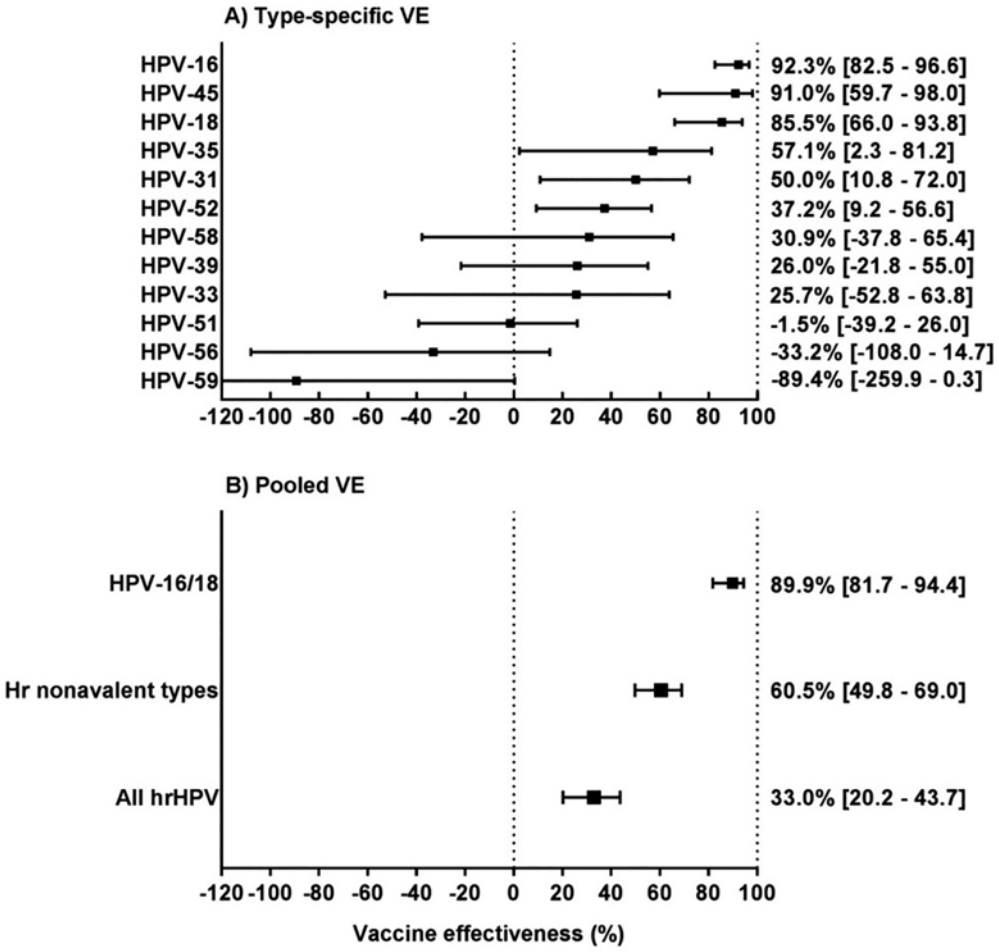

Figure 7.4.4 Vaccine effectiveness in the PASSYON study for at least one dose corrected for demographics and risk behaviour against: A) type-specific high-risk (hr) HPV DNA positivity and B) pooled estimates

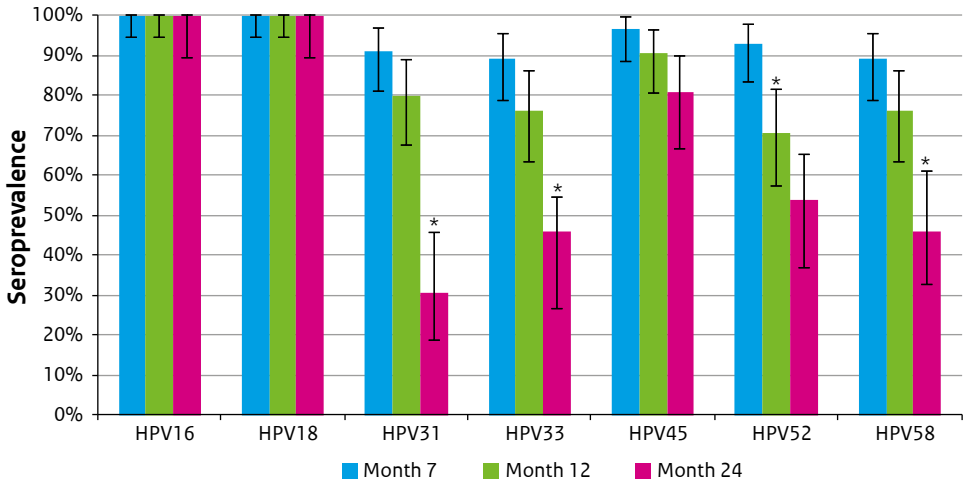

Figure 7.4.5 Seroprevalence among HPV2D participants of HPV types 16/18/31/33/45/52/58 following a two-dose schedule (0, 6 months) at months 7, 12 and 24 after the first dose

* Statistically significant difference compared with the previous sampling

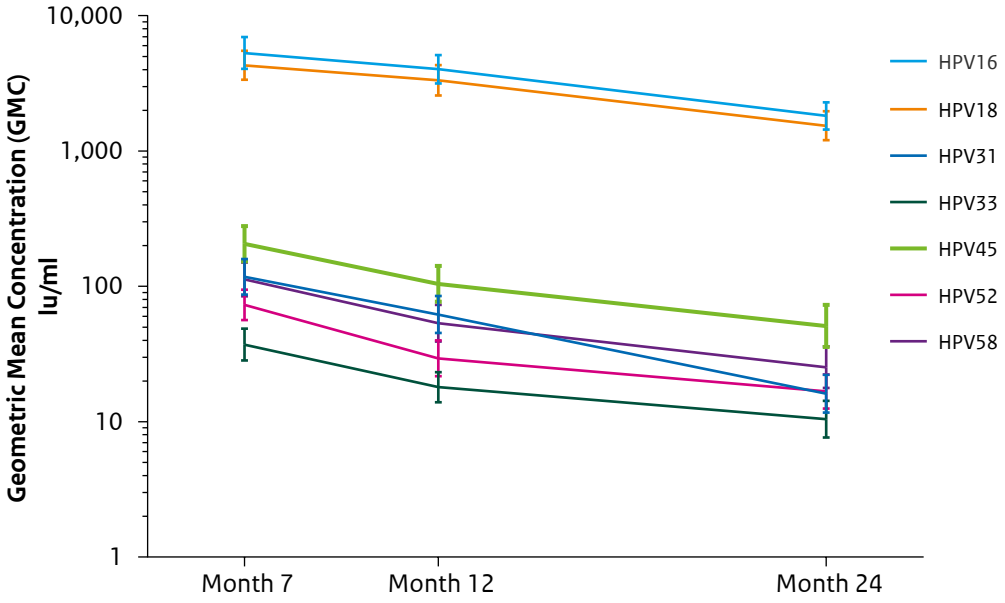

Figure 7.4.6 Geometric Mean Concentrations (GMC; lu/ml) among HPV2D participants of HPV types 16/18/31/33/45/52/58 following a two-dose schedule (0, 6 months) at months 7, 12 and 24 after the first dose

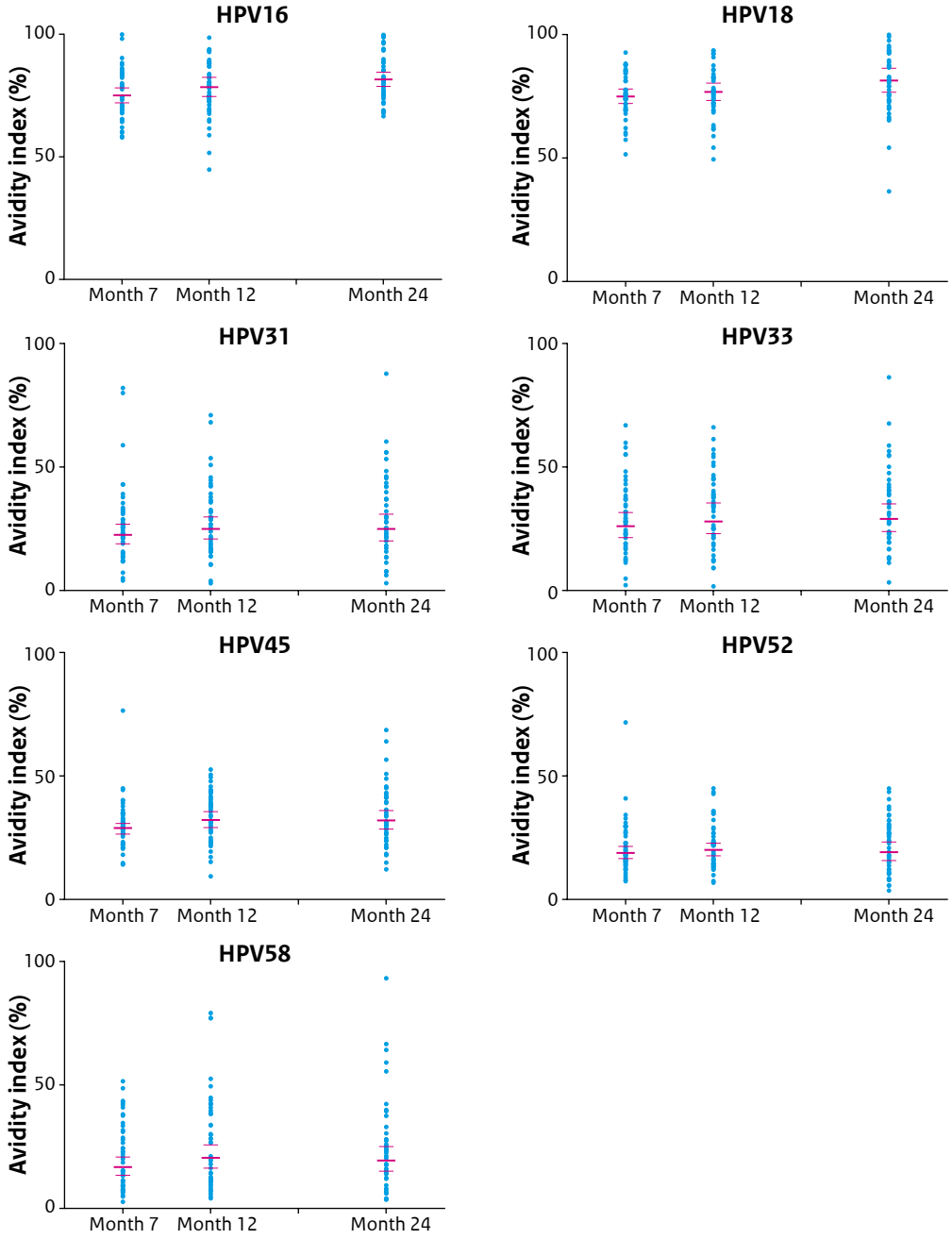

Figure 7.4.7 Antibody avidity among HPV2D participants of HPV types 16/18/31/33/45/52/58 following a two-dose schedule (0, 6 months) at months 7, 12 and 24 after the first dose

The lines indicate the mean antibody avidity index with a 95% confidence interval

7.4.3 Epidemiology

Persistent infection with a high-risk HPV (hrHPV) type is a necessary cause in the development of cervical cancer. It can also cause vaginal, vulvar, penile, anal, mouth/oral and oropharyngeal cancer (Table 7.4.1). Globally, 570,000 cancer cases (8.6% of all cancers) per year in women and 60,000 cases (0.8%) in men are attributable to HPV [2]. In Europe, this number is 43,500 in women and 9,500 in men [1].

The incidence of cervical cancer in the Netherlands increased in 2016 (preliminary data) to 9.25 per 100,000, compared with 7.67 per 100,000 in 2015 (Figure 7.4.1). The number of deaths due to cervical cancer only slightly increased in 2016 (2.67 per 100,000 in 2016 (preliminary data), compared with 2.43 per 100,000 in 2015; Figure 7.4.2). Incidences and deaths related to other HPV-associated cancers in the Netherlands have remained more or less stable over the last five years (Figure 7.4.1 and Figure 7.4.2). Annually 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 2016, the number of GW diagnoses at STI clinics was 1,785 [3]. The positivity rate of GW among women (1.0%) and heterosexual men (2.2%) has remained relatively stable since 2013, while the positivity rate continued to decrease among MSM (from 1.7% in 2013 to 0.9% in 2016). The number of diagnoses of GW by GPs was estimated at 36,800 in 2015, which was comparable to figures for the past three years.

In response to novel insights into penile, anal, vaginal, vulvar and oropharyngeal cancer, the Ministry of Health asked the Health Council to prepare an update of their recommendation in 2008 to vaccinate all girls in the Netherlands. To support the Health Council, the RIVM has collected and structured relevant national and international information. For example, information on the occurrence of HPV infections and HPV-related diseases in girls/women and boys/men, as well as information on the effectiveness and safety of the vaccines [4].

7.4.4 Research

7.4.4.1 Whole genome sequencing analysis of HPV16 and HPV18

We have recently investigated the naturally occurring diversity of HPV16 and HPV18 strains on the whole genome level. Samples from the Chlamydia trachomatis Screening and Implementation (CSI) study were used [5] for this. Participants in this study supplied follow-up samples annually for up to 3 years. The found diversity was remarkably large. HPV16 infections from 115 study participants were sequenced, leading to 109 unique sequence variants. HPV18 infections from 51 study participants were sequenced, leading to 52 unique sequence variants. For both HPV16 and HPV18, a single reinfection event was found, in which the initial sample from a participant was different from the follow-up sample.

Using the available follow-up, both persistent and clearing infections were identified. A single nucleotide polymorphism (SNP) analysis was then performed to identify any SNPs associated

with infections, either clearing of persisting. No correlation was found between any nucleotide position and the clearing or persisting of infections. However, our SNP analysis did lack in power for both HPV16 and HPV18, due to a limited number of infections. As a result, only SNPs with very strong-acting properties could be identified. A sliding window analysis of persistent HPV16 genomes compared with clearing HPV16 genomes did not identify any regions that differed between the groups. The same was true for HPV18. Based on our results, we have no indication that genome differences could explain why HPV16 or HPV18 infections are clearing or persisting. Further research on larger studies is required to assess more nuanced effects of SNPs on infection outcome.

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, that were eligible for the catch-up campaign, is still ongoing [6]. The primary aim of this study is to monitor the effect of the bivalent HPV vaccination on HPV-type-specific presence amongst vaccinated and unvaccinated young women. A search of literature identified five different statistical approaches that are used to estimate the vaccine effectiveness (VE) against persistent HPV infections. These approaches differ with respect to their underlying assumptions. Still, the VE against persistent infections with vaccine types and cross-protective types (HPV16/18/31/33/45) was quite similar in young women eligible for routine HPV vaccination and seems resistant to violations of underlying assumptions. Based on our findings and available literature, at this point the Prentice Williams and Peterson total time (PWP-TT) seems to be the most appropriate method for monitoring routine HPV vaccination. Further confirmation of our findings could be obtained by applying these methods when follow-up time increases in our study, as well as by using these methods in a different study population. Applying this method to the data of the HAVANA-study showed significant type-specific VE against incident infections with HPV16/18/31/35 and 45 and 12-month persistent infections up to six years post-vaccination by HPV16/18/31.The VE up to six years post-vaccination against both incident and persistent infections is shown in Table 7.4.2.

Since the autumn of 2016, a second prospective cohort study has also been carried out among vaccinated and unvaccinated girls born in 2001 who were eligible for a two-dose schedule in 2014 (HAVANA2). Annual follow-up of this cohort is planned for at least five years. Each year, girls will be asked to fill out a questionnaire and hand in a vaginal self-swab. For the first round of this study, 23,540 girls (50% vaccinated, 50% unvaccinated) were initially invited to participate. Because the participation rate among unvaccinated girls lagged behind, an additional 15,721 unvaccinated girls were approached. Overall, 2,489 girls confirmed their intention to participate in the study, 53% of whom were vaccinated and 47% unvaccinated.

7.4.4.3 Effect of bivalent HPV vaccine on viral load of vaccine and non-vaccine HPV types

Vaccine recipients are protected against persistent HPV16 and HPV18 infection, but protection against incident infections of these types is lower. This implies the presence of a mechanism in which HPV16 and HPV18 in vaccinated persons are not able to establish infections efficiently. As a result, these infections can be cleared by the host before they persist. To elucidate the mechanism behind this finding, fifteen type-specific quantitative HPV assays were developed

(for HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 6 and 11). Initial results have been obtained for HPV16 and HPV18. In incident HPV16/18 infections, vaccinated HAVANA-study participants show significantly lower viral loads than non-vaccinated HAVANA-study participants. This finding could help explain the reduced occurrence of both incident and persistent HPV16 and HPV18 infections in vaccinated individuals in this study.

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

Using data from the PASSYON study, a biennial cross-sectional survey conducted among 16- to 24-year-old STI clinic visitors in the Netherlands [7], we estimated the direct VE against hrHPV positivity. Data was used from all women who were eligible for HPV vaccination and with a self-reported vaccination status (cohorts born from 1993 onwards, n=1,087). We used Odds Ratios (ORs) to estimate the VE, which has been suggested to be a suitable measure for the relative reduction in the expected time a woman will be positive for HPV from cross-sectional data [8]. We calculated the ORs using a logistic mixed model, incorporating a random intercept to account for residual dependence between type-specific infections within individuals. VE was calculated as 1 minus the adjusted OR times 100%. Of the women included, 53% tested positive for a high-risk type and 60% reported to have been vaccinated at least once. The adjusted VE against hrHPV positivity is presented in Figure 7.4.4. The VE against HPV16/18 was high (90%) and in line with previous efficacy estimates from the vaccine trials. In addition, significant cross-protection against types 45 (91%), 35 (57%), 31 (50%) and 52 (37%) was found.

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

To monitor the effects on immunogenicity of the change from a three to a two-dose schedule, a cohort study among girls who received a two-dose schedule was initiated in 2014. Annually, girls fill in a questionnaire and supply a blood sample to assess the quantity and quality of the generated immune response.

Interim results have showed high antibody levels, with high avidity (>75%), against vaccine-types HPV16/18 after 24 months of follow-up, despite a waning in levels over two years (Figure 7.4.5 and Figure 7.4.6). The high antibody avidity remained stable for up to 24 months (Figure 7.4.7). Antibody levels and avidity were considerably lower for cross-protective types (HPV 31, 33, 45, 52, 58), with a somewhat higher level of waning for up to 24 months.

7.4.4.6 Modelling

Vaccinating boys may be a complementary strategy for the prevention of HPV-related diseases, especially since uptake among girls in the Dutch immunisation programme in 2015 seemed to have reached a plateau. We expanded a previously published Bayesian evidence synthesis framework [9] in order to evaluate the efficiency of vaccinating boys relative to increasing uptake among girls and assessing the cost-effectiveness of a gender-neutral programme relative to a girls-only programme [10]. We estimated that increasing the uptake in girls from 60% to 80% would yield the same gain in life-years (LYs) as vaccinating 40% of boys along with 60% of girls. Hence, vaccinating boys along with girls is modestly less efficient than increasing uptake among girls. The ICER of vaccinating boys under a 3% discounting was €9,134/LY gained (95%CrI: 7,323-11,231), assuming similar costs per vaccinated boy as previously published for the girls-only programme [11, 12]. The ICER of vaccinating boys was

€4,390/LY gained (95%CrI: 3,617-5,253) under a 1.5% discounting of future health gains and a 4% discounting of future costs and savings, as recommended in Dutch guidelines for health economic evaluation. The ceiling vaccination costs at which the ICER remained below the per capita gross domestic product was €240 (95%CrI: 200-280) per vaccinated boy if uptake among girls continued at 60%. If girls' uptake increased to 90%, the ceiling costs decreased to €70 (95%CrI: 40-100) per vaccinated boy. In conclusion, a gender-neutral programme is highly likely to be cost-effective under published vaccine costs and uptake among girls in the Netherlands.

7.4.5 International developments

A current review of Sankaranarayanan et al. stated that more than 80 countries around the world have introduced HPV vaccination and an additional 25 have introduced HPV vaccination in pilot demonstration programmes [13]. Most programmes predominantly used a school-based approach.

7.4.5.1 Impact of HPV vaccination

A pooled analysis of 20 studies in high-income countries with >50% HPV vaccination coverage showed a significant decrease of 68% in HPV 16 and 18 infections between the pre-vaccination and post-vaccination periods (RR 0.32; 95%CI 0.19-0.52) [13]. In addition, significant reductions in cross-protective HPV types 31, 33 and 45 were recorded for girls (RR 0.72; 95%CI 0.54-0.96). A French study conducted among females under 25 years of age that were undergoing chlamydia testing demonstrated a VE against vaccine types (HPV 6, 11, 16, 18) of 95.9% (95%CI 90.2-98.3%) and 38.4% (95%CI 12.7-56.5%) against cross-protective genotypes (HPV 31, 33, 45) [14]. Another British study conducted in 2010-2012 among sexually-experienced women showed a lower prevalence of HPV 16 and 18 among 18- to 20-year-old women, for whom three-dose vaccine coverage was 52.0%, compared with the same study conducted in 1999-2001 (5.8% vs. 11.2%; age-adjusted prevalence ratio 0.48, 95%CI 0.24-0.93) [15]. Prevalences of HPV types 6 and 11 and cross-protective types 31, 33 and 45 remained unchanged between both periods, as well as prevalences of HPV 16 and 18 among women aged 21 to 44.

The quadrivalent vaccine was shown to be highly effective against GW, the incidence of which dropped shortly after the introduction of vaccination among young females and their male partners in Australia and Denmark [16]. In a pooled analysis of studies conducted in high-income countries with >50% HPV vaccination coverage, anogenital warts (AGW) decreased significantly in 13- to 19-year-old girls by 61% (RR 0.39; 95%CI 0.22-0.71) [13]. In addition, significant reductions of warts in boys younger than 20 (RR 0.66; 95%CI 0.47-0.91) and in women aged 20-39 (RR 0.68; 95%CI 0.51-0.89) were observed, which suggests a significant herd immunity. An observational study conducted in Italy showed a significant drop in hospitalisations for GW after 2007 among females (average annual percent changes: -6.1%; 95%CI -8.4--3.7%) [17]. For males, the hospitalisation rate for GW increased over the study period (average annual percentage changes: 3.8%; 95%CI 1.2-6.4%). In a study that evaluated the early population impact up to 6 years post implementation of Ontario's school-based HPV vaccination programme, the incidence of AGW decreased by 6.5% in females aged 18-20 [18]. The total health service utilization for AGWs decreased by 13.8%, 11.1% and 10.0% in females 15-17, 18-20 and 21-23 years of age, respectively, in the vaccine era compared with the

pre-vaccine era. In contrast, male AGW incidence rates increased, suggesting no early evidence of herd effects in males. For Valencian girls and women aged 14-19 years, the effectiveness of a three-dose regimen of the quadrivalent HPV vaccine against GW was 77% (95% credible interval (CrI) 66-85%) and the effectiveness of a single dose was 61% (95%CrI 20-87%) [19]. No effectiveness against GW was seen for a three-dose regimen with the bivalent HPV vaccine [19].

Niccolai et al. measured trends in cervical lesions during 2008-2015 in Connecticut, US, which showed that rates of CIN2+ declined by 30%-74% among women aged 21-26 years, with greater declines observed in the younger women [20]. Ecological comparisons revealed substantial increases in HPV vaccination during this period and more modest reductions in cervical cancer screening and sexual risk behaviours, suggesting that declines in CIN2+ are most likely driven by HPV vaccination. In European countries with high vaccination coverage, significant reductions of CIN3 were observed, regardless of HPV type [16]. In Denmark, using the quadrivalent vaccine, a reduction of up to 80% was seen and in Scotland, where the bivalent vaccine was used, the reduction was 55%.

An observational study that measured patterns of clinical activity at colposcopy before and after vaccinated women entered the Scottish Cervical Screening Programme showed a downward trend in the proportion of those referred with abnormal cytology at 20-21 years of age (2008-2009: 91.0%; 2013-2014: 90.3%; linear trend P = 0.03) [21]. Women were more likely to have no biopsy (2008-2009: 19.5%; 2013-2014: 26.9%; linear trend P < 0.0001) or no treatment (2008-2009: 74.9%; 2013-2014: 91.8%; linear trend P < 0.0001).

7.4.5.2 Reduced dose schedules

Based on immunobridging studies, in which immune responses after a two-dose schedule in young girls were non-inferior compared with immune responses following a three-dose schedule in young adult women, two doses of the HPV vaccines for girls below 15 years of age are recommended. By February 2017, 25 high-income countries and 23 low and middle-income countries had adopted a two-dose HPV vaccination schedule [22].

A systematic review and meta-analysis showed that, in randomised comparisons among adolescent girls, GMCs of HPV16 and 18 antibodies were non-inferior or inconclusive up to 24 months after a two-dose schedule, compared with a three-dose schedule [22]. Other studies showed comparable antibody responses at 60 months for the bivalent and quadrivalent vaccine [23, 24]. In non-randomised comparisons, GMCs in adolescent girls receiving the two-dose schedule were non-inferior or superior compared with women receiving the three-dose schedule up to at least 21 months after vaccination [22]. In non-randomized clinical trials as well, comparable protection against incident and persistent infections was demonstrated with two doses versus three doses [22, 25]. However, a review of the efficacy of less than three doses of HPV-vaccines concluded that population-based ecological and nested-case control studies seems to indicate reduced vaccine efficacy of two doses against virological and disease endpoints [25]. On the other hand, recent studies showed similar effectiveness against GW after receiving two doses compared with three doses of the quadrivalent vaccine [26, 27].

Some recent studies suggested a protective effect of a single dose of HPV vaccine [25]. A single dose of the quadrivalent vaccine elicits antibodies, which persist for at least six years and induce immune memory [28]. Efficacy of a single dose against incident and persistent HPV infections has been shown in analyses of clinical trial data from women intended to receive three doses [29]. However, receipt of one dose was associated with more genital warts than was the case for receipt of three doses [26]. Further evidence for the effectiveness of one dose is required [30].

7.4.5.3 Male vaccination

More and more countries are contemplating the inclusion of boys in preadolescent HPV vaccination programmes. Within Europe, boys' vaccination is being implemented in Austria, Liechtenstein and Switzerland. It is being considered in Sweden, Germany and the Netherlands. However, the cost-effectiveness profile of boys' vaccination in formal health economic assessments is still strongly debated internationally. Various models have estimated the incremental cost-effectiveness of vaccinating boys next to girls, with results that mainly advise against implementation [31-36] (but see [37, 38] for exceptions). It should be noted that most studies have likely underestimated the health impact of boys' vaccination by excluding some HPV-related cancers from the analysis and by ignoring the concentrated burden of male HPV-related diseases among men who have sex with men. Likewise, most evaluations have overestimated the incremental costs of boys' vaccination, by assuming three-dose schedules and market prices for the vaccines (€85-150 per dose), thereby neglecting the impact of tender negotiations and two-dose schedules [39]. A Norwegian study did account for reduced vaccine prices due to tender negotiations, but still assumed three-dose vaccination schedules for preadolescents [38]. Likewise, a New-Zealand study reported administration costs of €80-90, which played a decisive negative role in cost-effectiveness calculations [35].

7.4.5.4 Nonavalent vaccine

The nonavalent vaccine was developed from the quadrivalent vaccine and includes five additional HPV types – HPV 31, 33, 45, 52 and 58 – which could increase the level of protection against HPV-related cancers. The nonavalent vaccine provides non-inferior immune responses for HPV type 6, 11, 16 and 18, compared with the quadrivalent vaccine, with seroconversion rates close to 100% [29, 40, 41]. Efficacy data from women aged 16-26 showed an efficacy of the nonavalent vaccine against persistent infection and disease related to HPV types 31, 33, 45, 52 and 58 of approximately 96% [29, 40, 41]. The incidence of persistent infection and low and high-grade disease related to HPV type 6, 11, 16 and 18 was similar for the nonavalent and quadrivalent vaccines [29, 40].

Immune responses in men aged 16-26 years and girls and boys aged 9 15 years were assessed in order to support immunobridging. At month 7, seroconversion rates in those groups were close to 100%. Non-inferiority was demonstrated for all new types included in the nonavalent vaccine, but immune responses were slightly higher in the younger age groups, compared with women and men 16-26 years of age [40, 41].

The immunogenicity of the nonavalent vaccine has also been assessed in 9- to 14-year-old boys and girls receiving a two-dose schedule. At month 7, seroconversion for those boys and girls was more than 97% [40]. GMTs for all nine vaccine types were higher in girls and boys who received a two-dose schedule (at either 0 and 6 or 0 and 12 months) than they were for 16- to 26-year-old women who received a three-dose schedule of the nonavalent vaccine [40, 42]. GMTs were numerically lower for vaccine types 18, 31, 45, and 52 after a two-dose schedule at 0 and 6 months and for type 45 after a two-dose schedule at 0 and 12 months than they were after a three-dose schedule in 9- to 14-year-olds [40]. In girls and boys given doses at 0 and 12 months, GMTs were higher than they were in girls and boys given doses at 0 and 6 months [42].

In addition, the immunogenicity of the nonavalent vaccine was assessed in females who had previously received the quadrivalent vaccine. Of those females aged 12-26 years who were previously vaccinated with three doses, between 98.3% and 100% seroconverted to the new types included in the nonavalent vaccine [40]. The nonavalent vaccine can be used to complete an incomplete vaccination schedule or can be added to a previous completed schedule to extend the protection to other HPV types [43]. The number of doses and timing depends on the number of doses already given and the age of the recipient.

7.4.5.5 Cost-effectiveness

Favato et al. reviewed the ecological validity, specifically the consideration of sexual behaviours and population mixing, of the HPV vaccination cost-effectiveness models in the published literature [44]. Eight published economic evaluations were reviewed, but none of the studies showed due consideration of the complexities of human sexual behaviour and the impact this may have on the transmission of HPV. None of the studies considered the impact of sexual partners from other countries, sex that was paid for, or the frequency of unprotected sex. Only one of the models considered men who have sex with men. The included dynamic transmission models might be affected by a different degree of ecological bias, such as over-estimating the outcomes of girls' only vaccination. These findings indicate that the girls' vaccination programme is likely to fail to achieve the expected level of herd immunity at population level. A relatively small (15-20%) overestimation of QALY-gained through girls' vaccination programmes could induce a significant error in the estimate of the cost-effectiveness of universal immunisation, making the option of vaccinating boys cost-ineffective. To minimise potential ecological bias, population characteristics and sexual behaviours of the modelled population should be more in line with real-life scenarios.
In another review, the cost-effectiveness of different HPV prevention strategies based on screening and vaccination was assessed [45]. Among the strategies modelled in the 18 studies included, HPV DNA testing followed by cytological triage of HPV positive women in combination with HPV vaccination was found to be the optimal strategy, with a comparable cost to other screening strategies and a greater QALY gain. Strategies with shorter screening intervals were more costly and offered limited added benefit compared with those with longer intervals. New prevention strategies involving multi-valence vaccination, HPV DNA test screening, delayed beginning and frequency of screening could be implemented in the future. Assessing the interaction between screening and vaccination is difficult. So appropriate modelling techniques will be needed to assess the most cost-effective strategies.

Langeron et al. evaluated the cost-effectiveness of universal nonavalent vaccination for the German setting [46]. Compared with the current vaccination programme, the nonavalent vaccine extended to boys shows further reductions of 24% in the incidence of cervical cancer, 30% and 14% in anal cancer for males and females, as well as over a million cases of genital warts avoided after 100 years. The new strategy shows favourable results: in the case of universal vaccination, the ICER is €22,987 per QALY gained, decreasing to €329 when considering the vaccine switch for a girls-only vaccination programme.

The nonavalent HPV vaccine is being introduced in several countries. The cost-effectiveness of cervical screening in cohorts offered nonavalent vaccines and the optimal number of screening tests were assessed for four countries: the USA, New Zealand, Australia and England [47]. Local factors including vaccine uptake rates, attributable fractions of types included in the nonavalent vaccine, demographic factors, costs and indicative willingness-to-pay (WTP) thresholds were included. In the USA, four screens per lifetime was the most likely scenario, with a 34% probability of being optimal at WTP US$50,000/Life Years Saved (LYS). In New Zealand, five screens per lifetime was the most likely scenario, with a 100% probability of being optimal at NZ$42,000/LYS. In Australia, two screens per lifetime was the most likely scenario, with a 62% probability of being optimal at AU$50,000/LYS. In England, four screens per lifetime was the most likely scenario, with a 32% probability of being optimal at GB£20,000/LYS. The authors concluded that some cervical screening will remain cost-effective, even in countries with high vaccination coverage.

Men who have sex with men (MSM) have a high risk of anogenital warts and cancers related to infection with HPV. They also benefit less from herd protection than heterosexual males in settings with female-only HPV vaccination. The cost-effectiveness of offering vaccination to MSM who visit genitourinary medicine (GUM) clinics in England was evaluated [48]. Offering vaccination to HIV-positive MSM up to age 40 is likely to be cost-effective, with an ICER below £20,000/QALY gained, if vaccine costs are below £96.50 a dose. At £48 a dose, offering vaccination to all MSM up to age 40 is likely to be cost-effective. In conclusion, HPV vaccination of MSM via GUM clinics is likely to be an effective and cost-effective way of reducing the burden of HPV-related disease in MSM.

Therapeutic HPV-vaccines may improve the treatment of (pre)-malignant cervical neoplasia because no surgical treatment is needed. It can trigger the immune system to recognise HPV-infected cells and enhance the immune system to eliminate these cells. Luttjeboer et al. examined the potential price for a therapeutic vaccine against HPV 16 and 18 (pre)-malignant cervical lesions [49]. Based on data on cervical cancer screening and HPV prevalence in the Netherlands, cohorts were created with HPV 16 or 18 positive women with CIN 2 or 3 or cervical cancer stage 1A (FIGO 1A). In the base case, break-even vaccine prices of €381, €568 and €1,697 were found for CIN 2, CIN 3 and FIGO 1A, respectively. The sensitivity analysis showed vaccine pricing below €310, €490 and €1,660 will be cost saving with a likelihood of 95% for CIN 2, CIN 3 and FIGO 1A, respectively. The vaccine price proved to be very sensitive for inclusion of QALY gains, the HPV-type-specific test into the Dutch screening practice, and vaccine efficacy.

7.4.5.6 Screening of vaccinated women

Three recent studies evaluated the participation of HPV vaccinated girls in cervical screening. In a cohort of women in Alberta born between 1994 and 1997, vaccinated women had a higher screening rate than unvaccinated women (13.0% vs. 11.4%, p<0.001) [50]. Boone et al. found that 14- to 26-year-old women who had been vaccinated were more likely to screen than unvaccinated women (unvaccinated 53%, one dose 62%, two doses 59% and three doses 61%) [51]. Paynter et al. found the highest screening rate of 84% among women who had been vaccinated with three doses and screened at or after 21 years of age, which is a six times higher screening participation than for unvaccinated women (adjusted OR 5.94; 95%CI 3.77-9.35) [52]. Results suggest that women who receive HPV vaccination closer to age 21 are more likely to participate in cervical cancer screening.

To determine whether HPV vaccination has affected the prevalence of HPV genotypes and colposcopic features of CIN in young women referred for colposcopy, Munro et al. conducted an observational study among vaccinated and unvaccinated women aged 20-25 years attending colposcopy following an abnormal cervical cytology result from routine cervical screening [53]. They found that the prevalence of HPV16 was significantly lower in vaccinated women than in unvaccinated women (8.6% vs. 46.7%; P=0.001). The number of CIN2+ cases was also significantly lower in vaccinated women (P=0.006). In addition, there was a slight reduction in the positive predictive value of colposcopy for CIN2+, from 74% (unvaccinated) to 66.7% (vaccinated).

7.4.6 Literature

7.4.6.1 References

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7.5 Measles

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

7.5.1 Key points

- In 2016, the number of reported measles cases remained low (n=6) and was comparable to 2015. In 2017 up to July, 10 cases were reported.
- In Europe, a resurgence of measles was observed in 2016 (n=3,767), which continued in 2017 (n=2,480 up to March). Most cases were reported in Romania, Italy and Germany.

7.5.2 Tables and figures

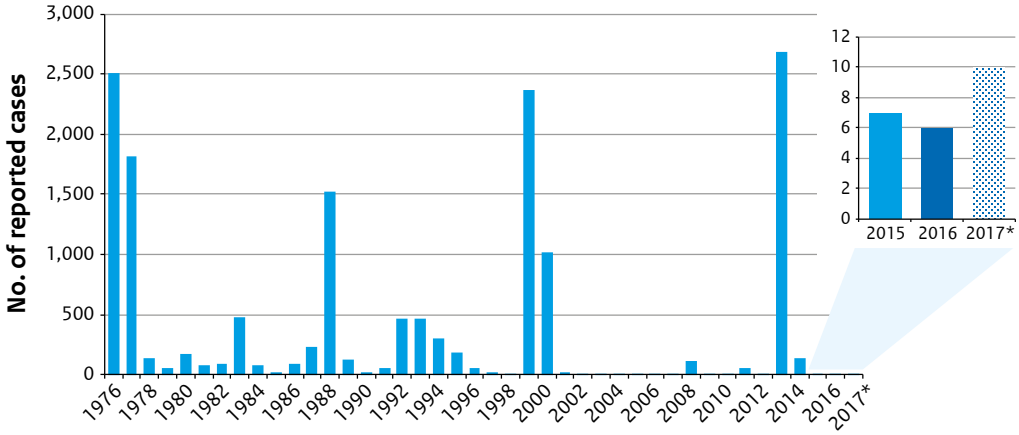

Figure 7.5.1 Reported measles cases since the introduction of measles vaccination programme in the Netherlands

* up to July

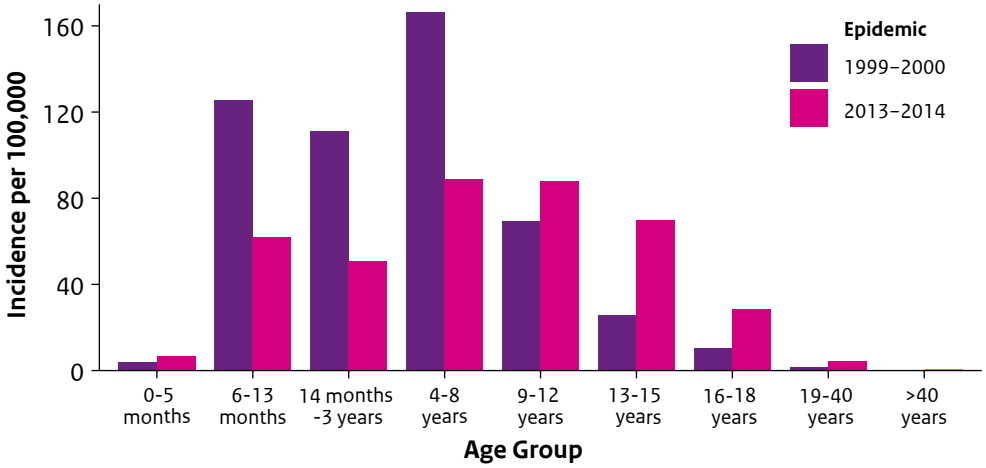

Figure 7.5.2 Incidence of reported cases by age group for the 1999-2000 epidemic (n = 3,170) and the 2013-2014 epidemic (n= 2,700), the Netherlands

7.5.3 Epidemiology

In 2016, we experienced the lowest number of measles cases since the last epidemic in 2013/2014 (Figure 7.5.1). Six cases were confirmed and reported to the national registry and to ECDC and WHO. However, in the first half of 2017, ten measles cases were notified.

Most cases from 2016 and 2017 were imported or were import-related cases related to traveling to and from countries in the European region and countries in South-East Asia, where major outbreaks of measles had been reported in the same period. Imported cases were mostly unvaccinated adults that sometimes caused one or two secondary cases among unvaccinated household members or contacts that attended the same GP or hospital.

7.5.4 Pathogen

Four out of six reported cases could be genotyped in 2016. All four were identified as genotype D8, with a molecular and epidemiological signature pointing to separate importations from Indonesia (n=3) and Thailand (n=1). The fifth case was a secondary case related to one of these four cases. For the sixth case, no molecular data were available nor was there a known source of infection.

From the ten cases reported up to 1 July 2017, the first case, which occurred in April, was genotyped B3, which is a common genotype in outbreaks occurring in Romania and Italy. Four cases were genotyped as D8 with a sequence currently only matching recent outbreaks in India. The first case could be epidemiologically linked to Spain, but this specific D8 sequence has not yet been reported among cases in Spain, or in any other European country to date. Another case found in a tourist had a D8 genotype matching a strain reported in Germany and closely matching the D8 strain seen in 2016.

7.5.5 Research

7.5.5.1 *Epidemic 2013-2014*

In a recently published study [1], the measles outbreaks of 1999-2000 and 2013-2014 were compared in terms of age distribution (Figure 7.5.2). The median age was 10 years in 2013-2014, four years higher than the median age in 1999-2000. This is probably caused by a longer inter-epidemic interval of some 14 years preceding the last epidemic, compared with an interval of around 6 years preceding the 1999-2000 epidemic. The higher median age of cases reported during the 2013 2014 epidemic was also partly caused by the lower incidence of cases involving children under 8, compared with the incidence of cases involving children under 8 from the 1999-2000 outbreak. A plausible explanation could be the improved vaccination coverage among orthodox Protestants [2]. An increase in the vaccination coverage among orthodox Protestants may lead to longer inter-epidemic periods, resulting in future outbreaks that affect older age groups, which is expected to lead to more complications.

7.5.5.2 *Evaluation of coverage and effects of early MMR vaccination*

During the outbreak of 2013-2014, all infants between 6 and 14 months old living in municipalities with vaccination coverage below 90% were invited for an early MMR vaccination. Regularly, the first MMR is given at 14 months.
The coverage was suboptimal, 57% (n=5,800) of the invited infants received a MMR vaccination before the age of 13.5 months. The uptake was extremely low (1%) among those without a previous DTaP vaccination, while the uptake was 70% among those with three previous DTaP vaccinations. Those who were vaccinated had a lower risk to contract measles than unvaccinated infants [3]. The vaccine effectiveness was 94% (95%CI 79-98%). Part of the effect, however, was caused by herd immunity. Vaccinated infants were more likely to be surrounded by vaccinated individuals. The vaccine effectiveness decreased to 71% (95%CI -72-95%) when adjusted for religion and the vaccination status of siblings.

7.5.5.3 *Measles outbreak among previously immunised health care workers, the Netherlands, 2014*

In a measles outbreak among previously immunised healthcare workers (HCWs) in 2014 [4], we assessed laboratory characteristics, measles vaccine effectiveness and serological correlates for protection. Eight HCWs were notified as measles cases, 6 had been vaccinated twice, 1 had been vaccinated once and 1 was unvaccinated. None of the twice-vaccinated cases had severe measles and none caused onward transmission, consistent with laboratory findings suggesting a secondary immune response. We concluded that improving 2-dose MMR coverage among HCWs is crucial in reducing outbreaks. WHO and CDC recognized the importance of the results of this study as it thoroughly describes and defines the occurrence and diagnostics of measles among vaccinated persons and the lack of secondary virus transmission from vaccinated HCWs.

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

Children who received an additional early measles immunisation between the age of 6 and 12 months during the latest measles epidemic participated in a clinical study with the aim of assessing the short and long-term immunological effects of lowering the age for the first immunisation. Virus neutralization assays were performed to determine neutralizing antibody concentrations against measles in children up to 2 years old.
A lower neutralizing antibody response and a lower total measles-specific IgG response after MMR vaccination at 14 months of age were observed when lowering the age for the first immunisation, most significantly for children who received the additional vaccine dose between the age of 6 months and 9 months. This negative correlation between lowering the age of vaccination and the antibody concentrations against measles has been reported in the literature [5]. Currently, functional properties of the antibodies (avidity, memory repertoire), as well as cellular immunity up to the age of 4 are being assessed.

7.5.5.5 Implementation of measles pre-exposure and post-exposure measures in Dutch hospitals

This study examined adherence to national recommendations on measles pre-exposure and post-exposure measures [7]. These included immunisation of HCWs in Dutch hospitals during the 2013/2014 measles epidemic and an assessment of which hospital characteristics and organisational issues hampered implementation. Most hospitals took measures to prevent measles in HCWs, but less than half implemented the minimum set of measures required. Implementation strategies in hospitals need to be improved, especially in large hospitals and hospitals that have several locations, as do the assignment of responsibilities for infection prevention policies as well.

7.5.6 International developments

In 2016, the number of reported cases (n=3,767) in Europe remained stable in comparison with previous years [8]. However, the number of reported cases increased throughout the year, primarily caused by an outbreak in Romania. The resurgence of the number of reported cases continued in 2017. In the first three months of 2017, a total of 2,480 cases were observed, whereas in the first three months of 2016 only 530 cases were reported. In the first three months of 2017, most measles cases were observed in Romania (n=749), Italy (n=684) and Germany (n=411) [9]. More efforts are needed to increase the vaccination coverage in Europe. Measles immunisation programmes are not only associated with large health benefits, but also with economic benefits, as been described in a recently published systematic review of economic analyses of measles immunisation programmes [10].
WHO has consulted RIVM and CDC/Atlanta as an expert laboratory in 2016 and 2017 in order to contribute and to provide guidelines for the use of serological tests for measles and rubella in defining seroprevalence and seroprotection from an international perspective, in which RIVM operates as an expert lab on multiplex (MIA/Luminex) serology and virus neutralization. This will be incorporated into a revised version of the International Laboratory Manual for measles and rubella, which will be published in 2017, and includes a contribution of RIVM to the diagnosis of measles and rubella cases in the elimination phase.

7.5.7 Literature

7.5.7.1 *References*

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* RIVM publication

7.5.7.2 *Other recent RIVM publications*

1. Nic Lochlainn L, Ruijs WL, Swaan C, de Melker H, Hahné S. Response to Lim et al regarding "In-flight transmission of measles: Time to update the guidelines?" American Journal of Infection Control. 2017 Jan 1;45(1):95-96.

7.6 Meningococcal disease

M.J. Knol, G. Berbers, P. Kaaijk, A. Suijkerbuijk, C. van Els, A. van der Ende, H.E. de Melker

7.6.1 Key points

- The number of cases involving meningococcal serogroup C disease is still very low; there was one vaccine failure in 2017.
- After more than two decades of decrease, meningococcal serogroup B (MenB) disease seems to be increasing again, especially in <5 year olds.
- In the UK, the initial results of the MenB vaccination programme showed high vaccine effectiveness of 83% after two doses.
- In 2016 and 2017, an ongoing increase in the number of cases involving meningococcal serogroup W (MenW) disease was observed with 50 cases in 2016 and 34 up to May 2017. Because of the increasing incidence of MenW disease, the Dutch minister of Health decided to replace MenC vaccination at 14 months of age by MenACWY vaccination, and to introduce a MenACWY vaccination at 12-14 years of age. These changes will be actualized in 2018.
- The current incidence of MenW disease is highest in persons aged 65 or older (0.60 per 100,000), followed by 15-24 year olds (0.55 per 100,000) and <5 year olds (0.41 per 100,000).
- The increase in MenW disease is due to an increase in finetype P1.5,2:F1-1, which is associated with the hypervirulent clonal complex 11.
- In the UK, the initial results of the MenW vaccination programme among school leavers with a 37% uptake show a 69% reduction of MenW cases and high vaccine effectiveness.
- The number of cases involving meningococcal serogroup Y (MenY) disease in 2016 was somewhat higher than it had been in the previous five years, mainly in persons aged 65 or older.

7.6.2 Figures

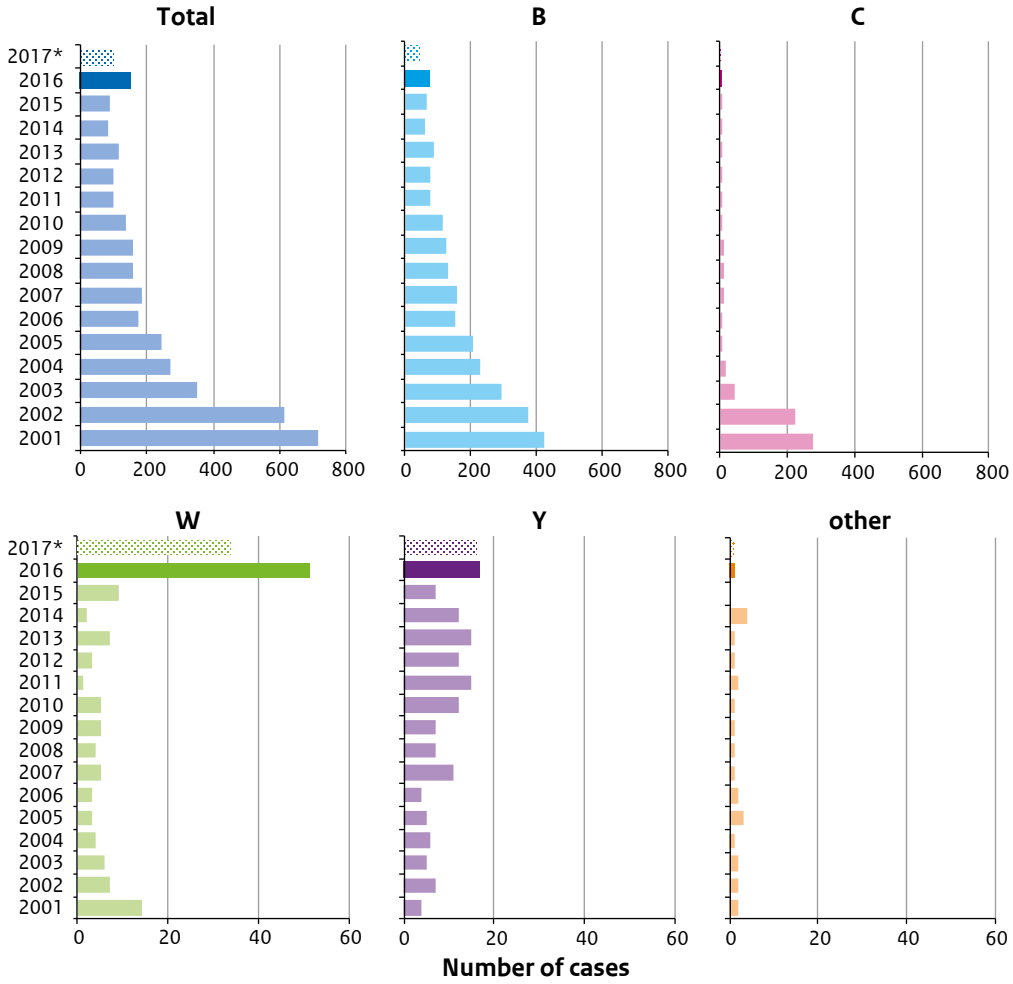

Figure 7.6.1 Number of cases of meningococcal disease per serogroup, 2001-2017* (*up to May)

Note: The scale distribution of the upper figures and lower figures is not equal.

Source: NRLBM

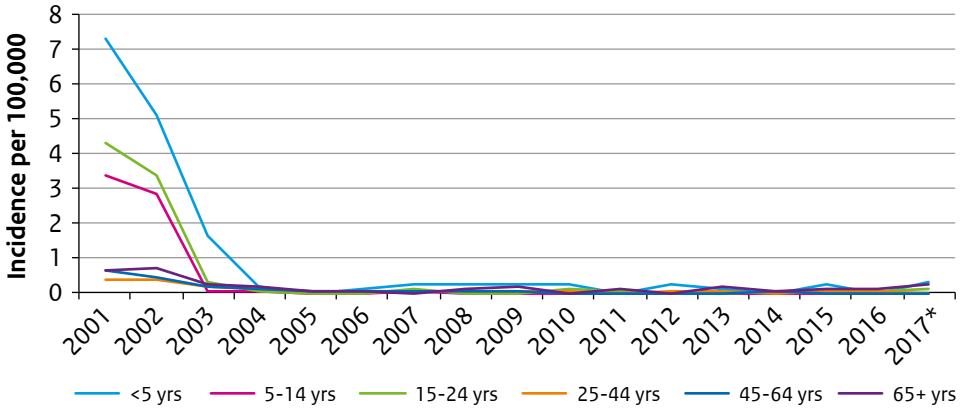

Figure 7.6.2 Age-specific incidence of meningococcal serogroup C disease, 2001-2017* (*up to May)
Source: NRLBM

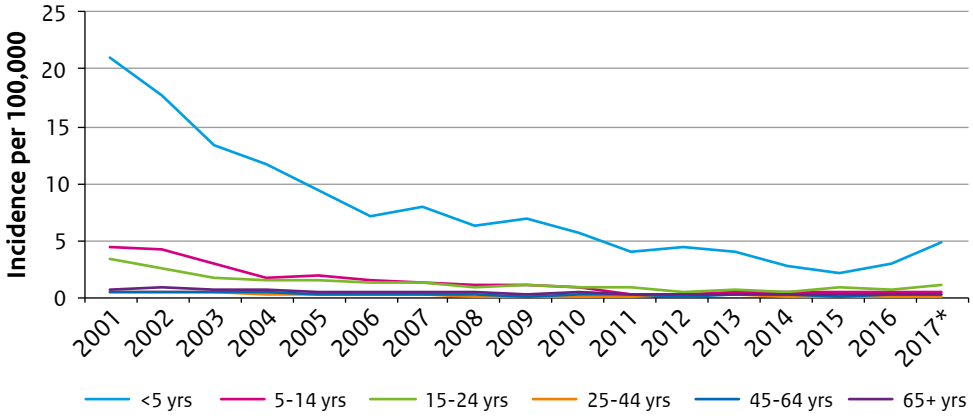

Figure 7.6.3 Age-specific incidence of meningococcal serogroup B disease, 2001-2017* (*up to May)
Source: NRLBM

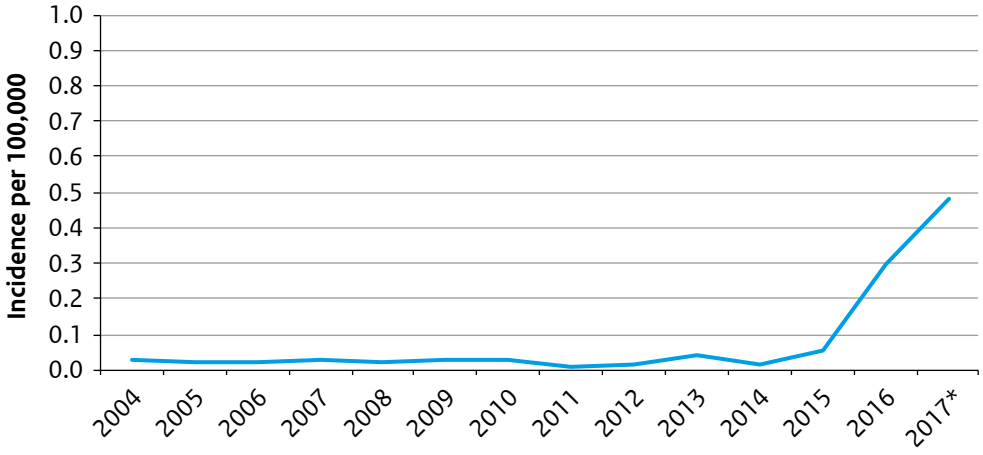

Figure 7.6.4 Incidence of meningococcal serogroup W disease, 2004-2017* (*up to May)
Source: NRLBM

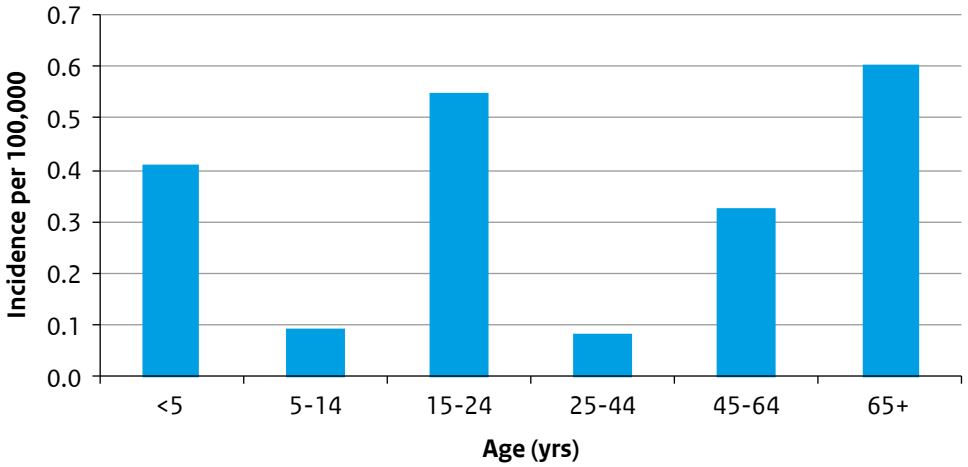

Figure 7.6.5 Age-specific incidence of meningococcal serogroup W disease for the period October 2015 up to May 2017 (n=91)
Source: NRLBM

7.6.3 Epidemiology

7.6.3.1 Meningococcal serogroup C

Since the introduction of the conjugated MenC vaccine in 2002, administered at 14 months of age, with a catch-up for one- 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 six cases per year since 2005 (Figure 7.6.1). The incidence of MenC decreased in all age groups due to herd protection (Figure 7.6.2).

In 2016, 4% of all meningococcal cases were serogroup C. Six cases of MenC were reported (Figure 7.6.1): two males aged 29 and 38, and four females aged 17, 79, 80 and 81. Only the 17-year-old was reported to have been vaccinated. She participated in the Polish vaccination programme.
Up to May 2017, five MenC cases were reported: three males aged 16 and 65 (n=2), and two females aged 9 months and 93 years. The 16 year-old was vaccinated with NeisVac-C when he was 16 months old and therefore constitutes a vaccine failure. The patient did not have an underlying disease. This is the fifth case of vaccine failure since the introduction of the conjugated MenC vaccine in 2002. With respect to the two other vaccine failures, it was known that they had an immune deficiency. None of the MenC cases in 2016 and 2017 died.

7.6.3.2 Meningococcal serogroup B

In 2016, 51% of all meningococcal cases were serogroup B. A total of 77 cases of meningococcal serogroup B (MenB) disease were reported (Figure 7.6.1), somewhat more than in 2014 (n=61) and 2015 (n=65). In 2017, up to May, 42 MenB cases were reported, which was slightly higher than in the same period in 2016 (n=36). The incidence of MenB was still highest in children under 5 years old in 2016 (3.0 per 100,000, n=26) and 2017 (4.9 per 100,000, n=18 up to May). After more than two decades of decrease, MenB disease seems to increase again, especially in children under 5 (Figure 7.6.3).
Mortality data are available for 90-95% of cases. Mortality was 1.4% (1/72) in 2016 and 4.9% (72/1,470) from 2004-2017.

7.6.3.3 Meningococcal serogroup W

In 2016, 33% of all meningococcal cases were serogroup W. A total of 50 cases of meningococcal serogroup W (MenW) disease were reported in 2016 and 34 were reported up to May 2017 (Figure 7.6.1). The incidence increased from 0.02 per 100,000 per year in 2005-2014 to 0.29 per 100,000 in 2016 and 0.51 per 100,000 in 2017 up to May (Figure 7.6.4). Between October 2015 and May 2017, 91 MenW cases were reported. The incidence was highest in persons 65 and older (0.60 per 100,000), followed by 15-24 year olds (0.55 per 100,000) and <5 year olds (0.41 per 100,000) (Figure 7.6.5). Ten out of 90 cases for which mortality data were available died (11%). Four of the deceased patients were 15-24 years old, three were 45-64 years old and three were 65 or older. Thirty-eight patients (48%) had septicaemia, 15 (19%) had meningitis and seven (9%) had meningitis and septicaemia. The other patients had less typical clinical manifestations for meningococcal disease, including bactaeremic pneumonia (n=13, 16%), septic arthritis (n=4, 5%), pericarditits (n=1), necrotizing fasciitis (n=1 [1]) and phlegmon mouth floor (n=1). To our knowledge, three patients with septicaemia, one of whom died, were presented primarily with gastrointestinal symptoms [2]. The vast majority of patients had finetype P1.5,2:F1-1 (77/84; 92%), which is associated with the hypervirulent clonal complex 11. Whole genome sequencing was performed on 77 of 91 MenW cases and revealed clonal complex 11 in 92% (n=71). Because of the increasing incidence of MenW disease, the Dutch minister of Health decided to replace MenC vaccination at 14 months of age by MenACWY vaccination, and to introduce a MenACWY vaccination at 12-14 years of age. These changes will be actualized in 2018.

7.6.3.4 Meningococcal serogroup Y

In 2016, 17 cases of meningococcal serogroup Y (MenY) disease were reported (Figure 7.2.1), which was somewhat higher than in the previous five years (7-15 cases). Up to May 2017, 16 MenY cases had already been reported. Most cases were involved patients that were 65 or older (9/17 in 2016 and 13/16 in 2017).

7.6.3.5 Other meningococcal serogroups

In 2016, one case of meningococcal serogroup X (MenX) disease was reported in an 83-year-old woman. Up to May 2017, one case of meningococcal serogroup E disease was reported in a 16-year-old girl.

7.6.4 Pathogen

The most common finetype among MenC cases in 2016 and 2017 was P1.5,2:F3-3 (n=5). There were two adult male cases with finetype P1.5 1,10-8:F3-6, which is the finetype that currently causes an outbreak in Tuscany, Italy [3]. This finetype has also been associated with several outbreaks among MSM in past years in various countries [4].
In 2016 and 2017, a regional increase was observed in the number of MenB cases with finetype P1.22,14:F5-1, which caused three MenB cases in 2016 and six cases in 2017. Previously, this finetype was only detected in one MenB case in 2009 and two cases in 2014. Of the nine cases in 2016 and 2017, eight lived in the south-west part of the Netherlands, five of whom lived in the Rotterdam region. One of the patients died. Six cases involved patients that were 15-24 years old and three cases involved patients that were 40-60 years old.
We observed a sustained increase in the number of MenW cases with finetype P1.5,2:F1-1 in 2016 and 2017, where this finetype caused the vast majority of the cases.

7.6.5 Research

7.6.5.1 Meningococcal disease

The RIVM published a report on meningococcal disease in the Netherlands, which can be used by the Health Council for determining the advice they give on whether and how the current immunisation programme against meningococcal disease should be adapted [5]. The report includes the most recent scientific information available on meningococcal disease in general, the burden of disease of meningococcal disease in the Netherlands, the effectiveness, safety, acceptance and cost-effectiveness of available vaccines against meningococcal disease, and aspects surrounding the implementation of meningococcal vaccination.

Since 2009, the incidence of MenW disease increased rapidly in the UK due to a single strain (the 'original UK strain') belonging to the hypervirulent ST-11 clonal complex (cc11), with a variant outbreak strain (the '2013 strain') emerging in 2013. We assessed the temporal and phylogenetic associations between the MenW outbreak in the Netherlands and the MenW outbreak in England, and the historical MenC outbreaks in both countries [6]. Cases due to MenW:cc11 emerged in 2012/13 in the Netherlands; most cases (32/35, 91%) were caused by the 2013-strain. For both the current MenW outbreak and the historical MenC outbreak, the increase in incidence started several years later in the Netherlands than in England, the rate of increase was higher in the Netherlands, and a similar age distribution was observed in both countries.

Based on core-genome multilocus sequence type (MLST) data of MenW cases, minimum spanning trees (MSTs) have been made, showing high similarity and links of MenW disease in Europe to earlier MenW cases in South America. MSTs however do not contain rates and directions of transmission between countries. The discrete-trait model in BEAST was used to characterize spatial transmission between countries, with timed sequence data. Core MLST data were downloaded from the pubMLST database for two South American countries (Argentina, Brazil) and seven European countries (France, Finland, Italy, Ireland, the Netherlands, Sweden and the UK). The analysis placed the root of the MenW:cc11 outbreak around 2000. Furthermore, it suggests multiple introductions into Europe, through Italy and the UK. Cases tended to be more clustered in the Netherlands, Italy and the UK, which acted as the main sources for multiple independent introductions into Finland, France and Sweden. Ireland was infected through the UK. Our analysis suggests differences between countries with respect to the level of sustained transmission. This is possibly due to different contact structures in the adolescent populations, where carriage is most prevalent.

7.6.5.2 Meningococcal vaccination

Adolescents are considered the key transmitters of meningococci in the population. MenC antibody levels wane rapidly after MenC conjugate vaccination in young children, leaving adolescents with low antibody levels. In the JIM study, we compared MenACWY immune responses after booster vaccination in adolescence with either tetanus toxoid conjugated MenC (MenC-TT) or MenACWY (MenACWY-TT) vaccine to establish an optimal age for this booster [7, 8]. Healthy 10-, 12- and 15-year-olds (n=464) that received a single dose of MenC-TT vaccine in early childhood were randomised to receive MenC-TT or MenACWY-TT vaccine. Blood samples were collected before the vaccination, as well as at one month and at one year after the vaccination. At one month after the booster, all participants developed high MenC rabbit serum bactericidal activity (rSBA) titres (>24,000 in all groups) and MenC-PS-specific IgG levels. Non-inferiority was not demonstrated one year after the booster with higher MenC GMTs after the monovalent MenC vaccine, compared with the tetravalent Men ACWY vaccine. Almost all participants (99.6%, 462/464), however, maintained protective MenC rSBA titres.

Between one month and one year, the highest MenC antibody decay rate was observed in the 10-year-old children. The MenACWY-TT vaccine elicited robust antibody responses against MenA, MenW and MenY, and the majority (94%) of the participants maintained rSBA titres ≥128 one year after the vaccination against all three serogroups. After one year, higher MenW rSBA GMTs were observed in the 12- and 15-year-olds compared to the 10-year-olds, while rSBA GMTs against MenA and MenY were similar between age groups.
In conclusion, both MenC-TT and MenACWY-TT vaccines induced robust protective immune responses after the booster and primary vaccination up to one year. The persistence of individual protection seems to increase with the age. Our results indicate that 12 or 15 years seems to be an optimal age for a primary quadrivalent MenACWY-TT vaccination to protect against the rapid increase of MenW disease and a booster MenC vaccination to protect against MenC disease in the long-term and maintain herd immunity.

Using data of two clinical studies (TIM and JIM study), immune responses following booster vaccination against MenC were compared between adolescent girls and boys. A total of 342 girls and 327 boys aged 10, 12 and 15 years, who had been primed with MenC vaccine between 14 months and 6 years of age, received a monovalent MenC or quadrivalent MenACWY vaccination. SBA titres were significantly higher for girls than boys for MenC one month after vaccination (GMT ratio: 1.17) and one year after vaccination (GMT ratio: 1.22), and for MenY one month after vaccination (GMT ratio: 1.32) and for MenA and MenW one year after vaccination (GMT ratio: 1.47 and 1.34). The percentage of participants with titres ≥8 or ≥128 was very high (95-100%) and did not significantly differ between boys and girls. Because of the high protection levels, the differences in average titres between boys and girls are unlikely to be relevant for adolescent meningococcal vaccination strategies.

To determine vaccine reponse in the older population, a cohort of 200 older adults between 50 and 65 years of age were enrolled in the so-called Stimulage study [9]. They were vaccinated with the quadrivalent MenACWY vaccine and blood samples were obtained just before (T0), 7 days (T1), 28 days (T2) and one year (T3) after vaccination. After 28 days, 94%, 99% and 97% of the participants possessed a protective SBA titre for MenC, MenW and MenY, respectively, which was maintained in 76%, 94% and 86% one year post-vaccination. Overall, protective antibody titres were predicted to persist after 10 years in 40-60% of the participants. Primary immunisation with a quadrivalent meningococcal vaccine was highly immunogenic in middle-aged adults, inducing protective antibody titres in the vast majority of the participants lasting for at least one year.

7.6.6 International developments

7.6.6.1 Overall meningococcal disease

A study from the US estimated the risk of meningococcal disease among MSM [10]. All meningococcal disease cases among men aged 18-64 years reported to the National Notifiable Disease Surveillance System between January 2012 and June 2015 were reviewed. Seventy-four cases of meningococcal disease were reported among MSM and 453 among non-MSM. Annualised incidence of meningococcal disease among MSM was 0.56 cases per 100,000 population, compared with 0.14 among non-MSM, resulting in a relative risk of 4.0 (95% CI: 3.1-5.1). Among the 64 MSM with known status, 38 (59%) were HIV-infected. HIV-infected MSM had 10.1 times (95% CI: 6.1-16.6) the risk of HIV-uninfected MSM. All isolates from cluster-associated cases were serogroup C sequence type 11.

The epidemiology of meningococcal disease in EU/EEA countries during the 2004-2014 period has been described [11]. The overall incidence was 0.9/100,000 population and it decreased by 6.6% annually. Infants had the highest incidence (16.0/100,000) and there were decreasing trends in all age groups <50 years. There were decreasing trends in serogroup B and serogroup C and an increasing trend in serogroup Y. Countries that introduced MenC vaccination before, and between 2004 and 2014, saw decreasing trends of MenC disease, but countries without routine meningococcal C conjugate (MCC) vaccination did not. The findings support evidence that routine MenC vaccination was the driving force behind the decreasing MenC disease trend.

7.6.6.2 MenB disease and vaccination

The UK introduced the MenB vaccine 4CMenB (Bexsero) in their national immunisation programme in September 2015 as a two-dose priming schedule offered to infants at age two and four months with a catch-up for three- and four-month-olds. Coverage of 4CMenB in infants eligible for routine vaccination was high with 95% for one dose and 89% for two doses by six months of age [12]. Two-dose vaccine effectiveness determined by the screening method was 83% (95%CI 24-95) against all MenB cases. Compared with the pre-vaccine period, there was a 50% IRR reduction in MenB cases in the vaccine-eligible cohort (37 cases vs an average of 74 cases; IRR 0.50 [95%CI 0.36-0.71]; p=0.0001). Similar reductions were observed even after adjustment for decreasing disease trends before MenB vaccine introduction in vaccine-eligible and vaccine-ineligible children.

MenB disease increased in The Saguenay-Lac-Saint-Jean (SLSJ) region in Quebec, Canada, with a rate of 3.4 per 100,000 population in 2006-2013 [13]. In May 2014, an immunization campaign for individuals between two-months-old and 20 years was launched in SLSJ, using the 4CMenB vaccine. Vaccination uptake was 82%. After the initiation of the campaign, no MenB case occurred among vaccinees, whereas two cases were reported among unvaccinated adults. These results suggest a high level of protection provided by the 4CMenB vaccine following mass vaccination at regional level.

The Meningococcal Antigen Typing System (MATS) was used to estimate coverage by the 4CMenB vaccine of MenB isolates obtained during the 2014-15 period (before introduction of vaccination) in England, Wales and Northern Ireland [14]. One hundred sixty-five of 251 (66%; 95%CI 52-80) meningococcal group B isolates were estimated by MATS to be covered by 4CMenB, compared with 391 of 535 (73%; 95%CI 57-87) in 2007-08. This effect reflected changes in circulating strains, particularly ST-269 clonal complex strains. MATS coverage increased with age, varied by geographical region and was associated with more severe disease. Temporal changes in MATS coverage underscore the need for continued monitoring of antigen expression and diversity.

Since May 2017, a new MenB vaccine Trumenba (Pfizer) has been licensed in the EU. Trumenba is indicated for individuals that are 10 years old and older. At least two doses with a six-month interval should be administered. The efficacy of Trumenba has not been evaluated through clinical trials. Vaccine efficacy has been inferred by demonstrating the induction of serum bactericidal antibody (SBA) responses to four MenB test strains that express fHbP variants A and B. Safety and efficacy of Trumenba in children under 10 have not been established.

7.6.6.3 MenW disease

Because of the continuing increase in MenW disease, the UK introduced an adolescent MenACWY conjugate vaccination programme targeting 14- to 18-year-olds and new undergraduate university entrants in August 2015. Coverage among persons who left school in 2015, the first cohort to be vaccinated, was 36.6% [15]. During the first 12 months of the MenACWY vaccination programme for teenagers, there were six confirmed MenW cases among ≈650,000 persons who left school, compared with a projected 19.4 cases (69%

decrease, 95%CI 18-88%). None of these six eligible case-patients had received the MenACWY vaccine. Based on population coverage of 36.6% among persons who left school, early estimated vaccine effectiveness was 100% (95%CI −47-100%).

Since 2013, there has been an increase in the number of notified cases of invasive meningococcal disease (IMD) due to MenW in Australia [16]. The proportion of MenW has increased from an average of 2% of all IMD cases annually (range 0% to 5%) between 1991 and 2012 to 8% (12/149) of all cases in 2013, 10% (17/169) in 2014, and 19% (34/182) of all cases in 2015. MenW has affected older populations, with a median age between 2003 and 2015 of 44 years. During this period, case fatality was 10.7% (17/159), 2.3 times higher than for all IMD serogroups combined (4.7%, 173/3720). There were seven deaths due to MenW in 2015 (case fatality rate (CFR) 21%). Whole genome sequencing (WGS) has found the majority of Australian isolates clustered within a group of W:P1.5,2:F1-1:ST11 isolates from the UK and South America.

7.6.6.4 Cost-effectiveness

Since September 2015, infants in England have been routinely offered a vaccine (Bexsero) against MenB disease at two, four and 12 months of age. The cost-effectiveness of offering catch-up vaccination with Bexsero against meningococcal disease to children too old to receive the vaccine was evaluated [17]. Catch-up vaccination of one-year-old children could be cost-effective, incremental on the infant programme with a vaccine price of ≤£8 per dose. Extending vaccination to two-year-olds could only be cost-effective (incremental on infant and one-year-old catch-up) with a vaccine price of ≤£3 per dose. Extending catch-up further to 3- and 4-year-olds was not cost-effective. In conclusion, even with low vaccine prices, only catch-up vaccination in one-year-old children could be cost-effective, when considered incrementally on the infant programme. Providing catch-up vaccination to older birth cohorts is less economically attractive due to a decreasing disease burden.

Between 2001 and 2005, almost all Canadian provinces and territories introduced monovalent conjugate meningococcal vaccines against MenC into the routine immunisation schedule. The MenC vaccine programme includes an infant vaccination and a booster dose in adolescence. Two economic evaluations were performed to assess the cost-effectiveness of replacing MenC by the MenACWY vaccine for the infant and/or adolescent dose in Canada. According to Delea et al., using the MenACWY vaccine instead of the MenC vaccine for the adolescent booster, following universal meningococcal C vaccination in infancy, may be cost-effective and should be considered [18]. Although replacing infant MenC vaccination with infant MenACWY vaccination was cost-effective in base-case analyses, in probabilistic sensitivity analyses the probability that such a strategy would be cost-effective was less than 50%. On the contrary, de Wals et al. found a switch to MenACWY vaccination for the province of Quebec not to be cost-effective [18]. This difference is mainly based on a different disease epidemiology in Quebec, with a low incidence rate for meningococcal disease.

7.6.7 Literature

7.6.7.1 References

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* RIVM publication

7.6.7.2 Other recent RIVM publications

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7.7 Mumps

S. Monge, S. Gouma, N. Rots, C.A.C.M. van Els, P. Kaaijk, W.L.M. Ruijs, R. van Binnendijk, I.K. Veldhuijzen

7.7.1 Key points

- The incidence of mumps in 2016 was low (0.4 per 100,000), and comparable to the previous two years.
- Although at low level, molecular typing indicated mumps endemic transmission was present in 2016 and 2017.
- Most of the mumps cases in the Netherlands were caused by genotype G.

7.7.2 Tables and figures

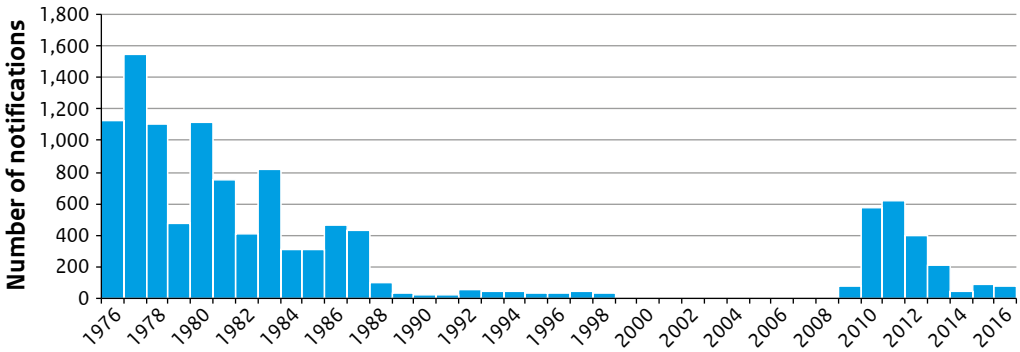

Figure 7.7.1 Number of notified mumps cases in the period 1976-2016
Source: Osiris

7.7.3 Epidemiology

In 2016 the incidence of mumps has remained stable, with 71 reported cases (Figure 7.7.1). More than half of these were male (57.8%) and the mean age was 25 years (range 1-69). Forty-one percent had been vaccinated twice, 17% had been vaccinated once, 3% had been vaccinated with an unknown number of doses, 32% were unvaccinated and for 7% the vaccination status was unknown. Only 28% of cases were students. Eleven per cent of the cases were imported or likely to be imported. Three patients were hospitalised, one of which had meningitis; only one of the three had been vaccinated once. Another two patients (one of them vaccinated once) reported orchitis, but were not hospitalised.

Six outbreak clusters were identified in 2016. The first two clusters were reported between late February and April in the south of the Netherlands (Brabant). One was linked to a carnival event and included eight reported mumps cases (cluster 1) and the other was linked to a local football team and included seven cases (cluster 2) [1]. The other four clusters included only two cases each and, in two of them, the index case was imported.

In 2017, up to the 30st of June, 25 mumps cases were reported, which is fewer than in the previous year. Most were sporadic mumps cases, except three limited transmission clusters of two cases each. 72% of the cases were male with a mean age 27.5 years (range 1-58), 16% were students and 24% were imported or likely to have been imported. As around two-thirds of mumps infections in vaccinated persons are asymptomatic, the actual number of infections is expected to be higher.

7.7.4 Pathogen

Since 2010, most of the mumps cases in the Netherlands have been caused by mumps virus genotype G. This genotype caused 82% of the 22 mumps cases with known genotype in 2016 and 100% of the three cases with known genotype in 2017. Molecular typing tools based on the mumps haemagglutinin-neuraminidase (HN) and fusion (F) genes [2] have shown that the two larger epidemiological clusters in 2016 and the three cases with known genotype in 2017 were linked and caused by the same cluster of mumps virus genotype G (molecular cluster C). Based on this new molecular tool, we could confirm the endemic transmission of the mumps virus within a defined region and period.

7.7.5 Research

7.7.5.1 Cellular immunity

Multiparametric flow cytometry analysis was performed to investigate the cellular immune response, in detail, in clinical samples derived from the BofTrans-cellular and Immfact studies [3]. High frequencies of mumps-specific CD8+ T cells, which produced interferon-γ one to two months after disease onset were observed, declined over time (7-10 months), but were still elevated compared to healthy individuals that were vaccinated >10 years ago (average age of 22 years). Interestingly, natural killer (NK) cells dominated the IFN-γ response of healthy vaccines [4]. Thus, innate immune cells prevailed in the mumps virus (MuV)-specific IFN-γ response in healthy vaccinees, whilst the adaptive CD8+ T cell response dominated after disease, even after three years. After disease, the activated CD8+ T cells reacting against mumps virus showed strong polyfunctionality, which appeared to be maintained for up to three years. By contrast, hardly any polyfunctionality was observed in mumps-specific T cells of healthy vaccinees. This lack of polyfunctional CD8+ T cells in vaccinees could be indicative of an increased susceptibility to mumps in this age group. These data show for the first time a more detailed profile of MuV-specific cellular responses over time after mumps infection, which differs from the profile seen 10 years post-vaccination.

7.7.6 International developments

In many countries around the world, mumps outbreaks have occurred in recent years, often in highly vaccinated populations in school and student settings [5-8]. The waning of vaccine induced immunity and strain differences are proposed as explanations for vaccine failure. In the US in 2016, the highest number of mumps cases in 10 years was reported [9], the majority of which were linked to different outbreaks at University campuses, which has motivated the creation of a working group to review the national mumps control policies [10].

A serosurvey conducted among young adults in Italy demonstrated that 10% of people aged 18-26 years are susceptible to mumps, adding concerns about the long-term immunogenicity of the mumps vaccine and the effect of the accumulation of susceptibles in future outbreaks [11]. In Portugal, where the second dose of the MMR vaccine was changed from 10-13 years to 5-6 years for those born in 1994 and afterwards, no difference was found in the concentration of mumps antibodies with either schedule [12]. A mathematical model suggested that the current two-dose protocol (MMR1 at 1 year and MMR2 at 3 years) used in the UK is optimal: while there are periodic large outbreaks, the severity of disease in vaccinated individuals is lower, and the size of the outbreaks did not decrease sufficiently with a third booster to make economic sense [13]. A study in England demonstrated that the true burden of hospitalised mumps-related orchitis was 2-2.5 times greater than the number of cases actually coded as mumps in hospital databases during an outbreak in 2004/05 [14].

In an outbreak investigation in Canada where all cases were vaccinated and experienced milder symptoms, only 25% of buccal and 21.4% of throat swabs tested by RT-PCR and only 3.3% of urine cultures were positive. IgM response was delayed or absent, illustrating the challenges and limitations in interpreting mumps diagnostic tests in the context of mumps in vaccinated individuals [5]. In an outbreak response in New York City, an advertisement campaign was launched targeting Facebook users aged 20-59 years in the affected zip codes. Information about mumps and the outbreak was included and persons with symptoms were instructed to stay home. Social media provided a timely and inexpensive means for communicating with a large population successfully and rapidly [15].

7.7.7 Literature

7.7.7.1 References

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* RIVM publication

7.8 Pertussis

N.A.T. van der Maas, A. Buisman, G.A.M. Berbers, N. Rots, A.W.M. Suijkerbuijk, C.A.C.M. van Els, E. Pinelli, H.E. de Melker, M. van Gent

7.8.1 Key points

- The 2016 pertussis epidemiology fits within the long-term epidemiology. IR was 32.6 per 100,000 compared to 38.8 in 2015. However, six people died from pertussis.
- Data of a maternal pertussis vaccination trial showed that pertussis-specific antibody titres are higher at birth and at two and three months of age in children of mothers that were vaccinated during pregnancy than they are in control children of mothers that were vaccinated immediately after delivery. This means that, in combination with maternal pertussis vaccination, antibody titres are sufficient to postpone the start of the infant vaccination to the age of three months.
- The prevalence of pertactin-deficient (i.e. a component of acellular vaccines) strains was 12% in 2016, compared with 15% in 2015.

7.8.2 Tables and figures

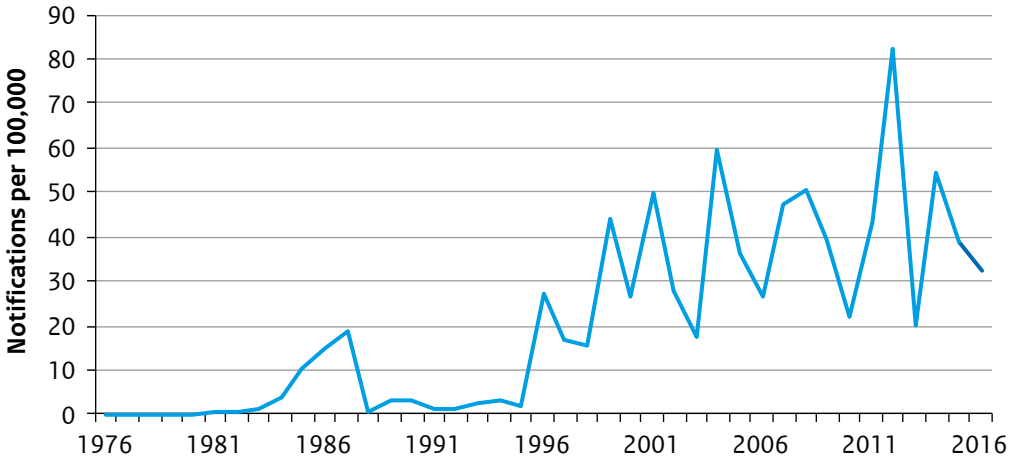

Figure 7.8.1 Pertussis notifications per 100,000 for 1976-2016

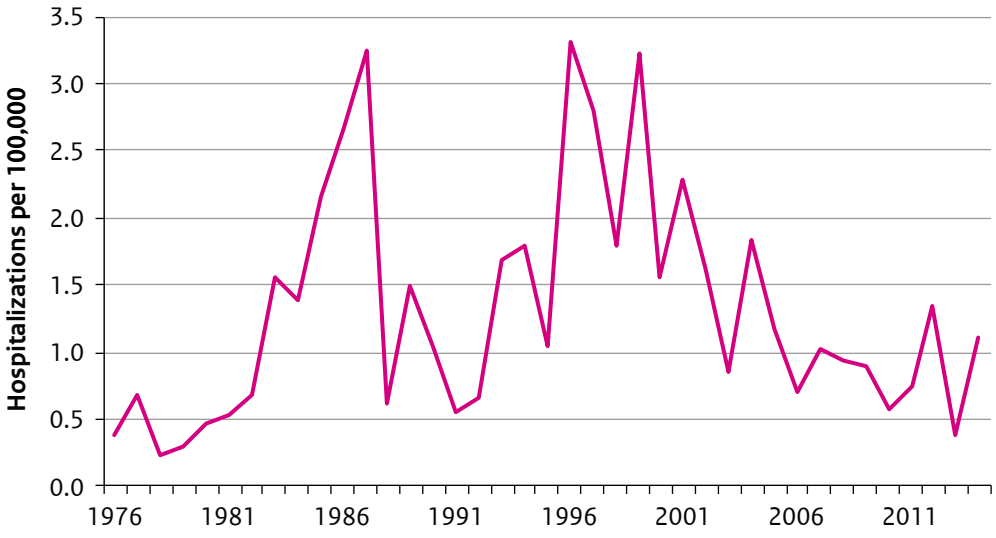

Figure 7.8.2 Pertussis hospitalisations per 100,000 for 1976-2014
Note: hospitalisation data from 2015 onwards is not yet available.

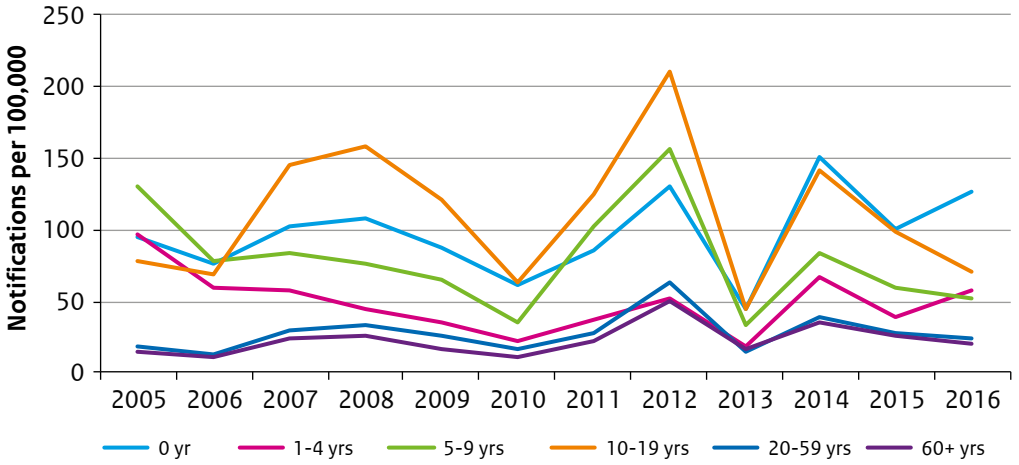

Figure 7.8.3 Pertussis notifications per 100,000 per age category for 2000-2016

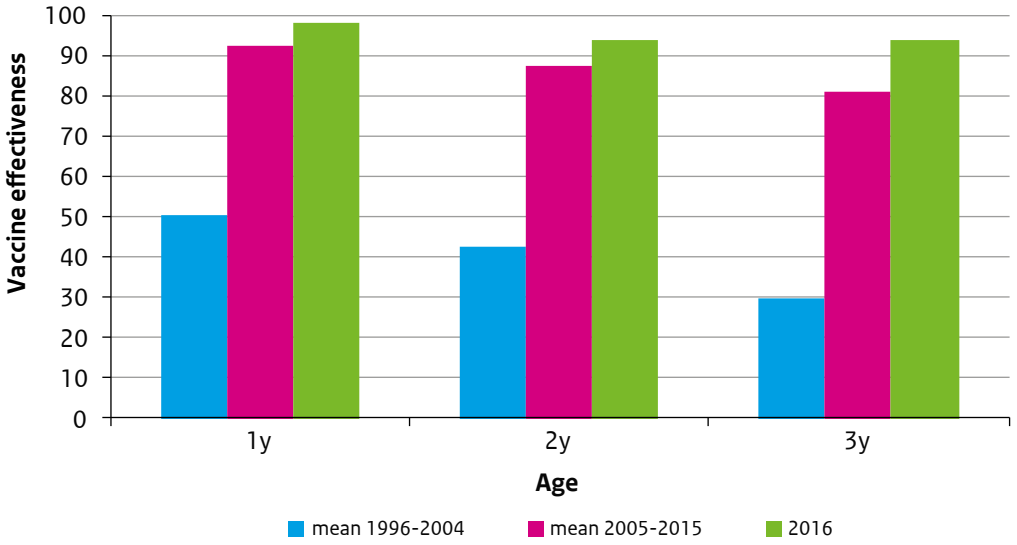

Figure 7.8.4 Vaccine effectiveness estimated for 1-, 2- and 3-year-olds during use of whole-cell pertussis vaccination (mean 1996-2004) and during use of acellular pertussis vaccination (mean 2005-2015 and 2016 separate)

Table 7.8.1 Estimation of vaccine effectiveness of the preschool booster by the 'screening method' for 5- to 15-year-olds per birth cohort

Birth cohort	Age (years)													
	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1998		74	68	77	73	60	-	45	-	18	-	-	-	-
1999	77	70	71	75	63	-	11	3	-	-	-	20	26	
2000	71	80	68	56	36	13	-	14	-	15	30	36		
2001	82	79	71	47	49	24	5	-	-	36	28			
2002	86	71	51	35	34	59	-	27	-	21				
2003	80	61	61	72	69	-	63	23	-					
2004	84	89	67	80	82	64	21	9						
2005	83	87	86	93	67	0	-							
2006	93	90	82	81	48	17								
2007	89	86	79	-	4									
2008	85	87	66	31										
2009	92	78	73											
2010	88	90												
2011	93													

7.8.3 Epidemiology

7.8.3.1 Disease

In 2016, the overall incidence rate (IR) of pertussis notifications was somewhat lower than in 2015 (32.6 per 100,000 population vs 38.8; Figure 7.8.1). This fits in with the epidemic pattern with peaks every 2-3 years, with the last epidemic peaks in 2014 (IR 54.7) and 2012 (IR 82.6). Among children, adolescents, adults and the elderly, we also found somewhat lower IRs in 2016 than were found in 2015. However, in infants and children up to four years of age, IRs in 2016 were higher than they were in 2015 (127.4 vs. 99.6 and 56.8 vs. 38.4, respectively; Figure 7.8.3). A slight decrease in notifications is observed in the first quarter of 2017, compared with 2016.
Hospitalization data for 2015 and 2016 are not available yet (Figure 7.8.2).

Within the notifications, six deaths were reported in 2016. Three deaths concerned infants that were too young for vaccination. The other three deaths concerned adults, i.e. a 62-year-old female, an 80-year-old male and an 85-year-old female. In 2017, up to July 1st, no deaths were reported. Within the data of Statistics Netherlands in 2016, one 0-year-old girl and one 80- to 85-year-old male were reported to have died from pertussis.

7.8.3.2 Vaccine effectiveness

In Figure 7.8.4, the VE, estimated through the 'screening method' for the infant vaccination series, is shown. We would like to emphasize that the presented VEs should not be interpreted as 'true' absolute efficacies, but rather are used to study trends in VE estimations. In 2005, an infant combination vaccine with an acellular pertussis component replaced the Dutch whole-cell pertussis vaccine containing a combination vaccine and was introduced in the NIP, which resulted in an increase of the VE of the primary series for one- to three-year-olds [1]. Since then, the VE of the primary series has been continuously high.
The VE for the booster dose at four years of age seems to decrease when children have reached the age of eight years, i.e. four to five years after the booster vaccination, especially in epidemic years (Table 7.8.1).

7.8.4 Pathogen

Strain surveillance focuses primarily on the analysis of Bordetella pertussis antigens that are used in acellular pertussis vaccines: pertussis toxin (Ptx), pertactin (Prn), filamentous hemagglutinin (FHA), serotype 2 fimbriae (Fim2) and serotype 3 fimbriae (Fim3). Both changes in genotype and phenotype are monitored to identify novel antigenic variants and strains that are deficient in one or more vaccine components, respectively.

The first shift we have found, when compared with previous years (2010-2016), is the emergence of strains that are deficient in vaccine components Prn and FHA. The Prn-deficient strains were observed for the first time in 2010. The prevalence increased from 1% to 15% in the years 2010-2015. A slight decrease was found in 2016, 12% of the strains did not produce Prn. Up to July 2017, one Prn-deficient strain had been found so far, but this is based only on 17 strains. *B. pertussis* can use different mutations to inactivate Prn [2]. Moreover, based on a phylogenetic tree, Prn-deficient strains were found in different branches, which indicated

positive selection. In addition, FHA-deficient strains have been detected in recent years, but at low prevalence; 2% in 2015, 2% in 2016 and no FHA-strains have been found in 2017 so far. The second shift concerned the Fim3 genotype. Since 2010, an increase of fim3-2 strains has been observed. In 2010, only 4% of the strains had the fim3-2 allele, but an increase was observed of up to 25% in 2013 and 66% in 2016. In coincidence with the increase of fim3-2 strains, we also observed an increase of strains with the Fim3 serotype since 2010. Besides these two shifts, no other major shifts were found compared with previous years. In the previous years (2010-2016), almost all strains had the following alleles; ptxP3, prn2 and ptxA1.

7.8.5 Research

7.8.5.1 Epidemiology

The results of a medical record study performed in 2015-2016 among 676 zero- to two-year-old infants who were hospitalised for pertussis in 2005-2014 showed an overrepresentation of preterm infants (12%-17%, compared with 7.4% in the general Dutch population). Preterms were older (median 3.0 months vs 2.0 months) and more often vaccinated at admission (62.7% vs 44.3%) than term infants. Among term and preterm infants, vaccination decreased the duration of hospitalisation (median three days vs nine days). Furthermore, vaccinated infants had a lower risk of complications and needed less intensive treatment, e.g. artificial respiration or admission to Paediatric Intensive Care Unit. The age-specific vaccine effectiveness of the first vaccination, assessed with the screening method, was 73% for preterms vs 95% for term infants.

7.8.5.2 Immunology

7.8.5.2.1 Maternal pertussis vacccination

Maternal pertussis vaccination was advised by the HC in December 2015. The effect of maternal pertussis vaccination is being evaluated in a study that measures the effect of maternal pertussis vaccination on pertussis-specific humoral and cellular immune response of the infants (MIKI study). Infants were vaccinated, according to a reduced dose NIP schedule, with vaccinations at three, five and 11 months of age. Initial data show that pertussis-specific antibody titres are higher at birth and at two and three months of age in children of mothers that were vaccinated during pregnancy than they were in control children of mothers that were vaccinated immediately after delivery. Maternal antibody titres pre-infant vaccination, at three months of age in the maternal vaccination group were still significantly higher than in the control group at two months of age, the age of first vaccine dose according to current RVP. This data support that, after maternal vaccination, the first infant vaccine dose can safely be postponed until three months of age, which is expected to result in a better immune response. Antibody responses after infant immunisation are currently being analysed.

7.8.5.2.2 Asymptomatic and unreported pertussis infections

In order to investigate the incidence of pertussis infections, including asymptomatic and unreported infections, the pertussis toxin (Ptx) antibody levels in longitudinal serum samples from Dutch adolescents were assessed [3]. These adolescents participated in a meningococcal C vaccine booster study and their samples encompassed the pertussis epidemic in 2012, with a follow-up in 2014. Blood was sampled from 10 to 18-year-olds in October 2011 (n=239), after

one (n=228) and three (n=168) years. Ptx-IgG concentrations ≥50 IU/ml were assumed to be indicative for an infection in the preceding year. During the 2012 epidemic, 10% of the participants became seropositive, while this was just 3% after the epidemic. In 2012, pertussis notifications among adolescents nationwide were 228/100,000 (0.23%), which is at least 40 times lower than the percentage of seropositivity. The pertussis acquisition rate among adolescents proved to be sixfold higher during the 2012 epidemic compared with a low-epidemic period. Remarkably, 17 of the 22 seropositive participants in 2011 were still seropositive in 2012 and nine remained seropositive for at least three years. A Ptx-IgG concentration ≥50 IU/ml as indication for recent pertussis infection may lead to an overestimation of these numbers in cross-sectional serosurveillance studies and should therefore be used carefully.

7.8.5.2.3 Cellular immune response

A study on Pertussis-specific humoral, memory B-cell and T-cell responses after both pre-school DTaP and pre-adolescent Tdap booster vaccinations have been finished. In a cross-sectional study, blood was collected from wP- and aP-primed children up to two years after the pre-school DTaP booster at age four years (study period 2006-2010). In a second study, paired blood samples were collected after a pre-adolescent Tdap booster at 9 years of age in wP- and aP-primed children (2009-2014). After the pre-school booster vaccination, IgG levels were significantly higher in aP-primed children as compared with wP-primed children up to 6 years of age. Before the pre-adolescent Tdap booster at 9 years of age, immune responses were similar in aP- and wP-primed children. Importantly, the Tdap booster vaccination induced fewer vaccine antigen-specific IgG, B-cell and Th1 responses, resulting in a significantly lower Th1/Th2 ratio in aP-primed compared with wP-primed children. These results indicate that replacement of the Dutch DTwP-combination vaccine by DTaP-combination vaccines enhanced both humoral and cellular immune responses up to 6 years of age, but quickly waned afterwards. After an additional Tdap booster at age 9 years, better immunity with a more Th1 profile was observed in DTwP- versus DTaP-primed children. This is in line with epidemiological data showing that DTaP-primed adolescents are less protected against clinical pertussis than wP-primed children are.

Several clinical and experimental immunological studies further underpinned our understanding of the emergence of new *B. pertussis* strains and of the suboptimal duration or effectiveness of immune responses after current vaccination as compared with natural infection. Recent findings indicate that emerging *B. pertussis* strains, particularly those circulating after the introduction of the acellular vaccine, induce a stronger activation of specific innate immune receptors and higher levels of the anti-inflammatory cytokine IL-10 by dendritic cells [4]. Ongoing studies include identifying the bactericidal mechanism of innate immune cells that are crucial in limiting *B. pertussis* infection and the strategies used by this pathogen to escape being killed by the complement system [5].

Studying a large cohort of (ex-) pertussis cases revealed the significant impact of the type of primary vaccination and of age on the immune responsiveness to and memory of *B. pertussis* [6].

7.8.6 International developments

Within the framework of the EUPertstrain group, a collaboration between the European experts on whooping cough concerning a technical proposal for the serosurveillance of pertussis was approved by ECDC. RIVM will lead the part of the proposal on the reference method of anti-Ptx ELISA and MIA and the possible cut-off for serological diagnosis of pertussis in Europe for standardization and harmonisation, as well as the organisation of a seroprevalence study in the participating countries of pertussis and diphtheria. For the serosurveillance study, a protocol was written and momentarily 16 European countries have agreed to participate in this study.

Internationally the scientific community calls for the development of a next generation pertussis vaccine with an improved immunological signature [7-11].

A large consortium of pertussis experts from 16 European universities and four national institutes (called Periscope), including the RIVM, and two vaccine companies received support for their Pertussis research IMI-2 proposal early in 2016 from the European Union's Horizon 2020 research and innovation programme, as well as EFPIA and the Bill & Melinda Gates Foundation (BMGF). The main objective of this extensive IMI-2 proposal is to unravel the reduced protective properties of the acellular vaccines compared with whole-cell vaccines and natural infection, touching on a large range of disciplines. Besides human neonatal/maternal vaccine studies and booster studies focused on older age groups, the mouse model, baboon model, human challenge and naturally infected studies are also a part of this 28 million € proposal. The main role of the RIVM is to perform clinical studies that involve participants from various age groups that have received different existing pertussis vaccines, or participants who were naturally infected by B. pertussis. In addition, the effect of priming with a whole-cell vaccine versus an acellular vaccine on the development of pertussis immunity will be studied in a neonatal/maternal clinical study. By using blood samples from all these participants, biomarkers of immune responses specific to *B. pertussis* can be investigated.

7.8.6.1 Cost-effectiveness

The cost-effectiveness of an intervention to improve adult vaccination rates, the so-called 4 Pillars Practice Transformation Program, was evaluated [12]. The intervention is a primary care practice improvement aid in the US focusing on changing behaviour by using evidence-based strategies organised into four domains. The pillars are convenient vaccination services, communication with patients about the importance of immunisation and the availability of vaccines, enhanced office systems to facilitate immunisation, and motivation through an office immunisation campaigner who monitors progress and encourages adherence to vaccination-promoting office procedures. The programme has been tested in several trials and found to be moderately effective at increasing immunisation rates in adults and children. In the model QALYs, public health outcomes and costs with respect to influenza, pertussis and pneumococcal disease were assessed. Extrapolating over 10 years, there would be approximately 60,920 fewer influenza cases, 2,031 fewer pertussis cases and 13,842 fewer pneumococcal illnesses in adults aged 65 and older in the US. Total per-person vaccination and illness costs with the intervention were $23.93 higher than they were without the intervention, with ura concurrent increase in effectiveness of 0.0031 QALYs, or $7,635 per QALY gained for the three diseases combined.

Currently, new vaccines against pertussis are under development. A previously validated dynamic cost-effectiveness model was used to evaluate the potential health benefits and economic value of developing a next-generation pertussis vaccine [13]. Three potential improvements were considered: 1) increased efficacy of the childhood vaccination series, 2) extended duration of protection for the childhood series, and 3) extended duration of protection for the adult booster, as well as combinations of improvements. The maximum cost-effective price increase (MCPI) was assessed, which estimates the per-dose price increase that would maintain the cost-effectiveness of pertussis vaccination.
A new theoretic vaccine that could achieve 100% efficacy for the childhood series would permit an MCPI of $18 per dose. Vaccine improvements that extend the duration of protection to an average of 75 years would allow for an MCPI of $22 per dose for the childhood series or $12 for the adult booster. Due to the short duration of vaccine effectivity induced by the adult booster, improvements to the childhood series are more valuable than improvements to the adult booster. A childhood series with perfect efficacy and average duration of 75 years would permit an MCPI of $39 per dose, the highest of any scenario evaluated.

7.8.7 Literature

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7.8.7.2 Other recent RIVM publications

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7.9 Pneumococcal disease

M.J. Knol, H.J. Bootsma, G. Berbers, A. Suijkerbuijk, H. Korthals Altes, A. van der Ende, H.E. de Melker

7.9.1 Key points

- Introduction of pneumococcal conjugate vaccination (PCV) led to a significant decrease in overall invasive pneumococcal disease (IPD) in children under five years of age, five- to 49-year-olds and in the elderly aged 65 years and older.
- The incidence of PCV7 type invasive pneumococcal disease (IPD) remained very low in 2016/2017, with an incidence of 0.6 per 100,000.
- There were no cases of IPD caused by the additional serotypes in PCV10 (PCV10-7: serotype 1, 5 and 7F) in children younger than five years in 2016/2017. In other age groups, the incidence of PCV10-7 type IPD further decreased in 2016/2017, thanks to herd protection.
- The increasing trend in incidence of non-PCV10 type IPD continued in 2016/2017.
- The incidence of PCV13-10 type IPD (3.2/100,000), including serotype 19A, was significantly higher in 2016/2017 than before the introduction of PCV7 (76% increase) and PCV10 (29% increase). It was similar to the incidence in 2015/2016 (3.2/100,000).
- The incidence of PPV23-PCV13 type IPD in persons aged 65+ has increased steadily over recent years from 10.6 per 100,000 in 2004/2005 to 25.8 per 100,000 in 2016/2017.
- The vaccine effectiveness (VE) of at least two doses of PCV10 was 85% (95%CI 41-96%) against vaccine type IPD and 91% (95%CI 33-99%) against serotype 7F.

7.9.2 Tables and figures

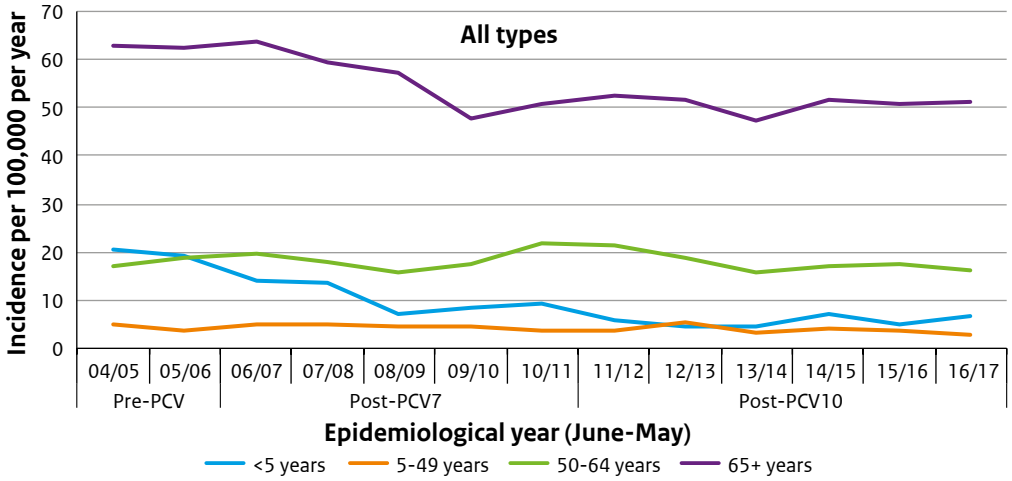

Figure 7.9.1 Incidence of invasive pneumococcal disease (IPD) caused by all serotypes, presented by epidemiological year (e.g. 04/05 = June 2004-May 2005)

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

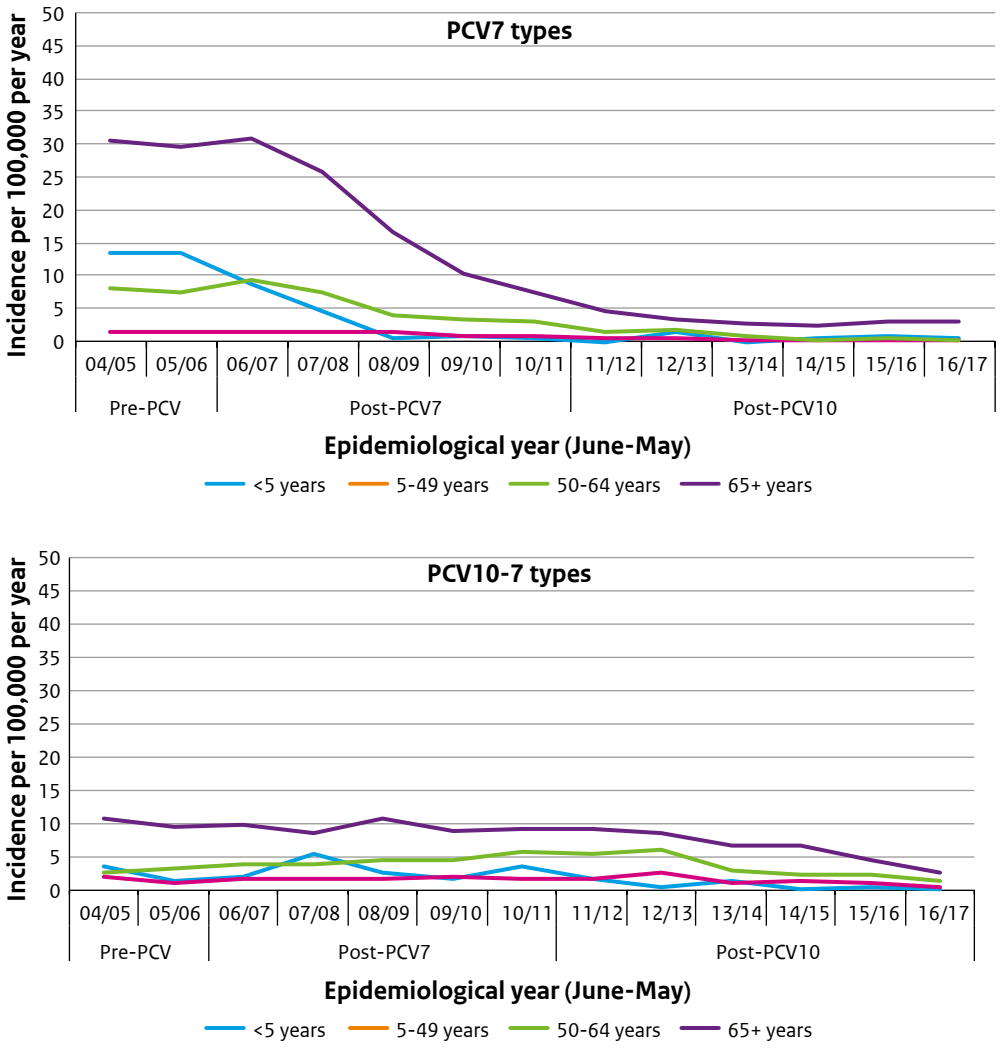

Figure 7.9.2 Incidence of invasive pneumococcal disease (IPD) caused by PCV7 serotypes, PCV10-7 serotypes, PCV13-10 serotypes and non-PCV10 serotypes, presented by epidemiological year (e.g. 04/05 = June 2004-May 2005)

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

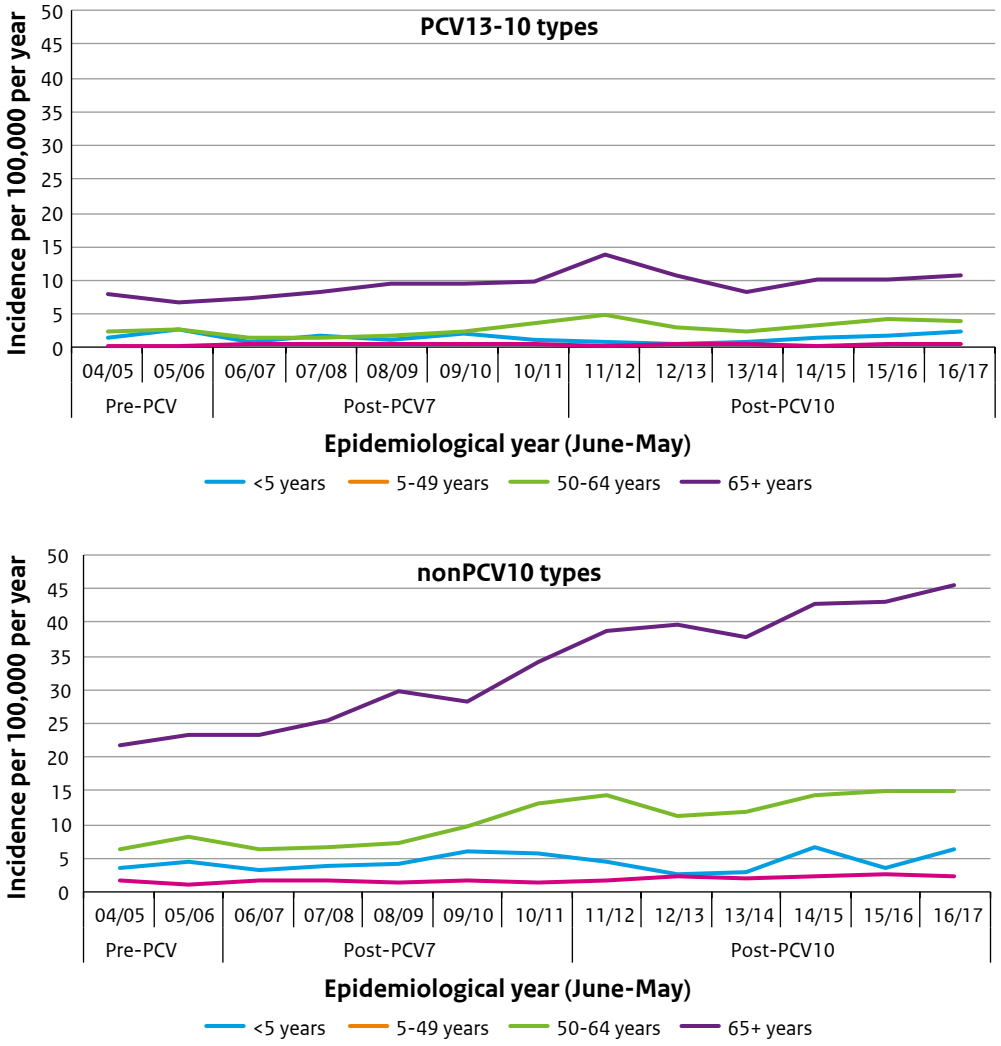

Figure 7.9.2 *(continuation)* Incidence of invasive pneumococcal disease (IPD) caused by PCV7 serotypes, PCV10-7 serotypes, PCV13-10 serotypes and non-PCV10 serotypes, presented by epidemiological year (e.g. 04/05 = June 2004-May 2005)

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

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 with vaccine type invasive pneumococcal disease (IPD) that 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 March 2016

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

Source: NRBM, Praeventis, Osiris

7.9.3 Epidemiology

7.9.3.1 Overall invasive pneumococcal disease (IPD) incidence

In the epidemiological year 2016/2017, 624 IPD cases were reported by the nine sentinel laboratories (covering 25% of the Dutch population). This resulted in an overall IPD incidence of 14.7 per 100,000 population in 2016/2017 (Figure 7.9.1). The incidence in 2016/2017 was significantly lower than it was before the introduction of the 7-valent pneumococcal conjugate vaccine (PCV7) in <five-year-olds (65% reduction), five- to 49-year olds (32% reduction) and persons aged 65+ (19% reduction). There was no significant change in incidence in 2016/2017 compared with 2015/2016 (15.0 per 100,000).

7.9.3.2 Vaccine type IPD incidence (see Table 7.9.1)

In 2016/2017, 27 of 624 reported IPD cases (4.3%) were caused by a PCV7 serotype, resulting in an incidence of 0.6 per 100,000 population (Figure 7.9.2). The incidence of PCV7 type IPD in 2016/2017 was significantly lower than it was before the introduction of PCV7 in all age groups (overall reduction of 91%). In 2016/2017, PCV7 type IPD incidence was similar to that in 2015/2016 (0.8 per 100,000) in all age groups.

In 2016/2017, 45 (7.2%) reported IPD cases were caused by the three additional serotypes included in PCV10 (serotype 1, 5 and 7F, Table 7.9.1), resulting in an incidence of 1.1 per 100,000 for PCV10-7 type IPD (Figure 7.9.2). The incidence of PCV10-7 type IPD in 2016/2017 was significantly lower than it was in the two years prior to PCV10 introduction in all age groups (overall reduction of 71%). Compared with 2015/2016 (1.8/100,000), there was a significant decrease of PCV10-7 type IPD incidence in 2016/2017 by 41%.

7.9.3.3 Non-vaccine type IPD incidence

In 2016/2017, 552 (88%) reported IPD cases were caused by serotypes not included in PCV10, resulting in an incidence of 13.0 per 100,000 population (Figure 7.9.2). The incidence of non-PCV10 type IPD in 2016/2017 was significantly higher than it was before the introduction of PCV7 and PCV10 in all age groups, except for <five-year-olds (overall increase compared with pre-PCV7 period was 131%). There were no significant differences between 2016/2017 and 2015/2016 (12.5/100,000) in the incidence of non-PCV10 type IPD, although the increasing trend continued.

Of special interest is the group of non-PCV10 type IPD caused by the three additional serotypes included in PCV13, i.e. serotype 3, 6A and 19A (Table 7.9.1). In 2016/2017, these serotypes caused 22% (n=135) of the reported IPD cases, resulting in an incidence of 3.2 per 100,000 for PCV13-10 IPD (Figure 7.9.2). The incidence in 2016/2017 was significantly higher than it was before the introduction of PCV7 (76% increase) and PCV10 (29% increase) and similar to the incidence in 2015/2016 (3.2/100,000). In children <five years of age, there was no significant difference in incidence between 2016/2017 and prior to the introduction of PCV10.

In 2016/2017, 199 (51%) of the IPD cases among persons 65 and older were caused by serotypes included in the 23-valent pneumococcal polysaccharide vaccine (PPV23), but not in PCV13 (PPV23-PCV13) (Table 7.9.1). The incidence of PPV23-PCV13 type IPD in persons 65 and older increased steadily over recent years from 10.6 per 100,000 population in 2004/2005 to 25.8 per 100,000 in 2016/2017.

7.9.3.4 Vaccine failure

Since the introduction of PCV7, 37 cases of vaccine-type IPD have been reported among vaccine-eligible children (born after April 1, 2006 and at least two months old) in the nationwide surveillance. Of these, 18 children (49%) were vaccinated with at least two doses (with the second dose given at least two weeks before diagnosis) and therefore they were considered vaccine failures (Table 7.9.2). Most vaccine failure cases had serotype 19F (n=7, 39%). There were two vaccine failure cases in 2016, both vaccinated with PCV10.

7.9.3.5 Vaccine effectiveness (VE) against IPD

The 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 eligible for PCV10 vaccination aged at least 2 months, and with known serotype and vaccination status. Seven of the 11 patients (64%) in vaccine type IPD cases were vaccinated with at least two doses and 129 of the 140 (92%) non-vaccine type IPD cases. This resulted in a VE of 85% (95%CI 41-96%) for at least two doses of PCV10 compared with zero doses. Serotype-specific VE was 91% (95%CI 33-99%) for serotype 7F. VE against PCV10-related IPD (type 6A, 6C, 6D, 7A, 7B, 7C, 9A, 9L, 9N, 18A, 18B, 18F, 19A, 19B, 19C, 23A, 23B) was 50% (95%CI -74-86%) and, specifically, the VE against serotype 19A was 60% (95%CI -8-91%). From these results, cross-protection of PCV10 against vaccine-related IPD, including serotype 19A, seems plausible but cannot be confirmed.

7.9.3.6 IPD mortality

From 2014 to 2017, 183 IPD cases among children under 5 years of age were reported nationally. The mortality status was known for 120 cases (66%). Eight of the 120 (7%) cases died. These eight cases had non-vaccine type IPD (serotypes 3 (n=2), 8, 12F, 15C, 23A, 22F, 24F) and two had known co-morbidity.

7.9.4 Pathogen

The impact of vaccination on the clonal composition of the pneumococcal population causing IPD was examined using multiple locus variable number of tandem repeat analysis (MLVA) on isolates from pre-PCV (2004-2005; n=1154), post-PCV7 (2008-2011; n=1775) and post-PCV10 (2013-2016; n=1844) periods. No obvious changes in the genetic background of isolates over time were observed, with 442, 557 and 483 MLVA types, respectively, detected in the three study periods. Of the current predominant serotypes, type 8 and 22F strains were found to be both largely of a single clonal lineage across time periods, while serotype 19A strains were genetically more diverse, with seven different clonal lineages detected in the 133 isolates obtained post-PCV10 period, compared with four pre-PCV (n=29) and five post-PCV7 (n=102). One potential capsular switch event occurred in 2016: 23B capsular locus with a 7F genetic background.

7.9.5 Research

The temporal relationship between influenza-like illnesses (ILI) and IPD was assessed in the Netherlands, while correcting for temporal autocorrelation [1]. The correlation between the time series was assessed, pre-whitening the dependent time series with the best-fit seasonal autoregressive integrated moving average (SARIMA) model to the independent time series. When correcting for the common seasonal pattern in ILI and IPD and other autocorrelations by pre-whitening, no cross-correlations were apparent anymore. This study suggests that ILI occurrence does not seem to be the major driver of IPD incidence in the Netherlands.

Pneumococcal carriage in the elderly with and without symptoms of ILI was investigated using both molecular and conventional diagnostic methods. Nasopharyngeal and saliva samples collected during the 2012/2013 influenza season from 247 elderly persons at ILI-onset and at recovery 7-9 weeks later, and from 339 healthy elderly persons were all cultured for S. pneumoniae. Pneumococcal absolute and relative abundancies were determined in minimally processed and culture-enriched samples by lytA- and bacterial-16S-specific qPCRs. Only four individuals (<1%) were identified as pneumococcal carriers by the gold standard method of nasopharyngeal culture, two healthy and two at ILI-onset [2]. Using qPCR on culture-enriched saliva samples, pneumococcus was detected in 52 (15%) healthy elderly persons, 50 (20%) elderly persons at ILI-onset, and 41 (17%) at recovery. When minimally processed saliva samples from carriers were tested (i.e. DNA extracted from raw saliva), differences between groups in overall density of *S. pneumoniae* (absolute abundance) were also not significant (Kruskal-Wallis, p=0.18). However, total bacterial load in raw saliva from pneumococcal carriers was significantly lower at ILI onset and at recovery compared with health (Mann-Whitney, p<0.001) [3]. Consequently, relative pneumococcal abundance was significantly higher at ILI-onset compared with health, suggesting that it may be more relevant for disease outcome than the absolute abundance.

In the VIP study, 504 Venezuelan Warao children aged six weeks – 59 months residing in nine geographically isolated Warao communities were vaccinated with a primary series of PCV13 according to CDC-recommended age-related schedules [4, 5]. While PCV13 was highly immunogenic in Warao children aged <24 months, children aged 24-59 months did not reach adequate antibody concentrations for a majority of serotypes after one catch-up dose. Higher antibody concentrations in younger children were accompanied by a significant decrease in nasopharyngeal carriage of vaccine-type pneumococci. Surprisingly, stunted Amerindian children showed generally higher antibody concentrations than well-nourished children following PCV13 vaccination, indicating that chronic malnutrition influences vaccine response.

7.9.6 International developments

7.9.6.1 IPD

The Streptococcus pneumoniae Invasive Disease network (SpIDnet) actively monitors IPD incidence at nine sites in seven European countries that use PCV10 and/or PCV13 [6]. IPD incidence four years after the introduction of PCV10/13 was compared with the average incidence during the PCV7 period. The pooled IRR was 0.53 (95%CI 0.43-0.65) for IPD in children younger than five years caused by any serotype, 0.16 (95%CI 0.07-0.40) for disease caused by PCV7 serotypes, 0.17 (95%CI 0.07-0.42) for disease caused by 1, 5 and 7F serotypes (PCV10-7), and 0.41 (95%CI 0.25-0.69) for that caused by 3, 6A and 19A serotypes (PVC13-10). A similar pattern was observed when the analysis was restricted to sites where only PCV13 was used. The pooled IRR for IPD caused by non-PCV13 serotypes was 1.62 (95%CI 1.09-2.42).

7.9.6.2 Pneumococcal pneumonia

Suzuki et al. assessed the VE of PPV23 against pneumococcal pneumonia in people aged 65 or older using the test-negative design [7]. Of 2,036 hospitalised pneumonia patients, 419 (21%) were positive for pneumococcal infection based on sputum, urine or blood. Five hundred twenty-two (26%) patients were vaccinated with PPV23. The VE of PPV23 was 27% (95%CI 3.2-46%) against pneumococcal pneumonia, 34% (95%CI 5.6-53%) against pneumococcal pneumonia caused by PPV23 serotypes, and 2.0% (95%CI –79-46%) against pneumococcal pneumonia caused by non-PPV23 serotypes.

A post-hoc subgroup analysis of the CAPiTA study found that the VE of PCV13 against vaccine-type pneumococcal pneumonia was significantly higher in elderly patients with diabetes mellitus (89.5% (95%CI 65.5-96.8)) than in elderly patients without diabetes mellitus (24.7% (95%CI 10.4-48.7)) [8]. There was no evidence of a different VE in patients with or without respiratory disease, heart disease or any comorbidity.

7.9.6.3 Cost-effectiveness

In June 2015, the 13-valent pneumococcal conjugate vaccine (PCV13) was introduced in the Portuguese immunisation programme for infants. The cost-effectiveness of PCV13 vaccination versus no vaccination for preventing IPD and pneumococcal pneumonia was evaluated taking herd immunity effects and productivity losses into account [9]. PCV13 proved to be cost-saving compared with no vaccination, and was associated with better health outcomes at lower costs. In another study, the cost-effectiveness of pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV/PCV10) was assessed in comparison with the ongoing PCV13 vaccination in the UK [10] in infants/children. Given the model assumptions, both vaccines had a similar impact on IPD and pneumonia, but PHiD-CV generated a greater reduction in acute otitis media cases (AOM), AOM-related general practitioner consultations, and tympanostomy tube placements. Assuming an equal vaccine price, the PHiD-CV vaccination was dominant, gaining more QALYs and saving costs.

Porchia et al. reviewed the cost-effectiveness of the pneumococcal vaccination of adults [11]. Both vaccination with PCV13 or PPV23 have an economically advantageous profile and are considered good value for money. PPV23 has a limited duration of protection and may need a

booster, leading to an increase in vaccination costs. On the other hand, PPV23 protects against 10 additional pneumococcal serotypes. PPV23 has a lower price than PCV13, whereas PCV13 offers a guaranteed protective effect on all pneumococcal diseases without the need for revaccination, according to current evidence. According to Newall, the conflicting results found in cost-effectiveness studies are due to differences in the level of herd protection resulting from infant pneumococcal vaccination programmes in different countries [12]. Other critical parameters are: the incidence of pneumococcal disease in older adults and the serotypes involved, the efficacy of each vaccine against invasive and non-invasive pneumonia, the duration of vaccine protection, and differences in vaccine price. The cost-effectiveness of PCV13 vaccination compared with no vaccination was evaluated in elderly people in Italy, taking new effectiveness data reported by the CAPiTA Study into account [13]. Vaccinating the elderly at 65, 70 or 75 years of age were all cost-effective; the ICERs ranged from €14,605 to €15,412 per QALY gained. The authors strongly recommend vaccination of the elderly in Italy with PCV13.

7.9.7 Literature

7.9.7.1 References

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* RIVM publication

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7.10 Poliomyelitis

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

7.10.1 Key points

- In 2016 and in 2017 up to July 1st, no cases of poliomyelitis were reported.
- In April 2017, two fully vaccinated employees were exposed to a wild poliovirus type 2 (WPV2) spill in a Dutch vaccine manufacturing plant. Four days later, WPV2 was found in the stool of one of them and later on in sewage samples. Strict isolation was applied. Shedding stopped 29 days later. No transmission was detected.
- In the three polio-endemic countries (Afghanistan, Nigeria and Pakistan), reports of wild poliovirus type 1 have decreased substantially.
- By the end of May 2016, all countries with oral polio vaccine (OPV) in their immunisation programmes switched from trivalent to bivalent OPV.
- WHO advised the inclusion of at least one dose of IPV in countries with a complete OPV-schedule. However, due to an IPV shortage, not all countries managed to include at least one IPV in their vaccination programmes.

7.10.2 Tables and figures

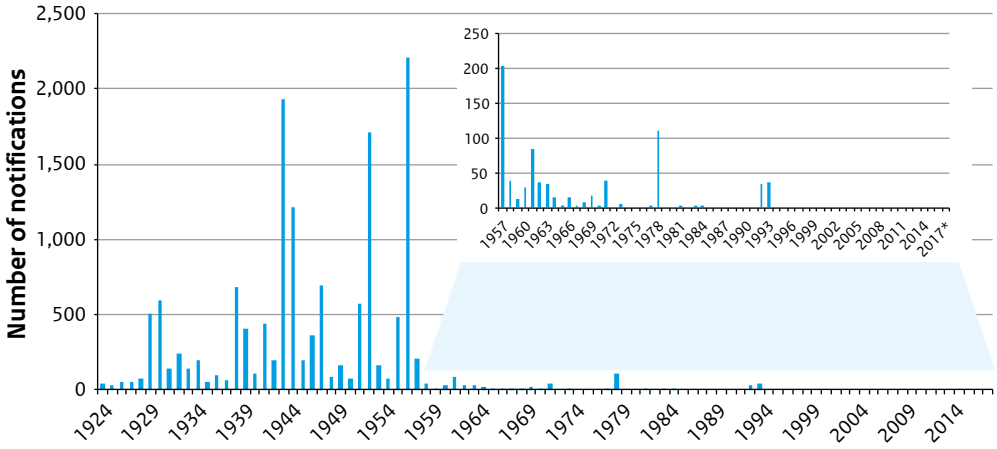

Figure 7.10.1 Notifications of poliomyelitis in the Netherlands from 1924 to 2017
For 2017, reports up to July 1st are included

7.10.3 Epidemiology

In 2016 and in 2017 up to July 1st, no cases of poliomyelitis were reported in the Netherlands. (Figure 7.10.1)

7.10.4 Pathogen

On 3 April 2017, a wild poliovirus type 2 (WPV2) spill occurred in a Dutch vaccine manufacturing plant. Two fully vaccinated operators with risk of exposure were advised on maintaining stringent personal hygiene and were monitored for virus shedding. Poliovirus (WPV2-MEF1) was detected in the stool of one, 4 days after exposure, and later also in sewage samples. The operator was isolated at home and followed up until shedding stopped 29 days after exposure. No further transmission was detected [1]. Lessons learned will be used to update the national guidelines following the introduction of poliovirus in the Netherlands.

7.10.5 Research

The National Polio Laboratory (NPL) at the RIVM participates in several projects of the WHO Global Polio Laboratory Network (GPLN), including the 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. The NPL is currently involved in reference testing and the sequencing of samples from the ongoing VDPV2 outbreaks in Syria.

7.10.6 International developments

In 2016-2017, polio remained endemic in three countries – Afghanistan, Nigeria and Pakistan. In 2016 and 2017 up to week 24, no importation of polio in non-endemic countries was observed. Currently, only WPV1 is circulating, WPV2 and WPV3 stopped circulating in 1999 and 2014, respectively.

The number of circulating vaccine-derived polioviruses (VDPV) decreased in 2016 (n=5), compared with 2015 (n=32). Four VDPVs were reported in 2017 up to May 30. To boost a further reduction in VDPVs, all countries with oral polio vaccine (OPV) in their immunisation programme switched from trivalent OPV to bivalent OPV, which does not contain poliovirus type 2, before June 2016. To comply with the WHO global action plan for poliovirus containment (GAPIII), all materials containing poliovirus type 2 should be destroyed or contained in poliovirus essential facilities (PEFs). In the Netherlands, the inventory of facilities maintaining poliovirus materials yielded 7-9 would-be PEFs.
To strengthen protection through vaccination, WHO advised that all countries should include at least one dose of inactivated polio vaccine (IPV) in their immunisation programme from 2015 onwards. Unfortunately, due to IPV shortage, not all countries managed to implement this to date.

7.10.7 Literature

7.10.7.1 References

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* RIVM publication

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7.11 Rubella

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

7.11.1 Key points

- In the year 2016 and in the first six months of 2017, no cases of rubella were reported.

7.11.2 Epidemiology

In the calendar year 2016 and in the first half of 2017, no rubella cases were reported. The last outbreak in the Bible Belt took place in 2004 2005, in which almost 400 cases were reported. In 2013, a small outbreak around an orthodox Protestant school involving over 50 cases occurred. In 2014 and 2015, only three cases were reported in total.

7.11.3 Research

In the Netherlands, there is no uniform policy on rubella screening during pregnancy. A study in the East of the Netherlands showed that some midwives screen all pregnant women, some screen only risk groups and others do not screen at all [1]. Given the high vaccination coverage and low incidence of rubella, screening of all pregnant women is not cost-effective [2].

7.11.4 International developments

Since the large rubella outbreak in Poland with over 38,000 cases reported in 2013, the number of cases in Europe continues to decline. In 2016, 28 EU/EEA countries reported 1,307 rubella cases, 1,144 (88%) of which were from Poland [3]. Other countries reporting significant numbers of rubella cases in 2016 were Germany (94 cases) and Italy (29 cases) [3].

WHO initiated a rubella IgG standardisation workgroup in 2013/2014 in order to provide a guideline for appropriate rubella IgG screening during pregnancy. The standardisation of rubella virus IgG assays is required because many women currently gain immunity from MMR immunisation and not from natural infection, which results in different IgG levels [4]. Follow-up studies and recommendations for the use of serological tests for rubella from this international group will be incorporated into a revised version of the International Laboratory Manual for measles and rubella, with a contribution from RIVM on the diagnosis of measles and rubella cases in the elimination phase [5].

7.11.5 Literature

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* RIVM publication

7.12 Tetanus

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

7.12.1 Key points

- In 2016 one case of tetanus was reported. No cases were reported in 2017 up to July 1st.

7.12.2 Tables and figures

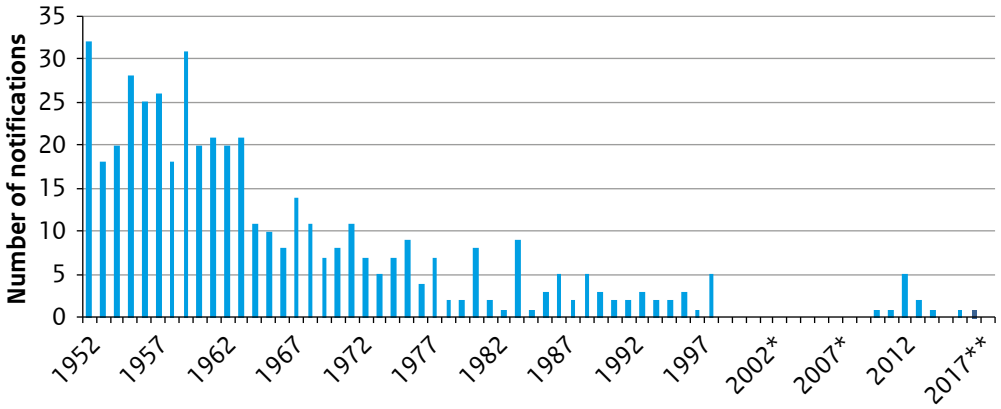

Figure 7.12.1 Reported cases of tetanus in the Netherlands by year, 1952-2017

* Between 1999 and 2009 tetanus was not notifiable.

** For 2017, notifications up to July 1st were counted.

7.12.3 Epidemiology

In 2016, an unvaccinated 72-year-old male with signs of tetanus was hospitalised and reported. His birth cohort was not eligible for routine vaccination with Tetanus Toxoid (TT). Nine days before disease onset, he wounded himself with a saw. At admittance, he received Tetanus Immuno Globulins (TIG) and TT, but nevertheless developed signs of tetanus. He recovered after treatment. In 2017 up to July 1st, no tetanus cases were reported.

7.12.4 Pathogen

No isolates of Clostridium tetani were submitted for PCR toxin gen testing. Clostridium tetani is rarely isolated, so the diagnosis mostly depends on clinical recognition. Serological diagnosis is not possible, because infection does not lead to an antibody response.

7.12.5 International developments

7.12.5.1 Cost-effectiveness

WHO updated the tetanus position paper [1]. One of the items in this paper concerns the cost-effectiveness of universal tetanus vaccination. According to WHO, universal tetanus vaccination is cost-saving. In an economic impact analysis performed in the US in 2009, the costs of a single non-neonatal tetanus case were estimated at $90,635 per hospitalisation. It was estimated that by vaccinating one birth cohort with DTP through routine immunisation, 169 tetanus cases and 25 deaths could be prevented in the US. The direct and societal costs saved for one birth cohort were estimated to be $12 million and $45 million, respectively.

7.12.6 Literature

7.12.6.1 References

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8
The immunisation programme on Bonaire, St. Eustatius and Saba

J. van Slobbe, K. Hulshof, R.A. Vos, A. Janga-Jansen; M. Luinstra-Passchier, H. van den Kerkhof

8.1 Key points

- Since 2016, the NIP on Bonaire, Statia and Saba has contained the same target diseases as the NIP in the European Netherlands.
- On Bonaire during the past five years, one Hib case and, in 2016, several pertussis cases were reported.
- Saba recently experienced a large varicella outbreak, with approximately 200-250 inhabitants affected.
- From May to August 2017, the PIENTER survey, as part of the so-called Health Study, was conducted on Bonaire, Statia and Saba in order to assess how well the islands are protected against infectious diseases, among other things.

8.2 Tables and figures

Table 8.1 Response rates Health Study Caribbean Netherlands (01-09-2017*)

	Bonaire	St. Eustatius	Saba	Total
Invited	4,797	2,135	1,133	8,065
Eligible for participation	4,675 (97.5%)	2,058 (97.7%)	1,050 (92.7%)	7,810 (96.8%)
Included	1,199 (25.6%)	431 (20.7%)	225 (21.4%)	1,855 (23.8%)

*Last update from St. Eustatius is from 01-08-2017

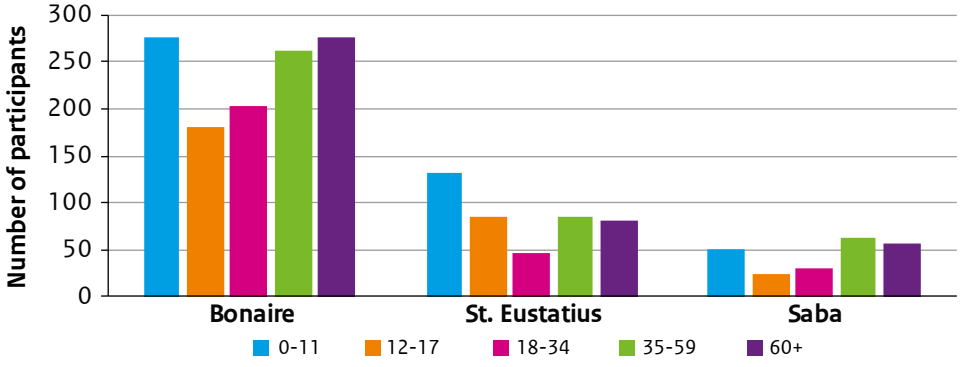

Figure 8.1 Number of participants, by age and island, enrolled in the Health Study Caribbean Netherlands (01-09-2017)
*Last update from St. Eustatius is from 01-08-2017

8.3 Developments in the immunisation programmes

The immunisation programme on Bonaire has changed over the years since its start at the end of the 1950s. The first immunisations on Bonaire were given following the example of Curaçao, where an immunisation programme had started a few years earlier. Initially, the organisation of the immunisation programme was not centralised on Bonaire. District nurses, obstetricians and GPs, which belonged to the public health department of the government, vaccinated children at different locations in the neighbourhoods. From the early 1990s, the immunisation programme became centralised at the child welfare centres (CWCs) and a central registration system was developed and maintained. The CWCs moved from the Public Health and Hygiene Service of the local government to the hospital premises of Fundashon Mariadal and, later on in 2011, to the Centre for Youth and Family (CJG). Since then, the CJG has effectuated (or executed) the immunisation programme on Bonaire under the responsibility of the Public Entity of Bonaire. Since 2011, with the introduction of the Public Health Law for the BES, this task of the Public Entity of Bonaire has been legally defined.
On Saba, a similar evolution of the immunisation programme has taken place, whereby in 2015 the responsibility for the immunisation programme of the Saba Healthcare Medical Centre was transferred to the Municipal Health Services (GGD), and thus to the local government.

In response to the advice of the Health Council and in consultation with the Public Entity of Bonaire, the Minister of Health, Welfare and Sport decided in 2012 to adjust the national immunisation programme in the overseas territories as much as possible to correspond with the NIP in the European Netherlands. Shortly before, Bonaire had included hepatitis B and pneumococcal immunisations in the programme. Following the advice of the Health Council, immunisation against meningococci group C was added to the programme and the whole-cell pertussis vaccine was replaced by the acellular pertussis vaccine. The oral polio vaccine was also replaced by the inactivated polio vaccine (IPV). After the introduction of HPV immunisation in 2016, the immunisation programme in the overseas territories contained the same target diseases as the NIP in the European Netherlands. The main difference between both programmes is that HPV immunisation on Bonaire and Saba is given at the age of 9 years and at the age of 10 years on St. Eustatius, in contrast to the practice in European Netherlands, where it is given at the age of 12 years. Since 2017, the first MMR on Saba has been given at the age of 12 months.

Since 2014, RIVM-DVP also supplies vaccines for the immunisation programme in our overseas territories. This means that our colleagues on these islands not only vaccinate against the same diseases, but also use the same vaccines as are used in the European Netherlands. The Public Health Departments on the islands, which have an intensive collaboration with RIVM, also frequently consult with the Pan American Health Organization (PAHO), which has a closer focus on the specific needs and problems in the Caribbean region.

8.4 Epidemiology of diseases included in the NIP

8.4.1 Epidemiology on Bonaire

Annually, an average of 200 children are born on Bonaire. The immunisation coverage among infants is between 90% and 95%. Bonaire has about 19,000 inhabitants. There are hardly any recent epidemiological data available for Bonaire. In the past 5 years, one case of Hib has been reported and in 2016 a number of cases of pertussis were reported, including two newborns and a single one-year-old child. All of these cases involved (partially) unvaccinated children. These numbers probably represent serious underreporting and are also due to a lack of laboratory facilities necessary to confirm such diagnoses.

8.4.2 Epidemiology on Saba

Saba has a population of about 2,000 inhabitants and annually 15-20 children are born. The immunisation coverage for infants has been over 95% for years. In 2016, there were no reports of patients with NIP diseases. However, few diagnostics were used or available, such as for complaints that might indicate pertussis.

Recently, Saba had a large varicella outbreak, with between 200-250 inhabitants contracting chickenpox. In tropical countries, varicella dynamics are different from those in countries with moderate climates, with seroprevalence at 12 years of age often under 50% (in the Netherlands this is more than 95%). During the outbreak, many adults also fell ill, as did some pregnant women and elderly people. This led to a lot of unrest, discomfort and absenteeism from work. Fortunately, the number of complications remained limited to two varicella pneumonia cases. Especially for the Caribbean Netherlands, a thorough evaluation of the addition of Varicella immunisation to the Island immunisation programme would be appreciated.

8.4.3 Epidemiology on St. Eustatius

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

8.5 Research

From May to Augustus 2017, the PIENTER survey has been extended to include the Dutch Caribbean Islands of Bonaire, St. Eustatius and Saba. In this Health Study, as it is referred to here, RIVM partnered with Statistics Netherlands (CBS) and the local Public Health departments on the islands. The main goal was to assess how well people living on the islands are protected against infectious diseases. However, this study took a wider-range than the Dutch PIENTER version because it aimed to investigate lifestyle and chronic illness as well. The results will be shared with the islands in order to support public health policy in the Dutch Caribbean Islands, thus enabling illnesses to be prevented and controlled more effectively in future.

An age-specific sampling technique was used to draw a representative sample of the population (Ntotal=8,092: Bonaire 4,821; St. Eustatius: 2,135; and Saba: 1,136). Age strata were 0-11, 12-17, 18-34, 35-59 and 60-89 years of age. Participants were invited by mail and were asked come to a community centre in their neighbourhood to take part in the study.

Promotional efforts prior to and during the survey were undertaken to increase participation. The study involved testing blood samples to detect antibodies in order to obtain insight into the age-specific seroprevalence of NIP-targeted diseases, as well as local tropical pathogens in the Dutch Caribbean population. Additionally, nasopharyngeal and oropharyngeal (starting from 8 years) swabs were taken to investigate the presence of bacteria and viruses in the nose and throat. Stool samples were collected to be able to analyse the microbiome of the gut and to investigate antibiotic resistance. Finally, height, weight and blood pressure were measured and the participants were asked to complete a questionnaire about risk factors, lifestyle and chronic illness.

Of the total population that were invited, 7,810 people (96.8%) were eligible to participate. To date, a total of 1,855 people (23.8%) have been enrolled in the study, 1,199 (25.6%) of which lived on Bonaire, 431 (20.7%) on St. Eustatius, and 225 (21.4%) on Saba (Table 8.1 and Figure 8.1).

9
Future NIP candidates

9.1 Hepatitis A

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

9.1.1 Key points

- In 2016, the number of reported hepatitis A patients (81 cases) remained low (2015: 80 cases), compared with previous years (2011-2014: 105-125 cases).
- Fifty-six per cent of the patients were aged 20 or older, hospitalisation in this group was higher (42%) than in cases involving patients younger than 20 years (8%).
- Fifty-eight percent of the Dutch cases were reported to be travel-related, with Morocco reported most frequently.
- An international outbreak of hepatitis A among MSM, ongoing since July 2016, also affects the Netherlands (~100 Dutch cases in one year).

9.1.2 Tables and figures

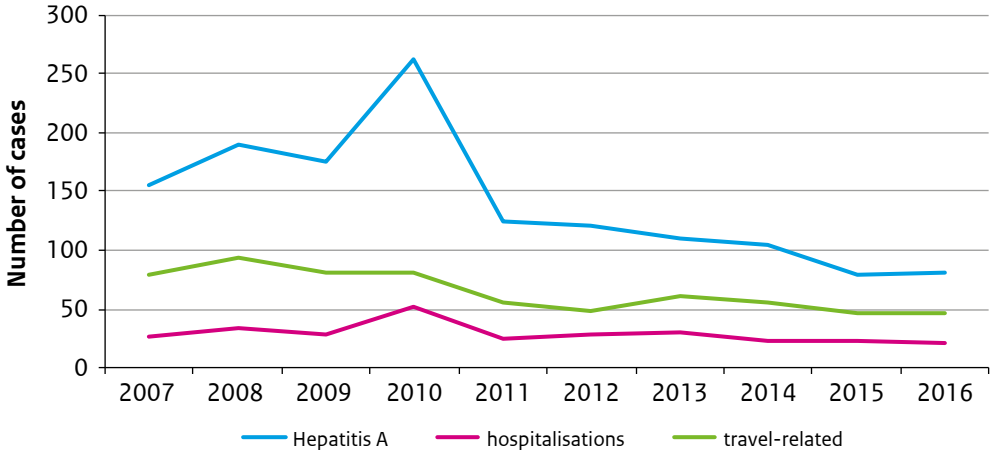

Figure 9.1.1 Number of reported, hospitalised and travel-related cases of hepatitis A, 2007-2016
Source: Osiris

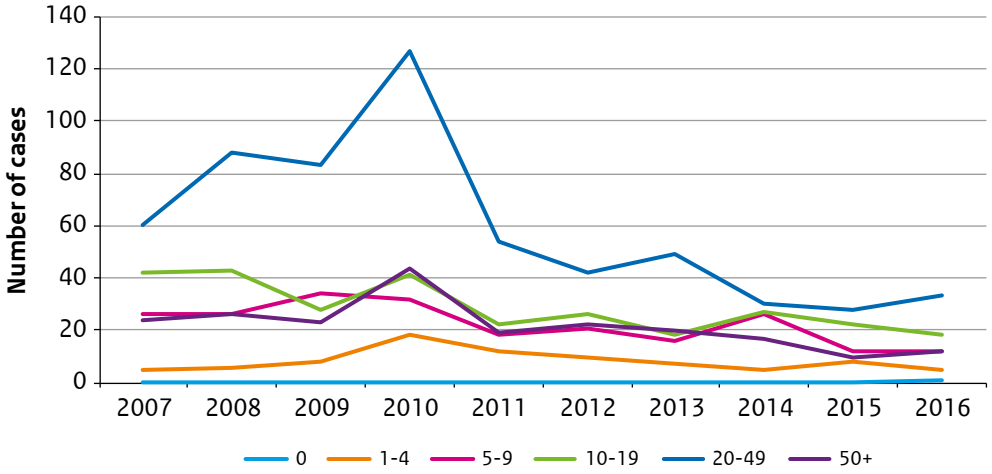

Figure 9.1.2 Age distribution of hepatitis A cases, 2007-2016
Source: Osiris

9.1.3 Epidemiology

In 2016, 81 cases of hepatitis A were reported in the Netherlands, corresponding to 0.5 cases per 100,000 population. Together with 2015 (80 cases), this is the lowest number since hepatitis A became notifiable in 1999 (Figure 9.1.1 / Appendix 2). No mortality due to hepatitis A was reported. The age distribution over the years 2007-2016 is given in Figure 9.3.2. After two years with more than half of the patients aged under 20 years, in 2016 there were more adult cases than children. In total, 22 patients were hospitalised (27%); of those aged under 20 this percentage was 8% (3/36), compared with 42% of the patients aged 20 years or older (19/45). Based on the reports, 12 epidemiologically linked clusters with a total of 22 cases could be deduced. A further case could be linked to a case in 2017.

The percentage of travel-related cases was 58% in 2016 (Figure 9.1.1). This is similar to 2015 (59%), but higher than it was in the previous years: 31-51% (2007-2012) and 53-55% (2013-2014). Morocco (21/47; 45%) was reported most frequently; all other countries were reported a maximum of three times. Most of the clusters (10/13) were at least partly travel-related, especially from Morocco (five clusters) and Afganistan (three clusters).

After several years without cases involving MSM, nine cases were registered in the second half of 2016. In 2017, the number of MSM cases increased sharply (~100 cases between July 2016 and July 2017). These cases are part of an ongoing international outbreak among MSM, with three different strains dominating. England, Germany and the Netherlands have published preliminary data on the outbreak [1-3]. Sixteen European countries reported a total of 1,466 confirmed cases and 2,658 probable and suspected cases related to this outbreak between June 2016 and June 2017 [4].

9.1.4 Pathogen

Hepatitis A virus (HAV) specific IgM-positive samples can be sent to the IDS of the RIVM for typing as part of the molecular surveillance of this virus. In 2016, samples were submitted for 62 out of 81 reported cases (77%) for the purpose of virus typing and the samples of 58 cases were found to be positive by PCR and could be sequenced. The lab or Municipal Health Service (GGD) probably reasoned, for the remaining 19 cases, that it was not necessary to submit a sample because the source was clear. 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.
A total of 126 serum and faecal samples from cases and contacts were tested. HAV RNA was detected in 59 (47%) and 58 of reported cases could be typed, which resulted in 47 unique sequences, eight of which were detected in clusters of two to three cases. One cluster of three and two unique strains were detected in MSM cases, a well-known risk group for hepatitis A. Since 2011, there has been no major epidemic in this risk group in Europe. At the beginning of 2017, it became apparent that a large outbreak was ongoing in this risk group in Europe.

9.1.5 Research

An international study led by Spain, RIVM and ECDC is underway and focused on the ongoing MSM outbreak. Epidemiological information on the cases and strain data are gathered to monitor and analyse the development of the outbreak.

9.1.6 International developments

In 2013, a total of 165 persons from 10 states were reported with hepatitis A in the largest outbreak in the United States in 10 years. The outbreak was caused by consumed pomegranate arils imported from Turkey. A high number of persons, i.e. 69 (42%), were hospitalised [5]. Individual comorbid conditions were significantly associated with hospitalisation, including excessive alcohol use, inflammatory bowel disease, and cardiovascular disease. Total outbreak costs were estimated at $1.7 million (including a liver transplant at the cost of $183,680). Based on these findings, the authors recommend hepatitis A vaccination for adults with chronic medical conditions, in addition to persons with chronic liver disease.

In countries with moderate HAV endemicity, the mean age of HAV infection has increased, resulting in an increase in the number of symptomatic and severe cases. For those countries, WHO has recommend universal vaccination for children aged ≥1 years and suggests the use of single-dose HAV vaccines in immunisation schedules. A one-dose HAV vaccine was included in the national immunisation programme in Argentina and additional countries in Latin America are considering this option [6]. In Argentina, this universal single-dose hepatitis A vaccination was introduced for children aged 12 months in 2005 [7]. In 2013-2014, 1,088 children that had been vaccinated at least six years prior were included in the study. The median interval between vaccination and enrolment was 7.7 years (range 6.3-9.2 years). A total of 97.4% of these children had anti-HAV antibody levels of ≥10 mIU/mL with a GMC of 170.5 mIU/mL (95%CI 163.2-178.2 mIU/mL). Curran et al. [8] reviewed the cost-effectiveness of one-dose versus two-doses of HAV vaccination in a limited resource environment. The results for a one-dose vaccine strategy appear promising, especially over a short time horizon (e.g., 25 years). However, exploring a longer time horizon (i.e. 75 years), with a one-dose strategy, may

result in more deaths than a no vaccination strategy. If one assumes that vaccine-induced immune protection lasts for 50 years or more, then a one-dose strategy would lead to an overall HAV reduction and cost savings. Further data on the long-term impact of a single dose of HAV is required.

Stuurman et al. [6] reviewed the effect of a countrywide universal mass vaccination of children with monovalent inactivated vaccines. In the countries with intermediate levels of endemicity, the incidence of acute hepatitis A showed a clear decline. And because a decrease in incidence in the non-vaccinated age groups was seen, a herd immunity effect seems to occur. In Greece, a country with low endemicity, universal mass vaccination had less effect.

In January 2005, 130 Nicaraguan children found to be seronegative for hepatitis A in 2003 received one dose of the virosomal vaccine Epaxal [9]. After 7.5 years, the children received a booster dose (Havrix Junior or Havrix). Blood samples were collected prior to and one to two months after the booster vaccination. The VE was estimated to be 98.3% (95%CI 87.8-99.8%). The booster vaccination resulted in an almost 30 fold increase of anti-HAV levels. Even in the children with very low or undetectable antibody levels at the end of the follow-up, a strong immune response to the booster vaccine was seen. Another study reports the effect of vaccination on healthy adults with two doses of Epaxal with a one-year interval after a follow-up period of 20 years, done in Switzerland [10]. Of the 256 participants who had received two doses of Epaxal, 103 attended the 20-year follow-up visit and 95 of them could be included in the analyses. The seroprotection rate was 100% (95%CI 96.2-100%) and with 95% of the vaccinees predicted to be protected for at least 41.5 years.

The impact of the inclusion of a 2-dose hepatitis A vaccination in the national immunisation programme for indigenous children aged 12-24 months in 2005 in Australia was reviewed [11]. In 2000-2005, the notification rate of HAV infections among Indigenous people was 8.41 per 100,000 population (95%CI 5.03-11.79), which declined to 0.85 per 100,000 (95%CI 0.00-1.99) in the period 2006-2014. This post-vaccine notification rate is similar to the non-indigenous rate.

In Alaska, 144 children who had received three doses of Havrix were followed up at 20 years [12]. The children had been randomised to one of three groups with the time between the first and the third dose varying between two, six and 12 months. At a 20-year follow-up, 52 participants were available, equally distributed over the three groups. Eighty-nine percent had ≥20 mIU/mL anti-HAV antibody concentrations. After adjusting for peak antibody levels post-vaccination, no differences between the three groups were seen. Modelling of the results of the study lead to the prediction that protective anti HAV-levels will remain for at least 25-30 years after vaccination in childhood.

The live attenuated H2 strain vaccine is a Chinese vaccine also available in India, Thailand, the Philippines, Guatemala and Bangladesh. Rao et al. [13] reviewed the randomised controlled trials and cohort studies, analysing the immunogenicity and tolerability of the H2 vaccine. All reviewed studies were done in children, with follow-up periods varying from two months to 15 years. The authors concluded that the vaccine is highly immunogenic with efficacy similar to

that of inactivated vaccines. As a single dose can provide long-term immunogenicity, it can be a preferred option for developing countries.

The effectiveness of administering one dose of hepatitis A vaccine and immune globulin as a post-exposure prophylaxis (PEP) in susceptible, exposed persons during outbreaks was examined in Catalonia [14]. Information from 112 outbreaks occurring between 2006 and 2012 involving 3,550 exposed persons was used. No significant differences were seen between the two methods: the effectiveness of the HAV vaccine was 97.6% (95%CI 96.2-98.6%) and 98.3% (95%CI 91.3-99.9%) of immune globulin.

9.1.7 Literature

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* RIVM publication

9.2 Respiratory syncytial virus infection

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

9.2.1 Key points

- In the season 2016/2017 (week 40 trough week 20) 12% positive RS-samples were found in the GP sentinel surveillance on ILI and ARI compared to 5.0-8.6% in the previous four seasons.
- Currently, 14 vaccine candidates are at least in phase 1 clinical trials, but only one has reached phase 3 trials.
- This vaccine candidate in phase 3 trials aims to vaccinate pregnant women to protect the newborn. The trial will probably continue to 2021.
- The same vaccine was tested in the elderly, but was not effective.

9.2.2 Tables and figures

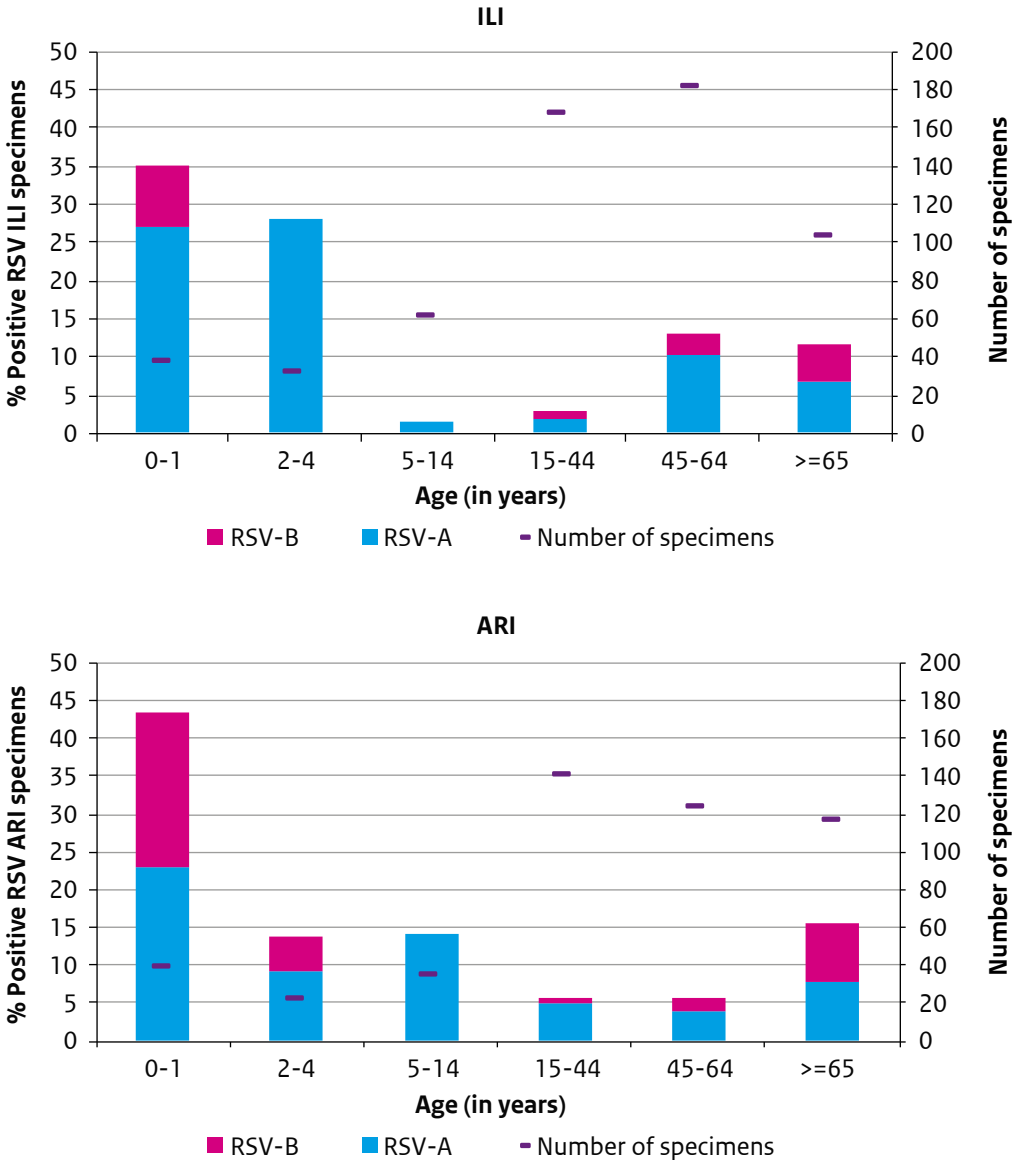

Figure 9.2.1 Percentage of RSV-A and RSV-B positive influenza-like illness (ILI) specimens (upper graph) and acute respiratory infection (ARI) specimens (lower graph), and the number of tested specimens, taken by sentinel GPs during the respiratory season of 2016/2017 (week 40 of 2016 - week 20 2017), displayed for six age categories

Source: NIVEL Primary Care Database, NIC location RIVM

9.2.3 Epidemiology

Respiratory Syncytial Virus (RSV) is the most common cause of acute lower respiratory infections in children <5 years of age worldwide. In Western countries, it is the most frequent reason for the hospitalisation of infants [1]. For frail elderly people, RSV infection can be as severe as an influenza virus infection, with similar morbidity and mortality [2]. Using a systematic review and modelling, Shi et al. [3] estimated globally in 2015 that 33.1 million episodes of acute lower respiratory infection (ALRI) due to RSV in children under 5 years of age resulted in approximately 3.2 million hospital admissions and nearly 60,000 in-hospital deaths. In children younger than 6 months, 1.4 million hospital admissions and 27,300 in-hospital deaths were due to RSV-ALRI.

The current Dutch RSV surveillance is primarily based on the GP surveillance of patients with influenza-like illness (ILI) and other acute respiratory infections (ARI). For this purpose, nose swabs and throat swabs of a subset of patients are collected and tested for the influenza virus, RSV, rhinovirus and enterovirus. Furthermore, the weekly reporting of virological laboratory surveillance by 20 virologic laboratories provides insight into the number of positive RSV tests, reflecting the RSV circulation.

In the 2016/2017 season, 123 RS-viruses were detected in 1,060 nose swabs and throat swabs (12%) of ILI and other ARI patients, which were collected by sentinel GPs. The percentage of positive specimens from the GP sentinel surveillance was higher in this season than it was in the same period (week 40 through week 20) of the previous four seasons (range 5.0% - 8.6%). The percentage of positive samples was highest in the age group below 2 years old (35% in ILI cases and 44% in other ARI cases) (Figure 9.2.1). The percentages were lower in the older children and young adults and then increased again in older adults.
The number of positive RSV diagnoses reported by 20 virologic laboratories in the Netherlands (virological laboratory surveillance) in week 40 of 2016 through week 20 of 2017 (n=1937) was higher than it was in the previous three seasons (range 1,348 - 1,661 diagnoses), but still lower than it was in most seasons before that period (range week 40, 2007-week 20, 2013: 1,838 – 3,075 diagnoses per season).
For more information on epidemiology in the Netherlands, see the annual report 'Surveillance of Influenza and Other Respiratory Infections in the Netherlands: winter 2016/2017' [4].

9.2.4 Pathogen

RSV is divided into two types, RSV-A and RSV-B, mainly based on the variation in the attachment protein, the G-protein. These two types can circulate simultaneously in the population. In the 2016/2017 season in the Netherlands, RSV-A was detected more than RSV-B in the GP-specimens of all age groups. Both the G-protein and the F-protein (especially the pre-fusion form) are targets for vaccine development and undergo genetic drift, which might lead to vaccine escape. Although relatively stable, monitoring their evolution is important [5].

9.2.5 Research

The number of RSV vaccines in development has increased considerably in the last decade [6, 7]. These candidates aim to target RSV naïve young infants, RSV naïve infants >4-6 months old, pregnant women and the elderly with different issues related to vaccine development. With respect to naïve young infants, there is a lack of knowledge on how the neonatal immune system would react to such vaccines or even how infants are protected against RSV disease [8]. Many infants suffer from RSV disease at a young age, despite receiving antibodies against RSV from their mothers. Research at CIb (IIV) focuses on studying the characteristics of protection by antibodies against RSV in neonates to gain greater insight into the workings of maternal immunity. In collaboration with Radboud MC in Nijmegen, we initially analyzed RSV antibodies from a group of infants hospitalized with RSV disease [9]. We found that the levels of antibody, particularly those received from the mother, do not predict disease severity in infants and therefore cannot be used to predict the risk of RSV disease. This is an important finding for the assessment of vaccines. We also showed that RSV-specific antibodies have the capacity to help RSV to infect the cells of the cellular arm of the immune system, a phenomenon called antibody-dependent enhancement of infection, which is known to occur with respect to the Dengue virus [10]. Although this effect could only be shown in cell cultures, it should be taken into account when assessing vaccine strategies because the infection of immune cells may negatively influence the immune response and thus promote disease.

Finally, we found that, in human serum, virus neutralization is predominantly mediated by antibodies against the viral F protein, which is included in many candidate vaccines [11]. In addition, we examined the immune response to different regions of the F protein in cotton rats after vaccination with formalin-inactivated RSV in order to learn what went wrong with this vaccine when it was used in children in the 1960s. We found that this vaccine could only induce antibodies to a specific region of F that neutralises poorly and is therefore non-protective. This might have played a role in the vaccination-induced enhancement of disease that was observed in the past with these preparations and again is an important characteristic to assess in candidate vaccines.

9.2.6 International developments

Using a systematic review and modelling Shi et al. [3] estimated globally in 2015, 33.1 million episodes of acute lower respiratory infection (ALRI) due to RSV in children under 5 years of age, resulting in about 3.2 million hospital admissions and nearly 60,000 in-hospital deaths. In children younger than 6 months, 1.4 million hospital admissions and 27,300 in-hospital deaths were due to RSV-ALRI.

RIVM is partner in the RESCEU project (*http://resc-eu.org/*) that runs from 2017 to 2021 and aims to explore the burden (clinical, economic and social) of RSV populations that are at high-risk of developing severe (complications from) RSV infection, and strengthening RSV surveillance and European/international collaboration on RSV surveillance and research.
Routine health care databases, including GP-consultations and hospitalisations, will be used as a source of information to assess the burden of RSV in the Netherlands.

Also, an RSV pentaplex immune assay (RSV-MIA) is currently under development at the RIVM as a part of this project. Using this assay, a population-based sero-survey will be performed with samples of the PIENTER studies.

Currently, ECDC is developing a joint protocol for activities related to the surveillance of RSV. RIVM works closely together with ECDC and other public health institutes, specifically SSI (Denmark), in order to strengthen international collaboration on RSV surveillance and improve the surveillance of RSV.

There are currently many RSV vaccine concepts under development. Updates of these developments are shown at *http://www.path.org/vaccineresources/details.php?i=1562*. It should be noted that most concepts in phase 1 would take at least four years to reach market approval and those in phase2/3 at least three years. In particular, vaccines intended for maternal vaccination have a long clinical trial path. The Novavax nanoparticle vaccines were tested in the elderly, but failed to show a level of protection [12]. The same vaccine is currently being tested for maternal vaccination in a long-running phase-3 clinical trial (at least until 2021).

9.2.7 Literature

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* RIVM publication

9.3 Rotavirus infection

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

9.3.1 Key points

- In 2016, a second low-endemic rotavirus season was observed, similar to the one in 2014, while 2015 and 2017 showed average rotavirus epidemics, comparable to the years prior to 2014. Together, these observations suggest a possible transition from an annual to a biennial rotavirus epidemic pattern in the Netherlands.
- G9P[8] was the most prevalent genotype in 2016.
- The Dutch Health Council has recommended to the Ministry of Health, Welfare and Sport to vaccinate high-risk group children (premature children, children with low birth weight or congenital pathology). In addition, they state that the Health Council is positive towards mass vaccination incorporated in the NIP, however, they mention that this will not be cost-effective seen the current vaccine prices. The RIVM has published a background document providing up-to-date information to facilitate the Health Council in preparing their recommendation.

9.3.2 Tables and figures

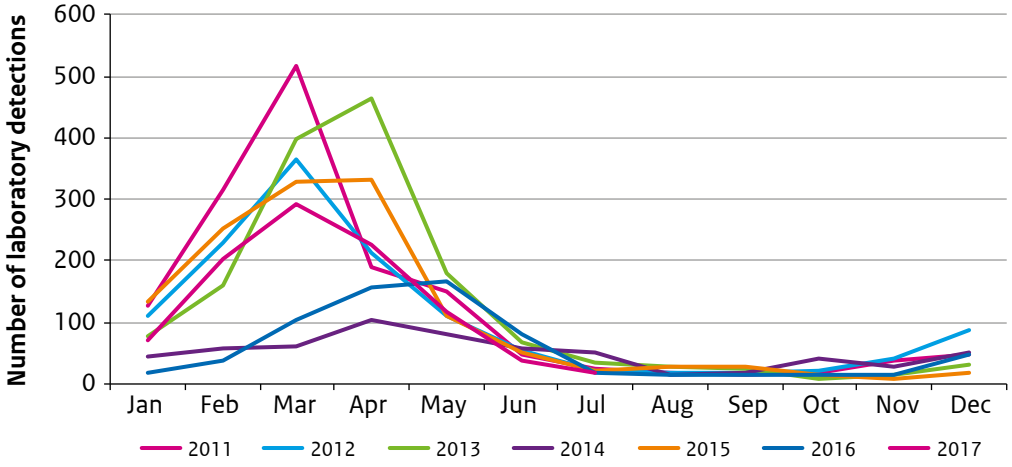

Figure 9.3.1 Reported laboratory detections of rotavirus per month, the Netherlands, 2011-2017

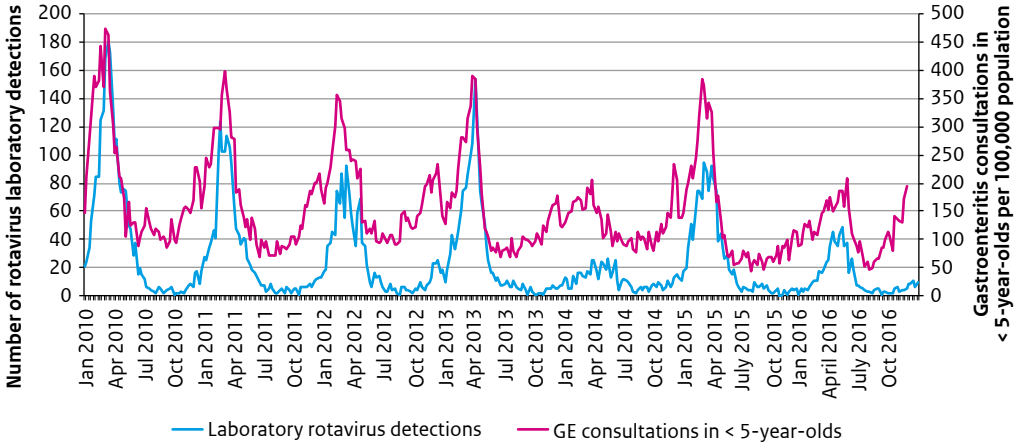

Figure 9.3.2 Rotavirus laboratory detections and general practice gastroenteritis consultation rates in children under 5 years old, the Netherlands, 2010-2016

Table 9.3.1 Number of rotavirus samples typed per year, the Netherlands, 2012-2016

Type	2012	2013	2014	2015	2016	Total
G12P8	4	1	6	2	0	13
G1P8	48	**83**	20	25	9	185
G2P4	23	41	29	34	12	139
G3P8	50	51	7	14	23	145
G4P8	39	35	12	**137**	3	226
G9P8	**71**	23	**49**	32	**59**	234
Other	36	53	16	28	12	145
Total	271	287	139	272	118	

Note: the bold figures represent the most prevalent genotype in a year.

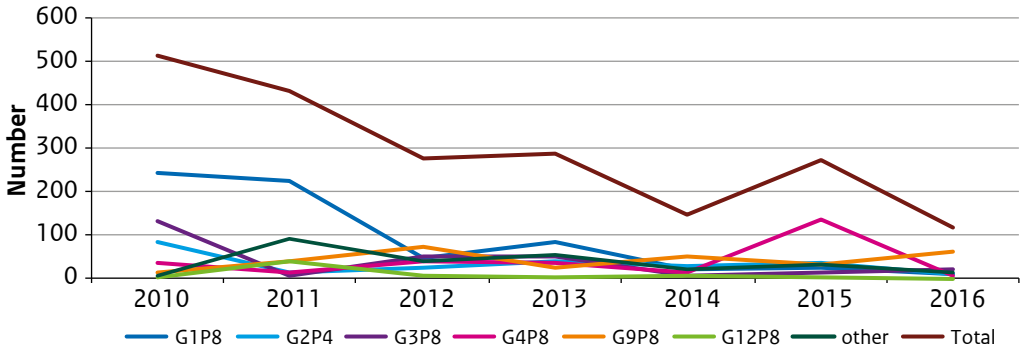

Figure 9.3.3 Distribution of rotavirus genotypes per year, the Netherlands, 2010-2016

9.3.3 Epidemiology

For the surveillance of rotavirus, weekly laboratory detections of rotavirus are used, reported on by the Working Group Clinical Virology. These data show a change in the rotavirus seasonal pattern in the Netherlands over the last four years. In 2014, the rotavirus season was exceptionally low: only 607 positive laboratory detections for rotavirus were reported that calender year, compared with 1,288 and 1,496 detections in 2012 and 2013, respectively. Besides, the epidemic peak was delayed (mid-April and beginning of May). The 2015 season followed a usual pattern with the epidemic peak occurring in March and an average number of total rotavirus laboratory detections (N=1,323). For 2016, we observed a low rotavirus season again (N=679), with the epidemic peak occurring in May (Figure 9.3.1) [1]. Observations for the 2017 season up to week 30 show a similar season and pattern as seen in 2015 (Figure 9.3.1). The observed pattern since 2014 could indicate a possible transition to biennial rotavirus epidemics in the Netherlands (Figure 9.3.2). A biennial pattern has also been reported in Belgium and the United States [2, 3]; countries with moderate to high rotavirus vaccine coverage rates. However, the origin of such a change in epidemic pattern in the Netherlands, in the absence of vaccination, is still unknown and a focus of research.
Close monitoring of future years is needed to see whether the pattern of the past four years will continue.

NIVEL GP consultations for all-cause gastroenteritis (GE) in children under the age of 5 years confirm the seasonal pattern observed by the rotavirus laboratory detections in 2016 (Figure 9.3.2) [4]. The mean weekly, all-cause GE consultation rate in the calendar year 2016 was 125 per 100,000 persons involving children under five (range 46-215 per 100,000 persons), as compared with 135/100,000 persons and 130/100,000 persons in 2015 and 2014, respectively. The estimated number of hospital admissions attributable to rotavirus in children under five was 1,778 in 2016, compared with 3,508 in 2015 and 1,613 in 2014 (see Appendix 1).

Further epidemiological analysis was done that compared rotavirus detections for the 2014, 2015 and 2016 rotavirus seasons with the average over the period 2010-2013 [5]. In both 2016 and 2014 a reduced rotavirus incidence was confirmed (IRR 0.41; 95%CI 0.29-0.56; p<0.001 and IRR 0.34; 95%-CI 0.25-0.47, respectively; p<0.001) compared with 2010-2013. In addition, an age-stratified analysis was performed on all-cause GE consultations rates in primary care during the months of the rotavirus epidemic among children under five years old. This analysis compared similar years, but excluded 2016, as primary care data were incomplete for that year. A statistically significant increase in rates of GE consultations was observed for two- and three-year-olds in 2015 (IRR 1.66; 95%CI 1.34-2.07 and IRR 1.52; 95%CI 1.21-1.90, respectively), compared with 2010-2013. The IRR in one- and four-year-olds in that same year remained unchanged. These observations could indicate a shift of rotavirus infections towards older age groups, following a year with low rotavirus activity (2014), due to an increased accumulation of older susceptible children who remained uninfected during the low activity year.

9.3.4 Pathogen

For the 2016 rotavirus season, the IDS/RIVM received 145 faeces samples tested for rotavirus from laboratories participating in the Working Group Clinical Virology. One hundred eighteen of these samples could be typed (Table 9.3.1). The most prevalent genotype in 2016 was G9P[8], which accounted for half of the typed strains (n=59, 50%) (Figure 9.3.3). The proportion of G1P[8] further decreased to less than 10% of the strains that were typed. G3P[8] increased to almost 20%. The dominant strain of last year (G4P[8]) dramatically decreased to less than 4%.

9.3.5 Research

The RotaFam study is a prospective household study on the transmission of rotavirus within households with young children. This study, conducted during the 2016 and 2017 rotavirus seasons, closely monitored enrolled households during 10 consecutive weeks for the occurrence of acute rotavirus gastroenteritis. The data have only partly been analysed, but show an epidemic pattern consistent with observations from virological surveillance. In both 2016 and 2017, around 300 randomly sampled households participated with equal follow-up duration. The number of rotavirus acute gastroenteritis cases detected in 2016 was 17, while the number in 2017 was 73.

9.3.6 Cost-effectiveness

Yamin et al. evaluated the cost-effectiveness of universal pentavalent rotavirus vaccination for France, taking indirect effects into account and considering a vaccine coverage of 75% [6]. The ICER for universal vaccination compared with no vaccination was €28,500 and €39,500 per QALY gained at the costs of €115 and €135 per vaccine course, respectively. The uncertainty analysis suggests that findings were sensitive to various assumptions, including the number of hospitalisations, outpatient visits and the extent of QALY losses per rotavirus episode.

In Australia, universal vaccination against rotavirus was included in the national immunisation programme in 2007. A retrospective economic evaluation of the Australian rotavirus programme was performed using national level post-implementation data on vaccine uptake, before and after measures of programme impact and published estimates of excess intussusception cases [7]. Relative to the baseline period (1997-2006), over the six years (2007-2012) after implementation of the rotavirus programme, 77,000 hospitalisations (17,000 coded rotavirus and 60,000 unspecified acute gastro-enteritis) and three deaths were prevented, compared with an estimated excess of 78 cases of intussusception. The programme was cost-saving when observed declines in both hospitalisations coded as rotavirus and as unspecified acute gastro-enteritis were attributed to the rotavirus vaccine programme. The authors concluded that the rotavirus vaccination programme was economically far more favourable than predicted by pre-implementation models. The main reason for the differences was the larger number of prevented hospitalisations found, compared with previous studies.

For the Netherlands, the cost-effectiveness analysis published in 2013 [8] has been updated based on more recent data on rotavirus disease burden in the Netherlands and on international evidence of herd-protection in cases of universal infant vaccination. The initial results have been recently communicated to the Dutch Health Council. In brief, the updated

analysis showed that the targeted rotavirus vaccination of infants with medical risk conditions is cost-saving under all tested scenarios. Universal rotavirus vaccination is cost-effective when vaccine costs per vaccinated child are less than €48 and cost-saving at costs of less than €16/vaccinated child.

9.3.7 International developments

A recent systematic review assessed the effectiveness of rotavirus vaccination based on data from studies from 2006 to 2016 [9]. They showed a median vaccine effectiveness (VE) of 84%, 75% and 57% in low, medium and high child mortality countries for Rotarix, respectively, and for RotaTeq a VE of 90% in low and 45% in high child mortality countries. It is known that the effectiveness and impact of the rotavirus vaccines is reduced in developing country settings, where the burden and mortality is highest. The reasons for these differences in VE are unknown, but malnutrition, concomitant infections, RV strain diversity and host factors have been proposed [10]. The differences in vaccine effectiveness indicate that there is a need for improvement for the current rotavirus vaccines [11]. The recent discovery that human histo-blood group antigens (HBGAs) might be involved in rotavirus attachment to intestinal cells may provide new insights into the rotavirus epidemiology, diversity and the performance of the current rotavirus vaccines. The HBGA phenotypes differ by ethnic populations and the fact that the presence or absence of specific rotavirus genotypes differ by geographical scale may provide insights into the efficacy of both vaccines [10, 12, 13].

Worldwide, 81 countries have introduced rotavirus vaccination in their national immunisation programmes [14]. Some countries have introduced rotavirus vaccines in phased or regional introductions. In the Netherlands, rotavirus vaccination is currently not included in the NIP. In September 2017, the Dutch Health Council has published a recommendation on rotavirus vaccination [15]. They recommend vaccinating high-risk group children (premature children, children with low birth weight or congenital pathology). In addition, they state that the Health Council is positive towards mass vaccination incorporated in the NIP, however, they mention that this will not be cost-effective seen the current vaccine prices. The RIVM has published a background document providing up-to-date information on rotavirus disease in the Netherlands to facilitate the Health Council in preparing their recommendation [1].

9.3.8 Literature

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* RIVM publication

9.4 Varicella zoster virus (VZV) infection

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

9.4.1 Key points

- The VZV epidemiology (incidence of GP consultations, hospitalisations and deaths) is comparable to previous years.
- For the prevention of herpes zoster (HZ), HZ/su (or Shingrix®) might be a promising alternative for Zostavax® due to the higher sustained vaccine efficacy. It is now being submitted for regulatory approval in the USA, Canada, Japan and Europe.

9.4.2 Tables and figures

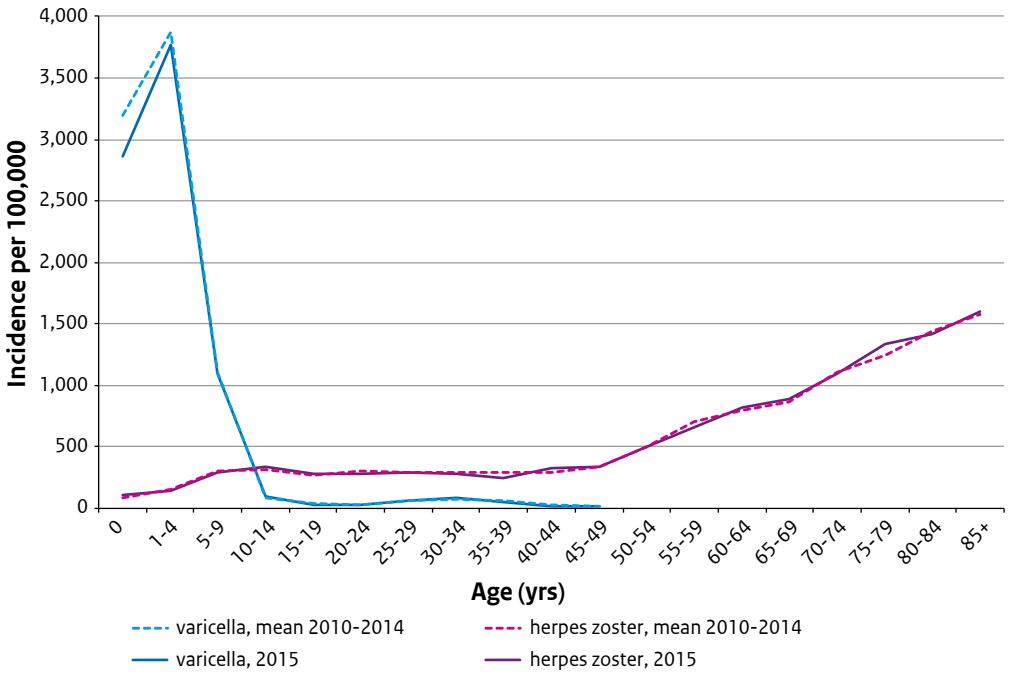

Figure 9.4.1 Estimated incidence per 100,000 of population of episodes of varicella (ICPC-code A72) and herpes zoster (ICPC-code S70) in 2015 versus mean 2010-2014 by age group [3]

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

Source: NIVEL

Table 9.4.1 Estimated incidence per 100,000 of population of episodes of varicella (ICPC-code A72) and herpes zoster (ICPC-code S70), based on NIVEL-PCD, using the old method (2005-2011) and the new method (2010-2015) (rounded off to closest ten)

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

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

** NIVEL-PCD, old method [2].

*** NIVEL-PCD, new method from 2012 onwards [3]; 2010-2012 recalculated.

Source: NIVEL

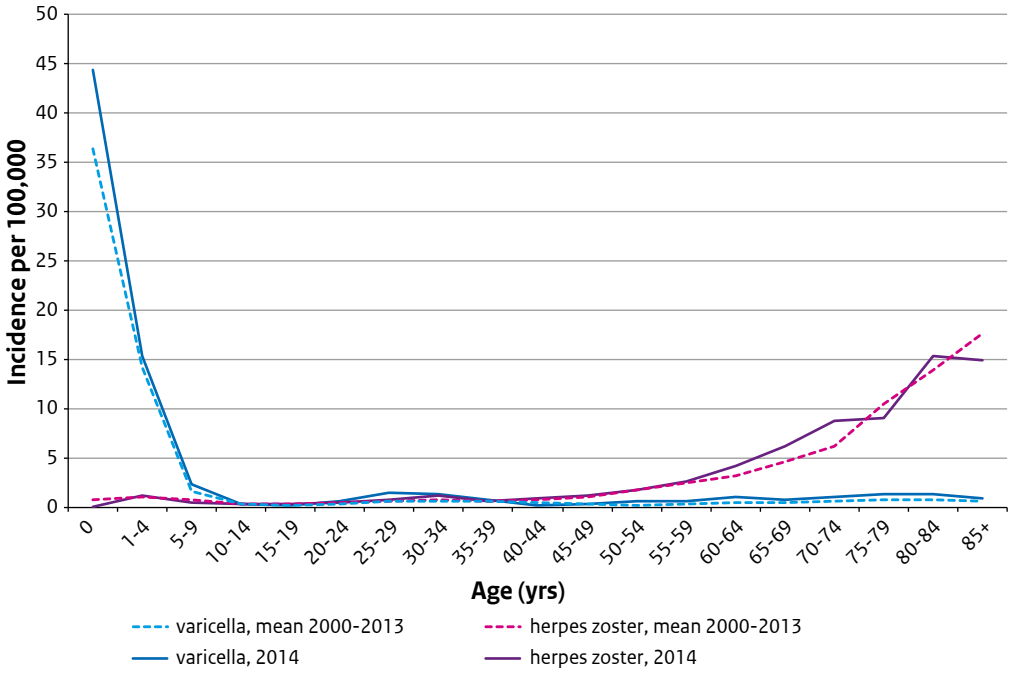

Figure 9.4.2 Incidence per 100,000 of population of hospitalisations due to main diagnosis of varicella (ICD-10 code B01) and herpes zoster (ICD-10 code B02) in 2014 versus mean incidence in 2000-2013 by age group [4]

Note: hospitalisation data since 2015 is not yet available.

Source: DHD

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

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

Notes:
1. In 2006/2007 a number of hospitals stopped their registration, causing an underestimation of hospital admissions from 2006 onwards (see Appendix 1).
2. Admissions for one day have been excluded.
3. 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.
4. Hospitalisation data since 2015 is not yet available.

Source: DHD

Table 9.4.3 Absolute number of deaths with main cause being varicella (ICD-10 code B01) and herpes zoster (ICD-10 code B02), 2005-2016 [5]

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

* Preliminary data

Source: CBS

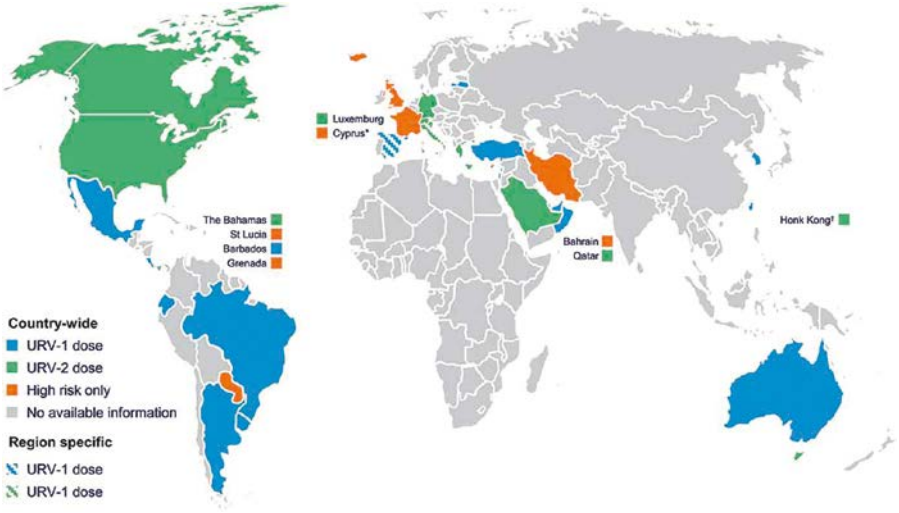

Figure 9.4.3 World map representing different national, universal routine vaccination (URV) schedules against varicella [6]

* In Cyprus, varicella vaccination is administered universally in the private sector.

† Varicella URV is recommended in Hong Kong, but not yet implemented

Source: Wutzler et al. [6]

9.4.3 Epidemiology

The VZV epidemiology is comparable to previous years (Table 9.4.1 and Table 9.4.3). Unfortunately, there is no update on hospitalisations for the years 2015-2016. The incidence of varicella episodes per 100,000 of population is highest in the age groups under five years, whereas the incidence of herpes zoster (HZ) episodes is highest in the age groups over 50 years (Figure 9.4.1). According to a new, more precise method for estimating morbidity rates used by NIVEL from 2012 onwards, the incidence of HZ is higher than it was according to the old method (Table 9.4.1) [3, 7]. The incidence of hospitalisations due to varicella is highest among new-borns, while the incidence of hospitalisations due to HZ is highest among the oldest age groups (Figure 9.4.2 and Table 9.4.2). Mahamud et al. found that national death certificate data tend to overestimate the number of deaths in which HZ is the underlying or contributing cause of death [8]. If we apply their rate of deaths for which HZ was validated as the underlying cause of death (0.25 (range 0.10-0.38) per 1 million population) to the Dutch population in 2016, we would expect 4.2 deaths (range 1.7-6.5) instead of the 27 deaths (preliminary data) that were reported in 2016 (Table 9.4.3).

9.4.4 Pathogen

Jensen et al. proposed a new SNP-based VZV genotyping scheme that can discriminate between all recognized VZV clades. The revised strategy provides redundancy in the number of confirmatory SNPs for each VZV clade, enhancing its robustness [9].
Kurapati et al. studied the mechanism by which VZV infects human neurons. They found that the c-Jun N-terminal kinase (JNK) pathway plays an important role in lytic infection and reactivation of VZV, and may provide an alternative target for antiviral therapy [10].

9.4.5 International developments

9.4.5.1 Varicella

Wutzler et al. reviewed the evidence for varicella vaccination and showed that, in December 2014, varicella vaccines were recommended in 33 countries (Figure 9.4.3) [6]. Riera-Montes et al. conducted a review to estimate the annual burden of varicella in Europe before the introduction of universal childhood immunisation: 5.5 million (95%CI 4.7-6.4) varicella cases resulting in 3-3.9 million primary care physician visits, 18,200-23,500 hospitalisations, and 80 deaths [11]. Leung et al. reviewed the occurrence of severe varicella in vaccinated persons (breakthrough varicella) and concluded that, although it can occur, it appears to be uncommon, especially in two-dose vaccinees [12]. A meta-analysis conducted by Marin et al., including 42 studies reporting original data on dose-specific varicella VE among immunocompetent children, showed that the pooled one-dose VE for varicella vaccines was 81% (95%CI 78-84%) against all varicella and 98% (95%CI 97-99%) against moderate/severe varicella. The pooled two-dose VE for monovalent varicella vaccines was 92% (95%CI 88-95%) against all varicella [13]. A German study not included in the above-mentioned review showed similar results with a one-dose VE of 81.9% (95%CI 81.4-82.5%) and a two-dose VE of 94.4% (95%CI: 94.2-94.6%) [14]. In Australia, with a single-dose varicella vaccine schedule, the varicella VE at preventing hospitalisation with a principal diagnosis of varicella among children aged 19 months to six years was 81.9% (95%CI 61.8-91.4%) [15].

Lopez et al. documented an 85% decline in varicella incidence from the two-year period 2005-2006 (end of one-dose programme) through 2013-2014, and a 97% decline since the varicella vaccination programme was implemented in the US. During 2013-2014, 55% of all reported varicella cases occurred in persons who had received the varicella vaccine [16]. In Quebec (Canada), a 70% reduction in the rate of varicella-associated invasive group A streptococcal infections was also found since the introduction of routine varicella vaccination in 2006 [17]. Streng et al. showed a 60% reduction in the incidence of varicella-associated neurologic complications in children during the first seven years after introduction of universal varicella vaccination in Germany [18]. Based on a transmission model using current vaccination rates of 87% (64%) with one (two) varicella dose(s), an 89% decrease in varicella cases for the year 2015 was estimated in Germany [19].

Before the introduction of varicella vaccination in Germany, the VZV seropositivity rate was 80.3% (95%CI 79.3-81.3%) in varicella-unvaccinated children and adolescents, which is lower than it was in the Netherlands [20, 21]. In Norway, the seroprevalence is also lower, revealing substantial susceptibility during the childbearing period (85.5% immune at 20 years of age and 90.5% at 30 years of age) [22]. Compared with other modelling studies of the natural history of VZV, Norwegian estimates indicate that varicella transmission in Norway is slower than it is in the Netherlands and Belgium, but faster than in Central and Southern European countries [23]. A recent seroprevalence study in Italy showed an increase of seropositivity in children aged one-four years, as a result of vaccine interventions already adopted in some regions [24]. Duncan et al. showed that US basic military trainees who received varicella vaccine in childhood were 24% less likely to be seropositive for VZV than trainees who were exempt from vaccine due to a history of varicella disease. The odds of a vaccinated trainee being seropositive for VZV decreased by 8% with each year elapsed since vaccination. Seroprevalence declined below estimated herd immunity thresholds in vaccinated trainees born after 1994 and in the cohort as a whole for trainees born after 1995 [25].

Wu et al. explored a novel monochimeric VLP combined vaccine for children to prevent both enterovirus 71 (EV71) and VZV. It could simultaneously neutralise VZV and EV71 and cross-neutralise coxsackievirus A16 and could be a promising candidate to prevent both hand, foot and mouth disease and varicella [26].

9.4.5.2 Herpes zoster

Hobbelen et al. estimated the hospital burden of VZV infection in England for the period 2004-2013. The average annual incidences of admissions due to varicella and HZ were 7.6 and 8.8 per 100,000 population, respectively. The authors conclude that most of the hospital burden due to VZV in England occurs in the immunocompetent population and is potentially vaccine-preventable [27]. In England, where HZ vaccination was introduced in 2013, vaccination coverage was estimated at 59.5% (95%CI 59.3-59.7%) [28]. In contrast, coverage has remained rather low in the US after recommendation since 2006: by 2013, vaccination coverage among adults aged ≥60 years was estimated at 19.5% [29] based on a claims database.

Based on the 2014 Behavioral Risk Factor Surveillance, the coverage was higher with 31.8% (95%CI 31.4-32.2%) but varied considerably by state from 17.8% (95%CI 15.8-20.0%) in Mississippi to 46.6% (95%CI 44.3-48.8%) in Vermont [30].

Izurieta et al. found a VE for Zostavax® of 33% (95%CI 32-35%) against community HZ, 57% (95%CI 52-61%) for postherpetic neuralgia (PHN) and 74% (95%CI 67-79%) for HZ hospitalisation for the first three years post-vaccination [31]. The VE declined over time with a VE of 19% (95%CI 17-22%) against community HZ, 45% (95%CI 36-53%) for PHN and 55% (95%CI: 39-67%) for hospitalisation for four+ years post-vaccination. Guzzetta et al. reviewed predictions of three modelling approaches regarding the effect of exogenous boosting: 1) progressive accumulation of immunity following repeated re-exposures, 2) partial protection that wanes over time, 3) full but temporary immunity against HZ. All models predict a qualitatively similar, but quantitatively heterogeneous, transient increase of HZ incidence [32]. A German transmission model predicted a temporary increase in HZ incidence of up to 20% for around 50 years (with limited effect of additional HZ vaccination), while HZ incidence is shown to decrease in the long term by 58% [19]. In British Columbia, Canada, HZ incidence increased from 3.2 per 1,000 population in 1997 to 4.5 in 2012, but no significant increase in HZ incidence was seen during the publically funded varicella vaccination programme compared with the non-publicly funded period [33].

Lelic et at. showed that Zostavax® induces VZV immunity in elderly nursing home residents (aged 80-102 years) that is similar to that produced in community-dwelling seniors (aged 60-75 years). However, the absolute levels of VZV responses before and after vaccination were lower in the nursing home cohort than they were among the community-dwelling seniors. Upon further examination of the elderly nursing home residents, they found that higher frequencies of regulatory T-cells and cytomegalovirus-specific CD4+ T cells correlated negatively with the magnitude of VZV-specific responses. This suggests that the accumulation of these cells with age might impact vaccine responsiveness [34]. In a pilot study conducted among grandparents re-exposed to varicella, Ogunjimi et al. found that VZV-specific antibody titres did not systematically show boosting after re-exposure. Furthermore, the antibody boosting occurred exclusively in cytomegalovirus-positive participants. Ogunjimi stated that the protective effect of re-exposure to varicella is likely limited, as boosting only occurred in 17-25% of the re-exposed grandparents and for less than one year [35]. Weiberg et al. studied the VZV-specific cellular immune response of HZ vaccination in young and older adults and concluded that high proportions of senescent and exhausted VZV-specific T cells in the older adults contributed to their poor effector responses (lower and slower) to a VZV challenge, which may underlie their inability to contain VZV reactivation and prevent the development of HZ [36].

A randomized, placebo-controlled, phase 3 trial (ZOE-70) conducted in 18 countries involving adults aged 70 years or older showed an efficacy of two doses of the HZ subunit vaccine (HZ/su, also known as Shingrix®) of 89.8% (95%CI 84.2-93.7%). In pooled analyses of data from participants aged 70 years or older in ZOE-50 and ZOE-70, vaccine efficacy against HZ was 91.3% (95%CI 86.8-94.5%) and against PHN 88.8% (95%CI 68.7-97.1%) [37]. Curran et al. compared the public health impact of Zostavax® (40% coverage) and HZ/su (first dose 40%,

second dose 70% coverage) in the German population. They estimated that over the remaining lifetime since vaccination, the vaccines would reduce the number of HZ cases by 1,745,179 (HZ/su) or 499,117 (Zostavax®), and the number of PHN cases by 309,795 (HZ/su) or 117,828 (Zostavax®), showing the superior public health impact of HZ/su due to the higher, sustained vaccine efficacy [38].

The results of this new HZ/su vaccine (not yet available for clinical use) are promising, although additional follow-up is required to assess the persistence of HZ/su-induced protection over a longer period. This subunit vaccine might also be suitable for immunocompromised people (in contrast to Zostavax®, which is a live-attenuated vaccine), but more research is needed in immunocompromised patients, especially phase III follow-up trials. The marketing authorisation application of HZ/su vaccine has been submitted in the USA, Canada, Europe (2016) and Japan (2017) [39]. HZ/su (or Shingrix®) is a candidate vaccine for the prevention of HZ and its complications in people aged 50 years or older. Regulatory approval is being sought for the vaccine to be given intramuscularly in two doses, with a two-to-six month interval between doses. The Dutch Healh Council advised in 2016 not to introduce routine vaccination against herpes zoster given the relatively low protection of the Zostavax® vaccine [40] She recommended to reconsider this advice when a new more effective vaccine has become available.

Different studies, systematic reviews and meta-analyses were conducted on HZ and the risk of stroke [41-47]. They all concluded that HZ is a risk factor for increasing the risk of (ischaemic) stroke, especially shortly after a HZ episode.

9.4.5.3 Cost-effectiveness

Several countries have assessed the cost-effectiveness of HZ vaccination for the elderly. In Switzerland, the cost-effectiveness of the HZ vaccine was re-evaluated, taking updated vaccine prices, a different age cohort, latest clinical data and burden of illness data into account. A Markov model was developed to simulate the lifetime consequences of vaccinating 15% of the Swiss population aged 65-79 years. Based on a vaccine price of CHF 162 (≈€97), the ICER was CHF 29,814 (≈€17,888) per QALY gained [48]. Also in Japan, an economic evaluation was performed to assess a vaccination programme for the elderly. The vaccination targeted different age groups: 65-84, 70-84, 75-84 and 80-84 years old. Vaccination costs were assumed at ¥10,000 (≈€80). ICERs ranged from ¥2,812,000 (≈€22,496) to ¥3,644,000 (≈€29,152) per QALY gained. A vaccination programme for persons 65-84 years old gave the most favourable results and seems to be cost-effective [49]. Vaccinating people aged between 60 and 79 years in Italy would result in an ICER of €11,943 per QALY gained [50]. In addition, Boccalini et al. estimated net costs for vaccinating cohorts of elderly at several ages over a five-year period. The net costs per vaccinated cohort (vaccination costs minus clinical savings) would be around €30 million per cohort, about €87 per vaccinated subject [51]. In France, starting vaccination in elderly individuals aged 65, 70 and 75 years old appears more cost-effective than vaccination for those aged 60, with a cost-effectiveness ratio between €30,000 and €35,000 per QALY gained. These results largely contributed to the recommendation to include the HZ vaccination in the French immunisation schedule. This recommendation was

endorsed by the Ministry of Health in 2015 and HZ vaccination has been included in the 2016 national immunisation schedule for all individuals aged 65 to 74, with a one-year catch-up for those aged 75-79 years [52].

In the US, a single dose of HZ vaccine in persons aged 60 or older is recommended, but the efficacy decreases to zero after approximately 10 years. In a cost-effectiveness analysis, the optimal vaccination schedule including a booster dose was evaluated. Vaccination at the age of 70 plus one booster was the most cost-effective strategy, with an ICER of $36,648 per QALY gained. Vaccination at the age of 60 plus two boosters was more effective, but had an unfavourable ICER of $153,734 per QALY gained [53].

9.4.6 Literature

9.4.6.1 References

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* RIVM publication

10
Vaccines under development for other potential future NIP target diseases

N.Y. Rots

10.1 Vaccines under development

An update of information with regard to vaccines under development against infectious diseases that have reached the clinical testing phase and that are relevant for the Netherlands is shown in the table below. Vaccine development takes 10-15 years. Only a small percentage (6%) of vaccines tested in phase I reach marketing authorization. On average, clinical development phase I takes one to two years, phase II takes two to three years and phase III four to six years. Relevant developments of combination vaccines are described in earlier chapters.
Compared with last year, several RSV vaccines reached the next clinical development phase. The trial conducted among the elderly using the RSV vaccine from Novavax failed, but the maternal trial is being continued. Results are expected in 2021. For several Ebola vaccine candidates, phase II trials have successfully been completed and phase III trials have begun. The first Zika vaccines are being tested in phase I trials.

10.2 Tables and figures

Pathogen	Vaccine	Status, clinical phase
Bacteria		
Chlamydia	Adjuvanted chlamydia vaccine CTH522 (SSI)	I
Clostridium difficile	Toxoid inactivated Recombinant toxoid VLA84, genetic fusion (Valneva)	III, FDA fast track (Sanofi Pasteur) II fast track (Pfizer) II completed
Helicobacter pylori	HP3 (Chiron/Novartis) Oral recombinant vaccine (China)	I, completed, limited protective immunity III
Lyme	Outer surface protein based vaccine (GSK) Subunit vaccine (Valneva)	Licensed but removed from market I
Shigella	• Live attenuated single-strain, • Inactivated trivalent whole-cell, • Chemical glycoconjugate • recombinant glycoconjugate (biconjugate) • conjugate outer membrane (GSK)	II I III III II

Pathogen	Vaccine	Status, clinical phase
Bacteria		
Staphylococcus aureus	Conjugate (SA4Ag, 4 antigen), fast track FDA (Pfizer) Protein	II Previous phase I-III with different single antigen vaccine candidates all failed, safety concerns and low efficacy I
Streptococcus group A & B	• Group A: N-terminal M protein-based multivalent vaccines (26-valent and 30-valent vaccines) Conserved M protein vaccines (the J8 vaccine and the StreptIn-Cor vaccine) • Group B: CPS-protein conjugate (mono and trivalent) (GSK) Protein	II I II maternal I
Tuberculosis (all forms all ages)	• Live attenuated vaccine BCG • 2, 3 or 4 antigen adjuvanted fusion protein (GSK/Areas, Areas) • Modified recombinant BCG • recombinant subunit (GSK, Sanofi) • Live attenuated (TBVI) • Lysate of NTM • killed whole-cell (booster) (Areas) • viral vector (Oxford)	On market but low efficacy II(b) II II II III I I
Moraxella catarrhalis, non-typeable *Haemophilus influenzae*	Recombinant, COPD reduction (GSK)	II

Pathogen	Vaccine	Status, clinical phase
Viruses		
Chikungunya	Live recombinant Measles Virus based Virus-like particle (NIAID)	II, Immunogenic and safe in adults
Cytomegalo (CMV)	Glycoprotein B DNA (Astellas/ Vical) eVLP transplant patients (Merck, Novartis, Helocyte)	I and III III III, I/II, II
Dengue	Live recombinant (tetravalent) (Butantan/NIAID) Live-attenuated (tetravalent) (Takeda) Inactivated (tetravalent)(Merck) Recombinant subunit (tetravalent) (GSK) Monovalent subunit DNA	III III I II Dengvaxia Sanofi registration approved for 9-45 years of age
Ebola	rVSV-ZEBOV 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 III ready to start III I III I
Epstein–Barr	Recombinant gp350 Glycoprotein subunit	II
Hepatitis C	Recombinant viral vector (GSK)	II
Hepatitis E	Recombinant protein	II, (Hecolin®, Xiamen China Approved in China not registered in EU)
Herpes simplex	HSV-2 replication defective (Sanofi)	I

Pathogen	Vaccine	Status, clinical phase
HIV	Recombinant protein (GSK) Viral vector Prime/boost (Sanofi) Ad26 Mos HIV vaccine (Janssen vaccines) DNA (GeoVax)	II II II II completed
Hookworm	iBio	I
Noro	Virus-like particles (bi-valent)	II
MERS-CoV	MVA-MERS-S DNA (GeneOne Life Scinence/ Inovio)	I
Parainfluenza type I	Live attenuated	I-II
Respiratory syncytial (RSV) (17 in clinical development)	Live attenuated (Sanofi) Inactivated whole-cell Nanoparticle based (Novavax) Particle BLP (Mucosis) Subunit, F-protein (GSK) Subunit, F-protien (NIH/NIAID/ VRC) Gene-based vector MVA (Bavarian Nordic) Gene-based vector AV (Janssen) Gene-based vector AV (Vaxart) Gene-based vector AV (GSK)	I (pediatric) 0 III (maternal data 2021), II (elderly, failed), I infants I (pediatric, elderly) II maternal I (maternal, elderly) II (elderly) I (elderly, pediatric) I (elderly) II (pediatric)
West Nile	Inactivated Live attenuated Recombinant subunit (Hawai Biotech)	I I completed
Zika	DNA (GeneOne Life Scinence/ Inovio) Inactivated (Sanofi)	I I

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

List of abbreviations

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

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

HPV2D	Study to monitor the immunogenicity of a two-dose schedule of HPV vaccination
hrHPV	high-risk human papillomavirus
HR	hazard ratio
HSV	herpes simplex virus
HZ	herpes zoster
IBD	invasive bacterial disease
ICD	International Classification of Diseases
ICER	incremental cost-effectiveness ratio
ICPC	International Classification of Primary Care
ICU	intensive care unit
IDS	Centre for Infectious Disease Research, Diagnostics and IDS Centre for Infectious Disease Research, Diagnostics and Screening
IDU	injecting drug use
IFN-γ	interferon γ
IgG	immunoglobulin G
ILI	influenza-like illness
IMD	invasive meningococcal disease
IMI	Innovative Medicines Initiative
IPD	invasive pneumococcal disease
IPV	inactivated polio vaccine
IR	incidence rate
IRR	incidence rate ratio
ITP	idiopathic thrombocytopenische purpura
IU/ml	international units per milliliter
JCVI	Joint Committee on Vaccination and Immunisation
JIM	Juveniele Immunisatie Meningokokken ACWY
JNK	c-Jun N-terminal kinase
LBZ	National Register Hospital care
LINH	the Netherlands Information Network of General Practice
LMR	National Medical Registration
lrHPV	low-risk human papillomavirus
LVC	low vaccination coverage
LYs	life years
LYS	life years saved
MATS	the meningococcal antigen typing system
MCC	meningococcal C conjugate
MCPI	maximum cost-effective price increase
MCV	measles-containing vaccine
ME	myalgic encephalomyelitis
MenACWY-D	quadrivalent meningococcal diphtheria toxoid conjugate vaccine
MenACWY-TT	tetravalent meningococcal tetanus toxoid conjugate vaccine
MenB	Meningococcal serogroup B
MenC	Meningococcal serogroup C
MenC-PS	Meningococcal serogroup C polysaccharide vaccine
MenC-TT	Meningococcal serogroup C polysaccharide-tetanus toxoid

MenW	Meningococcal serogroup W
MenX	Meningococcal serogroup X
MenY	Meningococcal serogroup Y
MERS-CoV	Middle East Respiratory Syndrome-coronavirus
MF	multiplication factor
MIA	multiplexed immuno assays based on Luminex technology
MLST	Multilocus sequence typing
MLVA	multiple locus variable number of tandem repeat analysis
MMR	combination of measles, mumps and rubella vaccines
MMRV	combination of measles, mumps, rubella and Varicella vaccines
MS	multiple scleroses
MST	minimum spanning tree
MSM	men who have sex with men
MuV	mumps virus
NIAID	National Institute of Allergy and Infectious Diseases
NIP	national immunisation programme
NIVEL	Netherlands Institute for Health Services Research
NIVEL-PCD	NIVEL Primary Care Database
NK	Natural killer
NKR	the Netherlands Cancer Registry
NPG	National Influenza Prevention Programme
NPL	National Polio Laboratory
NRBM	Netherlands Reference laboratory for Bacterial Meningitis
NTHi	nontypeable *Haemophilus influenzae* strains
NTM	neurotrimin
NVI	Netherlands Vaccine Institute
OPV	oral polio vaccine
OR	odds ratio
PASSYON	Papillomavirus Surveillance among STI clinic Youngsters
PCR	polymerase chain reaction
PCV	pneumococcal conjugate vaccine
PCV1	porcine circovirus type 1
PCV7	heptavalent pneumococcal conjugate vaccine
PCV10	10-valent pneumococcal conjugate vaccine
PCV10-7	additional types in PCV10 compared to PCV7
PCV13	13-valent pneumococcal conjugate vaccine
PCV13-10	additional types in PCV13 compared to PCV10
PEF	poliovirus essential facility
PEP	post-exposure prophylaxis
PHiD-CV	10-valent pneumococcal nontypeable Haemophilus influenza protein D conjugate vaccine
PIENTER	assessing immunisation effect to evaluate the NIP
POTS	postural orthostatic tachycardia syndrome
PPV	proportion of population vaccinated
PPV23	23-valent pneumococcal polysaccharide vaccine
PPV23-PCV13	additional types in PCV13 compared to PPV23

PPSV23	23-valent pneumococcal polysaccharide vaccine
Prn	pertactin
PRP	polyribosyl-ribitol-phosphate
Ptx	pertussis toxin
PWP-TT	Prentice Williams and Peterson total time
QALY	quality-adjusted life year
qPCR	real-time polymerase chain reaction
RIVM	National Institute for Public Health and the Environment, the Netherlands
RNA	ribonucleic acid
RR	relative risk
rSBA	rabbit serum bactericidal activity
RSV	respiratory syncytial virus
RT-PCR	reverse transcription polymerase chain reaction
RV	rotavirus
SARIMA	seasonal autoregressive integrated moving average
SBA	serum bactericidal antibody
SLE	systemic lupus erythematosus
SLSJ	the Saguenay-Lac-Saint-Jean region in Quebec, Canada
SNP	single nucleotide polymorphism
SpIDnet	The Streptococcus pneumoniae Invasive Disease network
SPR	RIVM strategic programme
STI	sexually transmitted infections
Tdap	tetanus, diphtheria and pertussis vaccine
TIG	tetanus immunoglobulins
TIM	second immunisation Meningococcal serogroup C study
TM	transverse myelitis
tOPV	trivalent oral polio vaccine
TT	tetanus toxoid
UA	under-ascertainment
UE	underestimation
UK	United Kingdom
UR	under-reporting
US	United States
VDPV	vaccine-derived poliovirus
VE	vaccine effectiveness
VLP	virus-like particle
VPD	vaccine-preventable disease
VZV	varicella zoster virus
VWS	Ministry of Health, Welfare and Sport
WGS	whole genome sequencing
WHO	World Health Organization
wP	whole-cell pertussis
WPV	wild poliovirus
WTP	willingness-to-pay
YLD	years lived with disability
YLL	years of life lost

Appendix

Appendix 1 Surveillance methodology

Disease surveillance

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

Mortality data

Statistics Netherlands (CBS) registers mortality data from death certificates on a statutory basis. The registration specifies whether it concerns a natural death, a non-natural death or a stillborn child. In the event of 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 been using the IRIS programme to automatically code the causes of death [1]. One of the advantages of this is that it increases the international comparability of the figures. The change in coding did however cause (once only) considerable shifts in the statistics.

Morbidity data

Notifications

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) [2]. 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 laboratory-confirmed diagnosis. Diseases in categories B1, B2 and C must be reported within 24 hours or one working day after laboratory confirmation. However, for several diseases there is under-reporting and a delay in reporting [3]. In each of the last three categories, different intervention measures can be enforced to prevent the spread of the disease.

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

Disease	Category	Periods of notification by legislation
Diphtheria	B1	from 1872 onwards
Pertussis	B2	from 1975 onwards
Tetanus	C	1950-1999, 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 diseasea	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

Hospital admissions

Until 2010, hospital data was managed by the research institute Prismant in the National Medical Register (LMR); since 2011, Dutch Hospital Data (DHD) has managed the LMR. Since 2013, the National Register Hospital Care (LBZ), managed by DHD, has received the discharge diagnoses of all patients admitted to hospital. Outpatient diagnoses are not registered. Diseases, including all NIP-targeted diseases, are coded as the main or subsidiary diagnosis according to the ICD-10 coding system. Up to 2012, discharge diagnoses were coded according to the ICD-9 coding system, thereafter according to ICD-10. The coverage of this registration was about 99% until mid-2005. Thereafter, coverage 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. 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 since 2015 is not yet available.

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

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

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

Data 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 [6]. Thus, for poliomyelitis and tetanus, notifications are a more reliable source of surveillance.
Also, for invasive *Haemophilus influenzae* disease and invasive pneumococcal disease (IPD), data on mortality and hospital admissions based on registration databases are not reliable. 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. Laboratory data from the Netherlands Reference Laboratory for Bacterial Meningitis (see below) are more reliable for these diseases. Data on mortality of IPD are collected every two to four years by means of a chart review study.

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 indirectly estimated according to a method proposed by Harris et al. [7]. By using this method, the proportion of hospitalisations for gastroenteritis attributable to RV is estimated by comparing the weekly RV laboratory detections (surveillance virological laboratories) to 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 was the scaling factor times the number of positive laboratory detections per week. For this report, the constant and scaling factor were estimated by fitting the model on hospitalisation data and weekly laboratory detections (laboratory surveillance) for the five previous years. The scaling factor estimated by this model was used to estimate the RV-attributed hospital admissions for the most recent year by multiplying it with the RV-positive laboratory detections of that year. Because hospitalisation data is available till 2015, the estimates for 2015 and 2016 are based on the five previous years (2010-2014).

Laboratory data

Laboratory diagnostics are very important in monitoring infectious diseases and the effectiveness of vaccination; about 75% of all infectious diseases can be diagnosed only by laboratory tests [8]. However, limited information on patients is registered and, in many cases, laboratory confirmation is not sought for self-limiting VPDs. The different laboratory surveillance systems for diseases targeted by the NIP are the Netherlands Reference Laboratory for Bacterial Meningitis (NRBM) and the virological laboratories, which are part of the Dutch working Group for Clinical Virology.

Netherlands Reference Laboratory Bacterial Meningitis (NRBM)

The NRBM is a collaboration between the National Institute for Public Health and the Environment (RIVM) and the Academic Medical Centre of Amsterdam (AMC). On a voluntary basis, microbiological laboratories throughout the Netherlands send isolates from the blood and cerebrospinal fluid (CSF) of patients with invasive bacterial disease (IBD) to the NRBM for further typing. For CSF isolates, the coverage is almost complete.

Furthermore, nine sentinel laboratories throughout the country are asked to send isolates from all their patients with invasive pneumococcal disease (IPD). Based on the number of CSF isolates, their overall coverage is around 25%. Positive results of pneumococcal, meningococcal and *Haemophilus influenzae* diagnostics and typing are relevant to NIP surveillance.

Virological laboratories

Each week, virological laboratories, which are part of the Dutch Working Group for Clinical Virology, send positive results of virological diagnostics to the RIVM. Approximately 22 laboratories send information regularly. Aggregated results are shown on the RIVM website. It is important to bear in mind that the presence of a virus does not automatically imply the presence of disease. Since 1 December 2014, information on the total number of tests done can be reported each week or each year.

NIVEL Primary Care Database

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

In 2012, there was a fourfold increase in the number of general practices that were 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: there were changes in the definitions of episodes and in calculations of incidence, which caused an increase in the 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 [9]. Because of these changes, we decided to report previously published incidence rates until 2011 based on the old method [10] and incidence rates from 2012 onwards using the new method [11]. Due to the new estimation method, the data for 2012 (based on 219 practices) and onwards is not comparable with that for previous years.

Burden of disease

The composite health measure, the disability-adjusted life year (DALY), has been developed to compare the impact of diseases. The idea behind this approach is that the impact of a particular disease can be divided 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 [12, 13].

Vaccine effectiveness

After the implementation of a vaccination in the NIP, vaccine effectiveness (VE) can be routinely estimated using the 'screening method' with the following equation:
VE (%) = 1- [PCV / (1-PCV) * (1-PPV/PPV], in which PCV = proportion of cases vaccinated, PPV = proportion of population vaccinated, and VE = vaccine effectiveness.
In addition, several study designs, including case-control and cohort studies, can be used to assess VE after implementation [14]. A specific type of case-control design used to estimate VE

is the indirect cohort design or Broome method [15]. 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 checks for biases in ascertainment between cases and controls, as both cases and controls are actually diseased. An assumption made for this design is that vaccinated people are at the same risk of non-vaccine-type infection as unvaccinated people. This means that the VE is underestimated in the case of cross-protection of the vaccine against non-vaccine-type disease. Conversely, if a replacement disease occurs only in vaccinated people, the VE is overestimated.

To evaluate the vaccine effectiveness against persistent HPV infections through the use of cohort studies, multiple statistical approaches are available. These approaches differ with respect to underlying assumptions [16]. 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 the most valid one 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 [17]. We estimated the VE as one minus the hazard ratio times 100%. When the VE is estimated against a combined endpoint of multiple HPV types, then instead of the total number of infections, rather being infected with one of these types at that time point is used as outcome.

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 insight into transmission dynamics.

Immunosurveillance

Monitoring the seroprevalence of all NIP-targeted diseases is a way to gather age- and sex-specific information on immunity to these diseases acquired through natural infection or vaccination. Towards this end, a random selection of people from the general population of the Netherlands is periodically asked to donate a blood sample and to fill in a questionnaire (PIENTER survey). This survey was performed in 1995 1996 (Nblood=10,128) [18] and in 2006-2007 (Nblood=7,904) [19]. People living in regions with low vaccine coverage and non-Western migrants are oversampled in order to gain greater insight into differences in immunity among specific groups. In February 2016, the third population-based cross-sectional seroepidemiological study started. This survey will continue until the end of 2017.

Vaccination coverage

Vaccination coverage data can be used to gain insight into the effectiveness of the NIP. Furthermore, this information can identify groups with low vaccine coverage who are at increased risk of contracting one of the NIP-targeted diseases. In the Netherlands, all vaccinations administered within the framework of the NIP are registered in a central electronic (web-based) database at the individual level (Præventis) [20].

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 [21].
As from 1 January 2011, this enhanced spontaneous reporting system of AEFI was taken over by the Netherlands Pharmacovigilance Centre (Lareb). Detailed information is available at *www.lareb.nl*. In view of this transition, comparisons between the period before 2011 and the period running from 2011 onward should be made with caution. Furthermore, in 2011 Lareb started a campaign among parents of vaccinated children to promote the reporting of AEFIs. In addition, the Centre for Infectious Disease Control (CIb) of the RIVM conducts systematic studies to monitor the safety of the NIP, e.g. questionnaire surveys and linkage studies between different databases.

Cost-effectiveness

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

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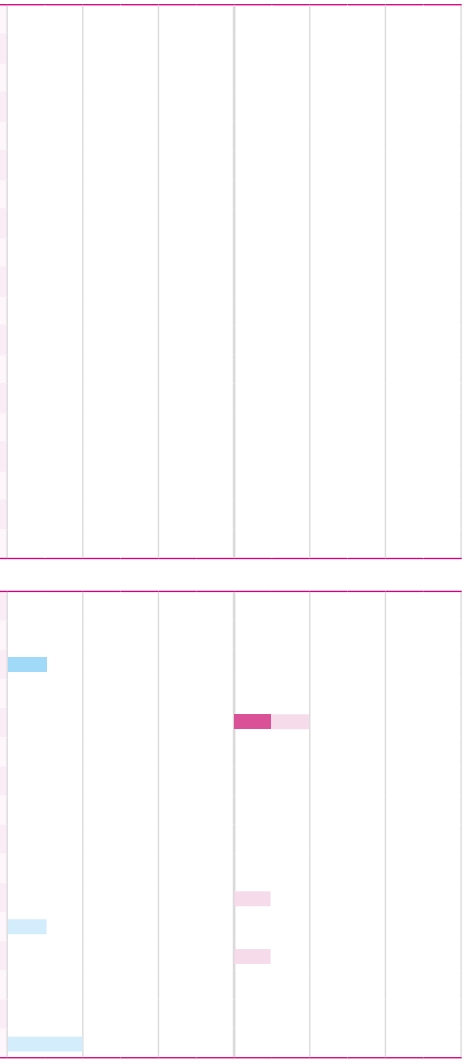
* RIVM publication

Appendix 2 Morbidity and mortality figures

Diseases included in the current NIP

Diphtheria								ICD10: A36
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (source: CBS)								
1998	0	0	0	0	0	0	**0**	
1999	0	0	0	0	0	0	**0**	
2000	0	0	0	0	0	0	**0**	
2001	0	0	0	0	0	0	**0**	
2002	0	0	0	0	0	0	**0**	
2003	0	0	0	0	0	0	**0**	
2004	0	0	0	0	0	0	**0**	
2005	0	0	0	0	0	0	**0**	
2006	0	0	0	0	0	0	**0**	
2007	0	0	0	0	0	0	**0**	
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	0	0	**0**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	0	**0**	
2015	0	0	0	0	0	0	**0**	
2016*	0	0	0	0	0	0	**0**	
*Hospitalisations** (source: Prismant/DHD)*								
1999	0	0	0	0	0	0	**0**	
2000	0	0	0	0	0	0	**0**	
2001	0	0	0	1	0	0	**1**	
2002	0	0	0	0	0	0	**0**	
2003	0	1	0	0	0	1	**2**	
2004	0	0	0	0	0	0	**0**	
2005	0	0	0	0	0	0	**0**	
2006	0	0	0	0	0	0	**0**	
2007	0	0	0	0	0	0	**0**	
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	1	**1**	
2010	0	0	0	0	0	1	**1**	
2011	0	0	0	0	0	1	**1**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	2	**2**	



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

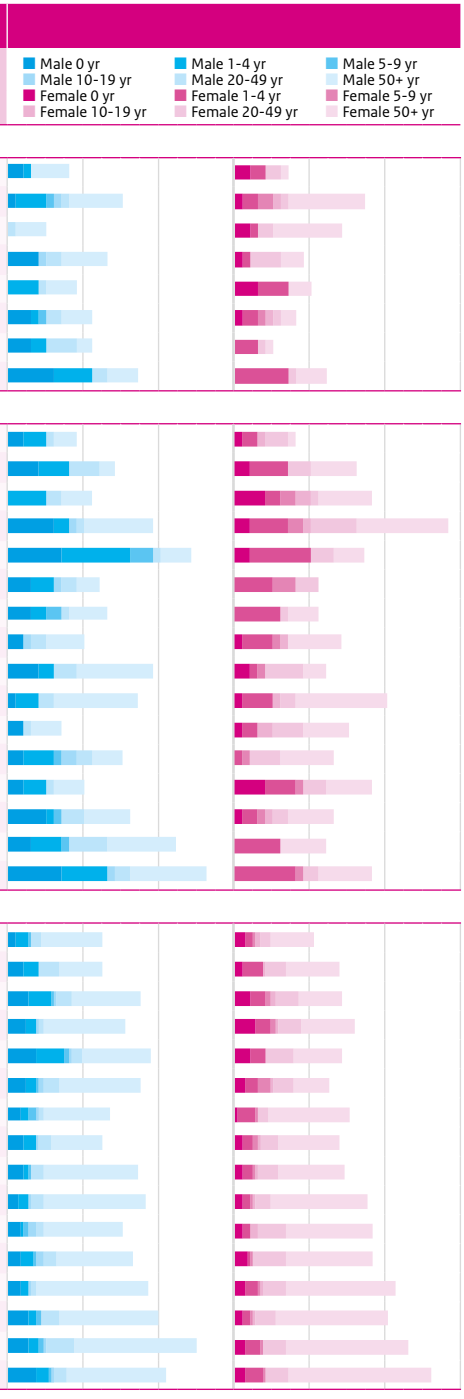
** Up to 2012, diseases are coded according to the ICD-9 coding system. From 2013 onward, diseases are coded according to the ICD-10 coding system. Hospitalisation data since 2015 are not yet available.

Diphtheria								ICD9: 032 ICD10: A36
Year	Age (years)						Total	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+		
Notifications (source: Osiris)								
1997	0	0	0	0	1	0	**1**	
1998	0	0	0	0	0	0	**0**	
1999	0	0	0	0	1	0	**1**	
2000	0	0	0	0	0	0	**0**	
2001	0	0	0	0	0	0	**0**	
2002	0	0	0	0	0	0	**0**	
2003	0	0	0	0	0	0	**0**	
2004	0	0	0	0	0	0	**0**	
2005	0	0	0	0	0	0	**0**	
2006	0	0	0	0	0	0	**0**	
2007	0	0	0	0	0	0	**0**	
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	0	1	**1**	
2012	0	0	0	0	0	1	**1**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	1	0	**1**	
2015	0	0	0	0	3	1	**4**	
2016	0	0	0	0	1	2	**3**	
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**	

* Number of diphtheria isolates.

Haemophilus influenzae

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Notifications (serotype b; source: Osiris)*							
2009	4	3	0	0	2	6	**15**
2010	2	6	3	2	2	17	**32**
2011	2	1	0	0	3	13	**19**
2012	5	1	0	1	6	9	**22**
2013	2	9	0	0	1	7	**19**
2014	4	3	2	1	3	6	**19**
2015	3	5	0	0	5	3	**16**
2016	6	12	0	0	3	8	**29**
Laboratory diagnoses (serotype b; source: NRBM)							
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**
Laboratory diagnoses (all serotypes; source: NRBM)							
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**



* Notifiable since 2009.

Hepatitis B								ICD9: 070.2-3 ICD10: B16, B17.0, B18.0, B18.1
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 (B16: Acute; source: CBS)								
1997	0	0	0	0	0	2	**2**	
1998	0	0	0	0	0	1	**1**	
1999	0	0	0	0	1	1	**2**	
2000	0	0	0	0	0	1	**1**	
2001	0	0	0	0	0	4	**4**	
2002	0	0	0	0	0	4	**4**	
2003	0	0	0	0	0	3	**3**	
2004	0	0	0	0	1	0	**1**	
2005	0	0	0	0	1	4	**5**	
2006	0	0	0	0	1	3	**4**	
2007	0	0	0	0	1	0	**1**	
2008	0	0	0	0	1	1	**2**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	0	3	**3**	
2011	0	0	0	0	0	2	**2**	
2012	0	0	0	0	0	2	**2**	
2013	0	0	0	0	1	3	**4**	
2014	0	0	0	0	1	3	**4**	
2015	0	0	0	0	1	2	**3**	
2016*	0	0	0	0	0	1	**1**	
*Hospitalisations** (source: Prismant/DHD)*								
1999	0	0	2	8	56	29	**95**	
2000	1	2	2	8	80	32	**127**	
2001	0	7	1	5	61	26	**104**	
2002	1	0	1	6	57	34	**102**	
2003	0	2	0	8	71	25	**106**	
2004	2	4	0	6	56	21	**92**	
2005	0	0	0	4	56	28	**89**	
2006	0	0	0	5	48	38	**92**	
2007	0	1	0	3	49	27	**81**	
2008	0	1	0	4	37	21	**63**	
2009	0	1	2	4	36	31	**74**	
2010	0	0	0	4	42	19	**66**	
2011	0	0	1	6	30	26	**63**	
2012	0	1	1	2	37	34	**76**	
2013	0	0	0	0	18	30	**48**	
2014	0	1	1	4	32	27	**66**	

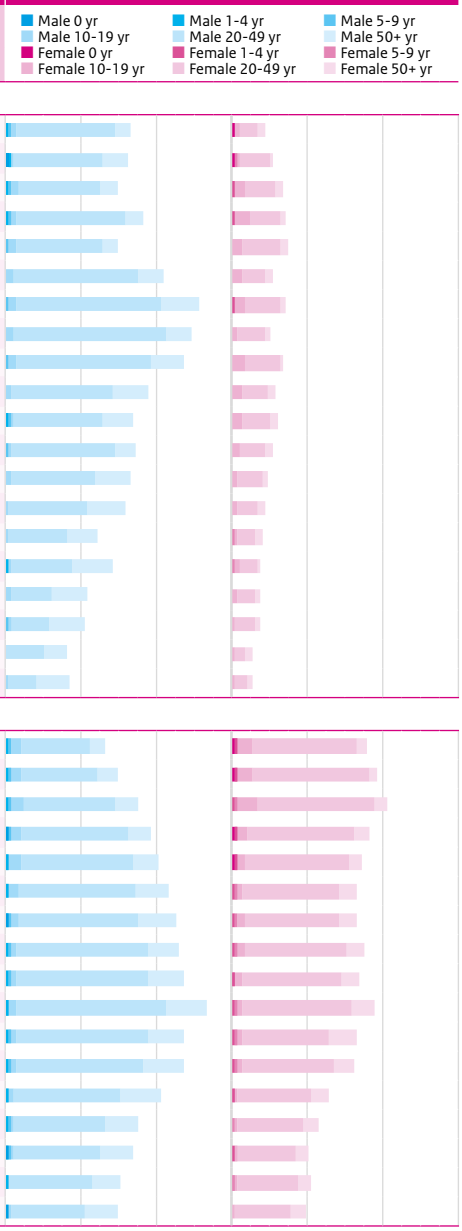
* Preliminary figures. From the statistical year 2013, the coding of the causes of death is partly automatic.

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

** For 18 patients, the age is unknown.

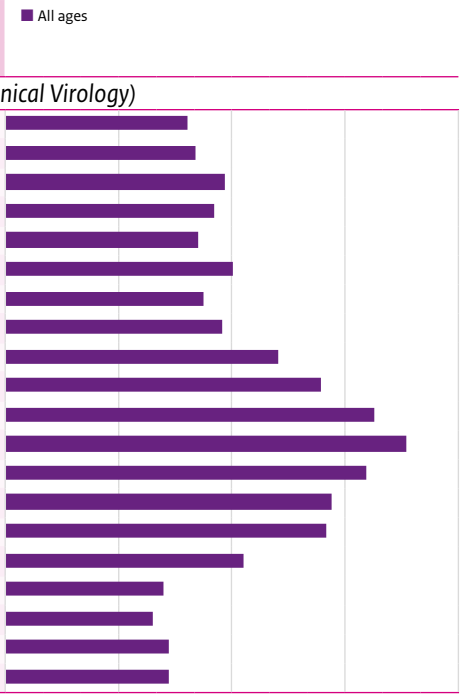
Hepatitis B

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Notifications (Acute; source: Osiris)							
1997	1	1	3	15	158	28	**206**
1998	3	1	5	10	157	37	**213**
1999	0	4	1	26	148	35	**214**
2000	0	3	1	31	186	26	**247**
2001	0	0	2	23	163	33	**221**
2002	0	0	0	22	193	44	**259**
2003	0	1	3	22	240	56	**322**
2004	0	1	0	15	240	40	**296***
2005	0	0	2	26	227	46	**301**
2006	0	0	0	20	166	56	**242**
2007	0	1	1	20	154	50	**226**
2008	0	0	1	13	170	41	**225**
2009	0	0	0	11	144	56	**211**
2010	0	0	0	10	129	60	**199**
2011	0	0	1	7	98	53	**159**
2012	0	1	2	9	108	54	**174**
2013	0	0	0	12	77	56	**145**
2014	0	0	1	3	81	56	**141**
2015	0	0	0	1	64	40	**105**
2016	0	0	0	5	54	51	**110**
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**



Hepatitis B

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Laboratory diagnoses (source: Dutch Working Group for Clinical Virology)							
1997							**787**
1998							**819**
1999							**950**
2000							**904**
2001							**827**
2002							**974**
2003							**849**
2004							**932**
2005							**1,174**
2006							**1,361**
2007							**1,588**
2008							**1,725**
2009							**1,553**
2010							**1,403**
2011							**1,377**
2012							**1,024**
2013							**677**
2014							**632**
2015							**708**
2016							**708**

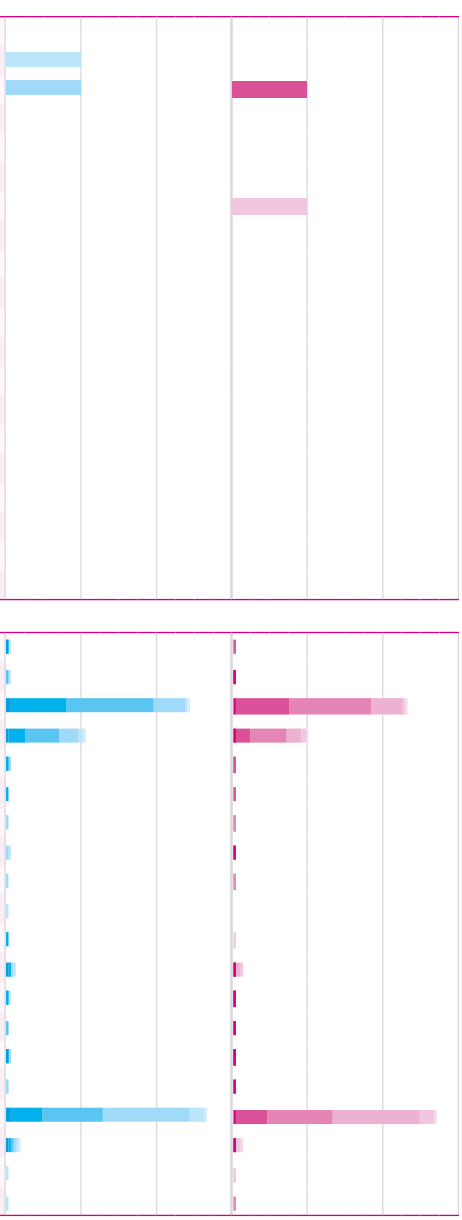


Human papillomavirus								ICD10: C53
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (cervical cancer; source: CBS)								
1997	0	0	0	0	58	176	**234**	
1998	0	0	0	1	56	219	**276**	
1999	0	0	0	0	64	189	**253**	
2000	0	0	0	0	73	185	**258**	
2001	0	0	0	0	66	177	**243**	
2002	0	0	0	0	45	142	**187**	
2003	0	0	0	0	47	167	**214**	
2004	0	0	0	0	49	154	**203**	
2005	0	0	0	0	52	183	**235**	
2006	0	0	0	0	44	170	**214**	
2007	0	0	0	0	57	147	**204**	
2008	0	0	0	0	51	193	**244**	
2009	0	0	0	0	40	169	**209**	
2010	0	0	0	0	43	162	**205**	
2011	0	0	0	0	46	143	**189**	
2012	0	0	0	0	42	173	**215**	
2013	0	0	0	0	47	176	**223**	
2014	0	0	0	0	50	148	**198**	
2015	0	0	0	0	49	158	**207**	
2016*	0	0	0	0	50	179	**229**	
Registrations (cervical cancer; source: NKR)								
1997	0	0	0	1	395	335	**731**	
1998	0	0	0	0	396	351	**747**	
1999	0	0	0	1	403	299	**703**	
2000	0	0	0	0	344	337	**681**	
2001	0	0	0	0	332	271	**603**	
2002	0	0	0	0	333	315	**648**	
2003	0	0	0	0	319	292	**611**	
2004	0	0	0	1	372	328	**701**	
2005	0	0	0	0	359	320	**679**	
2006	0	0	0	0	368	319	**687**	
2007	0	0	0	0	410	328	**738**	
2008	0	0	0	0	376	326	**702**	
2009	0	0	0	0	383	340	**723**	
2010	0	0	0	0	397	339	**736**	
2011	0	0	0	0	390	356	**746**	
2012	0	0	0	1	403	329	**733**	
2013	0	0	0	0	376	283	**659**	
2014	0	0	0	0	413	320	**733**	
2015	0	0	0	0	388	320	**708**	
2016**	0	0	0	0	466	381	**847**	

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

** Preliminary figures.

Measles								ICD10: B05
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (source: CBS)								
1997	0	0	0	0	0	0	**0**	
1998	0	0	0	0	1	0	**1**	
1999	0	1	0	1	0	0	**2**	
2000	0	0	0	0	0	0	**0**	
2001	0	0	0	0	0	0	**0**	
2002	0	0	0	0	0	0	**0**	
2003	0	0	0	0	1	0	**1**	
2004	0	0	0	0	0	0	**0**	
2005	0	0	0	0	0	0	**0**	
2006	0	0	0	0	0	0	**0**	
2007	0	0	0	0	0	0	**0**	
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	0	0	**0**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	0	**0**	
2015	0	0	0	0	0	0	**0**	
2016*	0	0	0	0	0	0	**0**	
Notifications (source: Osiris)								
1997	1	9	0	0	11	0	**21**	
1998	1	1	2	2	3	0	**9**	
1999	41	738	1,112	427	44	2	**2,364**	
2000	19	225	469	237	64	3	**1,017**	
2001	0	3	4	3	7	0	**17**	
2002	0	2	0	1	0	0	**3**	
2003	0	0	1	2	1	0	**4**	
2004	1	1	0	3	6	0	**11**	
2005	0	0	1	1	1	0	**3**	
2006	0	0	0	0	1	0	**1**	
2007	0	1	0	0	8	0	**9**	
2008	4	8	38	39	21	0	**110**	
2009	1	2	2	3	7	0	**15**	
2010	1	2	2	1	9	0	**15**	
2011	2	2	7	14	26	0	**51**	
2012	1	2	0	1	6	0	**10**	
2013	53	425	840	1,162	199	9	**2,688**	
2014	18	25	6	17	65	1	**134**	
2015	0	0	0	0	6	1	**7**	
2016	0	0	2	0	4	0	**6**	

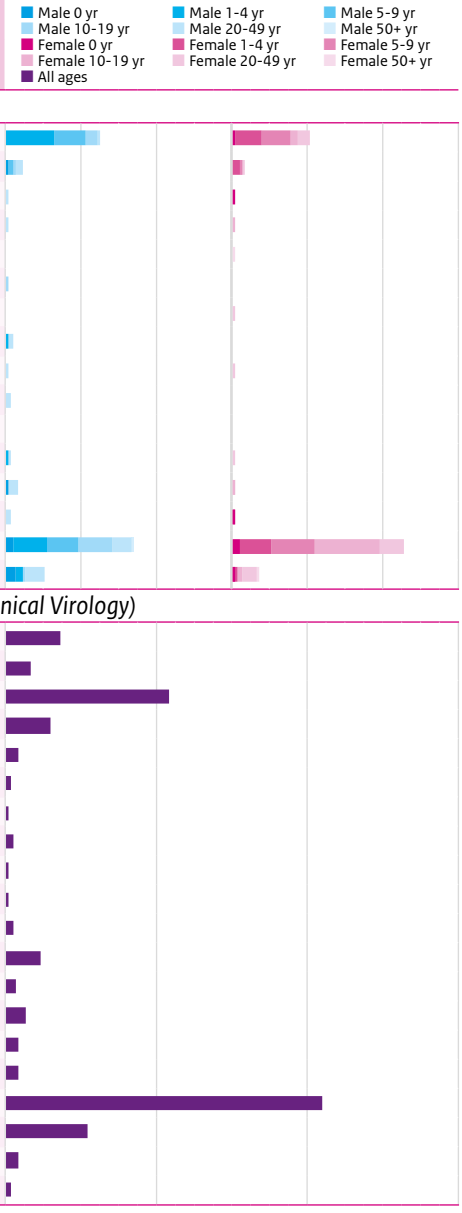


* Preliminary figures. From the statistical year 2013, the coding of the causes of death is partly automatic.

Measles

ICD9: 055
ICD10: B05

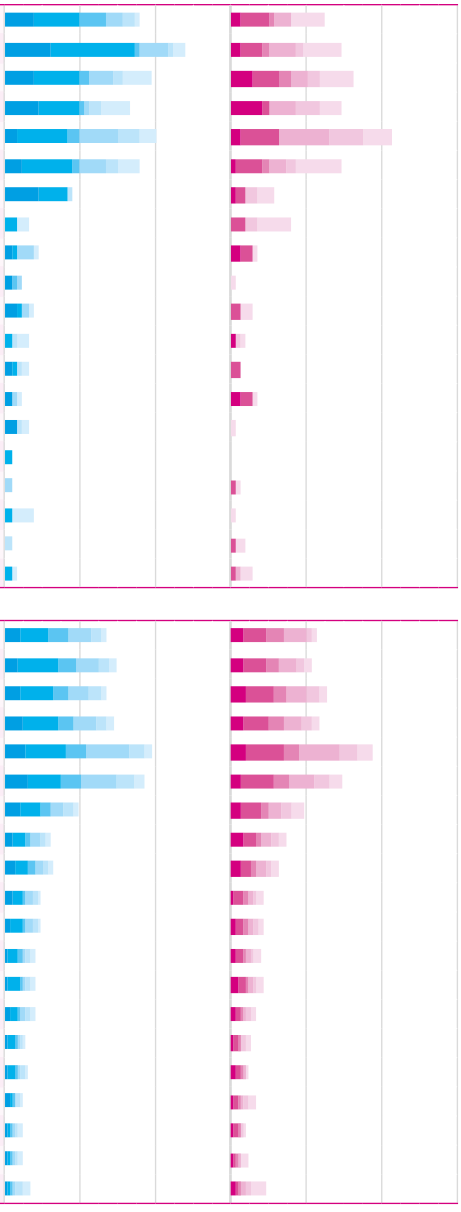
Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Hospitalisations (source: Prisman/DHD)*							
1999	2	39	33	9	8	0	**91**
2000	1	4	3	1	6	0	**15**
2001	1	0	0	0	2	0	**3**
2002	0	0	0	1	1	0	**2**
2003	0	0	0	0	0	1	**1**
2004	0	0	0	1	0	0	**1**
2005	0	0	0	0	1	0	**1**
2006	0	1	0	0	2	0	**3**
2007	0	0	0	0	2	0	**2**
2008	0	0	0	0	2	0	**2**
2009	0	0	0	0	0	0	**0**
2010	0	1	0	0	3	0	**4**
2011	1	0	0	1	6	0	**9**
2012	1	1	0	0	2	0	**4**
2013	8	34	41	52	23	1	**164**
2014	6	6	0	4	18	1	**35**
Laboratory diagnoses (source: Dutch Working Group for Clinical Virology)							
1997							**36**
1998							**17**
1999							**110**
2000							**30**
2001							**8**
2002							**4**
2003							**1**
2004							**5**
2005							**2**
2006							**1**
2007							**5**
2008							**24**
2009							**7**
2010							**13**
2011							**8**
2012							**9**
2013							**212**
2014							**55**
2015							**8**
2016							**4**



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

* For six patients, the age is unknown.

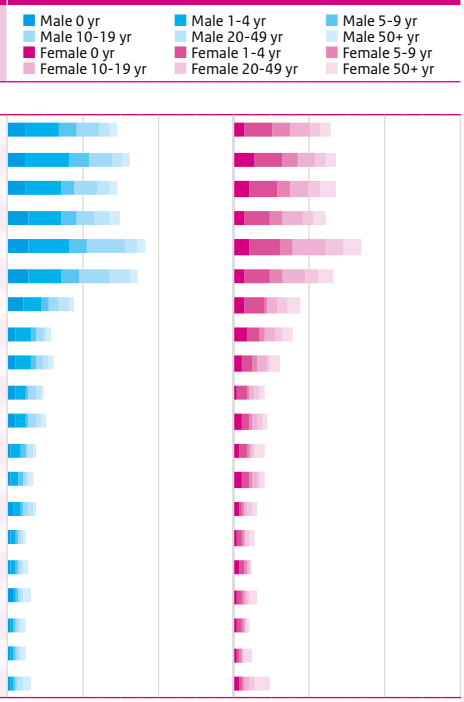
Meningococcal disease								ICD10: A39
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (source: CBS)								
1997	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**	
Notifications (source: Osiris)								
1997	64	145	95	118	45	28	**495**	
1998	63	170	82	107	44	35	**501**	
1999	72	166	69	118	57	42	**524**	
2000	79	154	84	104	58	42	**521**	
2001	88	211	93	224	87	63	**766**	
2002	82	173	93	166	91	56	**661**	
2003	62	110	44	64	60	46	**386**	
2004	42	80	25	50	35	34	**266**	
2005	44	71	30	48	30	29	**252**	
2006	25	50	20	34	24	27	**180**	
2007	26	49	24	32	27	23	**181**	
2008	17	47	19	19	17	36	**155**	
2009	23	50	18	25	16	28	**160**	
2010	22	34	14	21	22	28	**141**	
2011	13	25	4	19	20	18	**99**	
2012	18	32	6	15	17	16	**104**	
2013	16	22	6	14	20	32	**110**	
2014	10	17	9	14	10	22	**83**	
2015	13	10	9	13	14	33	**92**	
2016	13	17	8	27	33	58	**156**	



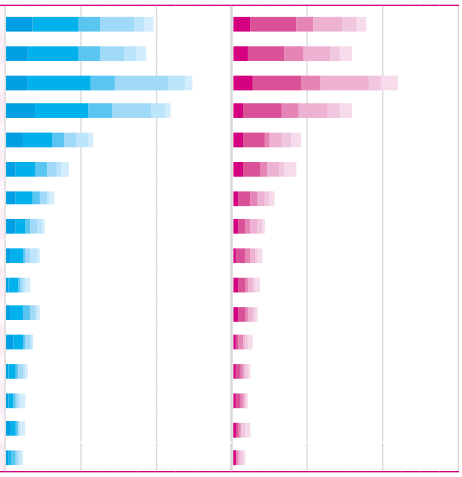
* Preliminary figures. From the statistical year 2013, the coding of the causes of death is partly automatic.

Meningococcal disease

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Laboratory diagnoses (all serogroups; source: NRBM)							
1997	75	164	101	123	59	46	**568**
1998	101	195	94	117	60	46	**613**
1999	88	175	71	110	66	57	**567**
2000	79	161	73	102	67	62	**544**
2001	91	197	82	194	86	69	**719**
2002	79	154	84	148	86	62	**613**
2003	61	98	37	54	56	45	**351**
2004	50	75	27	45	31	43	**271**
2005	41	63	29	45	30	34	**242**
2006	25	49	22	32	23	24	**175**
2007	30	51	20	30	27	28	**186**
2008	15	47	18	18	22	39	**159**
2009	25	47	18	23	16	28	**157**
2010	23	34	13	18	21	28	**137**
2011	15	23	4	18	19	22	**101**
2012	18	28	7	11	17	16	**97**
2013	19	21	6	15	19	37	**117**
2014	10	16	10	12	11	23	**82**
2015	12	10	5	14	15	33	**89**
2016	14	16	7	24	28	63	**152**
Laboratory diagnoses (serogroup C; source: NRBM)							
1997	6	16	11	25	8	14	**80**
1998	9	17	11	17	8	6	**68**
1999	9	20	5	21	10	16	**81**
2000	2	22	16	29	19	19	**107**
2001	20	53	27	105	43	29	**277**
2002	13	39	30	73	42	25	**222**
2003	11	6	0	1	16	8	**42**
2004	1	1	1	0	7	7	**17**
2005	0	0	0	0	2	2	**4**
2006	0	1	0	0	2	1	**4**
2007	2	0	1	1	4	2	**10**
2008	2	0	0	0	4	5	**11**
2009	1	1	0	0	2	5	**9**
2010	2	0	0	2	2	0	**6**
2011	0	0	0	0	1	2	**3**
2012	2	0	0	0	1	0	**3**
2013	0	1	0	0	1	4	**6**
2014	0	0	0	0	1	2	**3**
2015	2	0	0	0	3	3	**8**
2016	0	0	0	1	2	3	**6**



Meningococcal disease								ICD9: 036.0-4, 036.8-9 ICD10: A39
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Hospitalisations (source: Prismant/DHD)*								
1999	114	251	98	170	66	53	**755**	
2000	98	233	109	132	64	55	**694**	
2001	114	295	113	268	85	66	**949**	
2002	106	238	110	182	72	47	**767**	
2003	72	135	46	64	57	44	**421**	
2004	54	101	46	58	31	45	**336**	
2005	45	70	36	45	19	27	**244**	
2006	35	50	28	40	20	21	**196**	
2007	23	58	17	22	28	18	**166**	
2008	18	48	15	14	11	30	**136**	
2009	28	49	26	25	14	13	**156**	
2010	21	37	12	20	13	18	**122**	
2011	18	27	12	20	13	11	**103**	
2012	15	26	11	11	9	12	**84**	
2013	16	22	4	14	17	25	**99**	
2014	10	15	13	11	10	16	**75**	



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

* For 12 patients, the age is unknown.

Mumps								ICD10: B26
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (source: CBS)								
1997	0	0	0	0	0	0	**0**	
1998	0	0	0	0	0	0	**0**	
1999	0	0	0	0	0	0	**0**	
2000	0	0	0	0	0	0	**0**	
2001	0	0	0	0	0	0	**0**	
2002	0	0	0	0	0	2	**2**	
2003	0	0	0	0	0	0	**0**	
2004	0	0	0	0	0	0	**0**	
2005	0	0	0	0	0	1	**1**	
2006	0	0	0	0	0	0	**0**	
2007	0	0	0	0	0	0	**0**	
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	0	0	**0**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	0	**0**	
2015	0	0	0	0	0	0	**0**	
2016*	0	0	0	0	0	0	**0**	
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	19	63	3	**87**	
2016	4	1	7	20	33	6	**71**	

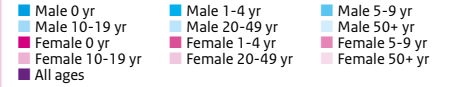
* Preliminary figures. From the statistical year 2013, the coding of the causes of death is partly automatic.

** Notifiable from 1 December 2008 onwards.

Mumps

ICD9: 072
ICD10: B26

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Hospitalisations (source: Prismant/DHD)*							
1999	0	1	0	0	1	0	**2**
2000	0	0	0	0	0	2	**2**
2001	0	0	0	0	0	1	**1**
2002	0	1	1	1	0	1	**4**
2003	0	1	0	0	0	1	**2**
2004	2	0	1	1	2	0	**6**
2005	0	0	0	1	2	1	**4**
2006	0	0	0	1	1	3	**5**
2007	1	0	0	0	1	2	**4**
2008	0	4	5	25	9	0	**43**
2009	0	0	1	2	6	1	**10**
2010	1	1	0	2	6	0	**10**
2011	0	1	0	4	7	0	**12**
2012	2	1	0	3	6	1	**14**
2013	0	0	0	0	3	2	**5**
2014	1	1	1	1	5	2	**11**
Laboratory diagnoses (source: Dutch Working Group for Clinical Virology)							
1997							**19**
1998							**9**
1999							**6**
2000							**8**
2001							**2**
2002							**8**
2003							**6**
2004							**7**
2005							**12**
2006							**9**
2007							**9**
2008							**80**
2009							**22**
2010							**144**
2011							**190**
2012							**95**
2013							**65**
2014							**24**
2015							**45**
2016							**43**



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

* For one patient, the age is unknown.

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

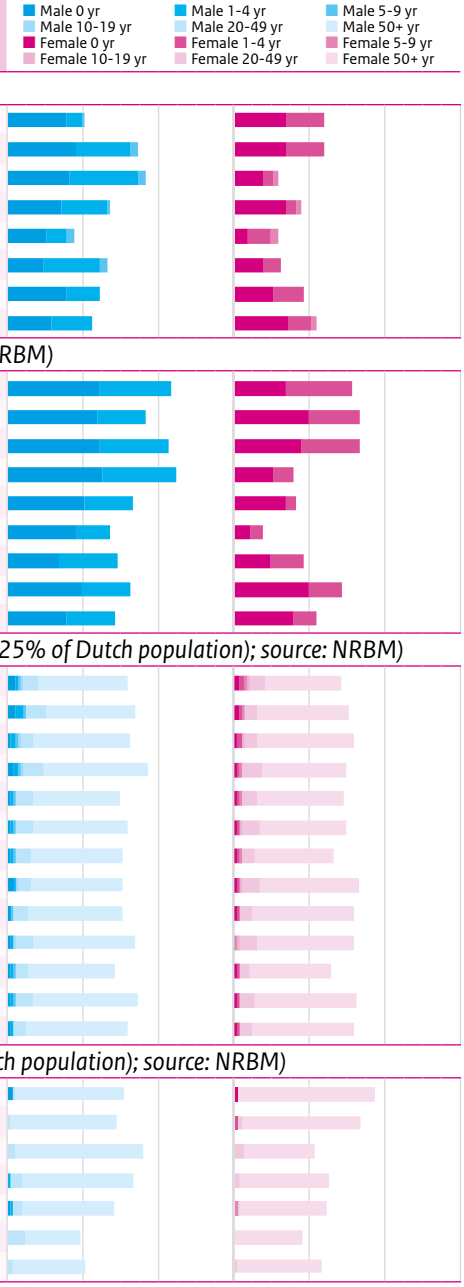
Pertussis								ICD9: 033 ICD10: A37
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Hospitalisations (source: Prismant/DHD)*								
1999	351	73	24	12	8	4	**472**	
2000	171	37	12	5	0	5	**230**	
2001	301	40	32	1	2	2	**378**	
2002	188	24	23	4	3	3	**245**	
2003	114	14	9	2	0	1	**140**	
2004	221	42	13	10	3	12	**301**	
2005	131	28	11	5	4	6	**185**	
2006	94	7	2	3	1	3	**110**	
2007	129	7	8	10	5	7	**166**	
2008	124	6	5	2	6	8	**151**	
2009	112	12	1	4	6	6	**141**	
2010	77	6	2	2	2	4	**93**	
2011	97	11	2	4	2	5	**121**	
2012	164	7	1	11	16	13	**213**	
2013	44	5	1	2	2	6	**60**	
2014	146	11	4	3	7	12	**185**	

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

* For three patients, the age is unknown.

Pneumococcal disease

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Notifications IPD (source: Osiris)*							
2009	27	15	1				**43**
2010	31	24	2				**57**
2011	23	20	4				**47**
2012	26	16	2				**44**
2013	11	13	4				**28**
2014	16	20	2				**38**
2015	25	17	0				**42**
2016	25	17	1				**43**
Laboratory diagnoses IPD (<5 years, nationwide; source: NRBM)							
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**
Laboratory diagnoses IPD (all ages, sentinel labs (covering 25% of Dutch population); source: NRBM)							
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	67	545	**630**
Mortality IPD (all ages, sentinel labs (covering 25% of Dutch population); source: NRBM)							
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

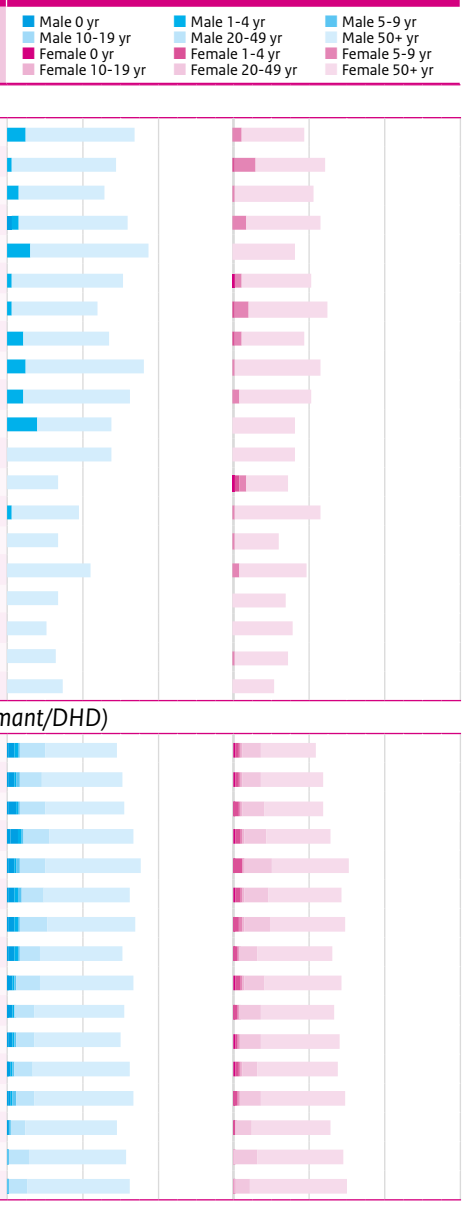


* Notifiable for 0- to 5-year-old children since 2009.

Pneumococcal disease

ICD9: 481
ICD10: J13

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Mortality pneumococcal pneumonia (source: CBS)*							
1997	0	0	0	0	8	47	**55**
1998	0	0	0	1	7	48	**56**
1999	0	0	0	0	4	46	**50**
2000	0	1	0	0	6	51	**58**
2001	0	0	0	0	6	51	**57**
2002	0	1	0	0	3	50	**54**
2003	0	0	0	1	5	46	**52**
2004	0	0	0	1	6	41	**48**
2005	0	0	0	0	6	57	**63**
2006	0	0	0	0	6	50	**56**
2007	0	0	0	0	8	39	**47**
2008	0	0	0	0	0	47	**47**
2009	0	0	1	1	2	37	**41**
2010	0	0	0	0	2	43	**45**
2011	0	0	0	0	1	26	**27**
2012	0	0	0	0	2	42	**44**
2013	0	0	0	0	0	29	**29**
2014	0	0	0	0	0	28	**28**
2015	0	0	0	0	1	28	**29**
2016*	0	0	0	0	0	27	**27**
*Hospitalisations pneumococcal pneumonia** (source: Prismant/DHD)*							
1999	35	74	48	37	394	1,126	**1,719**
2000	32	75	48	41	360	1,257	**1,817**
2001	24	102	39	34	421	1,215	**1,839**
2002	45	123	41	35	414	1,323	**1,987**
2003	28	115	34	49	454	1,523	**2,215**
2004	33	103	51	37	409	1,416	**2,051**
2005	29	95	57	36	461	1,446	**2,130**
2006	25	72	46	28	333	1,388	**1,893**
2007	10	87	41	33	382	1,502	**2,064**
2008	8	68	31	21	352	1,452	**1,938**
2009	28	59	30	36	332	1,465	**1,955**
2010	23	62	37	35	285	1,560	**2,009**
2011	17	40	46	38	337	1,631	**2,111**
2012	4	28	11	20	263	1,506	**1,835**
2013	0	4	7	17	384	1,606	**2,020**
2014	3	4	3	19	309	1,754	**2,095**



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

** Up to 2012, diseases are coded according to the ICD-9 coding system. From 2013 onward, diseases are coded according to the ICD-10 coding system. Hospitalization data since 2015 are not yet available.

** For 16 patients, the age is unknown.

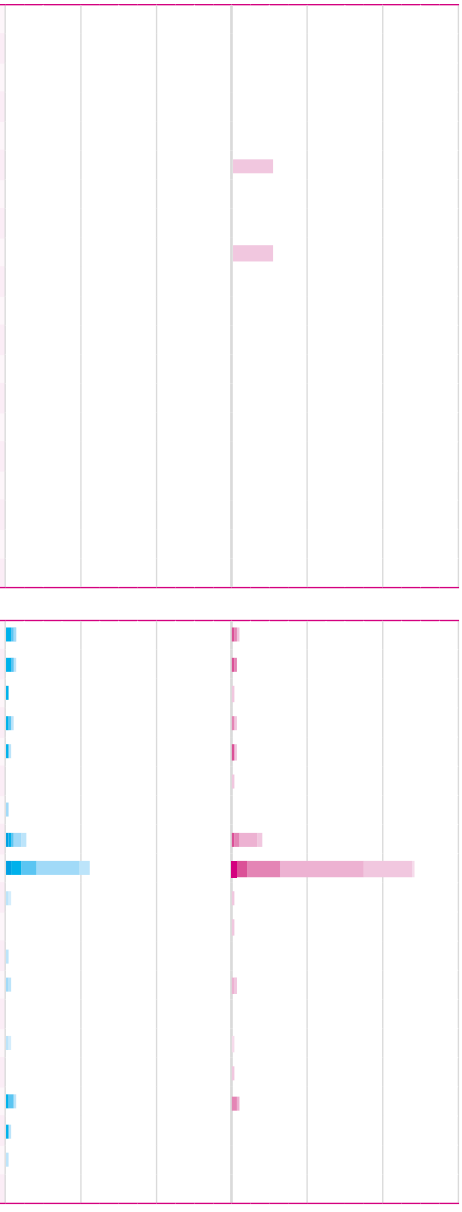
Poliomyelitis								ICD10: A80
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (acute; source: CBS)								
1997	0	0	0	0	0	1	**1**	
1998	0	0	0	0	0	0	**0**	
1999	0	0	0	0	0	0	**0**	
2000	0	0	0	0	0	2	**2**	
2001	0	0	0	0	1	0	**1**	
2002	0	0	0	0	0	1	**1**	
2003	0	0	0	0	0	3	**3**	
2004	0	0	0	0	0	0	**0**	
2005	0	0	0	0	0	0	**0**	
2006	0	0	0	0	0	0	**0**	
2007	0	0	0	0	0	0	**0**	
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	0	0	**0**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	0	**0**	
2015	0	0	0	0	0	0	**0**	
2016*	0	0	0	0	0	0	**0**	
Notifications (source: Osiris)								
1997	0	0	0	0	0	0	**0**	
1998	0	0	0	0	0	0	**0**	
1999	0	0	0	0	0	0	**0**	
2000	0	0	0	0	0	0	**0**	
2001	0	0	0	0	0	0	**0**	
2002	0	0	0	0	0	0	**0**	
2003	0	0	0	0	0	0	**0**	
2004	0	0	0	0	0	0	**0**	
2005	0	0	0	0	0	0	**0**	
2006	0	0	0	0	0	0	**0**	
2007	0	0	0	0	0	0	**0**	
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	0	0	**0**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	0	**0**	
2015	0	0	0	0	0	0	**0**	
2016	0	0	0	0	0	0	**0**	

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

Poliomyelitis								ICD9: 045 ICD10: A80
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Hospitalisations (source: Prismant/DHD)*								
1999	0	0	0	0	0	0	**0**	
2000	0	0	0	0	0	0	**0**	
2001	0	0	0	0	0	0	**0**	
2002	0	0	0	0	0	0	**0**	
2003	0	0	0	0	0	0	**0**	
2004	0	0	0	0	0	0	**0**	
2005	0	0	0	0	0	0	**0**	
2006	0	0	0	0	0	0	**0**	
2007	0	0	0	0	0	0	**0**	
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	0	0	**0**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	0	**0**	

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

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)								
1997	0	0	0	0	0	0	**0**	
1998	0	0	0	0	0	0	**0**	
1999	0	0	0	0	0	0	**0**	
2000	0	0	0	0	0	0	**0**	
2001	0	0	0	0	0	0	**0**	
2002	0	0	0	0	1	0	**1**	
2003	0	0	0	0	0	0	**0**	
2004	0	0	0	0	0	0	**0**	
2005	0	0	0	0	1	0	**1**	
2006	0	0	0	0	0	0	**0**	
2007	0	0	0	0	0	0	**0**	
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	0	0	**0**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	0	**0**	
2015	0	0	0	0	0	0	**0**	
2016*	0	0	0	0	0	0	**0**	
Notifications (source: Osiris)								
1997	0	8	6	1	4	0	**19**	
1998	0	5	7	0	6	0	**18**	
1999	0	2	0	0	1	0	**3**	
2000	0	1	4	0	7	0	**12**	
2001	0	2	0	0	2	0	**4**	
2002	0	0	0	0	3	0	**3**	
2003	0	0	0	1	0	0	**1**	
2004	2	4	12	33	14	0	**65**	
2005	9	28	66	166	78	2	**349**	
2006	0	0	0	0	4	1	**5**	
2007	0	0	0	0	1	0	**1**	
2008	0	0	0	0	2	0	**2**	
2009	0	0	0	4	2	1	**7**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	1	2	**3**	
2012	0	0	0	0	1	0	**1**	
2013	0	10	37	7	3	0	**57**	
2014	0	1	0	0	1	0	**2**	
2015	0	0	0	0	1	0	**1**	
2016	0	0	0	0	0	0	**0**	

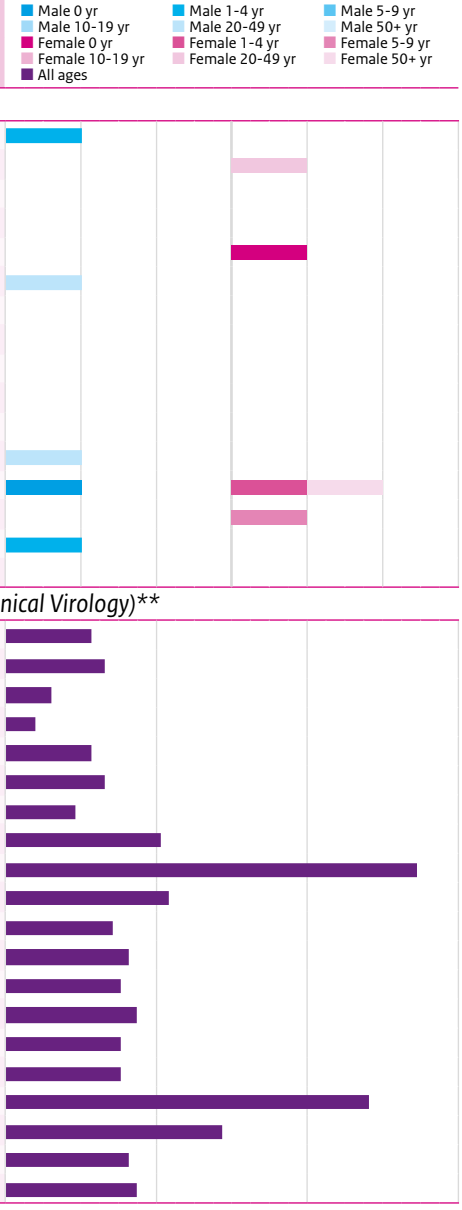


* Preliminary figures. From the statistical year 2013, the coding of the causes of death is partly automatic.

Rubella (acquired)

ICD9: 056
ICD10: B06

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Hospitalisations (source: Prismant/DHD)*							
1999	0	1	0	0	0	0	**1**
2000	0	0	0	0	1	0	**1**
2001	0	0	0	0	0	0	**0**
2002	0	0	0	0	0	0	**0**
2003	1	0	0	0	0	0	**1**
2004	0	0	0	0	1	0	**1**
2005	0	0	0	0	0	0	**0**
2006	0	0	0	0	0	0	**0**
2007	0	0	0	0	0	0	**0**
2008	0	0	0	0	0	0	**0**
2009	0	0	0	0	0	0	**0**
2010	0	0	0	0	1	0	**1**
2011	1	1	0	0	0	1	**3**
2012	0	0	1	0	0	0	**1**
2013	0	1	0	0	0	0	**1**
2014	0	0	0	0	0	0	**0**
*Laboratory diagnoses (source: Dutch Working Group for Clinical Virology)***							
1997							**11**
1998							**13**
1999							**6**
2000							**4**
2001							**11**
2002							**13**
2003							**9**
2004							**20**
2005							**53**
2006							**21**
2007							**14**
2008							**16**
2009							**15**
2010							**17**
2011							**15**
2012							**15**
2013							**47**
2014							**28**
2015							**16**
2016							**17**



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

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

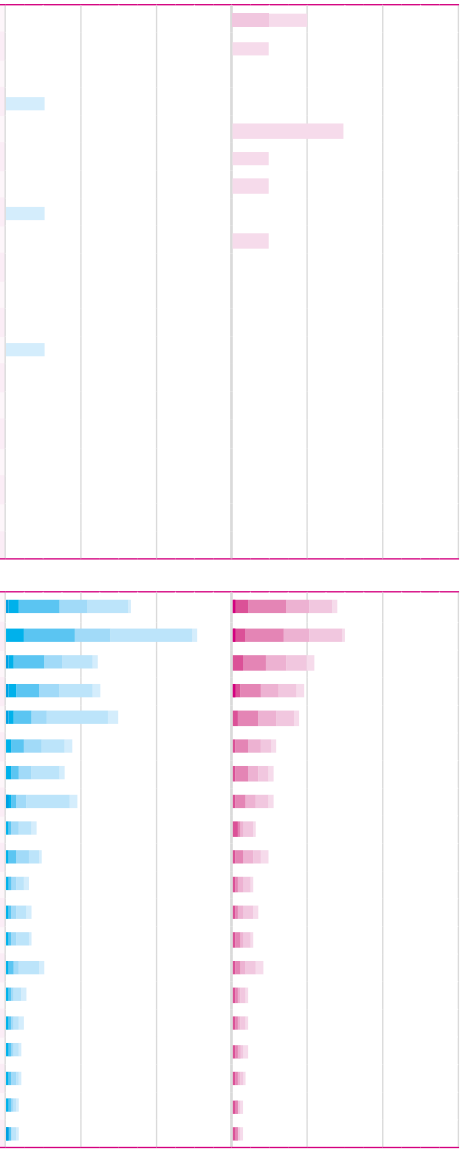
Tetanus								ID10: A33-35
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (source: CBS)								
1997	0	0	0	0	0	1	**1**	
1998	0	0	0	0	0	0	**0**	
1999	0	0	0	0	0	0	**0**	
2000	0	0	0	0	0	0	**0**	
2001	0	0	0	0	0	3	**3**	
2002	0	0	0	0	0	0	**0**	
2003	0	0	0	0	0	1	**1**	
2004	0	0	0	0	0	0	**0**	
2005	0	0	0	0	0	0	**0**	
2006	0	0	0	0	0	0	**0**	
2007	0	0	0	0	0	0	**0**	
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	0	1	**1**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	0	**0**	
2015	0	0	0	0	0	0	**0**	
2016*	0	0	0	0	0	0	**0**	
Notifications (source: Osiris)								
1997	0	0	0	0	1	3	**4**	
1998	0	0	0	0	0	0	**0**	
1999**								
2000**								
2001**								
2002**								
2003**								
2004**								
2005**								
2006**								
2007**								
2008**								
2009	0	0	0	0	0	1	**1**	
2010	0	0	0	0	0	2	**2**	
2011	0	0	0	0	0	5	**5**	
2012	0	0	0	0	1	1	**2**	
2013	0	0	0	0	1	0	**1**	
2014	0	0	0	0	0	0	**0**	
2015	0	0	0	1	0	0	**1**	
2016	0	0	0	0	0	1	**1**	

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

** No notifications in 1999-2008.

Potential NIP target diseases

Hepatitis A								ICD10: B15
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (acute; source: CBS)								
1997	0	0	0	0	1	1	**2**	
1998	0	0	0	0	0	1	**1**	
1999	0	0	0	0	0	0	**0**	
2000	0	0	0	0	0	1	**1**	
2001	0	0	0	0	0	3	**3**	
2002	0	0	0	0	0	1	**1**	
2003	0	0	0	0	0	1	**1**	
2004	0	0	0	0	0	1	**1**	
2005	0	0	0	0	0	1	**1**	
2006	0	0	0	0	0	0	**0**	
2007	0	0	0	0	0	0	**0**	
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	1	**1**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	0	0	**0**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	0	**0**	
2015	0	0	0	0	0	0	**0**	
2016*	0	0	0	0	0	0	**0**	
*Notifications** (source: Osiris)*								
1997	3	96	318	199	253	37	**913****	
1998	1	114	360	235	446	47	**1,210****	
1999	2	58	210	148	217	53	**694****	
2000	3	63	174	146	205	54	**647****	
2001	2	43	149	126	318	63	**704****	
2002	0	22	97	119	144	51	**433**	
2003	0	23	81	96	139	50	**389**	
2004	1	21	69	76	227	45	**439**	
2005	0	18	28	41	89	36	**212**	
2006	0	17	59	85	78	38	**277**	
2007	0	5	26	42	60	24	**157**	
2008	0	6	26	43	88	26	**189**	
2009	0	8	34	28	83	23	**176**	
2010	0	18	32	41	127	44	**262**	
2011	0	12	18	22	54	19	**125**	
2012	0	10	21	26	42	22	**121**	
2013	0	7	16	18	49	20	**110**	
2014	0	5	26	27	30	17	**105**	
2015	0	8	12	22	28	10	**80**	
2016	1	5	12	18	33	12	**81**	

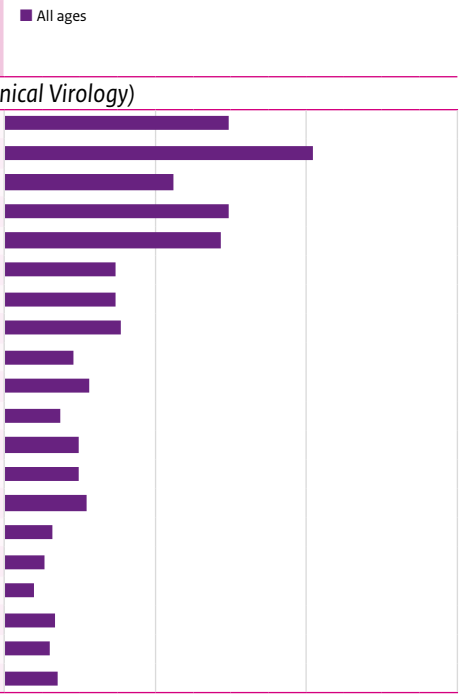


* Preliminary figures. From the statistical year 2013, the coding of the causes of death is partly automatic.

**For 25 patients, the age is unknown.

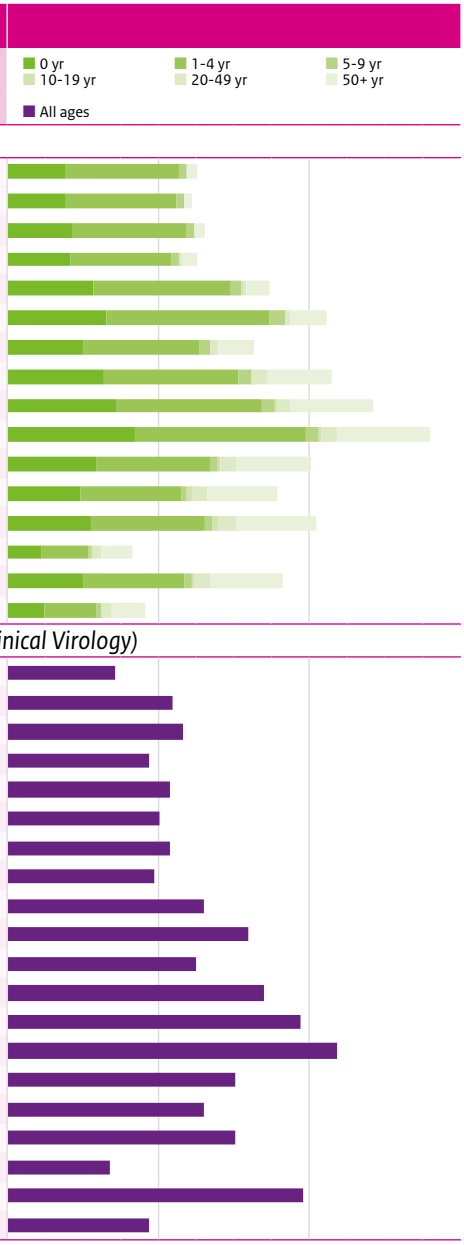
Hepatitis A

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Laboratory diagnoses (source: Dutch Working Group for Clinical Virology)							
1997							**295**
1998							**405**
1999							**223**
2000							**293**
2001							**284**
2002							**145**
2003							**146**
2004							**153**
2005							**91**
2006							**111**
2007							**72**
2008							**97**
2009							**96**
2010							**107**
2011							**63**
2012							**53**
2013							**38**
2014							**66**
2015							**59**
2016							**70**



Rotavirus

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Hospitalisations (estimation; source: Prismant/DHD)*							
2001	1,154	2,277	147	0	0	184	**3,762**
2002	1,180	2,208	148	0	0	160	**3,696**
2003	1,298	2,287	160	0	0	202	**3,947**
2004	1,240	2,011	160	16	51	298	**3,776**
2005	1,729	2,744	199	19	83	443	**5,217**
2006	1,990	3,254	272	26	109	737	**6,388**
2007	1,532	2,323	189	23	139	722	**4,928**
2008	1,933	2,702	211	47	274	1,288	**6,455**
2009	2,171	2,924	220	45	301	1,636	**7,297**
2010	2,534	3,398	262	60	329	1,845	**8,428**
2011	1,754	2,294	167	56	305	1,502	**6,078**
2012	1,470	1,985	148	71	329	1,392	**5,395**
2013	1,682	2,270	169	81	377	1,592	**6,171**
2014	686	927	69	33	153	650	**2,518**
2015	1,493	2,015	150	72	334	1,412	**5,476**
2016	757	1,021	76	36	169	716	**2,775**
Laboratory diagnoses (source: Dutch Working Group for Clinical Virology)							
1997							**712**
1998							**1,094**
1999							**1,163**
2000							**932**
2001							**1,067**
2002							**1,004**
2003							**1,079**
2004							**975**
2005							**1,304**
2006							**1,585**
2007							**1,251**
2008							**1,692**
2009							**1,935**
2010							**2,180**
2011							**1,505**
2012							**1,288**
2013							**1,496**
2014							**607**
2015							**1,323**
2016							**679**

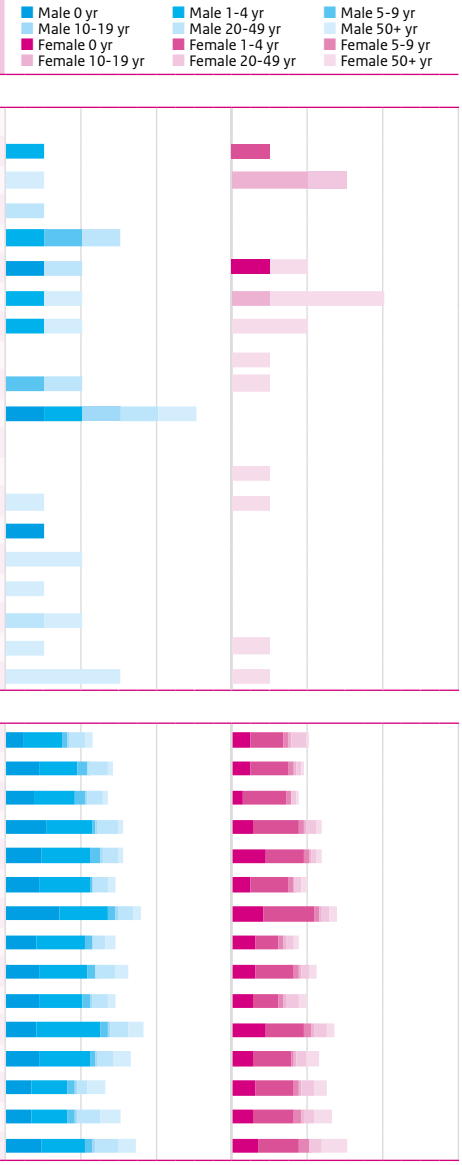


* Up to 2012, diseases are coded according to the ICD-9 coding system. From 2013 onward, diseases are coded according to the ICD-10 coding system. Hospitalisation data since 2015 are not yet available; therefore, data of the five previous years was used to estimate the number of hospitalisations in 2015 and 2016.

Varicella (chickenpox)

ICD9: 052
ICD10: B01

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Mortality (source: CBS)							
1997	0	0	0	0	0	0	**0**
1998	0	2	0	0	0	0	**2**
1999	0	0	0	2	1	1	**4**
2000	0	0	0	0	1	0	**1**
2001	0	1	1	0	1	0	**3**
2002	2	0	0	0	1	1	**4**
2003	0	1	0	1	0	4	**6**
2004	0	1	0	0	0	3	**4**
2005	0	0	0	0	0	1	**1**
2006	0	0	1	0	1	1	**3**
2007	1	1	0	1	1	1	**5**
2008	0	0	0	0	0	0	**0**
2009	0	0	0	0	0	1	**1**
2010	0	0	0	0	0	2	**2**
2011	1	0	0	0	0	0	**1**
2012	0	0	0	0	0	2	**2**
2013	0	0	0	0	0	1	**1**
2014	0	0	0	0	1	1	**2**
2015	0	0	0	0	0	2	**2**
2016*	0	0	0	0	0	4	**4**
*Hospitalisations** (source: Prismant/DHD)*							
2000	44	95	14	6	38	14	**211**
2001	62	104	19	3	36	9	**233**
2002	47	113	17	4	29	9	**219**
2003	78	121	10	6	41	17	**273**
2004	89	115	20	7	26	12	**269**
2005	64	119	9	1	28	17	**238**
2006	108	132	17	4	33	19	**313**
2007	69	92	19	4	24	23	**231**
2008	74	111	19	3	38	26	**271**
2009	67	92	18	6	37	22	**242**
2010	81	136	21	7	39	31	**315**
2011	67	118	13	5	34	40	**277**
2012	63	96	17	6	29	42	**253**
2013	58	102	18	7	45	51	**281**
2014	76	112	22	6	49	56	**321**



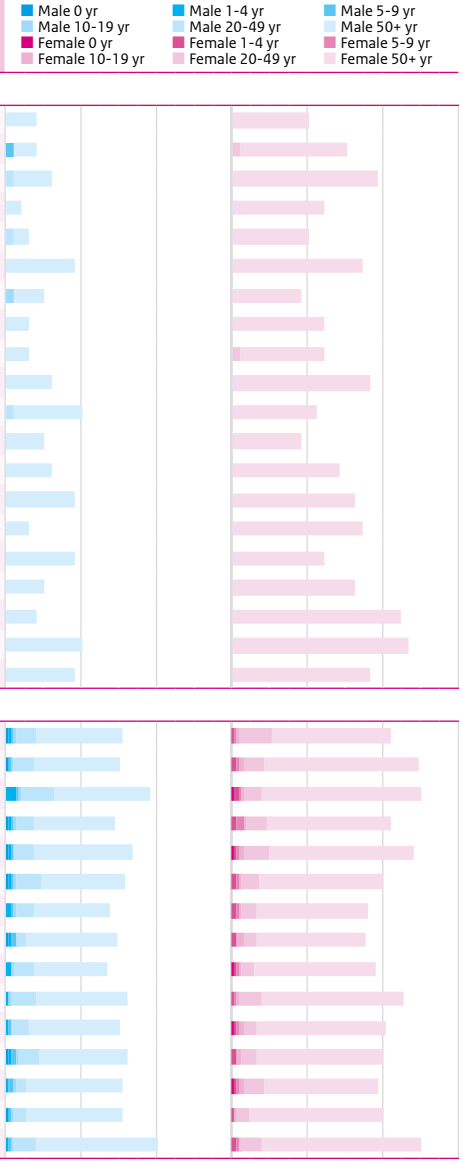
* Preliminary figures. From the statistical year 2013, the coding of the causes of death is partly automatic.

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

Herpes zoster (shingles)

ICD9: 053
ICD10: B02

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Mortality (source: CBS)							
1997	0	0	0	0	0	14	**14**
1998	0	0	1	0	1	17	**19**
1999	0	0	0	0	1	24	**25**
2000	0	0	0	0	0	14	**14**
2001	0	0	0	0	1	12	**13**
2002	0	0	0	0	0	26	**26**
2003	0	0	0	1	0	13	**14**
2004	0	0	0	0	0	15	**15**
2005	0	0	0	0	1	14	**15**
2006	0	0	0	0	0	24	**24**
2007	0	0	0	0	1	20	**21**
2008	0	0	0	0	0	14	**14**
2009	0	0	0	0	0	20	**20**
2010	0	0	0	0	0	25	**25**
2011	0	0	0	0	0	20	**20**
2012	0	0	0	0	0	21	**21**
2013	0	0	0	0	0	21	**21**
2014	0	0	0	0	0	26	**26**
2015	0	0	0	0	0	33	**33**
2016*	0	0	0	0	0	27	**27**
*Hospitalisations** (source: Prismant/DHD)*							
2000	2	6	4	9	68	274	**363**
2001	1	8	7	9	55	319	**399**
2002	2	18	7	8	67	340	**442**
2003	1	9	14	6	51	273	**354**
2004	4	8	6	7	60	324	**409**
2005	2	9	5	11	54	278	**359**
2006	0	11	7	7	43	249	**317**
2007	1	10	7	8	33	267	**326**
2008	2	8	5	6	43	259	**323**
2009	0	2	6	7	63	311	**389**
2010	1	6	6	8	39	292	**352**
2011	2	9	7	10	44	288	**360**
2012	1	6	11	8	42	279	**347**
2013	1	3	6	5	34	302	**351**
2014	0	9	4	7	58	373	**451**



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

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

Appendix 3
Overview of vaccin changes in the NIP since 2000

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

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

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

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

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

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

January 2006
→ HBVAXPRO (SP MSD)
🕒 birth
Children born on or after 1 January 2006
(specific risk groups [2])

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

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

June 2006
← Pediacel (SP MSD)
→ Infanrix hexa (GSK)
🕒 2, 3, 4 and 11 months of age
Children born on or after 1 April 2006
(specific risk groups [1])

February 2008
← Triaxis Polio (SP MSD) [4]
→ Infanrix IPV (GSK)
🕒 4 years of age
Children born on or after 1 February 2004

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

September 2008
← HBVAXPRO (SP MSD)
→ Engerix-B Junior (GSK)
🕒 birth
Children born on or after 1 September 2008
(specific risk groups [3])

September 2008
← MMR vaccine (NVI)
→ Priorix (GSK)
🕒 9 years of age
Children born on or after 1 September 1999

May 2011
← Prevenar (Wyeth)
→ Synflorix (GSK)
🕒 2, 3, 4 and 11 months of age
Children born on or after 1 March 2011

October 2011
← Pediacel (SP MSD)
→ Infanrix hexa (GSK)
🕒 2, 3, 4 and 11 months of age
Children born on or after 1 August 2011

December 2013
→ Synflorix (GSK)
🕒 2, 4 and 11 months of age
Children born on or after 1 October 2013

January 2014
→ Cervarix (GSK)
🕒 12 years [6]
Children born on or after 1 January 2001

January 2017
← Infanrix IPV (GSK)
→ Boostrix Polio (GSK)
🕒 4 years of age

Legend

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

[1] Only children at least one of whose parents was born in a country where hepatitis B is moderately or highly endemic and children whose mother had tested positive for HBsAg.

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

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

[4] Used until March 2008.

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

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

Appendix 4 Composition of vaccines used in the NIP

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

Vaccine	Composition
DT-IPV vaccine / BBio RVG 17641 Diphtheria (adsorbed), tetanus (adsorbed) and inactivated poliomyelitis vaccine 1 ml	Diphtheria-toxoid* > 5 IU Tetanus toxoid* > 20 IU Inactivated poliovirus type 1 > 40 DU Inactivated poliovirus type 2 > 4 DU Inactivated poliovirus type 3 > 7.5 DU *adsorbed to aluminium phosphate 1.5 mg Al3+
REVAXIS / SP RVG24534 Diphtheria, tetanus and inactivated poliomyelitis vaccine (absorbed; limited quantity of antigen(s)) 0.5 ml	Purified diphtheria-toxoid* > 2 IU Purified tetanus toxoid* > 20 IU Inactivated poliovirus type 1** 40 DU Inactivated poliovirus type 2** 8 DU Inactivated poliovirus type 3** 32 DU *adsorbed to aluminiumhydroxide 0.35 mg **produced on Verocells
Engerix-B Junior / GSK RVG24290 Hepatitis B vaccine (recombinant) 0.5 ml	Hepatitis B-virus surface antigen, recombinant* (S protein) absorbed 10 µg *produced on genetically engineered yeast cells (Saccharomyces cerevisiae)
HBVAXPRO / MSD RVG17316 Hepatitis B vaccine (rDNA) 0.5 ml	Hepatitis B virus surface antigen, recombinant (HBsAg)[1,2] 5 µg [1] Adsorbed on amorphous aluminium hydroxyphosphate sulfate (0.25 mg Al+) [2] Produced in Saccharomyces cerevisiae (strain 2150-2-3) yeast by recombinant DNA technology
Act-HIB / SP *Haemophilus influenzae* 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

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

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

Appendix 5 Overview of recent RIVM publications (01-08-2017 to 31-07-2017)

Vaccination coverage

1. Scheepers ED, van Lier A, Drijfhout IH, Berbers G, van der Maas NAT, de Melker HE, Knol MJ. Dutch national immunization schedule: compliance and associated characteristics for the primary series. European Journal of Pediatrics. 2017;176(6):769-78.
2. van Lier EA, Geraedts JLE, Oomen PJ, Giesbers H, van Vliet JA, Drijfhout IH, et al. Vaccinatiegraad en jaarverslag Rijksvaccinatieprogramma Nederland 2016. [Vaccination coverage and annual report National Immunisation Programme Netherlands 2016]. Bilthoven: National Institute for Public Health and the Environment (RIVM); 2017 (RIVM report 2017-0010).

Burden of disease

1. de Gier B, Nijsten DRE, Duijster JW, Hahné SJM. State of Infectious Diseases in the Netherlands, 2016. Bilthoven: National Institute for Public Health and the Environment (RIVM); 2017 (RIVM Report 2017-0029).
2. Colzani E, Cassini A, Lewandowski D, Mangen MJ, Plass D, McDonald SA, et al. A Software Tool for Estimation of Burden of Infectious Diseases in Europe Using Incidence-Based Disability Adjusted Life Years. PLOS ONE. 2017;12(1):e0170662.
3. McDonald SA, Devleesschauwer B, Wallinga J. The impact of individual-level heterogeneity on estimated infectious disease burden: a simulation study. Population Health Metrics. 2016;14:47.
4. McDonald SA, Qendri V, Berkhof J, de Melker HE, Bogaards JA. Disease burden of human papillomavirus infection in the Netherlands, 1989-2014: the gap between females and males is diminishing. Cancer Causes Control. 2017;28(3):203-14.

Acceptance of vaccination

1. Pot M, van Keulen HM, Ruiter RAC, Eekhout I, Mollema L, Paulussen TWGM. 2017. Motivational and contextual determinants of HPV-vaccination uptake: A longitudinal study among mothers of girls invited for the HPV-vaccination. Preventive Medicine. 2017 Jul;100:41-49.
2. Lehmann BA, de Melker HE, Timmermans DRM, Mollema L. Informed decision making in the context of childhood immunization. Patient Education and Counseling. 2017 June 26. pii: S0738-3991(17)30361-0. doi: 10.1016/j.pec.2017.06.015.
3. - Lehmann BA, Eilers R, Mollema L, Ferreira J, de Melker HE. The intention of Dutch general practitioners to offer vaccination against pneumococcal disease, herpes zoster and pertussis to people aged 60 years and older. BMC Geriatrics. 2017 June 7;17(1):122. doi: 10.1186/s12877-017-0511-7.
4. Visser O, Kraan J, Akkermans R, Ruiter RA, van der Velden K, Hautvast JL, Hulscher ME. Assessing determinants of the intention to accept a pertussis cocooning vaccination: A survey among Dutch parents. Vaccine. 2016 Sept. 7;34(39):4744-51. doi: 10.1016/j.vaccine.2016.07.024. Epub 2016 Aug. 11Vaccine.

5. Eilers R, de Melker HE, Veldwijk J, Krabbe PFM. Vaccine preferences and acceptance of older adults. 2017 May 15;35(21):2823-2830. doi: 10.1016/j.vaccine.2017.04.014. Epub 2017 Apr 12.

Adverse events

1. Gadroen K, Kemmeren JM, Bruijning-Verhagen PC, Straus SM, Weibel D, de Melker HE, Sturkenboom MC. Baseline incidence of intussusception in early childhood before rotavirus vaccine introduction, the Netherlands, January 2008 to December 2012. Euro Surveillance 2017;22;25.
2. Kemmeren JM, van der maas NA, de Melker HE. Comparison of the tolerability of newly intoduced childhood vaccines in the Netherlands. European Journal of Pediatrics 2017;176:757-768.

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

1. Curvers M, Tostmann A, Hautvast JLA, Ruijs WLM, de Melker HE, van der Klis F, et al. [Bescherming tegen infectieziekten bij volwassen asielzoekers]. Infectieziekten Bulletin. 2016;27(9):321-3.
2. Tielemans SMAJ, de Melker HE, Hahné SJM, Boef AGC, van der Klis FRM, Sanders EAM, van der Sande MAB, Knol MJ. Non-specific effects of measles, mumps, and rubella (MMR) vaccination in high income setting: population based cohort study in the Netherlands. BMJ. 2017 Aug 30;358:j3862.

Current NIP

Diphtheria

None

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

None

Hepatitis B

1. Hofman R, Nusselder WJ, Veldhuijzen IK, Richardus JH. [Mortality due to chronic viral hepatitis B and C infections in the Netherlands]. Nederlands Tijdschrift voor Geneeskunde. 2016;160(0):D511.
2. Mangen MJ, Stibbe H, Urbanus A, Siedenburg EC, Waldhober Q, de Wit GA, et al. Targeted outreach hepatitis B vaccination program in high-risk adults: The fundamental challenge of the last mile. Vaccine. 2017;35(24):3215-21.
3. Rijksinstituut voor Volksgezondheid en Milieu. Meer dan opsporen. Nationaal hepatitisplan: een strategie voor actie. Bilthoven: RIVM, 2016 2016-0166.
4. van Heiningen FM, Wijnands YHHM, Veldhuijzen IK, Hahne SJM. Verbeterslag nodig in de uitvoering van hepatitis B-serologie bij kinderen van moeders met chronische hepatitis B. Infectieziekten bulletin. 2016;27(4):131-3.

Human papillomavirus (HPV) infection

1. Alberts CJ, van der Loeff MF, Hazeveld Y, de Melker HE, van der Wal MF, Nielen A, El Fakiri F, Prins M, Paulussen TG. A longitudinal study on determinants of HPV vaccination uptake in parents/guardians from different ethnic backgrounds in Amsterdam, the Netherlands. BMC Public Health. 2017 Feb 21;17(1):220.
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Pertussis

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Pneumococcal disease

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Poliomyelitis

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Rubella

1. Ruijs WLM, van Harten-Gerritsen AS, Akkermans R, de Haan-Burggraaf H, Hautvast JLA. Rubellascreening bij zwangere vrouwen door verloskundigen. Infectieziekten Bulletin. 2016;27:233-5.

Tetanus

1. van der Maas NA, Donken R, Te Wierik MJ, Swaan CM, Hahne SJ, de Melker HE. Performance of a bedside test for tetanus immunity: results of a cross-sectional study among three EDs in the Netherlands in 2012-2013. Emergency Medicine Journal. 2016 Nov;33(11):763-768.

Potential NIP target diseases

Hepatitis A

1. Freidl GS, Sonder GJ, Bovee LP, Friesema IH, van Rijckevorsel GG, Ruijs WL, et al. Hepatitis A outbreak among men who have sex with men (MSM) predominantly linked with the EuroPride, the Netherlands, July 2016 to February 2017. Euro Surveillance. 2017;22(8).

Respiratory syncytial virus

None

Rotavirus

1. Verberk JDM, Bruijning-Verhagen P, de Melker HE. Rotavirus in the Netherlands - Background information for the Health Council. Bilthoven: National Institute for Public Health and the Environment (RIVM), 2017 Contract No.: RIVM Report 2017-0021.

Varicella zoster virus (VZV) infection

1. Lehmann BA, Eilers R, Mollema L, Ferreira J, de Melker HE. The intention of Dutch general practitioners to offer vaccination against pneumococcal disease, herpes zoster and pertussis to people aged 60 years and older. BMC Geriatrics. 2017;17(1):122.
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Appendix 6 Overview of relevant websites

General information for NIP professionals

RIVM website for professionals:
http://www.rivm.nl/Onderwerpen/R/Rijksvaccinatieprogramma/Professionals

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

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

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

General information for the public

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

www.rijksvaccinatieprogramma.nl

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:
http://www.rivm.nl/Onderwerpen/B/Bevolkingsonderzoek_baarmoederhalskanker

Other NIP-related RIVM reports

Immunisation coverage and annual report National Immunisation Programme in the Netherlands 2016: *http://www.rivm.nl/bibliotheek/rapporten/2017-0010.pdf*

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

Product information

Product information and package leaflets NIP:
http://www.rivm.nl/Onderwerpen/B/Bijsluiters_vaccins/Bijsluiters_Rijksvaccinatieprogramma

National organisations

General
Ministry of Health, Welfare and Sport:
http://www.rijksoverheid.nl/onderwerpen/vaccinaties

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

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

Safety of vaccines
Netherlands Pharmacovigilance Centre Lareb:
http://www.lareb.nl/

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

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

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

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

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

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

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

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

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

International organisations

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

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

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

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

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

Advisory Committees

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

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

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

Safety of vaccines

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

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

International vaccine schedules

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

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

International networks

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

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

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

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

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

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

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

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

Communication platforms

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

Vaccination of risk groups

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

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

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

Jaarrapportage Surveillance Respiratoire Infectieziekten:
http://www.rivm.nl/bibliotheek/rapporten/2016-0071.pdf

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

Jaarrapportage Surveillance Respiratoire Infectieziekten:
http://www.rivm.nl/bibliotheek/rapporten/2016-0071.pdf

Nationaal plan tuberculosebestrijding:
http://www.rivm.nl/bibliotheek/rapporten/2016-0028.pdf

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

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

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