



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 2015-2016



The National Immunisation Programme in the Netherlands

Surveillance and developments in 2015-2016

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Publiekssamenvatting

Het Rijksvaccinatieprogramma in Nederland

Surveillance en ontwikkelingen in 2015-2016

In 2015 kregen bijna 770.000 kinderen van 0 tot 19 jaar samen 1.547.000 vaccinaties binnen het Rijksvaccinatieprogramma (RVP). De deelname aan het RVP is met 92 tot 99 procent (afhankelijk van de vaccinatie) nog steeds hoog. Een uitzondering daarop is de vaccinatie tegen het humaan papillomavirus (HPV) met 61 procent. De deelname voor pasgeborenen is voor het tweede achtereenvolgende jaar met ongeveer 0,5 procent gedaald.

Meldingen van RVP-ziekten

Het aantal gemelde gevallen van de meeste ziekten waartegen via het RVP wordt ingeënt, was wederom laag. Dit gold ook voor het aantal meldingen van mazelen (7) na de grote epidemie in 2013/2014. Kinkhoest kwam in 2015 minder vaak voor (39 per 100.000) dan in het epidemische jaar 2014 (55 per 100.000). Eén zuigeling overleed aan kinkhoest. Het aantal gevallen van ernstige pneumokokkenziekte - veroorzaakt door de drie typen waarmee het pneumokokkenvaccin werd uitgebreid in 2011 - bleef bij kinderen jonger dan 5 jaar zeer laag (0,5 per 100.000). Door de indirecte bescherming kwam het bij andere leeftijdsgroepen ook minder vaak voor. In 2015 en de eerste helft van 2016 kwam de bof vaker voor dan in 2014 (bij respectievelijk 89, 45 en 40 mensen).

Meldingen van mogelijke bijwerkingen van vaccins

In 2015 is het aantal meldingen van mogelijke bijwerkingen van vaccins gestegen (1494 ten opzichte van 982 in 2014). Het betrof vooral meldingen van (heftige) lokale ontstekingsreacties en koorts bij 4-jarigen. Ook nam het aantal meldingen van vermoeidheid bij 12-jarige meisjes toe na media-aandacht over eventuele bijwerkingen van de HPV vaccinatie. De aard van de gemelde bijwerkingen was in vergelijking met voorgaande jaren niet ernstiger.

Meldingen van ziekten voor potentiële RVP-vaccins

In 2015 en 2016 steeg het aantal gevallen van meningokokkenziekte veroorzaakt door serogroep W (MenW); meestal waren dit personen van 65 jaar of ouder. Na het extreem lage aantal gevallen in 2014 had 2015 een gemiddeld rotavirus seizoen, met de piek in maart. Tot en met juni 2016 was het aantal gevallen van rotavirus weer laag, waarbij het 'seizoen' ook later begon dan normaal.

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

Synopsis

The National Immunisation Programme in the Netherlands

Surveillance and developments in 2015-2016

In 2015, nearly 770,000 children aged 0 to 19 years received a total of 1,547,000 vaccinations within the National Immunisation Programme (NIP). Participation in the NIP, which was between 92% and 99% (depending on the vaccination), was still high. An exception was vaccination against human papillomavirus (HPV), which was 61%. The participation of newborns dropped by about 0.5% for the second consecutive year.

Notifications of NIP target diseases

The number of reported cases of most NIP target diseases was again low. This was also true for the number of reported measles cases (7) after the great epidemic in 2013/2014. Pertussis was less frequently reported in 2015 (39 per 100,000) than in the epidemic year 2014 (55 per 100,000). One infant death due to pertussis was reported. The incidence of cases of invasive pneumococcal disease – caused by the three additional types which were included in the pneumococcal vaccine in 2011 – was very low in children under 5 years (0.5 per 100,000), and a decrease was seen in other age groups due to herd protection. In 2015 and the first half of 2016, mumps was more common than in 2014 (n=89, n=45 and n=40, respectively).

Notifications of adverse events following immunisation

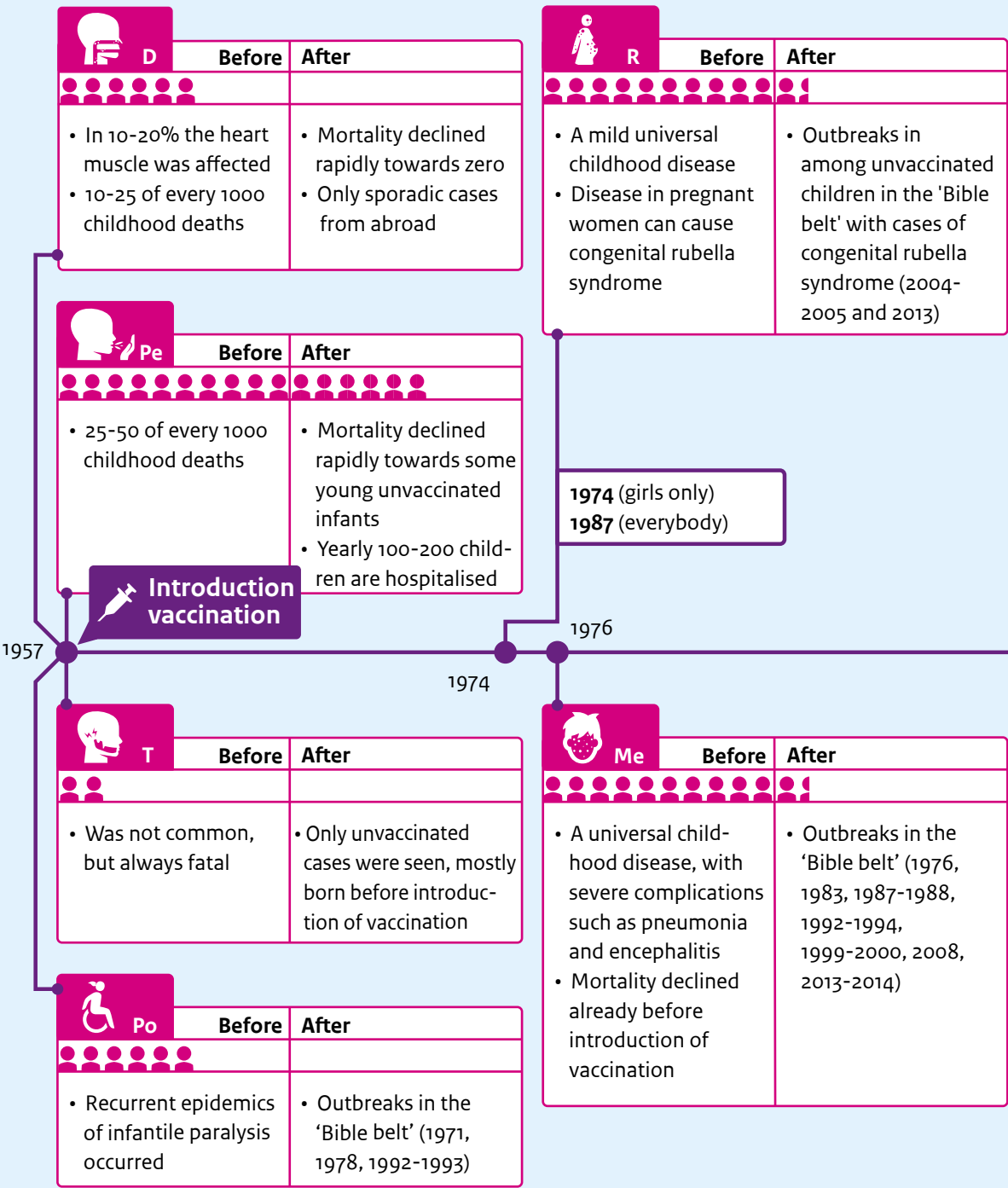
In 2015, an increased number of reports of possible side effects of vaccines was reported (1,494 versus 982 in 2014). These were mainly reports of (pronounced) local inflammation and fever in 4-year-olds. The number of reports of fatigue in 12-year-old girls increased after media attention on possible side effects of the HPV vaccination. The severity of the reported adverse events was comparable with previous years.




Notifications of potential NIP target diseases




In 2015 and 2016, the number of invasive meningococcal serogroup W (MenW) cases increased; these were mostly in people aged 65 years or older. After the extremely low number of cases in 2014, 2015 had an average rotavirus season with the peak in March. Until June 2016, the number of cases of rotavirus was also low, with a later start of the season than usual.




Keywords: National Immunisation Programme (NIP), diphtheria, *Haemophilus influenzae* type b (Hib), 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).

Effects of the National Immunisation Programme (NIP)






 Hib	Before	After
		
<ul style="list-style-type: none">• Infection caused epiglottitis, meningitis and sepsis	<ul style="list-style-type: none">• A few vaccine failures were seen yearly	

 MenC		Before	After
			
<ul style="list-style-type: none">• The disease mostly occurred in children with meningitis and sepsis• A sharp increase in incidence occurred in 2001		<ul style="list-style-type: none">• The number of cases in unvaccinated people also decreased due to less transmission/circulation	




HepB	Before	After
		
<ul style="list-style-type: none">• Cause livercirrhosis and livercarcinoma		<ul style="list-style-type: none">• Lowest rates since notification• Effect of universal vaccination become visible in the future



2003 (specific risk groups)

2011 (everybody)

 Pneu	Before	After
		
<ul style="list-style-type: none">• Cause invasive disease, such as pneumonia, meningitis and sepsis• Especially in children <2 and elderly >65 years	<ul style="list-style-type: none">• A strong decrease in cases caused by the 10 vaccine types was seen• Disease due to non-vaccine types increased	







1987 1993 2001 2003 2006 2010

Mu	Before	After
		
<ul style="list-style-type: none">• An universal childhood disease• mostly mild disease, but sometimes aseptic meningitis or encephalitis occurred	<ul style="list-style-type: none">• An epidemic in 2007-2009 among unvaccinated children in the 'Bible belt'• A countrywide epidemic in 2009-2012 affecting (partially) vaccinated students	

		(girls only)
HPV	Before	After
		Since 2023
	<ul style="list-style-type: none">• An universal infection among sexual active people• Every year 200-250 women died due to cervical cancer	<ul style="list-style-type: none">• The vaccine is effective against HPV16/18 and crossprotective types (HPV31/45)

Indication sick people before and after vaccination

	
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1X  = 2-10
 2X  = 10-100
 4X  = 100-1.000
 6X  = 1.000-10.000
 8X  = 10.000-100.000
 10X  = > 100.000

Highlights NIP surveillance 2015 - 2016



RIVM continuously monitors the effectiveness and safety of the National Immunisation Programme to optimise the programme.



Through routine enterovirus-surveillance in 2015, a VDPV type 3 was found in a young Syrian refugee without clinical symptoms

In 2015, Sabin 1 and 2 strains were detected in a child returning from Pakistan



Po



The incidence of PCV10 serotypes in children <5 years remained very low in 2015-2016

Due to herd protection the incidence of PCV10-7 type IPD in other age groups further decreased



Pneu



Start of a third population-based cross-sectional sero-epidemiological study (February 2016 - December 2017)



D



Pe



T



R



Me



Mu



Po



Hib



MenC



Pneu



HPV



HepB



A review of the EMA concluded no evidence of a causal link between the vaccines and CRPS or POTS



HPV



All patients in 2015 were imported or import related



Me



Immunity



Vaccination uptake



Disease



Adverse events



Pathogen

The bivalent vaccine is effective against HPV16/18/31/45 persistent infections at least 5 years post-vaccination



HPV

In 2015 and the first six months of 2016, mumps was more common than in 2014



Mu

The incidence of acute notifications decreased in 2015, which is the lowest since notification started in 1976



HepB

In 2015, there was an increase in reports of (severe) local inflammatory responses and fever at the 4-year-olds



D



Pe



T



Po

In December 2015, the Health Council advised to offer all pregnant women vaccination for better protection of their new-born



Pe

Children of whom at least one parent is born in a country where hepatitis B is common, do not always receive the vaccination



HepB

The estimated vaccine effectiveness was 97%



Hib

Preface









This report presents an overview of surveillance and developments in 2015–2016 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 serogroup C disease, mumps, pertussis, pneumococcal disease, poliomyelitis, rubella and tetanus. It also describes surveillance data concerning potential target diseases: hepatitis A infection, meningococcal non-serogroup C types, respiratory syncytial virus (RSV) infection, rotavirus infection and varicella zoster virus (VZV) infection. In addition, an overview of vaccines for infectious diseases undergoing clinical trials that are relevant for the Netherlands is included in this report.

Some changes were made in the structure of the report following an evaluation of last year's report. Diseases are now presented in alphabetical order. The report is structured as follows: Chapter 1 gives a short introduction. Recent results on vaccination coverage are discussed in Chapter 2 and the burden of diseases included in the NIP is the focus of Chapter 3. Public acceptance of vaccination and the communication of the NIP is described in Chapter 4 and adverse events following immunisation (AEFI) in Chapter 5. In Chapter 6 various research topics addressing the evaluation of the NIP in a broader sense are presented. These include a historical analysis of the effect of vaccination programmes on mortality, non-specific effects and age differences of vaccination as well as the start of a third seroepidemiological study. Chapter 7 focuses on the current target diseases of the NIP. For each disease, key points highlight the most prominent findings; these are followed by an update of information on epidemiology, the pathogen, the results of current and ongoing studies and international developments. Chapter 8 describes potential new target diseases that are under consideration for inclusion in the NIP. Finally, in Chapter 9, 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 for 1997 onwards, taken from various data sources, are reported. Appendix 3 gives an overview of changes in the NIP since 2000 and Appendix 4 presents the composition of the vaccines used in 2014–2015. Appendix 5 provides an overview of recent publications by the National Institute for Public Health and the Environment (RIVM) and Appendix 6 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* serotype b (Hib) disease, measles, mumps, rubella, meningococcal serogroup C (MenC) 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, meningococcal disease caused by serogroups other than C (i.e. A, B, W, X, Y, Z, 29E) and respiratory syncytial virus (RSV) infection.

Current vaccination schedule

Phase 1	Injection 1	Injection 2	Phase 2	Injection 1	Injection 2
 6-9 weeks	DTaP-IPV Hib HBV	PCV	 4 years	DTaP-IPV	
 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 3	Injection 1	Injection 2	Phase 4	Injection 1	Injection 2
 9 years	DT-IPV	MMR	 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	<i>Haemophilus influenzae</i> type b	R	Rubella		

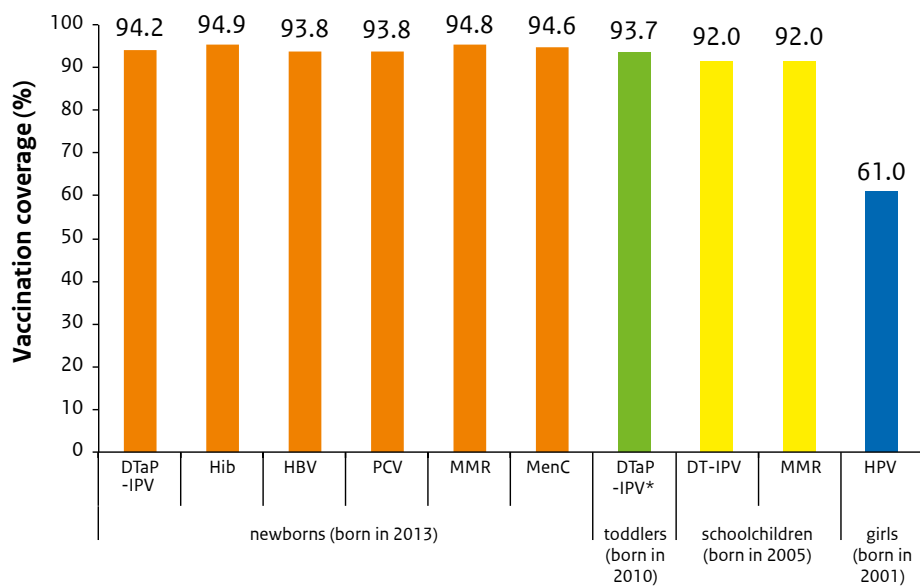


Figure 1 Vaccination schedule of the NIP

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

Vaccination coverage

Vaccination coverage in the Netherlands is high. Nevertheless, the participation of newborns for most vaccinations declined by about 0.5% for the second consecutive year.



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

Figure 2 Vaccination coverage per vaccine for age cohorts of newborns, toddlers, schoolchildren and adolescent girls in 2016

Source: Præventis

Burden of disease

National burden of disease estimates are expressed in disability-adjusted life years (DALY), which include both years lived with a disability (YLD) and years of life lost (YLL) due to the disease or infection. The estimated disease burden was highest for human papillomavirus infection, followed by invasive pneumococcal disease, pertussis and rotavirus infection. Compared with the estimated average annual burden for the period 2010–2014, the estimated burden in 2015 was considerably lower for measles, rubella, acute hepatitis B and hepatitis A infection, and meningococcal disease.

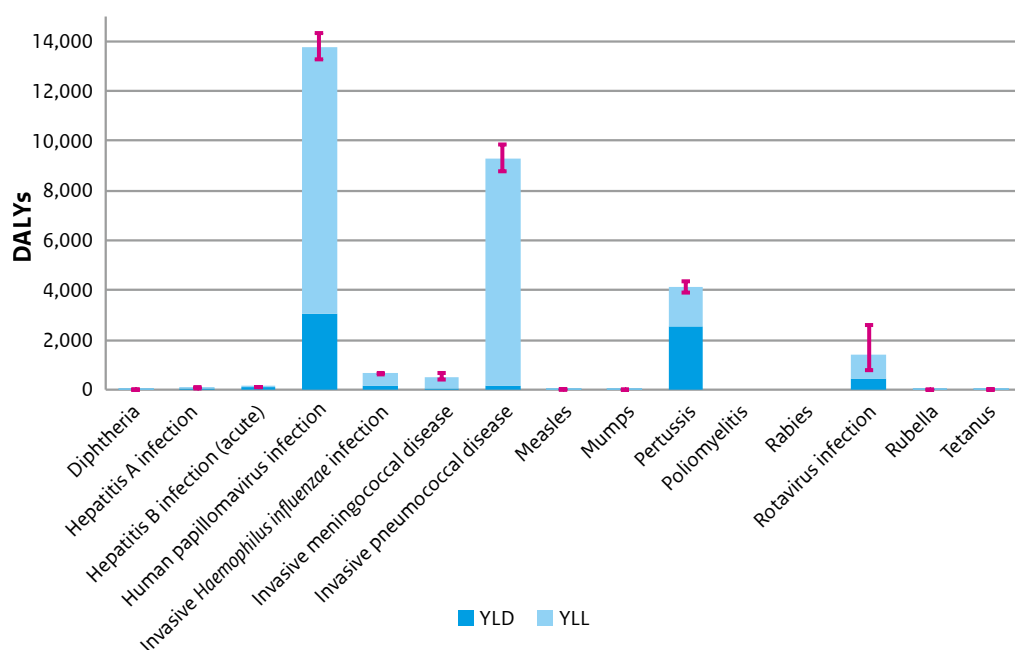


Figure 3 Estimated burden of new cases in the year 2015, with the years lived with disability (YLD) and years of life lost (YLL) components shown separately

Notes:

1. Red lines indicate 95% uncertainty intervals.
2. Vaccination against rabies, hepatitis A infection and rotavirus infection is not included in the NIP.
3. For the three invasive diseases there was only a vaccine available against certain serotypes in 2015: *Haemophilus influenzae* serotype b (Hib), meningococcal C and pneumococcal serotype 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F. For human papillomavirus (HPV) infection there was only a vaccine available against two types: HPV 16 and 18.
4. For HPV infection, the average annual burden in the period 2011–2014 is shown instead of that for the year 2015, based on the numbers of cases with cancer, anogenital warts and high-grade cervical lesions attributable to HPV.

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

Acceptance of vaccination

In 2015, the mean intention of parents to vaccinate their child was high. Based on our monitoring system for acceptance of vaccination, 21% of parents made an informed decision about childhood vaccinations included in the NIP, 'making an informed decision' being defined as having sufficient knowledge, showing a process of deliberation and being value-consistent in their choice. Mass media attention on the use of allegedly inferior needles, which was later refuted, appeared to have a negative impact on mothers' attitudes and intention towards HPV vaccination for their daughters. Awareness of the Ministry's decision to stop using these needles had a significant preventive impact on this decline.

With regard to the acceptance of vaccinations for the elderly, older adults themselves, general practitioners and elderly care specialists showed a generally positive attitude. Awareness of the existence of vaccination against pneumococcal disease, herpes zoster and pertussis was low as well as knowledge about the individual health benefits that can be achieved with these vaccines.

Adverse events

In 2015, Lareb received 1,494 reports of a total of 3,366 adverse events following immunisation (AEFI), which is an increase of about 50% over 2014. The spectrum of reported AEFI is in line with previous years. No signals emerged indicating that vaccines used in the NIP are unsafe.

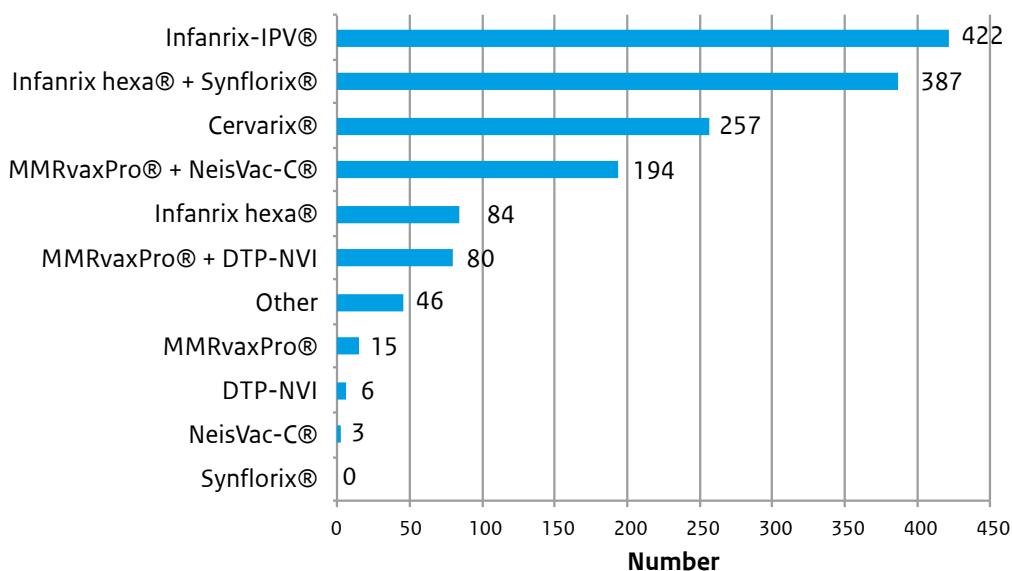


Figure 4 Number of reports of adverse events per suspected vaccine(s) in 2015

Source: Lareb

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

In a historical analysis of the effect of vaccination programmes on mortality burden among children and young adults in the Netherlands during the 20th century, a strong association between increasing vaccination coverage and diminishing mortality burden due to VPDs was shown (van Wijhe et al., the Lancet Infect Dis 2016).

In February 2016, a third population-based cross-sectional seroepidemiological study (PIENTER 3) was started. The survey will continue until the end of 2017. A serosurvey will also take place in the Dutch Caribbean in May 2017.

Current NIP

Diphtheria

In 2015, four diphtheria cases were reported. Furthermore, in 2016, up to 1st July, two notifications were received. All were cases of cutaneous diphtheria.

Results of the second nationwide serosurvey, performed by the RIVM in 2006/2007, showed that 91% of the general Dutch population had antibody levels >0.01 IU/ml.

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

The number of cases of Hib disease in 2015 (n=34) was similar to previous years, with the highest incidence among children under 5 years of age (1.5 per 100,000; n=13). Five Hib cases fulfilled the criteria of vaccine failure in 2015, resulting in a Hib vaccine effectiveness (VE) estimate of 97% (95% CI: 91–99%).

In 2015, 20 cases of Hi serotype f (Hif) were reported, which was more than in previous years (8 to 13 cases from 2011 to 2014).

Hepatitis B

The number of acute HBV infections in 2015 (n=105) was 20% lower than in 2014 (n=141). The incidence of acute HBV notifications in 2015 was 0.6 per 100,000. Almost 90% of the reported hepatitis B patients had a chronic infection (n=1,014), of which 90% were born abroad. In 2015, genotype A continued to be the dominant genotype among acute HBV cases.

Human papillomavirus (HPV) infection

Incidences of human papillomavirus (HPV)-associated cancers and death related to HPV-associated cancers has remained more or less stable in the past five years in the Netherlands. Ongoing surveillance among a cohort of vaccinated and unvaccinated adolescent girls showed that the bivalent vaccine remained effective against HPV-16/-18 incident and persistent infections for at least five years post-vaccination, significant cross-protection being observed against HPV-31/-45. The percentage of women positive for HPV-16 and/or -18 decreased from 23% in 2009, before vaccination was implemented, to 15% in 2015 among 16–24-year-old STI clinic attendees.

Measles

After the epidemic in 2013–2014 (n=2,700), seven measles cases were reported in 2015. Up to June 2016, no cases were reported. All seven cases were imported or import-related. One case reported having been vaccinated once; for one case the vaccination status was unknown; all the others were unvaccinated.

Meningococcal serogroup C (MenC) disease

Since the introduction of the conjugated MenC vaccine in 2002, the incidence of MenC disease has decreased enormously from 1.38 per 100,000 in 2002 to 0.05 per 100,000 in 2015. In 2015, eight cases were reported, one of which, a 75-year-old woman, died. There was one vaccine failure case in 2015. Up to August 2016, two MenC cases were reported.

Mumps

In 2015 and the first six months of 2016, indication of mumps endemic transmission was found. In 2015, 89 cases were reported, and two outbreak clusters were identified. Twenty of the cases were part of an outbreak cluster. Sixty per cent of the cases were vaccinated twice. In 2016, until 30th June, 45 mumps cases were reported, of which 15 were linked to one of two outbreak clusters. Most of the mumps cases in the Netherlands were caused by genotype G.

Pertussis

The incidence of pertussis notifications in 2015 was 39 per 100,000, which was lower than in the epidemic year 2014 (55 per 100,000). Since the introduction of acellular pertussis in the primary vaccine series in 2005, the effectiveness of infant vaccinations remains high until the preschool booster dose. In addition, the estimated effectiveness of the pre-school booster dose has remained high for about four to five years. Thereafter, vaccinated children are more susceptible to pertussis.

In December 2015, the Health Council advised offering all pregnant women a pertussis vaccination in the third trimester of pregnancy for better protection of their newborns.

Pneumococcal disease

The introduction of pneumococcal conjugate vaccination (PCV) led to a significant decrease in overall invasive pneumococcal disease (IPD) in children under five years of age and in adults aged 65 years and older. The incidence of PCV7 type IPD remained very low in 2015–2016, with an incidence of 0.9 per 100,000. The incidence of IPD caused by the additional serotypes in PCV10 (serotypes 1, 5 and 7F) was 0.5 per 100,000 in children under five years old in 2015–2016. Non-PCV10 type IPD incidence remained stable in 2015–2016 in all age groups.

The vaccine effectiveness (VE) of at least two doses of PCV10 was 87% (95% CI: 33–97%) against vaccine types.

Poliomyelitis

In 2015 and in 2016, up to 1st July, no cases of poliomyelitis were reported. However, in July 2015, a vaccine-derived poliovirus (VDPV) type3 was found in a young Syrian refugee without clinical symptoms. Furthermore, Sabin 1 and 2 strains were detected in December 2015 in a child returning from Pakistan.

Rubella

In the calendar year 2015 and in 2016, up to June, one rubella case was reported; the patient contracted rubella while visiting relatives in Namibia.

Tetanus

In 2015, one unvaccinated 18-year-old male with tetanus was reported. He probably contracted the bacterium after being wounded by a firework. In 2016, up to 1st July, no tetanus cases were reported.

Potential NIP target diseases

Hepatitis A

In 2015, 80 cases of hepatitis A were reported in the Netherlands, corresponding to 0.5 cases per 100,000 inhabitants. This is the lowest incidence since hepatitis A became notifiable in 1999. More than half of the cases were younger than 20 years old. Based on the reports, 14 epidemiologically linked clusters with a total of 29 cases could be deduced.

Meningococcal disease caused by non-serogroup C types

In 2015, 64 cases of meningococcal serogroup B (MenB) disease were reported, a similar number as in 2014 (n=60). Up to August 2016, 54 cases of MenB were reported, which was 1.4 times higher than in the same period in 2015. The incidence of MenB was highest in children under five years (2.1 and 3.4 per 100,000 in 2015–2016, respectively). In 2015–2016, a large increase in the number of cases with meningococcal serogroup W (MenW) disease was observed (26 cases up to August 2016 compared with 9 cases in 2015 and one to seven cases per year during 2005–2014). The recent MenW cases are mainly people aged 65 years or older (42%), and the increase is due to an increase in finetype P1.5,2:F1-1, which is associated with the hypervirulent clonal complex 11.

Respiratory syncytial virus (RSV) infection

In the season 2015/2016, RSV was detected in 8.6% (n=107/1238) of nose and throat swabs of ILI and ARI patients, collected by sentinel general practitioners (GPs). The percentage of positive specimens from the GP sentinel surveillance was highest in the age group 0–2 years old.

Rotavirus infection

In 2015, an average rotavirus season was observed, although a hyper-endemic season had been anticipated after the exceptionally low numbers in 2014. The 2015 season followed the usual pattern, with the epidemic peak in March. G4P[8] was the most prevalent genotype in 2015. Observations for the 2016 season up to 10th July showed again remarkably low numbers of reported rotavirus cases and a delayed start. Another low-endemic season in 2016 could indicate a transition to a biannual rotavirus epidemic pattern in the Netherlands, as has been observed in some countries with moderate to high rotavirus vaccine coverage rates. The origin of such a change in epidemic pattern in the Netherlands is currently unknown and is a focus of research.

The number of gastroenteritis hospitalisations attributable to rotavirus in children younger than five years was estimated at 3,508 patients in 2015.

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





The incidence of GP consultations (2014), hospitalisations (2014) and deaths (2015) is comparable to previous years, i.e. 270 per 100,000, 1.9 per 100,000, and 2 deaths, respectively for varicella and 530 per 100,000, 2.7 per 100,000 and 33 deaths, respectively for herpes zoster. The incidence of varicella episodes is highest in the age groups below 5 years, whereas the incidence of herpes zoster episodes is highest in the age groups above 50 years.

The Health Council of the Netherlands concluded that vaccination against herpes zoster should not be included in a public programme such as the NIP.

Uitgebreide samenvatting

In dit rapport worden surveillance data en wetenschappelijke ontwikkelingen in Nederland gepresenteerd voor ziekten waartegen binnen het Rijksvaccinatieprogramma (RVP) gevaccineerd wordt (difterie, kinkhoest, tetanus, polio, *Haemophilus influenzae* serotype b (Hib) ziekte, mazelen, bof, rodehond, meningokokken serogroep C-ziekte (MenC), hepatitis B, pneumokokkenziekte en infectie met humaan papillomavirus (HPV; Figuur 1). Ook worden surveillance data en wetenschappelijke ontwikkelingen beschreven voor ziekten waarvoor een vaccin (nog) niet is opgenomen in het RVP (rotavirusinfectie, infectie met varicella zoster-virus (VZV; waterpokken en gordelroos), hepatitis A, meningokokkenziekte veroorzaakt door serogroepen anders dan C (n.l. A, B, W, X, Y, Z, 29E) en infectie met respiratoir syncytieel virus (RSV)).

Huidig vaccinatieschema

Fase 1	Inenting 1	Inenting 2	Fase 2	Inenting 1	Inenting 2
 6-9 weken	DKTP Hib HepB	Pneu	 4 jaar	DKTP	
 3 maanden	DKTP Hib HepB				
 4 maanden	DKTP Hib HepB	Pneu			
 11 maanden	DKTP Hib HepB	Pneu			
 14 maanden	BMR	MenC			
Fase 3	Inenting 1	Inenting 2	Fase 4	Inenting 1	Inenting 2
 9 jaar	DTP	BMR	 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	<i>Haemophilus influenzae</i> type b	R	Rodehond		

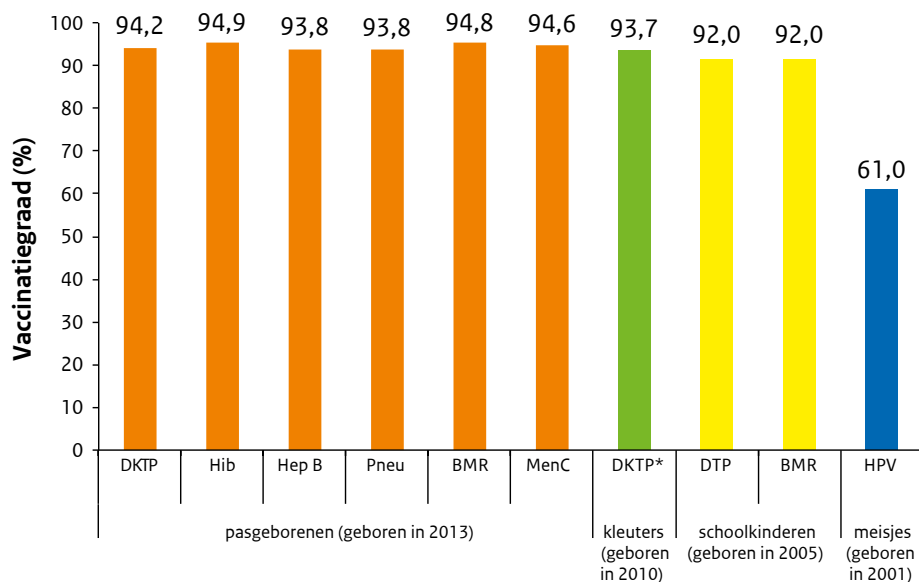


Figuur 1 Vaccinatieschema van het RVP

Bron: <http://www.rivm.nl/Onderwerpen/R/Rijksvaccinatieprogramma/Professionals>

Vaccinatiegraad

De vaccinatiegraad in Nederland is hoog. Toch is de participatie van pasgeborenen voor de meeste vaccinaties gedaald met ongeveer 0,5% voor het tweede achtereenvolgende jaar.



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

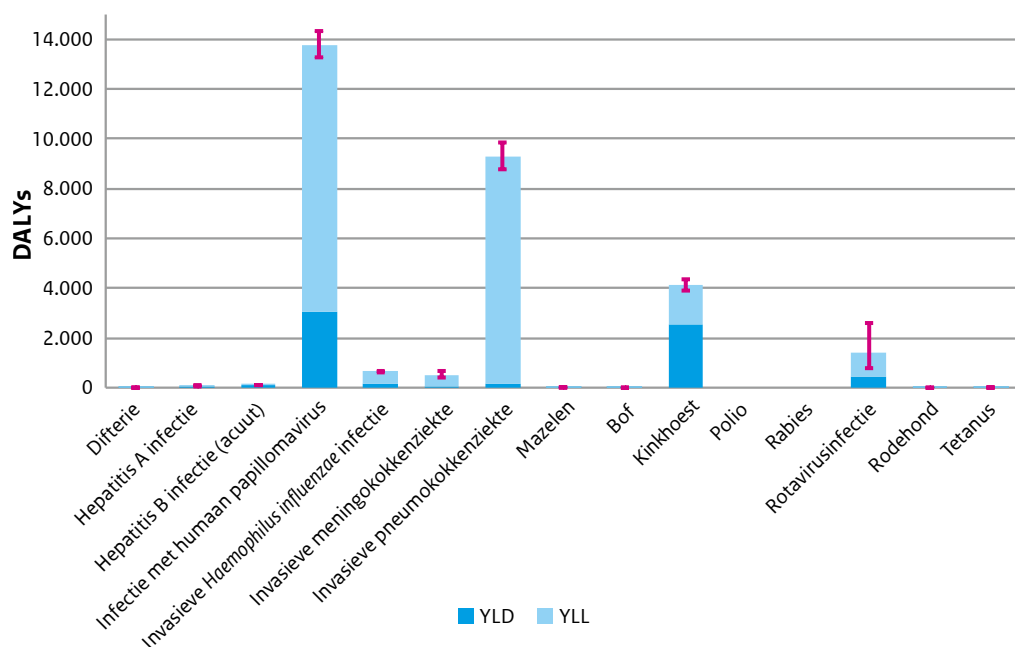
Figuur 2 Vaccinatiegraad per vaccin voor pasgeborenen, kleuters, schoolkinderen en adolescente meisjes in 2016

Bron: Præventis

In 2016 zijn alle aanpassingen afgerond om de vaccinatieprogramma's in Caribisch Nederland en Europees Nederland te harmoniseren.

Ziektelast

De schattingen van de ziektelast in Nederland worden uitgedrukt in Disability Adjusted Life Years (DALY), die bestaan zowel uit het aantal jaren geleefd met ziekte (YLD) als het aantal verloren levensjaren (YLL) door de ziekte of infectie. De geschatte ziektelast was het hoogst voor infectie met HPV, gevolgd door invasieve pneumokokkenziekte, kinkhoest en rotavirusinfectie. Vergeleken met de geschatte gemiddelde jaarlijkse ziektelast in de periode 2010-2014 was de geschatte ziektelast in 2015 aanzienlijk lager voor mazelen, rodehond, acute hepatitis B en hepatitis A infectie en meningokokkenziekte.



Figuur 3 Geschatte jaarlijkse ziektelast voor nieuwe cases in 2015, met jaren geleefd met ziekte (YLD) en verloren levensjaren (YLL) apart gepresenteerd

Ad 1: de rode lijnen geven het 95% betrouwbaarheidsinterval weer.

Ad 2: vaccinatie tegen rabies, hepatitis A infectie en rotavirusinfectie is niet opgenomen in het RVP.

Ad 3: voor de drie invasieve ziekten was in 2015 alleen een vaccin beschikbaar tegen bepaalde serotypen: *Haemophilus influenzae* serotype **b** (Hib), meningokokken serotype **C** en pneumokokken serotypen **1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F**. Voor infectie met humaan papillomavirus (HPV) was alleen een vaccin beschikbaar tegen twee types: HPV **16** en **18**.

Ad 4: voor infectie met HPV wordt de gemiddelde jaarlijkse ziektelast in de periode 2011-2014 in plaats van het jaar 2015 getoond, gebaseerd op het aantal gevallen van kanker, anogenitale wratten, en hooggradige cervicale laesies die zijn toe te schrijven aan HPV.

Bron: OSIRIS, NRBm, sentinel laboratorium surveillance, nationale kankerregistratie, PALGA, NIVEL-LINH

Acceptatie van vaccinatie

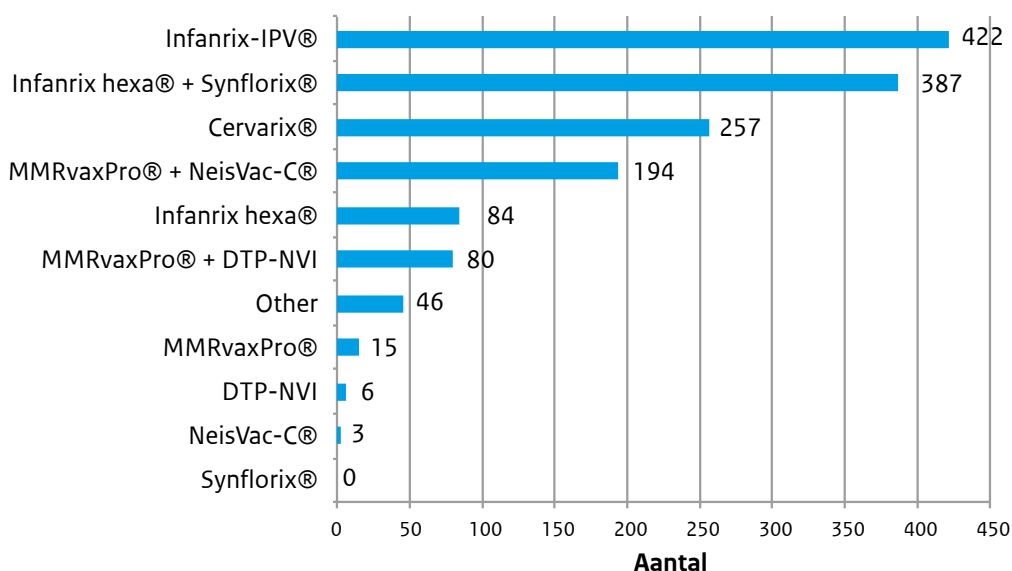
In 2015 was de gemiddelde intentie van ouders om hun kind te laten vaccineren hoog.

Gebaseerd op ons monitoringssysteem voor de acceptatie van vaccinatie maakte 21% van de ouders een geïnformeerde keuze over RVP-vaccinaties, d.w.z. zij hadden voldoende kennis, overwogen hun keuze en waren consistent in hun keuze. Media-aandacht over het gebruik van zogenaamde inferieure naalden, wat later werd weerlegd, bleek een negatief effect te hebben op de houding van moeders en de intentie tot het vaccineren van hun dochters tegen HPV. Bekendmaking van het besluit van het ministerie om te stoppen met het gebruik van deze naalden had een significant preventief effect op deze daling.

Met betrekking tot de acceptatie van vaccinaties voor ouderen bleken ouderen zelf, huisartsen en specialisten in de ouderenzorg een positieve houding te hebben. De bekendheid met het bestaan van vaccinatie tegen pneumokokken, gordelroos en kinkhoest was laag evenals kennis over de individuele gezondheidsvoordelen die kunnen worden bereikt met deze vaccins.

Bijwerkingen

In 2015 ontving Bijwerkingencentrum Lareb 1494 meldingen met 3366 mogelijke bijwerkingen van vaccins. Dit is een stijging van het aantal meldingen van ongeveer 50% ten opzichte van 2014. De aard van de gemelde bijwerkingen is vergelijkbaar met voorgaande jaren. De meldingen van vermoede bijwerkingen in 2015 hebben geen nieuwe signalen aan het licht gebracht.



Figuur 4 Aantal meldingen van bijwerkingen per vaccin(s) in 2015

Bron: Lareb

Verschillende onderzoeksonderwerpen over de evaluatie van het RVP in bredere zin

In een historische analyse naar het effect van vaccinatieprogramma's op sterfte onder kinderen en jongvolwassenen in Nederland tijdens de 20^e eeuw werd een sterke associatie gevonden tussen een stijgende vaccinatiegraad en vermindering van sterfte door ziekten waartegen gevaccineerd kan worden (van Wijhe et al., the Lancet Infect Dis 2016).

In februari 2016 is een derde sero-epidemiologische studie gestart onder de Nederlandse bevolking (PIENTER 3). De studie zal tot en met 2017 duren. Ook zal er in mei 2017 een sero-epidemiologisch onderzoek in Caribisch Nederland plaatsvinden.

Huidig RVP

Difterie

In 2015 waren er vier meldingen van difterie. In de eerste maanden van 2016, tot 1 juli, werden twee gevallen gemeld. Het waren allemaal meldingen van cutane difterie.

Resultaten van de tweede sero-epidemiologische studie, uitgevoerd door het RIVM in 2006/2007, lieten zien dat 91% van de Nederlandse bevolking een antistof niveau had >0,01 IU/ml.

Haemophilus influenzae ziekte veroorzaakt door type b (Hib) en andere serotypes

Het aantal gevallen van invasieve ziekte veroorzaakt door Hib in 2015 was met 34 vergelijkbaar met het aantal in het jaar daarvoor. De hoogste incidentie werd gevonden onder kinderen jonger dan 5 jaar (1,5 per 10.000; aantal=13). Er waren in 2015 vijf Hib vaccinalens, wat resulteerde in een schatting van de vaccineffectiviteit van 97% (95% betrouwbaarheidsinterval (BI): 91-99%).

In 2015 werden 20 gevallen van Hi serotype f (Hif) gerapporteerd. Dit was meer dan in voorgaande jaren (8 tot 13 gevallen in de periode 2011 tot 2014).

Hepatitis B

In 2015 is het aantal meldingen van acute HBV (n=105) 20% lager dan in 2014 (n=141).

De incidentie van meldingen van acute hepatitis B infecties in 2015 was 0,6 per 100.000 inwoners. Bijna 90% van de gerapporteerde hepatitis B patiënten had een chronische infectie (n=1014), waarvan 90% in het buitenland is geboren. In 2015 was genotype A nog steeds het dominante genotype onder acute hepatitis B gevallen.

Human papillomavirus (HPV) infectie

Incidenties van HPV-geassocieerde kankers en sterfgevallen bleven stabiel in de afgelopen 5 jaar in Nederland. Surveillance in een cohort van gevaccineerde en ongevaccineerde adolescente meisjes liet zien dat het bivalente vaccin in ieder geval tot 5 jaar na de vaccinatie effectief is tegen HPV-16/-18 incidente en persistente infecties. Ook werd significante kruisbescherming geobserveerd tegen HPV-31/-45. Onder 16- tot 24-jarige SOA-kliniek bezoekers is het percentage vrouwen dat positief is voor HPV-16 en/of -18 gedaald van 23% in 2009, voor implementatie van vaccinatie, naar 15% in 2015.

Mazelen

Na de epidemie in 2013/2014 (n=2700), werden zeven gevallen van mazelen gemeld in 2015. In 2016 werden tot en met juni geen mazelen gevallen gemeld. Alle zeven gevallen waren import gevallen of import-gerelateerd. Eén geval was eenmalig gevaccineerd en voor één geval was de vaccinatiestatus onbekend. Alle andere gevallen waren ongevaccineerd.

Meningokokken serogroep C (MenC)-ziekte

Sinds de introductie van het geconjugerd MenC vaccin in 2002 is de incidentie van MenC-ziekte drastisch gedaald van 1,38 per 100.000 in 2002 naar 0,05 per 100.000 in 2015. In 2015 werden 8 cases gerapporteerd, waarvan een 75-jarige vrouw overleed. Er was één patiënt met vaccinfalen in 2015. In 2016, tot en met augustus, werden twee MenC gevallen gerapporteerd.

Bof

In 2015 en de eerste zes maanden van 2016 is er endemische transmissie van bof gevonden. Er werden 89 gevallen van bof gerapporteerd in 2015, en twee uitbraak clusters konden worden geïdentificeerd. Twintig van de gevallen maakten deel uit van een uitbraakcluster. Van de gevallen was 60% twee maal gevaccineerd. In 2016, tot 30 juni, werden 45 gevallen van bof gemeld waarvan er 15 gelinkt waren aan één van twee uitbraakclusters. De meeste gevallen van bof worden veroorzaakt door genotype G.

Kinkhoest

De incidentie van meldingen van kinkhoest in 2015 was met 39 per 100.000 lager dan in het epidemische jaar 2014 (55 per 100.000). Sinds de introductie van het acellulair kinkhoestvaccin in de primaire serie in 2005 blijft de vaccineffectiviteit hoog tot aan de boostervaccinatie op 4-jarige leeftijd. De vaccineffectiviteit van de boostervaccinatie blijft ongeveer 4-5 jaar hoog. Daarna krijgen gevaccineerde kinderen makkelijker kinkhoest. In december 2015 heeft de Gezondheidsraad geadviseerd om alle zwangere vrouwen in het derde trimester van de zwangerschap een kinkhoestvaccinatie aan te bieden om pasgeborenen beter te beschermen.

Pneumokokkenziekte

Introductie van pneumokokkenvaccinatie (PCV) heeft geleid tot een significante daling in invasieve pneumokokkenziekte onder kinderen jonger dan 5 jaar en onder ouderen 65 jaar of ouder. De incidentie van PCV7-typen pneumokokkenziekte bleef met 0,9 per 100.000 erg laag in 2015–2016. De incidentie van pneumokokkenziekte veroorzaakt door de additionele typen in PCV10 (serotype 1, 5 en 7F) was 0,5 per 100.000 onder kinderen jonger dan 5 jaar. De incidentie van niet-PCV10 typen bleef in alle leeftijdsgroepen stabiel in 2015–2016. De vaccineffectiviteit van minimaal twee doses PCV10 was 87% (95% BI: 33 tot 97%) tegen pneumokokkenziekte veroorzaakt door vaccin typen.

Polio

In 2015 en 2016, tot 1 juli, werden geen gevallen van polio gerapporteerd. In juli 2015 werd wel een Vaccine Derived PolioVirus (VDPV) type 3 gevonden bij een jonge Syrische asielzoeker zonder klinische symptomen. Verder werden er in december 2015 Sabin 1 en 2 stammen gedetecteerd bij een kind die terug kwam uit Pakistan.

Rodehond

In 2015 werd 1 geval van rodehond gerapporteerd. Deze persoon heeft de ziekte opgelopen tijdens bezoek aan familieleden in Namibië. In 2016, tot en met juni, werden geen gevallen van rodehond gemeld.

Tetanus

In 2015 werd een melding gedaan van tetanus bij een 18-jarige ongevaccineerde man. Waarschijnlijk heeft hij de infectie opgelopen nadat hij gewond was geraakt door vuurwerk. Tot 1 juli 2016 werden geen meldingen van tetanus gedaan.

Potentiële RVP-kandidaten

Hepatitis A

Er werden in 2015 80 hepatitis A gevallen gerapporteerd in Nederland, wat correspondeert met een incidentie van 0,5 per 100.000 inwoners. Dit is de laagste incidentie sinds de invoering van de meldingsplicht voor hepatitis A in 1999. Meer dan de helft van de gevallen was jonger dan 20 jaar. Op basis van de meldingen konden 14 epidemiologisch gelinkte clusters geïdentificeerd worden.

Meningokokken niet-serogroep C ziekten

Er werden 64 gevallen van meningokokken serogroep B (MenB) ziekte gerapporteerd in 2015. Dit aantal was vergelijkbaar met het aantal in 2014 (N=60). Tot augustus 2016 werden 54 patiënten met MenB gemeld; dit is 1,4 keer zo veel als in dezelfde periode in 2015. De incidentie van MenB in 2015 en 2016 was het hoogst onder kinderen jonger dan 5 jaar (2,1 respectievelijk 3,4 per 100.000).

In 2015 en 2016 werd een stijging van het aantal gevallen van meningokokken serogroep W (MenW) gezien: 26 gevallen tot en met augustus 2016 vergeleken met 9 in 2015 en 1-7 per jaar in 2005-2014. Van de recente MenW gevallen waren de meeste 65 jaar of ouder (42%).

De stijging komt door een stijging van fijntype P1.5,2:F1-1 dat is geassocieerd met het hypervirulente klonaal complex 11.

Respiratoir syncytieel virus (RSV) infectie

In het seizoen 2015/2016 werd in 8,6% (n=107/1238) van de neus- en keelwabs van ILI en ARI patiënten, verzameld door sentinel huisartsen, RSV aangetoond. Het percentage positieve monsters was het hoogst onder kinderen jonger dan 2 jaar.

Rotavirusinfectie

2015 was een normaal rotavirus seizoen, ondanks dat er een hyperendemisch seizoen werd verwacht na het extreem lage aantal gevallen in 2014. Het seizoenspatroon in 2015 was echter normaal, met de endemische piek in maart. G4P[8] was het meest voorkomende genotype in 2015.

Tot 10 juli 2016 werd eveneens een extreem laag aantal gevallen van rotavirus gezien met een latere start van het seizoen. Een herhaald laag-epidemisch seizoen zou een overgang naar een tweejaarlijks epidemisch patroon kunnen betekenen, zoals wordt beschreven in sommige landen met een gemiddelde tot hoge vaccinatiegraad tegen rotavirus. De oorzaak van zo'n verandering in epidemisch patroon is tot nu toe onbekend en wordt momenteel onderzocht. Het geschatte aantal gastro-enteritis ziekenhuisopnames in kinderen jonger dan 5 jaar dat toegeschreven kan worden aan rotavirus is 3508 in 2015.

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

De incidentie van huisartsenbezoeken (2014), ziekenhuisopnames (2014) en sterfgevallen (2015) is vergelijkbaar met voorgaande jaren, namelijk 270 per 100.000, 1,9 per 100.000 en 2 sterfgevallen, respectievelijk voor waterpokken en 530 per 100.000, 2,7 per 100.000 en 33 sterfgevallen, respectievelijk voor gordelroos. De incidentie van waterpokken is het hoogst onder kinderen jonger dan 5 jaar terwijl de incidentie van gordelroos het hoogst is in de leeftijdsgroep 50 jaar en ouder.









De Gezondheidsraad heeft geconcludeerd dat vaccinatie tegen gordelroos niet in aanmerking komt voor invoering in een publiek vaccinatieprogramma zoals het RVP.

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	Pneumococcal disease	HPV	Human papillomavirus
T	Tetanus	M	Mumps		
IPV	Poliomyelitis	M	Measles	*	Only for girls
Hib	<i>Haemophilus influenzae</i> 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 2015 and 2016 up to October, no changes in the vaccination schedule of the NIP were made.

1.1.2 Number of vaccinated children

In 2015, almost 770,000 children from 0 to 19 years of age were immunised in the context of the Dutch NIP. They received a total of 1,547,000 vaccine doses. In 2015, 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 Sports (VWS) responded positive to the advice of the Dutch Health Council to offer all pregnant women in the Netherlands a pertussis vaccination to protect newborns against pertussis. A final decision by the Ministry is expected at the end of 2016.

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 on influenza and tuberculosis, we refer readers to the reports of the Centre for Infectious Disease Control (CIb), the Health Council and the KNCV Tuberculosis Foundation [1-4]. Besides the vaccination against HBV included in the NIP, an additional vaccination programme targeting groups particularly at risk of HBV due to sexual behaviour or profession is in place in the Netherlands.

1.4 Vaccination outside of public vaccination programmes

In addition to the childhood vaccinations in the NIP, influenza vaccination in the NPG and vaccination for risk groups, there are a number of registered vaccines in the Netherlands that are available outside of public programmes. In 2015, the Dutch Health Council expanded the evaluation of these vaccines and provided advice on them [5] to the Minister of Health, Welfare and Sports, who will decide whether a vaccine will be included in a public vaccination programme, will be reimbursed by basic health insurance or that the vaccine will remain available on the persons's own expense.

Vaccinations available for infants are those against gastro-enteritis caused by rotavirus infection, against varicella and against meningococcal B disease (MenB). For older children and adults, influenza and pertussis vaccinations are available. The Dutch Health Council has advised that maternal pertussis vaccination should be included in a national programme. For older people, vaccinations against herpes zoster, pneumococcal disease and pertussis are available. It has been advised that vaccination against herpes zoster should not be offered within a national programme but should remain available at the person's own expense. In addition, HPV vaccination for boys, hepatitis A vaccination for children with one or both parents coming from a country with a 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.

On the website www.rivm.nl/vaccinaties there is information on a number of vaccines available to the public. Professional guidelines are also available on herpes zoster and maternal pertussis vaccination. Others are currently under development.

1.5 Literature

- 1.* RIVM. Griepvrikk. Available from: www.rivm.nl/griepvrikk/voor_wie/.
- 2.* Slump E, Erkens CGM, van Hunen R, van Soolingen D, Teirlinck AC, de Vries G. Tuberculosis in the Netherlands 2014. Bilthoven: RIVM, 2015. RIVM report 2015-0168.
3. Tacken M, Jansen B, Mulder J, Tiersma W, Braspenning J. Monitoring Vaccinatiegraad Nationaal Programma Grieppreventie 2013. Nijmegen: LINH, IQ healthcare, 2014.
- 4.* Teirlinck CJPM, van Asten L, Brandsema PS, Dijkstra F, Donker GA, Euser SM et al. Surveillance of influenza and other respiratory infections in the Netherlands: winter 2014/2015. Bilthoven: RIVM, 2015. RIVM report 2015-0042.
5. Health Council of the Netherlands. The individual, collective and public importance of vaccination. The Hague: Health Council of the Netherlands, 2013 publication no. 2013/21.

* RIVM publication

2

Vaccination coverage



2.1 Key points

- Vaccination coverage in the Netherlands is high.
- Participation for most vaccinations declined by about 0.5% for newborns for the second consecutive year.

2.2 Vaccination coverage

As in previous years, the immunisation coverage (or participation) for the different vaccinations included in the NIP was with 92% to 99% high in report year 2016. However, participation for most vaccinations declined by about 0.5%. For newborns, this decline was observed for the second consecutive year. Such fluctuations were observed previously at regional level, but they are now for the first time being observed nationwide. An explanation is lacking. Participation for HPV vaccination has remained unchanged at 61%. Participation among newborns in the Caribbean Netherlands has also remained unchanged at 92% to 100%.

From 2012 onwards, not only children at risk but all children have been offered hepatitis B vaccination. However, children with at least one parent born in a country where hepatitis B is endemic did not always receive the vaccination. In addition, hepatitis B control testing to assess the effectiveness of the vaccine among the children of mothers who are carriers of the hepatitis B virus is not always conducted. Especially for these two risk groups, protection against hepatitis B is important.

2.3 Dutch Caribbean

In 2016, the immunisation programme in the Dutch Caribbean municipalities, Bonaire, St Eustatius and Saba (BES islands), was fully harmonised with the NIP in European Netherlands.

2.4 Tables and figures

Table 2.1 Vaccination coverage (%) per vaccine for age cohorts of newborns, toddlers, schoolchildren and adolescent girls in 2006–2016

	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	93.1

	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

* Vaccination coverage is assessed at the ages of 2 years (newborns), 5 years (toddlers), 10 years (schoolchildren) and 14 years (adolescent girls).

** Only for newborns born on or after 1 April 2006.

*** Key figure full participation newborns: received all NIP vaccinations at 2 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

2.5 Literature

2.5.1 References

- 1.* van Lier EA, Oomen PJ, Giesbers H, van Vliet JA, Drijfhout IH, Zonnenberg-Hoff IF et al. Immunisation coverage National Immunisation Programme in the Netherlands: Year of report 2016. Bilthoven: RIVM, 2016; RIVM report 2016-0064.

*RIVM publication

2.5.2 Other recent RIVM publications

1. Klomp JH, van Lier A, Ruijs WL. Vaccination coverage for measles, mumps and rubella in anthroposophical schools in Gelderland, The Netherlands. Eur J Public Health. 2015;25:501–5.

3 Burden of disease



3.1 Key points

- The estimated disease burden caused by vaccine-preventable diseases expressed in disability-adjusted life years (DALY) for the year 2015 was from high to low: invasive pneumococcal disease (9,292 DALYs/year), pertussis (4,114 DALYs/year), rotavirus infection (1,423 DALYs/year), invasive *Haemophilus influenzae* infection (644 DALYs/year), invasive meningococcal disease (521 DALYs/year), acute hepatitis B infection (106 DALYs/year), hepatitis A infection (65 DALYs/year), measles (14 DALYs/year), tetanus (8 DALYs/year), diphtheria (4 DALYs/year), mumps (1 DALYs/year), rubella (0.05 DALYs/year), rabies (0 DALYs/year), and poliomyelitis (0 DALYs/year).
- In a separate analysis, the average annual disease burden for HPV in the period 2011–2014 was estimated at 13,795 DALYs (76% among women), higher than any of the diseases mentioned above. For varicella, a model to estimate the disease burden is not yet available.
- Compared with the estimated average annual burden in the period 2010–2014, the estimated burden in 2015 was considerably lower for measles, rubella, acute hepatitis B and hepatitis A infection, and meningococcal disease, whereas the burden was higher for invasive *Haemophilus influenzae* infection.

3.2 Burden of disease

Here we present an update on the disease burden of vaccine-preventable diseases in 2015. We also calculated the burden separately for each of the years in the period 2011–2014. We used the same methodology and assumptions that were used in the State of Infectious Diseases in the Netherlands, 2013 [1, 2], except that for mumps, measles, pertussis and rubella multiplication factors to correct for underestimation (under-ascertainment and/or under-reporting) of the incidence were updated. Additionally we included the estimated disease burden of rotavirus infection based on methodology developed by Havelaar et al. [3, 4]. The average annual burden of HPV in the period 2011–2014 was also estimated in a separate analysis. Note that the calculation method for HPV is not fully comparable with that for the other diseases: a different period (2011–2014) and life table (Dutch life expectancy 2014) were used and instead of using the number of incident infections (which is unknown), we used the numbers of cases of cancer, anogenital warts and high-grade cervical lesions attributable to HPV. For varicella, a model to estimate the disease burden is not yet available.

The total annual number of reported cases in the period 2011–2015, the selected multiplication factors, and the estimated incident cases and deaths in the year 2015 for all diseases are provided in Table 3.1. Table 3.2 gives a comprehensive overview of the national burden estimates in the year 2015 for each of the diseases investigated. Data is presented both in

aggregated form (DALYs per year) and in disaggregated form (YLD and YLL per year), from a population perspective (DALYs per year) and from an individual perspective (DALYs per year per 100 infections).

The estimated burden for new cases in the year 2015 is shown in Figure 3.1. For poliomyelitis and rabies, the estimated disease burden was zero because no cases were reported in 2015. For rubella, mumps, diphtheria and tetanus the disease burden was estimated to be very low, while the highest burden was estimated for HPV infection (based on the average annual burden in 2011–2014 instead of 2015), followed by invasive pneumococcal disease, pertussis and rotavirus infection.

The relationship between individual-level burden (DALYs/100 infections) and population-level burden (DALYs) in 2015 is shown in Figure 3.2. Poliomyelitis and rabies could not be included because there were no cases reported in 2015, and HPV could not be included because the number of HPV infections is unknown. Rubella and mumps have a relatively low burden at both the population and the individual levels. Rotavirus infection and pertussis have a relatively low burden at the individual level, whereas the disease burden at the population level is rather high due to the high incidence. In contrast, tetanus and diphtheria have a relatively high burden at the individual level, but a low burden at the population level due to the small number of cases.

Compared with the estimated average annual burden in the period 2010–2014 (see annual report 2014/2015), the estimated burden in 2015 is considerably lower for measles (the last outbreak was in 2013/2014), rubella (no congenital rubella cases in 2015), acute hepatitis B and hepatitis A infection (fewer cases in 2015) and meningococcal disease (fewer cases <5 years of age), whereas the burden was higher for invasive *Haemophilus influenzae* infection (more cases in 2015). Figure 3.3 shows the estimated burden per year, revealing that in the period 2011–2015 the burden for invasive pneumococcal disease, measles, pertussis, rotavirus infection and rubella was more sensitive to annual fluctuations than the burden for other diseases.

It should be noted that the total disease burden for pneumococcal disease, meningococcal disease and *Haemophilus influenzae* infection is higher than presented here because we limited our analyses to *invasive* disease. The disease burden related to hepatitis B infection is also underestimated. Our analyses reflect only the (future) burden of new cases of hepatitis B infection in the year 2015, which means that the disease burden of (chronic) hepatitis B cases infected prior to this period is not included. Total mortality from chronic hepatitis B, including deaths from cirrhosis and hepatocellular carcinoma attributable to chronic hepatitis B infection, is estimated to be around 200 per year in the period 2008–2012 [9].

3.3 Tables and figures

Table 3.1 Total number of reported new cases in the years 2011–2015, multiplication factors (MFs) chosen to adjust for underestimation, and estimated number of new infections and deaths in the year 2015 (adjusted for underestimation), per disease

Disease	Total number of reported new cases					MF(s) chosen using Uniform or Pert distribution	Estimated number 2015	
	2011	2012	2013	2014	2015		Infections	Deaths
Diphtheria	1	1	0	1	4	UE: 1 ^d	4	<1
Hepatitis A infection	125	121	109	105	79	See Havelaar et al.[3, 4]	393	1
Hepatitis B infection (acute)	159	174	145	141	105	UA: 1.33 ^c UR: Uniform(1.20,1.22) ^c	518	2
Human papillomavirus infection ^h	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	417
Invasive <i>Haemophilus influenzae</i> infection ^a	139	140	159	160	190	UE: Uniform(1.05,1.20) ^c	214	16
Invasive meningococcal disease ^a	101	98	116	83	89	UE: 1.05 ^c	93	10
Invasive pneumococcal disease ^b	2,496	2,472	2,592	2,152	2,636	UE: Uniform(1.05,1.20) ^c	2,965	444
Measles ^a	51	10	2,688	140	7	UE: Pert(8.44,11.21,15.02) ^e	80	<1
Mumps ^a	614	397	205	39	88	UE: Pert(1.55,1.79,2.13) ^f	159	<1
Pertussis ^a	5,450	13,853	3,422	8,575	6,572	UE: Pert(23,41,66) (<1 yr) ^g Pert(17,25,34) (1-4 yrs) Pert(16,26,39) (5-9 yrs) Pert(6,10,15) (10-19 yrs) Pert(37,47,59) (20-59 yrs) Pert(49,69,96) (60+ yrs)	242,906	31
Poliomyelitis	0	0	0	0	0	-	0	0
Rabies	0	0	1	1	0	UE: 1 ^c	0	0
Rotavirus infection	3,947	3,363	3,913	1,607	3,448	See Havelaar et al.[3, 4]	259,288	43
Rubella ^a	3	1	57	2	1	UE: Pert(8.44,11.21,15.02) ^e (MF measles used as proxy)	11	<1
Tetanus	6	2	1	0	1	UE: Uniform(1.0,1.41) ^c	1	<1

UA=under-ascertainment, UR=under-reporting, UE=underestimation (UA+UR combined).

Notes:

^a Cases with unknown age and/or sex were imputed using the univariate method.

^b Corrected for 25% coverage of the sentinel surveillance system.

^c Same multiplication factor as used in State of Infectious Diseases in the Netherlands, 2013 [1].

^d No multiplication factor available.

^e New multiplication factor based on random effects meta-analysis of data from measles outbreaks in 1999/2000 [5] and 2013/2014 (preliminary data).

^f New multiplication factor based on random effects meta-analysis of data from mumps outbreaks in 2009/2010 [6] and 2012 [7].

^g New multiplication factor derived by evidence synthesis approach [8].

^h Estimated average annual number of deaths as a result of the cancer incidence in the period 2011–2014. The number of HPV infections is unknown.

Sources: OSIRIS, NRBm, sentinel laboratory surveillance, national cancer registry

Table 3.2 Estimated burden in the year 2015 for new cases in this period: mean (with 95% uncertainty intervals) YLD, YLL, DALYs, and DALYs/100 infections

Disease	YLD	YLL	DALYs	DALYs/100 infections
Diphtheria	0.07 (0.07-0.07)	3.48 (2.86-4.09)	3.55 (2.93-4.16)	89 (73-104)
Hepatitis A infection	23 (16-36)	41 (25-68)	65 (42-103)	17 (13-21)
Hepatitis B infection (acute)	76 (76-76)	30 (25-34)	106 (101-110)	20 (20-21)
Human papillomavirus infection ^d	3,045 (2,935-3,162)	10,748 (10,330-11,200)	13,795 (13,280-14,340)	n.a.
I. <i>H. influenzae</i> infection	151 (136-165)	493 (461-525)	644 ^a (608-680)	301 (285-318)
I. meningococcal disease	38 (30-47)	483 (378-602)	521 ^b (408-648)	558 (492-622)
I. pneumococcal disease	147 (145-149)	9,145 (8,611-9,703)	9,292 ^c (8,757-9,850)	313 (296-332)
Measles	1 (1-2)	13 (8-17)	14 (9-19)	18 (12-23)
Mumps	0.8 (0.8-0.8)	0.1 (0.04-0.1)	0.9 (0.8-0.9)	0.5 (0.5-0.6)
Pertussis	2,551 (2,447-2,661)	1,563 (1,403-1,749)	4,114 (3,884-4,365)	1.7 (1.6-1.8)
Poliomyelitis	-	-	-	n.a.
Rabies	-	-	-	n.a.
Rotavirus infection	464 (355-600)	959 (310-2,122)	1,423 (759-2,599)	0.6 (0.3-1.0)
Rubella	0.01 (0.01-0.02)	0.03 (0.02-0.06)	0.05 (0.03-0.07)	0.4 (0.3-0.6)
Tetanus	0.03 (0.02-0.03)	7.8 (6.4-9.2)	7.8 (6.5-9.2)	649 (622-676)

YLD=years lived with disability, YLL=years of life lost, DALYs= disability-adjusted life years.

Notes:

^a Proportion caused by the vaccine-preventable type b in 2015: 26%.

^b Proportion caused by the vaccine-preventable type C in 2015: 8%; proportion caused by type B in 2015: 82%.

^c Proportion caused by the vaccine-preventable types 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F in 2015: 24%.

^d Average annual burden in the period 2011–2014 instead of the year 2015. To estimate the burden the numbers of cases of cancer, anogenital warts and high-grade cervical lesions attributable to HPV were used. DALYs per 100 infections not calculated because the number of HPV infections is unknown.

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

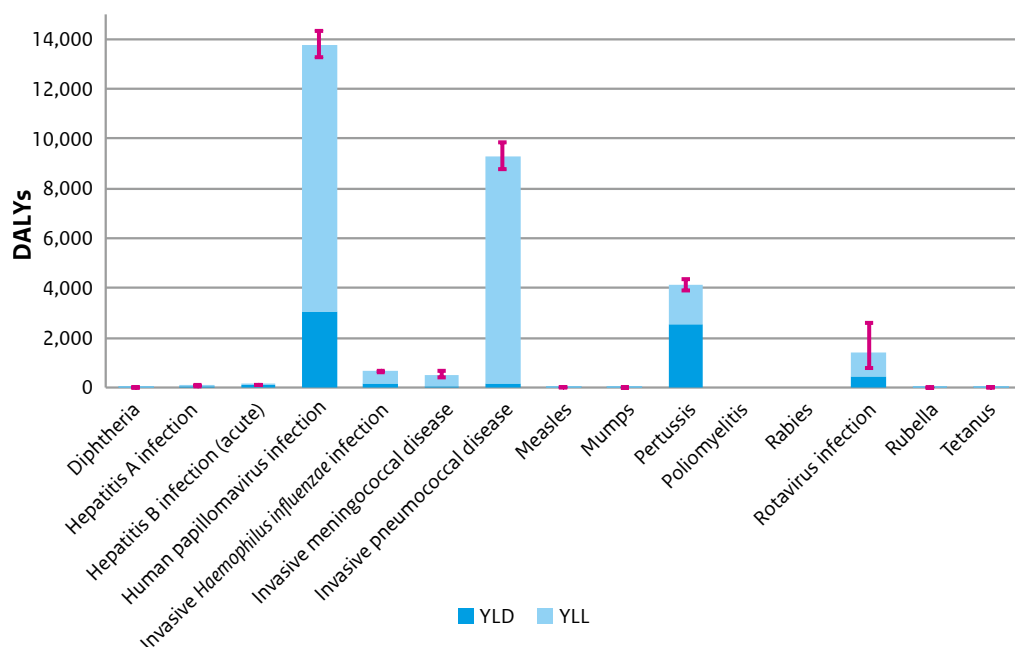


Figure 3.1 Estimated burden for new cases in the year 2015, with the years lived with disability (YLD) and years of life lost (YLL) components shown separately

Notes:

1. Red lines indicate 95% uncertainty intervals.
2. Vaccination against rabies, hepatitis A infection and rotavirus infection is not included in the NIP.
3. For the three invasive diseases there was only a vaccine available against certain serotypes in 2015: *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**.
4. For HPV infection, the average annual burden in the period 2011–2014 instead of that for the year 2015 is shown, based on the numbers of cases with cancer, anogenital warts and high-grade cervical lesions attributable to HPV.

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

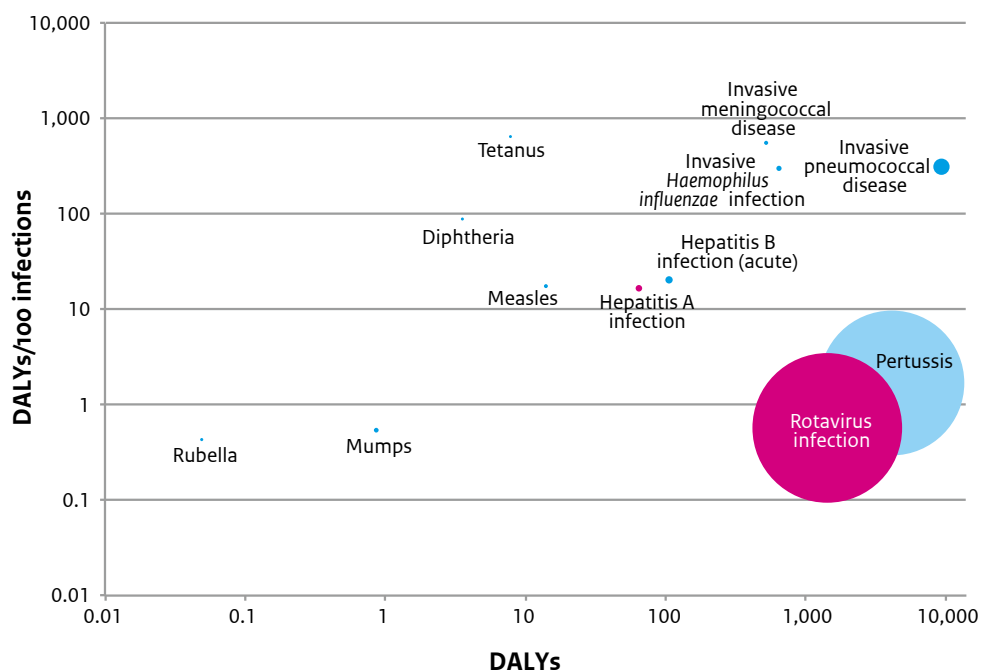


Figure 3.2 Ranking of diseases by estimated burden at population level (DALYs) and individual level (DALYs/100 infections) in the year 2015

Poliomyelitis and rabies could not be included because there were no cases reported in 2015. HPV infection could not be included because the number of HPV infections is unknown.

The area of each bubble is proportional to the number of estimated cases in 2015 (100 cases were added to each bubble to aid visibility).

Notes:

1. Both axes are on a logarithmic scale.
2. Blue bubbles = included in NIP, purple bubbles= not included in NIP.
3. For the three invasive diseases there was only a vaccine available against certain serotypes in 2015: *Haemophilus influenzae* serotype **b** (**Hib**), meningococcal **C** and pneumococcal serotype **1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F**.

Sources: OSIRIS, NRBM, sentinel laboratory surveillance

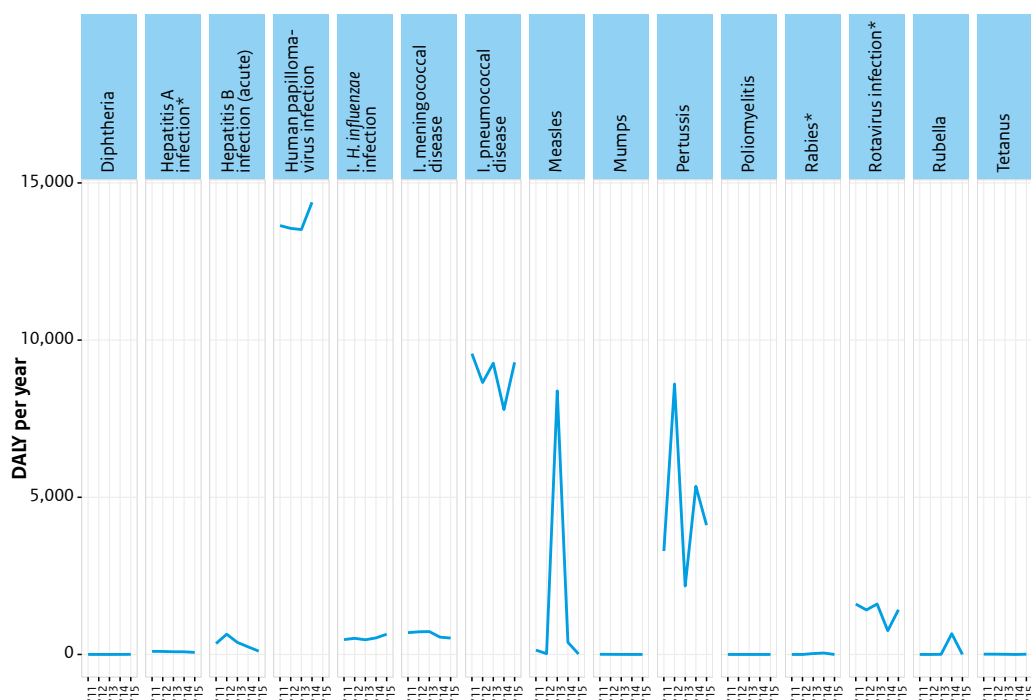


Figure 3.3 Estimated burden (DALYs) per year in the period 2011–2015

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

Notes:

1. For the three invasive diseases there was only a vaccine available against certain serotypes in 2015: *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**.

2. For HPV, the burden is based on the numbers of cases with cancer, anogenital warts and high-grade cervical lesions attributable to HPV.

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

3.4 Literature

3.4.1 References

- 1.* Bijkerk P, van Lier A, McDonald S, Kardamanidis K, Fanoy EB, Wallinga J et al. State of infectious diseases in the Netherlands, 2013. Bilthoven: RIVM; 2014. RIVM report 150205001. <http://www.rivm.nl/bibliotheek/rapporten/150205001.pdf>.
- 2.* Bijkerk P, van Lier A, McDonald S, Wallinga J, de Melker HE. Appendix: State of infectious diseases in the Netherlands, 2013. Bilthoven: RIVM; 2014. Appendix RIVM report 150205001. <http://www.rivm.nl/bibliotheek/rapporten/appendix150205001.pdf>.
- 3.* Haagsma JA, van der Zanden BP, Tariq L, van Pelt W, van Duynhoven YTPH, Havelaar AH. Disease burden and costs of selected foodborne pathogens in the Netherlands, 2006. Bilthoven: RIVM; 2009. RIVM report 330331001.
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- 7.* Ladbury G, Ostendorf S, Waegemaekers T, van Binnendijk R, Boot H, Hahne S. Smoking and older age associated with mumps in an outbreak in a group of highly-vaccinated individuals attending a youth club party, the Netherlands, 2012. *Euro Surveill*. 2014;19(16):20776.
- 8.* McDonald SA, Teunis P, van der Maas N, de Greeff S, De Melker H, Kretzschmar ME. An evidence synthesis approach to estimating the incidence of symptomatic pertussis infection in the Netherlands, 2005–2011. *BMC Infect Dis*. 2015;15:588.
9. Hofman R, Nusselder WJ, Veldhuijzen IK, Richardus JH. [Chronic hepatitis B and C virus infection related mortality in the Netherlands] Sterfte aan chronische hepatitis B en C virusinfectie in Nederland. *Ned Tijdschr Geneeskd*. 2016; in press.

*RIVM publication

3.4.2 Other recent RIVM publications

1. van Lier A, McDonald SA, Bouwknegt M, group EPI, Kretzschmar ME, Havelaar AH et al. Disease Burden of 32 Infectious Diseases in the Netherlands, 2007–2011. *PLoS One*. 2016;11(4):e0153106.
2. Kristensen M, van Lier A, Eilers R, McDonald SA, Opstelten W, van der Maas N et al. Burden of four vaccine-preventable diseases in older adults. *Vaccine*. 2016;34(7):942–9.

4

Acceptance of vaccination



4.1 Key points

- Both in 2013 and 2015 the mean intention of parents to vaccinate their child was high.
- Only 21% of parents reported making an informed decision about childhood vaccinations included in the NIP.
- Mass media attention on the use of allegedly inferior needles, which was later refuted, appeared to have a negative impact on mothers' attitudes and intention towards HPV vaccination for their daughters. Transparency by authorities had a preventive impact on this effect.
- HPV vaccination campaigns for non-Dutch parents should focus on the same aspects as for Dutch parents. However, delivery of the intervention should be tailored to different cultural backgrounds.
- The RIVM started to conduct studies within the project group 'extra vaccinations customised' to improve insight into the acceptance and information needs of the public and professionals with regard to vaccines that are available but not (yet) part of the NIP.
- With regard to the acceptance of vaccinations for the elderly, older adults themselves, general practitioners and elderly care specialists showed a generally positive attitude. Awareness of the existence of vaccination against pneumococcal disease, herpes zoster, and pertussis could be improved, as well as knowledge about the individual health benefits that can be achieved with these vaccines.
- With regard to maternal pertussis vaccination, the RIVM started to conduct studies to explore the information needs of pregnant women and professionals to develop communication materials for these groups.
- Studies about the determinants of the intention to get vaccinated against HPV among boys, their parents and young gay and bisexual men were conducted in order to prepare for the possible implementation of HPV vaccinations in these groups in the future.

4.2 Monitoring system for acceptance of vaccination

In 2013, a monitoring system was instigated with the aim of monitoring acceptance and trust in vaccination among the public and professionals. As part of this monitoring system, in 2013 and 2015, a questionnaire was sent to parents with at least one child between the ages of 3 months and 3.5 years. In both years the intention and attitude with regard to the NIP was high, and parents had a high perceived social and moral norm, did not perceive many barriers, had a high trust in the NIP, did not strongly believe that the use of combination vaccines was too much for the immune system of their child, believed vaccinate one's child is self-evident, had a high risk perception of the disease and a moderately high risk perception of the vaccine

(e.g. side effects), had positive beliefs about the vaccine (e.g. ‘Due to the NIP there are fewer infectious diseases in the Netherlands’) and less positive beliefs about the disease (e.g. ‘Experiencing infectious diseases provides better and lifelong protection than vaccination’), and perceived a high anticipated regret of not vaccinating their child (Table 4.1). With regard to the questionnaire in 2013, only some very small but significant differences were found in some factors that may influence parents’ decision to vaccinate their child or not, which were a small increase in intention to vaccinate, perception combination vaccines are good, trust, positive beliefs about vaccines and a somewhat higher anticipated regret not to vaccinate and a small decrease in barriers perceived and negative beliefs about diseases (Table 4.1).

Table 4.1 Mean (standard deviation) of socio-psychological determinants and its possible differences between sample 2013 (n=800) and sample 2015 (n=1,384)

	Mean (Standard Deviation)		p
	2013	2015	
1 Intention	6.01 (1.17)	6.31 (1.31)	<0.001
2 Attitude	5.44 (1.10)	5.52 (1.12)	0.091
3 Perceived norm	5.27 (1.05)	5.25 (1.28)	0.616
4 Barriers	2.19 (1.00)	2.01 (0.84)	<0.001
5 Perception combi vaccines	4.77 (1.27)	4.92 (1.62)	0.020
6 Trust	5.22 (1.00)	5.40 (1.03)	<0.001
7 Consideration	2.88 (1.30)	2.90 (1.46)	0.709
8 Moral norm	5.21 (1.29)	5.17 (1.33)	0.516
9 Risk perception disease	5.29 (0.92)	5.36 (0.97)	0.080
10 Risk perception side effects	3.74 (1.14)	3.69 (1.26)	0.304
11 Beliefs vaccine	4.76 (0.87)	4.92 (0.94)	<0.001
12 Beliefs disease	3.44 (1.30)	2.88 (1.44)	<0.001
13 Anticipated regret not vaccinating	5.90 (1.35)	6.12 (1.37)	>0.001

4.2.1 Childhood immunisation in the context of informed decision making

In September 2015, a second questionnaire to monitor the acceptance of the NIP was sent to parents with at least one child between the ages of 3 months and 3.5 years. This questionnaire contained some extra items to objectively assess parents’ level of informed decision making. Informed decision making was defined as choices that are based on sufficient knowledge, engaging in a process of deliberation and making a choice that is consistent with the decision maker’s values (e.g. attitude towards vaccination). A total of 1,615 parents were included in this study, of which 1,393 (86.3%) reported to have a completely immunised child (having had all vaccinations they should have had according to the NIP depending on the age of the child) and were classified as acceptors, 134 (8.3%) reported to have not immunised their child and were classified as decliners, and 84 (5.2%) reported to have immunised their child partially and were classified as partial acceptors. Only 21% of the parents met the criteria for informed decision making by having sufficient knowledge, showing a process of deliberation and being

value-consistent in their choice. Decliners more often made an informed decision than acceptors (33.3% vs 19.5%). The main reason decliners were considered to have made an uninformed decision was insufficient knowledge, which could mean that they based their decision on incorrect information. Among acceptors, the main reason for being considered to have made an uninformed decision was insufficient deliberation (see Table 4.2). Like the decliners, the partial acceptors showed low levels of knowledge and deliberation. Ways to increase knowledge among decliners (e.g. debunking vaccination myths) and to motivate acceptors to think more about their vaccination choices (e.g. by means of a decision aid) are currently under consideration.

Table 4.2 Mean percentages of sufficient knowledge, deliberated process and value consistency among decliners and acceptors who made an uninformed decision (n=1,206)

	Sufficient knowledge	Process of deliberation	Value consistency
Decliners (N=88)	7	88	94
Acceptors (N=1,118)	77	11	92
Chi-Square	$\chi^2(1)=196.3$, p<0.001	$\chi^2(1)=340.8$, p<0.001	$\chi^2(1)=0.5$, p=0.680

4.2.2 Impact on HPV vaccination intentions of mass media risk communication about the use of allegedly inferior needles

In spring 2015, Dutch mass media claimed that the use of inferior needles might represent a health risk for children who get vaccinated within the NIP. The glue that was used in assembling these needles was suspected of releasing a poisonous substance when children got vaccinated. This message was disseminated just after the start of the annual campaign in which all 12-year-old girls are invited to receive the HPV vaccination. The Ministry of VWS then decided to stop using these needles, until closer investigation confirmed or refuted the detrimental effect of their use. Based on investigations that were carried out after the completion of the study described below, it was concluded that these needles could be used safely. Before the media reports on the supposedly inferior needles, the TNO had been conducting a pre-post-test controlled field experiment to test the effectiveness of an experimental web-based tailored education intervention among mothers of girls who were invited for HPV vaccination in 2015. In this experiment, the mothers were randomly exposed either to an experimental web-based tailored intervention or to the general information usually provided within the annual HPV vaccination campaign. Before the mass media started publishing the possible health risks of certain needles, the mothers participating in that field experiment had completed the baseline and follow-up assessment of their attitudes, perceived decisional conflict and intentions towards the HPV vaccination of their daughters. To assess the impact of the mass media messages about inferior needles on these determinants of HPV vaccination behaviour, a brief second follow-up assessment was added to the educational experiment

already running. A random sub-sample of 472 mothers was invited to participate in the present study. We received a net response of 74% on this second follow-up, of which 155 were mothers (45%) exposed to the experimental intervention and 193 were mothers (55%) exposed to the control information. Besides attitudes, perceived decisional conflict and intention, the mothers were asked whether they were aware of the mass media messages about suspect needles and of the Ministry's decision to stop using them.

Mothers' attitudes and intentions towards the HPV vaccination of their daughters declined significantly between the first and second follow-up (from 4.86 to 4.71 and from 5.04 to 4.76 on a 7-point Likert scale, respectively ($p < 0.05$)). However, this overall decline did not differ between mothers that were or were not aware of the mass media messages about inferior needles. A possible explanation for the absence of a difference in degree of decline might be that the group of mothers who were aware of the messages about the inferior needles corrected their initially decreasing attitudes after becoming aware of the Ministry's decision to stop using the needles. In addition, the overall decline in intention did not differ between mothers that were or were not exposed to the experimental web-based tailored education. However, the decline in attitude and intention was less strong among mothers who were aware of the Ministry's decision to stop using these needles than among mothers who were not aware of that decision. The preventive effect of this awareness was even stronger among mothers that had previously been exposed to the experimental web-based tailored education than among their counterparts who had been exposed to the general information ($p = 0.03$). Finally, mothers that were aware of the Ministry's decision also reported lower levels of decisional conflict than those unaware of the Ministry's decision ($p = 0.01$) (see also TNO report for more results [1]).

Overall, mass media attention on the risks involved in using the allegedly inferior needles appeared to have had a negative impact on the mothers' attitudes and intentions towards the HPV vaccination of their daughters. Awareness of the Ministry's decision to stop using these needles had a significant preventive impact on this decline, even more so when mothers were previously exposed to the web-based tailored education. This underscores the importance of transparency and timely communication by the authorities about matters relating to the NIP, especially when something happens to cause concern among the target population about the possible risks of vaccination.

4.2.3 A longitudinal study on determinants of HPV vaccination uptake in parents/guardians from different ethnic backgrounds in Amsterdam, the Netherlands

HPV vaccination coverage among 12-year-old girls in the Netherlands is lower (61%) than coverage for other childhood vaccinations given at younger ages (>90%), and it is even lower among ethnic minorities, which is worrying, as these groups are known to have a higher incidence of cervical cancer than the native Dutch population. The Public Health Service of Amsterdam therefore decided to explore the possible impact of ethnicity on the determinants of HPV vaccination intention and uptake among parents/guardians having a daughter eligible for HPV vaccination.

Parents/guardians of girls that were invited for HPV vaccination in 2014 were asked to complete a questionnaire on socio-demographics and the social-psychological determinants of HPV vaccination uptake in 2014. For this study, four ethnic groups were distinguished: Dutch

(NL, n=723), Surinamese, Netherlands Antillean, and Aruban (Sur, n=126), Middle-Eastern and North-African (MENA, n=237) and Other (n=223). The MENA group was mainly composed of individuals with a Moroccan, Turkish or Egyptian background. In all ethnic groups, we found intention to be the strongest predictor of the daughters' HPV vaccination uptake. Explained variance is a measure of how well the assessed determinants predict the outcome. In this study, we found that the explained variance of uptake was highest in the NL group (56%) and lower in the other ethnic groups (ranging between 23% and 29%). The lower explained variance can be attributed to participants with a positive intention that did not opt for vaccination in the Sur group (11%) and MENA group (30%). Explained variance of intention to vaccinate (rather than actual vaccination) varied between 66% and 77% across ethnic groups, and was mainly explained by social-psychological determinants, namely attitude, beliefs, risk perception and social norms. The strength of association of the determinants on both intention and uptake were largely similar across ethnic groups.

We conclude that HPV vaccination campaigns can focus on the same determinants as used for the Dutch group when targeting non-Dutch groups, although the mode of delivery of the intervention needs to be tailored to the different cultural backgrounds (by personal communication or via social media and, if possible, in their own language). Further research is needed to explain the observed discrepancy between intention and uptake, especially among parents/guardians in the non-Dutch groups.

4.3 Vaccines not included in a public vaccination programme

Within the project group 'extra vaccinations customised', studies have been conducted to improve insight into acceptance and information needs among the public and professionals with regard to vaccines that are available but not (yet) part of a public vaccination programme. On the website www.rivm.nl/vaccinaties there is now information available on a number of vaccines available to the public. This information is being updated gradually in accordance with the most recent findings from ongoing research. Professional guidelines on herpes zoster and maternal pertussis vaccines are available, and others are currently being developed and reviewed by representatives of the different groups of professionals (e.g. child vaccine providers, general practitioners, paediatricians). Within the following year, professional guidelines for vaccination against rotavirus, pneumococcal disease, varicella, meningococcal disease B and W, HPV for boys, influenza for people under 60 years old, hepatitis B for migrants, and hepatitis A for migrant children are expected to be completed.

4.3.1 Vaccines for adults

4.3.1.1 Acceptance of four vaccines among Dutch older adults

In order to improve insight into the willingness of people aged 50 years and older to get vaccinated against influenza, pneumococcal disease, herpes zoster and pertussis, a questionnaire study was conducted; a total of 735 adults above 50 years of age completed the survey. The psychological concepts were measured on a 7-point Likert scale. Findings showed a positive attitude towards influenza vaccination ($M=5.28$, $SD=1.39$) and vaccination in general ($M=4.76$, $SD=1.01$), and a positive intention to get vaccinated ($M=4.90$, $SD=1.60$). The perceived severity of pneumococcal disease was highest ($M=5.98$, $SD=0.76$), which also resulted in the

highest willingness to get vaccinated against this disease ($M=5.47$, $SD=1.38$). The severity of herpes zoster and pertussis was perceived to be lower ($M=5.38$, $SD=1.03$ and $M=5.33$, $SD=1.06$, respectively), which also led to a lower willingness to get vaccinated against these diseases ($M=4.93$, $SD=1.50$ and $M=4.86$, $SD=1.50$, respectively).

Looking at the predictive value of different determinants of the intention to get vaccinated, findings showed that older adults are more willing to get vaccinated when they have positive outcome expectations (i.e. 'Getting vaccinated will prevent me from getting an infectious disease'), a positive attitude towards getting vaccinated in general, as well as against influenza, if they perceive themselves as susceptible to infectious diseases, when they have been vaccinated against influenza in the previous year, and if they did not mind the number of vaccinations they get. The determinants for attitude were similar to those for intention, and the following variables also had some predictive value: a positive belief about vaccinating people over the age of 50 against as many infectious diseases as possible, and a higher perceived severity of pneumococcal disease. With increasing age, participants perceived themselves to be more susceptible to the diseases and their attitude and intention were more positive. In order to ensure a positive attitude among the elderly, especially those aged between the ages of 50 and 60, they should be properly informed about the benefits of vaccination at their age. It should be highlighted that vaccination at their age might be more effective and more beneficial, considering that immunosenescence affects not only their immunity but also the effectiveness of the vaccine. In addition, they should be informed about the severity of the various diseases and the susceptibility to them according to their age; and additional vaccinations might be discussed and administered at the same time as influenza vaccination.

4.3.1.2 Acceptance of vaccination for the elderly among general practitioners

Possible expansion of the current influenza vaccination programme to include vaccination against pneumococcal disease, herpes zoster and pertussis partly depends on the willingness of general practitioners (GPs) to endorse additional vaccinations. GPs were therefore asked to fill in a questionnaire about the factors that influence their attitudes and willingness to offer vaccination – other than influenza vaccination – to the elderly. GPs were positive about vaccination in general ($M=5.43$, $SD=1.16$ on a 7-point Likert scale), but somewhat less positive about expanding the current programme ($M=4.22$, $SD=1.66$). Prediction analysis showed that the intention of GPs to offer additional vaccination was predicted by positive attitudes towards offering additional vaccination, towards vaccination as a preventive tool, towards offering vaccination during an outbreak and when they thought that they are suitable to offer additional vaccination. The attitude of GPs towards offering additional vaccination was predicted by the perceived severity of herpes zoster and pneumonia, as well as the perceived incidence of herpes zoster. The severity of diseases was ranked as an important argument to recommend vaccination, followed by effectiveness and expected health benefits for the individual. Comorbidity was seen as a more important selection criterion for vaccination than age. In order to ensure a positive attitude among GPs towards informing older people about and administering additional vaccinations, they need to have clear guidelines, including evidence-based information about the severity and incidence of the diseases, the effectiveness and health benefits of the vaccines, as well as about advising vaccination based on high-risk groups.

4.3.1.3 Consultants in elderly care

As well as GPs, other consultants in elderly care (e.g. nursing home physicians, clinical geriatric physicians) should be aware of the availability of additional vaccinations that might benefit older individuals. Semi-structured interviews with nursing home physicians were conducted to improve insight into their opinions, awareness and knowledge about vaccination against pneumococcal disease, herpes zoster and pertussis, how they perceive their role in the vaccination of the elderly and what their information needs are. Results showed that elderly care specialists in nursing homes have little knowledge about available vaccinations and they do not seem to perceive a role in informing the elderly about vaccination. Financial resources, additional time and clear guidelines with a focus on the elderly were stated as prerequisites for expanding their role in vaccination care.

4.3.2 Maternal pertussis vaccination

In December 2015, the Dutch Health Council recommended including maternal pertussis vaccination in the NIP. The Minister of Health will decide at the end of 2016 whether this recommendation is to be adopted. A number of studies have been conducted this year to improve insight into the current state of awareness, opinions, information needs and factors that could influence acceptance among pregnant women, as well as among midwives and other groups of professionals who might have a role in maternal pertussis vaccination.

4.3.2.1 Online forum about maternal pertussis vaccination

Online focus group discussions with three groups of pregnant women and three groups of midwives were conducted. Over a period of five days, pregnant women could log in to a forum and discuss with other pregnant women about 1. their opinion and reasons for or against vaccination during pregnancy, 2. pertussis and pertussis vaccination, 3. factors that affect the decision to get vaccinated or not, 4. their need for information and support in the decision, and 5. which professional should be administering the vaccine. Midwives had three days to discuss 1. their opinions about vaccination during pregnancy, 2. their information needs, 3. their perceived role in the vaccination of pregnant women, and 4. practical considerations (i.e. the role of other professionals, facilities, time concerns). The data is currently being analysed and results can be expected at the end of 2016.

4.3.2.2 Knowledge and opinion of general practitioners and child vaccine providers

In order to get a first impression of current knowledge, attitudes, intentions, role perception and information needs with regard to maternal pertussis vaccination among GPs and child vaccine providers (CVPs), a short questionnaire was handed out during a fair for GPs (huisartsenbeurs Utrecht, 2016) and the annual vaccination meeting for CVPs organised by the RIVM (Vasteprik-dag 2016). CVPs were found to have considerably more knowledge than GPs about maternal pertussis vaccination. However, it should be mentioned that they had already received information about this topic on the day the questionnaire was handed out. On average, the attitude of CVPs towards maternal pertussis vaccination was more positive than that of GPs (M=5.94 vs. M=4.89 on a 7-point scale). CVPs would also be more willing to offer vaccination if it is included in a public vaccination programme (M=6.18 vs. M=5.51). GPs perceived their role in maternal vaccination as to provide information and advice, while CVPs

considered themselves as the professionals who could administer the vaccine. Finally, both groups of professionals would like to receive more information about the risk of pertussis to the mother and child, the effectiveness of the vaccine and the possible side effects. The website of the RIVM was most often cited as a source of information. In addition, both GPs and CVPs considered e-learning as a good information source.

4.3.2.3 Interviews with professionals about maternal pertussis vaccination

A total of 22 semi-structured, in-depth interviews with CVPs, midwives, gynaecologists and paediatricians were conducted to improve insight into their opinions and knowledge with regard to pertussis and pertussis vaccination during pregnancy, how they perceive their role in vaccination during pregnancy and what their information needs are. Results showed that knowledge about maternal pertussis vaccination among key professionals should be improved – especially knowledge about the necessity for it and the long-term effects. Both midwives and CVPs reported to be most likely to administer the vaccination to pregnant women. All the professionals – paediatricians, gynaecologists, midwives and CVPs – believed they had a role in informing pregnant women. Providing information to key professionals is very important in order to increase their knowledge about maternal pertussis vaccination. Both the RIVM website and e-learning were mentioned as important information sources in order to inform professionals about maternal pertussis vaccination. A campaign to inform pregnant woman about maternal pertussis vaccination was also considered to be important. Pregnant women should particularly be informed about the safety of maternal pertussis vaccination for both themselves and their (un)born child and about the necessity of maternal pertussis vaccination, especially about the disease burden of pertussis.

4.3.3 HPV vaccination among 12-year-old boys and their parents and among MSM

4.3.3.1 Exploring factors influencing the HPV vaccination intentions of boys and their parents

In this study, focus group discussions (n=7, 87 boys in total) were conducted with 12-year-old boys and interviews with six parents of boys around this age, to assess the health beliefs, behavioural factors, communication preferences and information needs regarding the HPV vaccination of boys. The majority of parents (5 out of 6) and boys had a positive attitude towards the HPV vaccine and intended to (let their sons) receive the vaccine. However, most of the participants had little knowledge about HPV and HPV vaccination, especially about its effects in boys. Parents and boys had a low perceived risk of HPV infection and several participants were concerned about the side effects of the vaccine. Both parents and boys reported that parents would decide whether their sons would receive the vaccine or not. Most parents trusted the government to ensure that the vaccine was safe. Parents and boys would like to be informed about the HPV vaccination by a personal letter, via (several types of) (social) media and via information meetings at schools or community health services.

4.3.3.2 Young gay and bisexual men suggest more attention and free vaccines are needed to promote HPV vaccination

In the Netherlands, free vaccination against HPV is limited to young girls. In March 2016, Soa Aids Nederland carried out qualitative research amongst young gay and bisexual men in the Netherlands about their knowledge of HPV, their attitudes towards HPV vaccination and

their suggestions on ways to promote HPV vaccination amongst young gay and bisexual peers. Only young men who were (also) attracted to men were selected for the interviews. Participants were interviewed either individually (n=16) or in small focus groups (n=6 per group). Prior to reading a fact sheet with key information on HPV and HPV vaccination, the participants were asked what they already knew about HPV. After the fact sheet information was discussed, participants answered questions about their attitudes towards HPV vaccination. Finally, participants were asked what could be done to encourage HPV vaccination amongst gay and bisexual peers.

In total 28 adolescent men who have sex with men (MSM) were interviewed, with an average age of 20 years (range: 15–25 years). Their education level was above average (71% had higher education level). Half of the sample lived outside North-Holland (including Amsterdam) and Flevoland. Participants were completely unfamiliar with HPV and how HPV vaccination offers protection against genital warts and/or anogenital cancer. After reading the fact sheet, participants expressed low levels of willingness to receive vaccination. The current vaccine cost (over €300) was a major barrier for every participant. Respondents generally questioned the importance of HPV vaccination for themselves, primarily because of the perceived low prevalence of HPV-related cancer versus the high rates of HPV infection; the current non-existence of free vaccination programmes for gay and bisexual men; and the lack of information and campaigns about HPV focusing on gay and bisexual men. Sexually experienced boys wondered how effective the vaccine would still be for them and participants who had a steady partner perceived a lower risk of becoming infected with HPV.

In order to stimulate HPV vaccination uptake amongst (other) young gay and bisexual men, participants suggested the following: HPV vaccines should be offered free, by default, to boys and girls and preferably via sexual health clinics; more attention should be given to HPV, by providing information about HPV in schools and by promoting HPV vaccination via websites, social media and smartphone apps commonly used by young gay and bisexual men.

4.3.3.3 HPV vaccination intention among male clients of a large STI outpatient clinic in Amsterdam, the Netherlands

HPV vaccination coverage among girls is approximately 60% in the Netherlands, with some herd protection for men who have sex only with women (MSW). MSM are not protected through the indirect effects of girls' vaccination and have a higher risk of HPV-related diseases. In this study, we explored the socio-psychological determinants of the intention to get vaccinated against HPV among male clients of the sexually transmitted infections (STI) clinic in Amsterdam. From June until November 2015, men aged ≥18 years attending the STI clinic were asked to complete a web-based questionnaire about their demographic background, the socio-psychological determinants of their HPV vaccination-related intentions, and their sexual behaviour. The socio-psychological determinants of HPV vaccination that were included in the questionnaire were derived from the Theory of Planned Behaviour and Social Cognitive Theory. Additionally, the effect of different amounts of out-of-pocket payment (€50; €100; €200; €350) on intention was explored.

In total, 1,490 men participated; 1,053 (71%) were MSM. The median age was 33 years inter-quartile range (IQR) 25–44. The median HPV knowledge score was 5 (IQR 4–6) out of a maximum of 7.

HPV vaccination intention appeared very high: mean of 1.7 [SD=1.4] in MSW and mean of 2.4 [SD=1.1] in MSM (on a scale of -3 to +3). In a multivariable analysis of the responses of MSW, attitude towards HPV vaccination had the strongest association with HPV vaccination intention followed by self-efficacy. Additionally, anticipated regret and social influences were significantly associated with HPV vaccination intention (explained variance of 70%). Among MSM attitude and self-efficacy also were strongly associated with HPV vaccination intention. Anticipated regret, the number of friends that were expected to get vaccinated and outcome expectations were also associated with HPV vaccination intention (explained variance of 68%). Demographics and sexual behaviour variables did not much improve either model. With each step increase in the required out-of-pocket payment for HPV vaccination, HPV vaccination intention decreased by 0.81 (95% CI: 0.75–0.86) scale point on a scale of -3 to +3 among MSW and by 0.71 (95% CI: 0.67–0.75) among MSM.

HPV vaccination intention among male clients of the Amsterdam STI clinic is high. Most of the variance in HPV vaccination intention among men can be explained by socio-psychological factors such as attitude and self-efficacy. Out-of-pocket payment appeared to have a strong negative effect on HPV vaccination intention in both MSM and MSW.

4.4 Literature

4.4.1 References

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4.4.2 Recent RIVM publications

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2. Van Lier A, Tostmann A, Harmsen IA, de Melker HE, Hautvast JL, Ruijs WL. Negative attitude and low intention to vaccinate universally against varicella among public health professionals and parents in the Netherlands: two internet surveys. BMC Infect Dis. 2016 Mar 15;16(1):127.
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5 Adverse events



5.1 Key points

- In 2015, Lareb received 1,494 reports of a total of 3,366 adverse events following immunisation (AEFI), which is an increase of about 50% over 2014.
- The spectrum of reported AEFI was mostly in line with past years.
- No signals emerged to indicate that vaccines used in the NIP were unsafe.

5.2 Passive surveillance system

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 2015, Lareb received 1,494 reports of a total of 3,366 AEFI (Table 5.1) [1]. Compared with 2014, this is an increase of about 50%. Of the reports, 130 were classified as serious.

Table 5.2 summarises the adverse events per vaccination moment. The spectrum of reported AEFI is mostly in line with past years. The majority of the reports represent well known AEFI such as fever, crying and injection site reactions. Again, the most-reported ($n=405$) adverse event (AE), 'injection site reactions', occurred in 4-year-old children after the administration of the fifth DTP-IPV vaccine (Infanrix-IPV®). However, there was a clearly increase in reports of local inflammatory responses (114 in 2014 and 250 in 2015), fever (80 in 2014 and 120 in 2015) and extensive limb swelling (ELS) (76 in 2014 and 110 in 2015) among 4-year-olds. Whether this was a 'true' increase in the occurrence of AEFI or merely an increase in reporting rate is not known. No specific reason can be formulated why these events were reported more frequently in 2015 than in 2014.

The increase in reports after dT-IPV vaccination in 9-year-olds in past years (42 reports in 2012 vs. 78 in 2013 and 108 in 2014) did not continue in 2015 ($n=88$). A questionnaire-based study conducted by the RIVM could not confirm a potential increase in major local reactions after dT-IPV vaccination at 9 years of age in children either [2]. Compared with a previous survey in the Netherlands [3], the frequency of local reactions and systemic events remained similar. Therefore, it is useful to explore whether the introduction of low-dose fifth and sixth booster doses might reduce the amount of AEs, in which the efficacy of these different vaccines must also be considered. It is also important to monitor the number of reports of major local reactions after dT-IPV vaccination to the Netherlands Pharmacovigilance Centre Lareb.

In 2015 a higher number of reports ($n=257$) after administration of the HPV vaccine were received. Most of these reports were received after media attention surrounding HPV vaccines. In 192 of the 257 reports, the HPV vaccination had been administered before 2015. Fatigue was the most frequently reported long-term AEFI. Lareb has investigated these reports and concluded that a causal relation between HPV vaccination and long-term symptoms cannot be concluded or excluded on the basis of analysis of these reports [4]. These results are in line

with a UK study in 2013, which did not find an association between bivalent HPV vaccination and chronic fatigue syndrome [5]. The RIVM has started an epidemiological study into whether long-term fatigue occurs more often in vaccinated than unvaccinated girls.

5.3 International developments

5.3.1 Vaccines targeting diseases included in the current NIP

5.3.1.1 MMR

Three studies on the safety of MMR vaccines were published. No apparent differences in solicited or serious adverse events were found between MMRII, a human serum albumin-free vaccine, and MMR-RIT (i.e. Priorix) [6]. MMR vaccination was also well tolerated in children aged 6–14 months during a measles outbreak [7]. The safety of paediatric vaccine schedules in a non-human primate model was assessed by Curtis et al. [8]. This comprehensive five-year case-control study provided no consistent evidence of neurodevelopmental deficits or aberrant behaviour in animals vaccinated according to different schedules with or without MMR vaccine, or MMR only.

5.3.1.2 *Pneumococcal disease*

In the past year, research did not show safety issues for PCV7 in infants and children [9] or in children born to renal transplant recipients using immunosuppressive drugs during gestation [10]. Similar results were found for PCV10. This vaccine was well tolerated with or without co-administration with other paediatric vaccines to children from diverse ethnic and geographic backgrounds [11–14]. PCV13 was also safe and well tolerated in healthy children [15, 16] and in children with sickle cell diseases [17] or inflammatory bowel disease [18]. Several studies have shown a good safety and tolerability profile of PCV13 in adults and the elderly [19–22], even in people with underlying medical conditions [23–25]. A three-dose PCV13 followed by a booster dose of PPV23 was also well tolerated in recipients of allogeneic hematopoietic stem cell transplant [26] and HIV-infected individuals [27]. Furthermore, PPV23 was shown to be generally safe and well tolerated in studies in which the age of subjects ranged from two to over 80 years [28–31]. On the other hand, Han et al. demonstrated that the risk of developing severe adverse reactions to PPV23 is greater in patients with sickle cell disease than in patients with HIV or asthma, especially in paediatric and adolescent patients with sickle cell disease compared with their adult counterparts [32]. Song et al. found that local and systemic adverse events were more common in the elderly receiving PPV23 with or without an influenza vaccination than in those receiving the influenza vaccine alone [33]. The authors concluded that health care professionals might consider avoiding the simultaneous administration of other vaccines with PPV23.

In Cuba, a new vaccine candidate has been developed: PCV7-TT, a conjugate of tetanus toxoid with seven antigens [34]. A single dose of this candidate vaccine was found to be safe when used in healthy adults. The candidate PCV15 also displays an acceptable safety profile in healthy adults 18–45 years of age [35]. In a phase I study, a candidate trivalent pneumococcal protein vaccine was found to be safe in adults, toddlers and infants. The addition of aluminum adjuvant improved immunogenicity in infants without changing the safety profile [36]. In a

phase II study, the safety of a new 10-valent protein-based pneumococcal vaccine was assessed. A single dose of this vaccine, administered to Gambian children aged 2–4 years not previously vaccinated with a pneumococcal vaccine was well tolerated [37].

5.3.1.3 *Meningococcal C disease*

Several studies have been done on the safety profile of MenACWY-CRM [38–40], MenACWY-TT [41, 42] and MenACWY-D [43]. All vaccines were well tolerated, with no attributable serious AEs, when given as a single dose, two-dose series or booster dose. Despite differences in composition, the MenACWY-CRM and MenACWY-TT vaccines had comparable reactogenicity profiles [44, 45], even when combined with Hib vaccine [46]. Also, up to five years after the administration of Hib-MenC-TT, MenACWY-TT or MenACWY-PS, no vaccine-related serious AEs were reported [47–49].

5.3.1.4 *DTaP-IPV*

Many studies have been published on 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 [50–57], and no associations between maternal Tdap vaccination and infant outcomes were observed [55, 56], even after prior tetanus-containing vaccination [58], or when Tdap vaccine was concomitantly administered with influenza vaccine [57]. A review of the VAERS database over a period of 24 years found few cases of chorioamnionitis following receipt of any vaccine reported to the VAERS, including Tdap, which suggests no safety concern [59].

Other studies have demonstrated the safety of DTPa-IPV/Hib conjugate vaccine, DTaP vaccine, dTpa vaccine, Td-IPV, IPV and Hib PRP-CRM197 vaccine in different settings [60–68]. In a phase I clinical trial, Hong et al. showed the safety of a tetanus-diphtheria toxoid test vaccine (BR-TD-1001) in healthy Korean adults [69]. Furthermore, using different types of syringe for the administration of dTpa vaccine does not influence the reactogenicity of the vaccine [70].

5.3.1.5 *HPV*

Since the introduction of the HPV vaccines, several cases involving the exacerbation of autoimmune diseases following vaccination have been reported. After a Danish study demonstrated a possible link between postural orthostatic tachycardia syndrome (POTS) [71], the EMA performed a review of the evidence surrounding reports of this syndrome and complex regional pain syndrome (CRPS) in young women given HPV vaccines. In line with their initial recommendations, the EMA confirmed that the evidence does not support a causal link between the vaccines and development of CRPS or POTS [72].

In France the existence of a possible association between HPV vaccination and the occurrence of autoimmune diseases was studied in a large cohort of young girls [73]. For chronic inflammatory bowel disease and Guillain-Barré syndrome (GBS), significant associations were found with HPV vaccination, although the absolute number of cases that could be attributed to HPV was low.

Several reviews have described the safety of HPV vaccination [74–77]. Other reviews and summaries of published, post-licensure safety data from active and passive surveillance have also shown that HPV4 has a favourable safety profile [78–80]. Subelj et al. demonstrated the

safety of a school-based HPV4 vaccination programme [81]. Two other studies found no evidence of an increased risk of venous thromboembolism associated with HPV4 vaccination among females aged 9 years or older [82, 83]. HPV4 vaccination was also shown to be safe in late-stage chronic kidney disease [84]. However, a case report described a case of neuromyelitis optica spectrum disorder that was noteworthy because optic neuritis occurred in a very close temporal association with the first and second HPV4 vaccinations [85]. Another report described a case of interstitial lung disease associated with HPV2 vaccination [86]. The onset and spontaneous resolution of the disease showed a chronological association with the HPV vaccination. Further studies are needed to confirm or dismiss a causal link to the HPV vaccine from the results of these case reports.

No evidence has been found of an increased risk of spontaneous abortion and other adverse pregnancy outcomes after HPV4 or HPV2 vaccination in pregnant women [87–89].

Administration of a three-dose regimen of HPV9 vaccine was found to be generally well tolerated in females aged 9–26 years [90, 91] as well as in males and females in the same age category [92, 93], although the incidence of injection-site swelling was higher in the HPV9 group than in the HPV4 group [91]. The concomitant administration of HPV9 and other childhood vaccines also demonstrated a good safety profile [94, 95].

5.3.1.6 Hepatitis B

No safety issues were reported for hepatitis B vaccine [96, 97]. Also, for a new kind of recombinant hepatitis B vaccine (HepB-HPY) no serious or immediate reactions were found [98]. Leroux-Roels et al. showed that different adjuvants formulated with the same antigen induced different reactogenicity patterns in healthy naïve adults [99]. Tolerance of a recombinant HBV containing a new adjuvant system, AS04, was also good in patients undergoing regular dialysis [100]. Injection site pain was more frequent in the groups with AS01B, AS01E, AS03A and AS04 than in the alum group. No differences in tolerability were found between the standard three doses (20 µg) and two doses with higher-dosage (60 µg) regimens in healthy young adults [101]. Furthermore, HBV was shown to be safe in children with juvenile idiopathic arthritis [102] and in adults with diabetes mellitus [103], HIV-1 [104] or chronic kidney disease [105]. A study of people who had not responded appropriately to the intramuscular administration of HBV vaccine showed that the intradermal administration of HBV vaccine is a safe alternative [106].

Good tolerability and low rates of adverse events were also reported for a pentavalent DTP-HBV-Hib vaccine [107–109], with no differences between different ways of administration (auto-disables injection system vs. single-dose vial) [110].

As in previous years, Geier et al. reported that infants receiving increased mercury doses from Thimerosal-containing hepatitis B vaccines administered within the first month, the first two months, and the first six months of life were significantly more likely to be diagnosed with specific delays in development than infants receiving no mercury doses from this vaccine [111]. In the Netherlands, thimerosal is not used as a preservative in routinely recommended childhood vaccines.

5.3.2 Other potential future NIP target diseases

5.3.2.1 Meningococcal B disease

Six studies have been published on the safety and reactogenicity of 4CMenB. In general, 4CMenB was found to have an acceptable safety profile [112–114], although frequent solicited reactions after vaccination were commonly reported [113, 115, 116]. Systemic reactogenicity in toddlers was lower than in infants after a booster dose, and lower again in vaccine-naïve two-year-olds [116]. One severe AE was reported after administration of 4CMenB concomitantly with two routine vaccinations in a 5-month-old infant [117]. This child developed prolonged upper extremity dysfunction, which was resolved within two months after treatment. The authors concluded that clear recommendations for paediatricians are required because the increased reactogenicity of 4CMenB concomitantly administered with other childhood vaccines can lead to severe local reactions.

Three studies showed that the bivalent rLP2086 MenB vaccine is safe and tolerable in healthy individuals between 10 and 62 years of age [118–120]. Saez-Llorens et al. found that four investigational MenABCWY vaccine formulations were all well tolerated in healthy adolescents [121].

5.3.2.2 Varicella

Well tolerated safety profiles were demonstrated for MMRV and MMR+V in children ranging in age from less than 9 months to 14 months of age [122–126] although higher incidences of fever and a measles/rubella-like rash were found in MMRV groups [123, 125]. Due to limitations in manufacturing the licensed MMRV, MMRV is manufactured using an alternative process.

Marshall et al. showed that vaccine-related AEs were mostly mild to moderate in intensity for both vaccines, but somewhat more common after the alternative MMRV [127].

In a study by Toplak et al., varicella vaccination appeared to be safe in a group of six patients with juvenile idiopathic arthritis treated with biologicals [128]. Prymula et al. compared the safety of two doses of a new varicella vaccine without human serum albumin with two doses of a licensed vaccine with this component [129]. The incidence of solicited and unsolicited symptoms was similar after both vaccines, although that of low-grade fever was numerically higher after the first dose of the varicella vaccine without human serum albumin.

5.3.2.3 Hepatitis A

Two studies have been published on the safety of hepatitis A vaccine. Lau et al. showed that the combined hepatitis A and typhoid vaccine was well tolerated in children aged 2–16 years [130]. Bakker et al. described the safety of the combined vaccine against hepatitis A and hepatitis B. The safety profile of this vaccine was similar to that of the monovalent hepatitis A and B vaccines [131].

5.3.2.4 Herpes zoster

Several studies showed that herpes zoster vaccination in (older) adults is well tolerated and safe [132, 133] even for up to six years after vaccination [134]; it produces few system AEs and injection site adverse reactions of only mild to moderate intensity [135]. Furthermore, several studies have demonstrated that varicella zoster vaccine can be used safely in people with diabetes, in adults over 60 years old on chronic/maintenance corticosteroids, in people who

have had hematopoietic stem cell transplantation, and in patients taking immunosuppressant medications [136–139]. In addition, a large-scale analysis applying a case-centred method did not detect any association between sudden sensorineural hearing loss and herpes zoster vaccine [140]. However, a case report described a 53-year-old woman with no known immunodeficiency who developed a diffuse pruritic rash 17 days after receiving the varicella virus vaccine live [141]. After treatment, she recovered. Lai et al. concluded that herpes zoster vaccine is relatively safe and unlikely to exacerbate or induce autoimmune diseases, although increased risks were found of developing arthritis and alopecia after zoster vaccination [142]. A study of the reactogenicity of intradermal administration vs. subcutaneous administration of varicella-zoster vaccine showed that transient erythema and induration are more common after intradermal administration [143].

5.3.2.5 Rotavirus

Post-vaccination surveillance in several countries has established that the risk of intussusception after the first doses of RV1 and RV5 vaccination might be between 1:50,000 and 1:80,000 [144]. In the past year, two studies have assessed the risk of intussusception after RV1 vaccination. Both studies confirmed the already known increased risk after dose 1 [145–147]. Li et al. showed that RV1 was well tolerated in Chinese infants and did not interfere when co-administrated with routine childhood vaccines [148]. Mixed schedules of RV1 and RV5 were also demonstrated to be safe [149].

In a Phase IIa trial, the safety of a birth dose strategy with a vaccine developed from an asymptomatic neonatal rotavirus strain was assessed [150]. The results showed that this RV3-BB vaccine was well tolerated when administered in a three-dose neonatal or infant schedule.

In the Netherlands, two studies have calculated baseline incidences of intussusception with the purpose to observe any possible increase if rotavirus vaccination will be introduced in the Netherlands (Figure 5.1 and Figure 5.2). The first study used the hospital discharge register for the entire Dutch population [151]. The second study was conducted among the population that was registered in a general practitioner medical record database [152]. In a comparison with other countries, the incidence of intussusception in the Netherlands was lower than rates reported in the neighbouring countries of Germany and Denmark [153–155]. Whether this reflects a truly lower incidence or incomplete coding practices is currently unknown. Furthermore, data on the severity of intussusception among Dutch infants, including the rate of surgical procedures and resection, the occurrence of long-term sequelae or deaths, is lacking. Further research on this subject is needed.

5.4 Tables and figures

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

Vaccines	Total 2014	Total 2015	0m	2m	3m	4m	11m	14m	4yr	9yr	12-13yr
Infanrix hexa® + Synflorix®	323	387		168	1	87	131				
Infanrix hexa®	63	84		5	68		11				
Synflorix®	1										
MMRvaxPro® + NeisVac-C®	122	194						194			
MMRvaxPro®	15	15	2					11		2	
NeisVac-C®	3	3						3			
Infanrix-IPV®	274	422							422		
MMRvaxPro® + DTP-NVI	91	80								80	
DTP-NVI	16	6								6	
Cervarix®	59	257									257
Other	15	46									
Total	982	1494	2	173	69	87	142	208	422	88	257

Source: Lareb [1]

Table 5.2 Reported adverse events per vaccination moment

Event	Total 2015	2m	3m	4m	11m	14m	4yr	9yr	12-13yr	Other
Death	1					1				
Injection site reactions	678	26	17	35	72	23	405	42	37	21
Abnormal body temperature	575	84	15	44	80	135	134	34	21	26
Infections	55	8	1	0	4	18	3	3	14	3
Malaise and fatigue	365	30	5	13	13	45	23	9	218	9
Allergic reaction	24	2	1	2	3	5	2	3	5	1
Disorders or the immune system	16	0	1	0	1	6	1	1	5	1
Crying	289	75	23	37	48	56	40	3	3	4
Haematological disorders	7	1	1	1	0	1	0	2	1	0
Gastrointestinal complaints	267	28	10	16	24	64	28	22	63	12
Respiratory symptoms	55	9	2	4	5	9	6	5	14	1
Cardiovascular diseases	34	0	0	2	1	0	1	0	30	0
Muscle and joint disorders	131	3	1	3	2	8	21	17	71	5
Skin symptoms	255	21	14	21	21	105	38	13	16	6
Discoloured legs	25	7	7	6	3	2	0	0	0	0
Headache/dizziness	273	1	0	0	0	4	18	28	216	6
Complaints of reproductive organs	16	0	0	0	0	0	0	0	16	0
Faints	142	36	9	1	6	7	12	14	55	2
Fits	36	5	1	2	6	14	2	1	2	3
Other disorders of the nervous system	66	7	2	5	4	13	5	1	25	4
Other disorders	56	5	2	0	4	7	2	4	25	7

Source: Lareb [1]

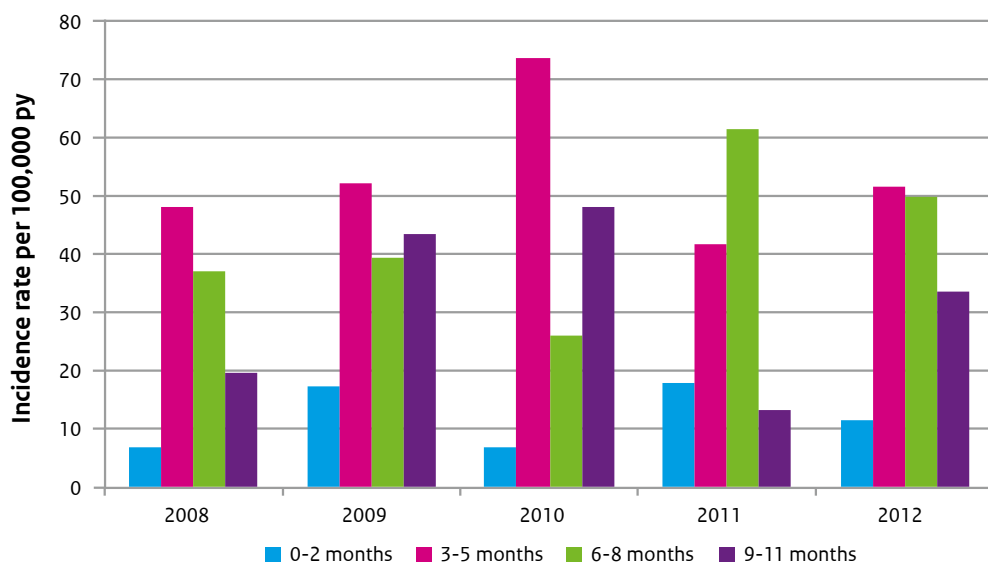


Figure 5.1 Intussusception incidence rate in children <1 year of age per 100,000 py, by age category and calendar year based on non-validated cases from the LBZ database

Source: LMR

*Adjusted for the estimated decline in national coverage of the Dutch Hospital Data from about 88% in 2008 to about 82% in 2012.

Sources: Statistics Netherlands (CBS) up to 2009 and Dutch Hospital Data (DHD) from 2010 onwards

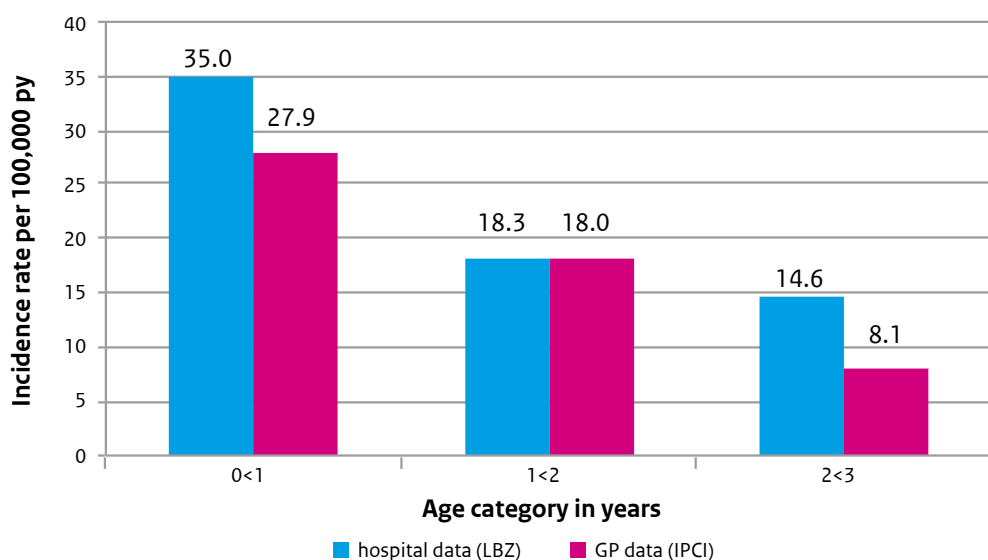


Figure 5.2 Intussusception incidence rate (95% CI) per 100,000 by age and database. Study period 1st Jan 2008 – 31st December 2012

5.5 Literature

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*RIVM publication

6

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



6.1 Key points

- In a historical analysis, a strong association between increasing vaccination coverage and diminishing mortality burden due to vaccine-preventable diseases was shown.
- The third population-based cross-sectional seroepidemiological study started in February 2016 and will continue until mid-2017.

6.2 Effect of vaccination programmes on mortality burden among children and young adults in the Netherlands during the 20th century: a historical analysis

Early in 2016 a paper was published on the impact of the Dutch National Immunisation programme on the childhood mortality burden [1]. During the 20th century, childhood mortality in the Netherlands declined rapidly. For many infectious diseases, including vaccine-preventable diseases, this decline was already ongoing before the start of mass vaccinations. The main question addressed by this research was to what extent mass vaccination programmes have contributed to lowering the mortality burden of vaccine-preventable diseases. The focus was mainly on vaccinations for diphtheria, pertussis, tetanus, polio and measles.

Data on all registered cause-specific deaths was obtained, stratified by age group from 1903 to 2012, as well as birth and population statistics from Statistics Netherlands (CBS). From this data, the cause-specific years of life lost (YLL) during childhood were derived for each birth cohort born between 1903 and 1992. For example, calculations indicate that, on average, someone born in 1903 would have lost nearly 4 years of life before he or she reached 20 years of age. To correct for the long-term decline in mortality burden, the contribution of each infection to the total childhood mortality burden was calculated.

Before mass vaccinations started, the contributions to the total mortality burden were constant for diphtheria (1.4%), pertussis (3.8%) and tetanus (0.1%). Around the start of mass vaccinations these contributions declined rapidly towards zero (Figure 6.1). Similar patterns were seen for poliomyelitis, mumps and rubella. The contribution of measles was already declining before the start of mass vaccinations. Extrapolating the pre-vaccination trends into the vaccination era, we estimated that around 9,000 deaths (6,000–12,000) have been averted by mass vaccination programmes among children born before 1992.

In this research we showed a strong association between increasing vaccination coverage and a diminishing mortality burden due to vaccine-preventable diseases.

6.3 Non-specific effects of vaccination

As part of the RIVM's strategic programme (SPR), 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

non-specific effects of measles-mumps-rubella- (MMR) and diphtheria-tetanus-pertussis- (DTP) containing vaccines originates from studies in low-income countries, which have high rates of infant mortality due to infectious diseases. The public health relevance of non-specific effects of vaccines in high-income countries, which have low infant mortality rates, is largely unknown. The first aim of the project on non-specific effects is to compare the risk of infectious disease related hospital admissions of having received the DTP-containing vaccine as 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. Data from the national vaccine register will be linked to hospital admission data using probability matching. The DTP-containing vaccine (recommended at 2, 3, 4 and 11 months) consists of vaccinations against diphtheria, tetanus, pertussis, polio and *Haemophilus influenzae* serotype b (Hib) and is administered simultaneously with a vaccination against pneumococcal disease (from 2013 onwards: three instead of four vaccines for pneumococcal disease). MMR vaccination (recommended at 14 months) is administered simultaneously with a vaccination against meningococcal serogroup C (MenC). Children will enter the present study from the moment of receiving the fourth DTP-containing vaccine and will be followed up until they are a maximum of 2 years old. The analyses will be stratified by date of birth (to fully control for age, season and calendar year) and adjusted for sex, chronic diseases, birth weight, gestational age, maternal age, educational level, parental country of birth and postal code. An additional analysis will be performed by investigating the risk of hospitalisation due to injury or poisoning as a negative control outcome. The results are expected in the autumn/winter of 2016. Moreover, this research will be extended by examining the DTP-containing vs. the MMR vaccine in relation to general practitioner consultations due to infection.

6.4 Sex differences in IgG levels following infant vaccinations

If immune responses to vaccination differ substantially between males and females, sex-specific vaccination schedules may be indicated. We systematically reanalysed clinical vaccination studies conducted by the RIVM for sex differences in IgG levels following vaccinations administered in infancy. Five studies of IgG measurements following infant pneumococcal (PCV7/PCV10/PCV13) and/or DTaP-IPV-Hib(-HepB) vaccinations on 1,118 children were included. We performed one-stage individual participant data meta-analyses of the effect of sex on log-transformed IgG levels per time point using linear mixed models. Pneumococcal serotype-specific IgG levels were generally higher in girls than in boys between the primary series and the booster vaccination. The geometric mean concentration ratio (GMC ratio) of IgG levels in girls versus boys pooled across serotypes was 1.15 (95% CI: 0.91–1.45) following the primary series (5–7 months), 1.16 (1.02–1.32) at 8 months and 1.12 (1.02–1.23) pre-booster (+/-11 months). However, following booster vaccination (+/-12 months), there was no difference in IgG levels between girls and boys, with a GMC ratio of 0.99 (0.89–1.10). This pattern was relatively consistent for the different serotypes. For diphtheria, tetanus and pertussis, there was no marked difference in the IgG levels of girls versus boys after the primary series (5–7 months), at 8 months, prior to booster vaccination (+/-11 months) or after booster vaccination (age +/-12 months). For Hib, anti-PRP IgG levels in girls were higher than in boys following booster vaccination with a GMC ratio of 1.24 (95% CI: 1.02–1.52). However,

there was no clear pattern across the measurement time points, with a GMC ratio of 0.93 (0.64–1.33) following the primary series (5–7 months), 1.14 (0.82–1.60) at 8 months, and 1.02 (0.83–1.27) pre-booster (+/-11 months).

An individual participant data meta-analysis using data from vaccine trials carried out by one UK research centre found either higher levels in girls or no difference between girls and boys in immunological parameters following vaccination in children under 3 years of age [2]. More specifically, levels of diphtheria toxoid IgG, meningococcal group A, W and Y serum bactericidal assay and pneumococcal serotype-specific IgG and opsonophagocytosis were higher for girls at one or more measurement time points (5 months, 12 months, 13 months or 24 months). No differences were found in diphtheria toxoid memory B-cells, *Haemophilus influenzae* type b anti-PRP IgG, tetanus toxoid IgG or memory B-cells, or meningococcal group C IgG, serum bactericidal assay or memory B-cells.

6.5 Immunosurveillance

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 NIP-targeted diseases in the Dutch general population. The first survey was performed in 1995–1996 ($n_{\text{blood}}=9,948$; 0–79 years) and the second in 2006–2007 ($n_{\text{blood}}=7,904$; 0–79 years) [3, 4]. In both studies, data were collected from the general population (national sample) and from eight low vaccination coverage (LVC) municipalities. In 12 of the municipalities in the nationwide sample (NS) non-Western migrants were oversampled. In February 2016, the third population-based cross-sectional seroepidemiological study started. A two-stage cluster sampling technique was used to draw a national sample. Forty municipalities were sampled within five regions proportional to size, and within each of these municipalities an age-stratified sample was drawn. Age strata were 0, 1–4, 5–9 up to 85–89 years of age. People living in LVC areas (nine municipalities) were oversampled. In addition, within the national sample, in ten municipalities non-Western migrants were oversampled. Oversampling is needed in order to obtain more information about these risk groups. As in the two previous studies, a blood sample and a questionnaire is collected from each participant. New in this third serosurvey is the option for participants to take part in additional research. For this additional research, participants are asked to optionally donate nasopharyngeal and oropharyngeal swabs, an oral fluid sample and a faecal sample and to fill in an additional questionnaire. These samples will be used for microbiome investigations and examination of antibiotic resistance. A small subset will be asked to donate an extra blood sample for cellular immunity analyses and to fill in a diary about contact patterns.

All participants give consent to check their vaccination history and participants of the additional study will be asked for permission to retrieve information on their use of medication in the last year. All participants are asked whether we may approach them in the future for follow-up research (nested cohort). Interim reports show that the response was about 20%. A major proportion of the participants (74%) also donated one or more samples for the purpose of additional research. The survey will continue until the end of 2017. In May 2017, also a PIENTER survey will be executed on the Dutch Caribbean islands to measure the seroprevalence of NIP-targeted diseases and other infectious diseases.

6.6 Tables and figures

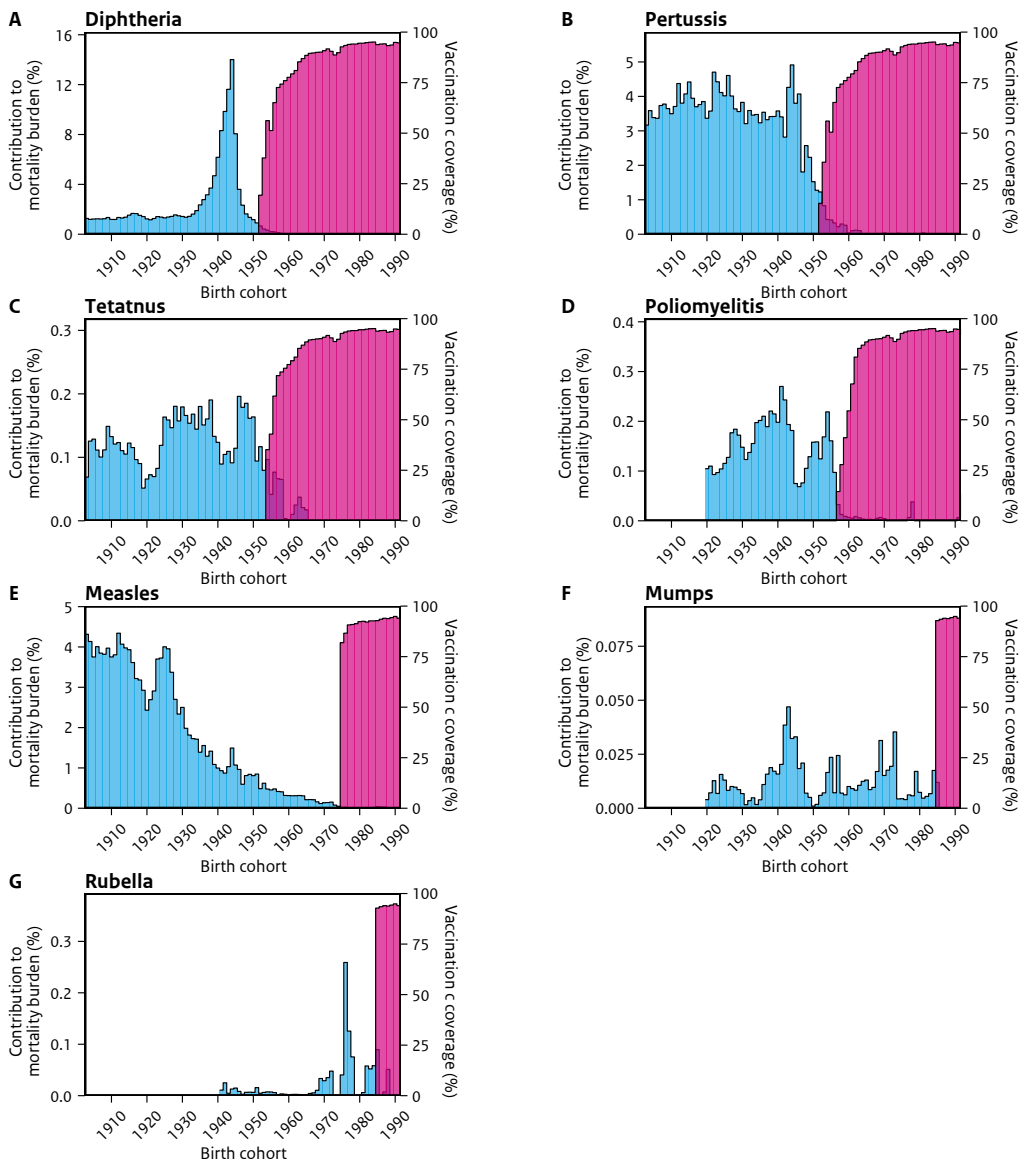


Figure 6.1 Vaccination coverage in the Netherlands and disease-specific contribution to childhood mortality burden

Data are for birth cohorts from 1903 to 1992, vaccination coverage (pink) and the contribution (as a percentage) to childhood mortality burden before the age of 20 (blue) for diphtheria, pertussis, tetanus, poliomyelitis, measles, mumps, and rubella.

Sources: CBS, Praeventis

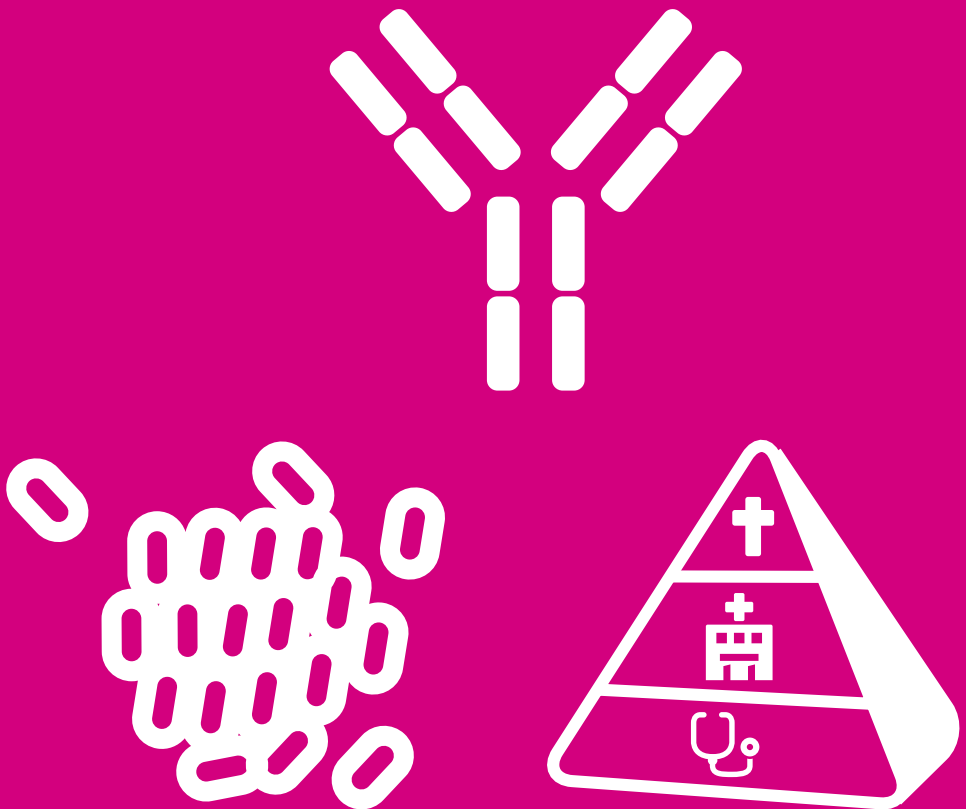
6.7 Literature

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2. Voysey M, Barker CI, Snape MD, Kelly DF, Truck J, Pollard AJ. Sex-dependent immune responses to infant vaccination: An individual participant data meta-analysis of antibody and memory B cells. *Vaccine*. 2016;34(14):1657–64.
- 3.* de Melker HE, van den Hof S, Berbers GA, Conyn-van Spaendonck MA. Evaluation of the national immunisation programme in the Netherlands: Immunity to diphtheria, tetanus, poliomyelitis, measles, mumps, rubella and *Haemophilus influenzae* type b. *Vaccine*. 2003;21(7-8):716–20.
- 4.* van der Klis FR, Mollema L, Berbers GA, de Melker HE, Coutinho RA. Second national serum bank for population-based seroprevalence studies in the Netherlands. *Neth J Med*. 2009;67(7):301–8.

*RIVM publication

7

Current National Immunisation Programme





7.1 Diphtheria

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

7.1.1 Key points

- In 2015 and 2016, up to 1st July, six diphtheria notifications were received.

7.1.2 Epidemiology

In 2015 four diphtheria notifications were reported (Figure 7.1.1). In 2016, up to 1st July, a further two notifications were received. All concerned cutaneous diphtheria.

7.1.3 Pathogen

In 2015, the RIVM received 11 *Corynebacterium* strains, seven with the suspicion of cutaneous diphtheria, four respiratory samples without a clear suspicion of diphtheria. Three strains were PCR positive; of these, the Elek test was not always conclusive.

Likewise, in 2016, up to 1st July, the RIVM received six *Corynebacterium* strains, five with the suspicion of cutaneous diphtheria and one isolated out of the trachea. Two strains were diphtheria-toxin-PCR positive; of these, one was also Elek-test positive. PCR positive strains must be notified.

7.1.4 Research

Results of the second nationwide serosurvey, performed by the RIVM in 2006/2007, showed that 91% of the Dutch general population had antibody levels >0.01 IU/ml compared to 88% in the first survey (1995/1996) [1]. Of all people born before the introduction of diphtheria vaccination in the NIP, 18% of the general population and 54% of Orthodox Protestants living in an area with low vaccination coverage had antibody levels below the protective level of 0.01 IU/ml.

7.1.5 International developments

Since 2015, an increase in people seeking asylum in Europe has been seen. Denmark, Sweden and Germany reported diphtheria among those refugees [2]. In the Netherlands, no increase in diphtheria has been seen among asylum seekers.

Furthermore, a 6-year-old Spanish child [3] and a Belgian 3-year-old child [4] died following diphtheria, in June 2015 and March 2016, respectively. Both children were not vaccinated.

7.1.6 Tables and figures

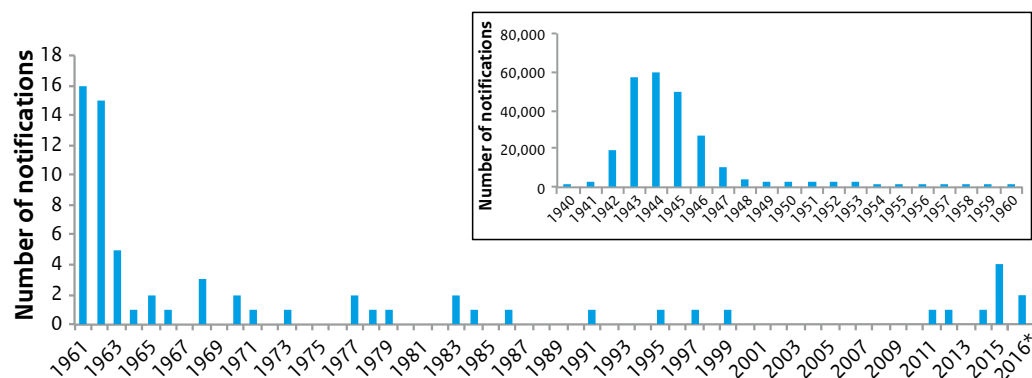


Figure 7.1.1 Diphtheria notifications per year for 1940–1960 and 1961–2016*

*reports up to 1st July 2016 are included

Source: Osiris

7.1.7 Literature

- 1.* Swart EM, van Gageldonk PG, de Melker HE, van der Klis FR, Berbers GA, Mollema L. Long-term protection against diphtheria in the Netherlands after 50 years of vaccination: Results from a seroepidemiological study. *PloS one*. 2016;11(2):e0148605.
2. European Centre for Disease Prevention and Control. Cutaneous diphtheria among recently arrived refugees and asylum seekers in the EU. Stockholm 2015; 30 July 2015; Available from: <http://ecdc.europa.eu/en/publications/Publications/Diphtheria-cutaneous-EU-July-2015.pdf>.
3. The Spain Report. Six-year-old boy with diphtheria in Catalonia dies. Jun 27, 2015; Available from: <https://www.thespainreport.com/articles/77-150627231118-six-year-old-boy-with-diphtheria-in-catalonia-dies>.
4. ECDC. A fatal case of diphtheria in Belgium underlines the importance of immunisation and access to diphtheria antitoxin. 1 Apr 2016; Available from: http://ecdc.europa.eu/en/press/news/_layouts/forms/News_DispatchForm.aspx?ID=1386&List=8db7286c-fe2d-476c-9133-18ff4cb1b568.

*RIVM publication



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

M.J. Knol, G. Berbers, A. van der Ende, H.E. de Melker

7.2.1 Key points

- The number of cases of *Haemophilus influenzae* type b (Hib) disease in 2015 (n=34) was similar to previous years, with the highest incidence among children under 5 years of age (1.5 per 100,000; n=13).
- There were five Hib cases with vaccine failure (38% of all vaccine-eligible Hib cases) in 2015, resulting in a Hib VE estimate of 97% (95% CI: 91–99%).
- Since 2004, the number of cases caused by nontypeable Hi (NTHi) strains showed a steady increase in (71 in 2004 to 127 in 2015).
- In 2015, 20 cases of Hi serotype f (Hif) were reported, which was more than previous years (8 to 13 cases from 2011 to 2014).

7.2.2 Epidemiology

7.2.2.1 Hib disease

7.2.2.1.1 Incidence

In 2015, the number of Hib cases was 34, which was similar to previous years, and in 2016 (up to May) there were 11 cases (Figure 7.2.1). The outcome was known for 10 and four cases in 2015 and 2016, respectively, and none of these patients died. In 2015, the incidence was still highest among children under five years of age (1.5 per 100,000; n=13; Figure 7.2.2).

7.2.2.1.2 Vaccine failure

In 2015 and 2016 (up to May), there were 14 and seven Hib cases, respectively, among cohorts eligible for vaccination (Figure 7.2.3). Of these, five (38%; for one case the vaccination status was unknown) and six cases (86%) were vaccine failures (i.e. they received at least two vaccinations with at least two weeks between the second vaccination and the date of diagnosis). Nine vaccine failure cases were younger than 5 years old, two were older than 5 years. On five of the eleven cases with vaccine failure, information on underlying diseases was available. One of these cases had a cerebral congenital disorder and the other four did not have an underlying disease.

7.2.2.1.3 Vaccine effectiveness

The estimated vaccine effectiveness (VE) of Hib vaccination using the ‘screening method’ was 97% (95% CI: 91–99%) for 2015 and 72% (-135–97%) for 2016 (up to May). The overall VE for 2003–2016 was 91% (87–93%).

7.2.2.2 Nontypeable Hi (NTHi) disease

In 2015, 127 cases of NTHi were reported, contributing to the increasing trend of NTHi since 2004 (Figure 7.2.1). Up to May 2016, there were 61 cases. In 2015, the incidence was still highest among those aged 65 years and older (2.0 per 100,000; n=60) and children under 5 years (1.4 per 100,000; n=12). Other countries also observe an increasing incidence of NTHi. The reason for this increase is unknown.

7.2.2.3 Disease due to other Hi serotypes

In 2015, there were eight Hi cases with serotype e (Hie), which was more than in 2013 and 2014 (both three cases) but similar to 2011 (n=8; Figure 7.2.1). In 2016 (up to May), there were two Hie cases.

In 2015, 20 cases of Hif were reported, which was more than in previous years (8 to 13 cases from 2011 to 2014). In 2016 (up to May), five Hif cases were reported.

In 2015 and 2016 (up to May), one and three Hi cases with other serotypes, respectively, were reported.

7.2.3 Pathogen

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

7.2.4 International developments

Two phase I studies in adults were conducted with a multi-component investigational vaccine based on three conserved surface proteins from NTHi (proteins D [PD], E [PE] and Pilin A [PilA]) [1]. The study found that the NTHi vaccine formulations had an acceptable reactogenicity and safety profile and were immunogenic in adults, justifying further clinical development of this NTHi vaccine candidate.

Desai and colleagues studied the epidemiology of HI non-serotype b disease in Ontario, Canada from 2004 to 2013 [2]. They found significant increases in the incidence of NTHi, Hif and Hi serotype a disease.

The clinical and molecular epidemiology of childhood (1 month to 10 years) NTHi disease in England and Wales was described by Collins and colleagues [3]. Detailed clinical follow-up of 214 cases showed that 52% of the cases had comorbidity and 11% died. Biotyping and MLST of 316 NTHi strains showed a genetically heterogeneous population (155 MLSTs) with diverse biotypes and no association with comorbidity status, clinical disease or outcome.

7.2.5 Tables and figures

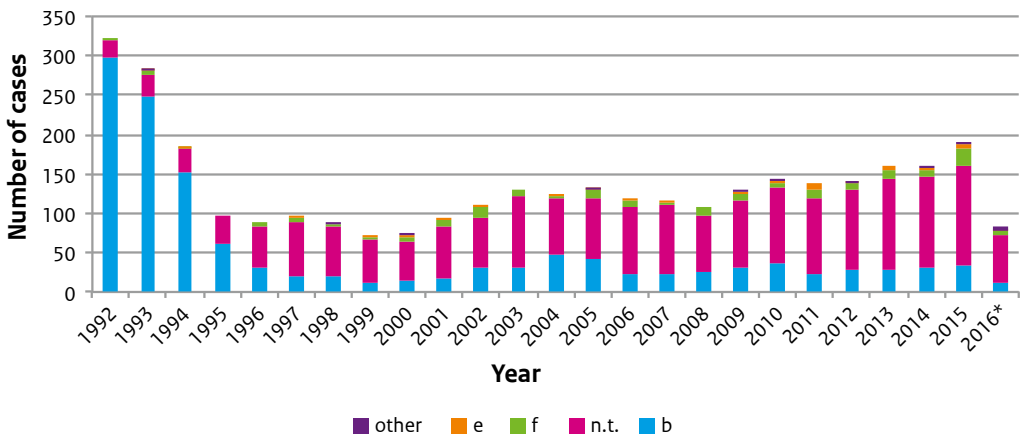


Figure 7.2.1 Absolute number of *Haemophilus influenzae* cases per serotype, 1992–2016* (*up to May)

Source: NRBM

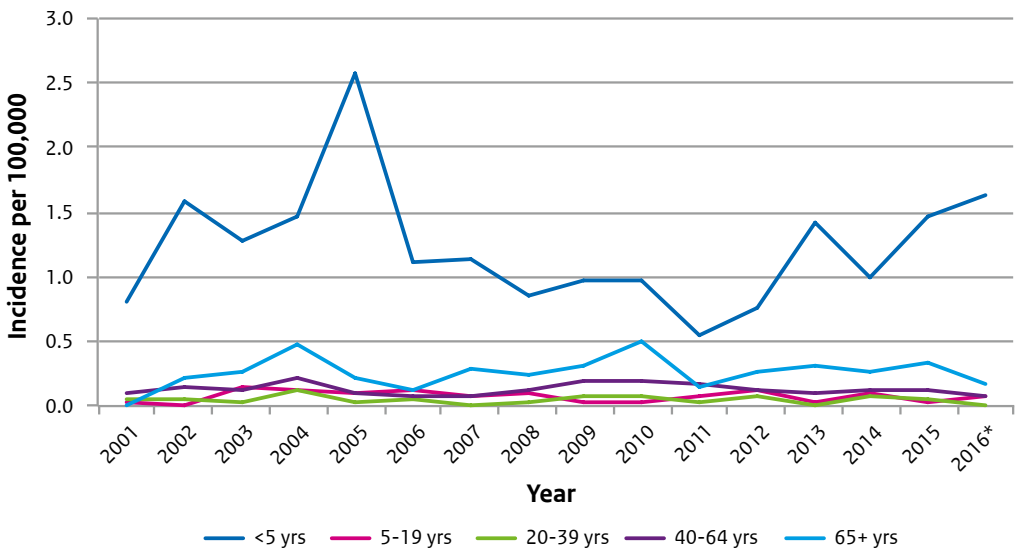


Figure 7.2.2 Age-specific incidence of *Haemophilus influenzae* type b (Hib) disease, 2001–2016* (*up to May)

Source: NRBM

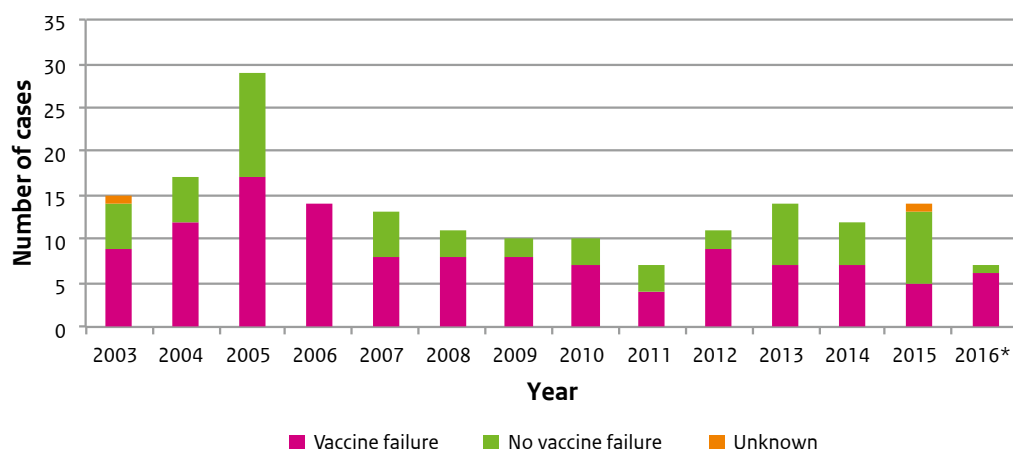


Figure 7.2.3 Absolute number of *Haemophilus influenzae* type b (Hib) cases in cohorts eligible for vaccination (i.e. born after 1st April 1993) by vaccine failure, 2003–2016* (*up to May)

Source: NRBM

7.2.6 Literature

1. Leroux-Roels G, Van Damme P, Haazen W, Shakib S, Caubet M, Aris E et al. Phase I, randomized, observer-blind, placebo-controlled studies to evaluate the safety, reactogenicity and immunogenicity of an investigational non-typeable *Haemophilus influenzae* (NTHi) protein vaccine in adults. *Vaccine*. 2016;34(27):3156–63.
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3. Collins S, Vickers A, Ladhani SN, Flynn S, Platt S, Ramsay ME et al. Clinical and molecular epidemiology of childhood invasive nontypeable *Haemophilus influenzae* disease in England and Wales. *The Pediatric Infectious Disease Journal*. 2016;35(3):e76–84.



7.3 Hepatitis B

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

7.3.2 Epidemiology

7.3.1 Key points

- The incidence of acute HBV notifications decreased in 2015 to 0.6 per 100,000 population.
- Among both men and women, heterosexual contact was the most frequently reported risk factor for acute HBV infection.
- In 2015, genotype A continued to be the dominant genotype among acute HBV cases.
- Almost 90% of the total number of reported hepatitis B patients had a chronic infection and, of those, 90% were born abroad.

In 2015, 1,133 cases of hepatitis B virus (HBV) infection were notified. Of these, 1,014 (89%) were chronic infections and 105 (9%) acute infections (14 cases unknown status).

7.3.2.1 Acute HBV epidemiology

The number of notified acute HBV infections was 20% lower than in 2014 (141 cases). The incidence of acute HBV notifications in 2015 was 0.6 per 100,000 population (2014: 0.8/100,000), 1.0/100,000 among men and 0.3/100,000 among women. The HBV incidence has been decreasing for men and women since 2004 (Fig. 7.3.1). In the first half of 2016, 43 cases of acute HBV were reported. In the past 10 years, the age at infection has been increasing for acute HBV cases (Figure 7.3.2). The mean age was 38 years in 2007 and 47 years in 2016. The mean age at infection is higher in men than in women.

In 2015, most cases of acute HBV infection (62%) were acquired through sexual contact. For 31% of reports of acute HBV infection the most likely route of transmission remained unknown, despite source tracing. Among men (81 cases), sexual contact between MSM accounted for 26% of acute infections and heterosexual transmission for 31%. Among women (24 cases), heterosexual contact accounted for two-thirds of cases.

7.3.2.2 Chronic HBV epidemiology

Since 2009, the number of chronic HBV notifications has decreased by 45% (n=1,820 in 2009 and n=1,014 in 2015). The reason for this decline is unknown, but as chronic hepatitis B is largely asymptomatic, it is likely to reflect changing testing practices. In 2015, 59% of the cases acquired chronic HBV infection through vertical transmission. Four per cent were infected by sexual contact. For 30% of reports of chronic HBV infection the most likely route of transmission was unknown. For the remaining 7%, transmission occurred via injecting drug use (IDU), via needle stick injuries or via other routes. Ninety per cent of the chronic HBV patients were born abroad (with Turkey, China and Syria as the three most frequently reported countries of birth).

7.3.2.3 HBV infection in children

Since the introduction of universal hepatitis B vaccination for all children in 2011, only five cases of acute HBV have been reported in children under 10 years of age. None of these children were born after 2011. In the period 2011–2015, 45 chronic HBV patients below 10 years of age were reported. Six of them (13%) were born in the Netherlands, and of those only one child was born after 2011. This child had a Chinese mother with chronic hepatitis B, and became infected despite vaccination.

7.3.2.4 HBV-related mortality

Mortality from acute HBV infection is low, with fewer than three patients per year in the past 10 years. However, most of the HBV-related mortality is due to chronic hepatitis B-related liver diseases such as cirrhosis and hepatocellular carcinoma, and is generally not registered in the mortality statistics with chronic HBV as the cause of death. By combining cause of death figures 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, including deaths from cirrhosis and hepatocellular carcinoma attributable to chronic HBV infection, is estimated to be around 200 per year in the period 2008–2015 [1].

7.3.3 Pathogen

Molecular sequencing and typing of 58 acute HBV cases (59%) and 10 chronic HBV cases was done in 2015. PCR amplification and sequencing gave results for 65 (96%) samples for the S-region. A basic maximum spanning tree on the basis of 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.

7.3.3.1 Molecular typing

Molecular typing of notified acute HBV cases and of chronic HBV cases in the target groups for selective vaccination will continue in 2016. A new genotyping PCR has been implemented that covers almost the entire HBV genome and enables a higher resolution on genetic data to identify clusters and aid in source/contact tracing. In addition, the molecular data are used to analyse the circulation of genetic variants, such as possible immune escape variants and antiviral resistant variants [2], to assess the current vaccination campaigns, diagnostic procedures and the impact of factors such as the influx of non-endemic strains, and to gain insight into transmission networks in the Netherlands. For efficient analysis and surveillance of these variants, the RIVM-Cib is working on implementing the molecular platform VIRO-TypeNed [3] for HBV, as well as hepatitis C virus, of both acute and chronic cases. The platform aims to combine molecular data with epidemiological and transmission data to allow a more efficient surveillance of HBV, source monitoring and detection of antiviral resistance and immune escape variants.

7.3.4 International developments

In July 2016, the ECDC published a report that included estimates of the chronic viral hepatitis burden in terms of infected cases among first-generation migrants in EU/EEA countries [4]. The study found that migrants account for an estimated 25% of the chronic hepatitis B (HBV) cases in the EU/EEA. This is higher than the proportion of migrants in the total population, which is 5% for migrants from HBV intermediate and high endemicity countries. In some countries (i.e. Ireland, the Netherlands and Sweden) the contribution of chronic viral hepatitis B cases among migrants coming from intermediate and high-endemicity countries to the overall burden in the host country was estimated to be exceptionally high. This is in line with the findings from the notifications that 90% of chronic HBV infections in the Netherlands are found among foreign born.

The cost-effectiveness of the different vaccination and antenatal screening strategies in the US was estimated by Fan et al. [5]. They compared the current strategy and two alternatives using a decision tree and a Markov model. In the current strategy, all pregnant women are screened for HBsAg. Infants of HBsAg-positive women receive HepB and HBIG within 12 hours after birth. All other infants receive HepB before hospital discharge. Alternative 1 is a universal hepatitis B vaccination (HepB) strategy whereby no pregnant women are screened for hepatitis B surface antigen (HBsAg) but all infants receive HepB before hospital discharge; no infants receive hepatitis B immunoglobulin (HBIG). Alternative 2 is an antiviral prophylaxis strategy whereby all pregnant women are screened for HBsAg. HBsAg-positive women have HBV-DNA load measured. Antiviral prophylaxis is offered for four months, starting in the third trimester, to women with a high viral load ($\geq 10^6$ copies/mL). HepB and HBIG are administered at birth to infants of HBsAg-positive women, and HepB is administered before hospital discharge to infants of HBsAg-negative women. Compared with the universal HepB strategy, the current strategy prevented 1,006 chronic HBV infections and gained 13,600 QALYs (ICER: \$6,957/QALY gained). Antiviral prophylaxis dominated the current strategy, preventing an additional 489 chronic infections, and saving 800 QALYs and \$2.8 million. In conclusion, the current US strategy for preventing perinatal HBV remains cost-effective compared with the universal HepB strategy. The antiviral prophylaxis strategy was cost saving compared with the current strategy and should be considered in order to continue to decrease the burden of perinatal hepatitis B in the United States. This finding supports improved implementation of the Dutch guidelines for specialists and primary care that recommend antiviral treatment for pregnant women with a high viral load.

7.3.5 Tables and figures

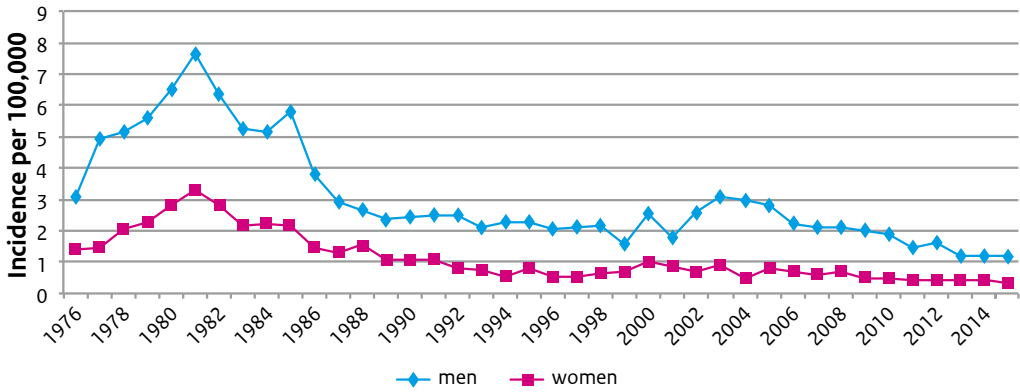


Figure 7.3.1 Incidence of acute HBV infections in men and women in the Netherlands between 1976 and 2015

Source: Osiris

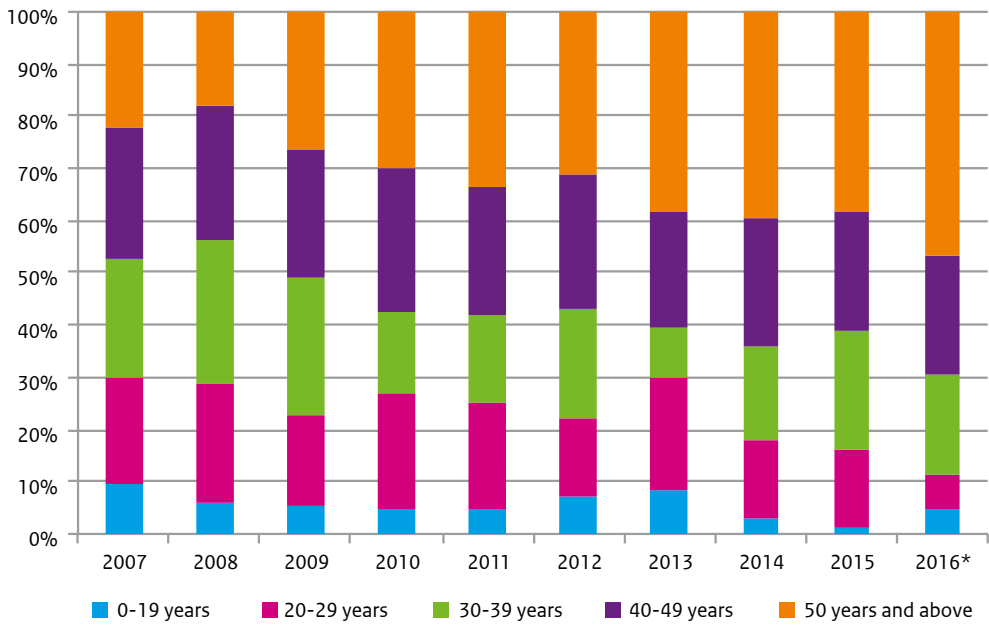


Figure 7.3.2 Age distribution of acute HBV infections in the Netherlands between 2007 and the first half of 2016

Source: Osiris

*first half of 2016

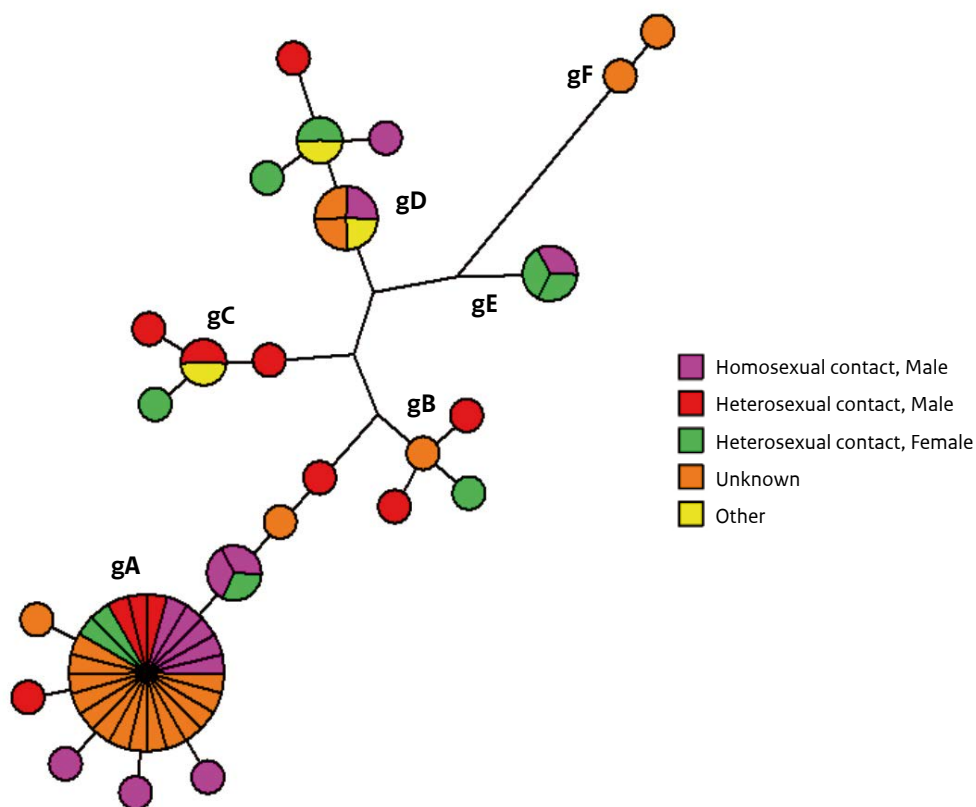


Figure 7.3.3 Basic maximum parsimony tree based on the S-region sequence of acute HBV cases in the Netherlands in 2015 by reported risk factor (n=57)

7.3.6 Literature

1. Hofman R, Nusselder WJ, Veldhuijzen IK, Richardus JH. Chronic hepatitis B and C virus infection-related mortality in the Netherlands [Sterfte aan chronische hepatitis B en C virusinfectie in Nederland]. *Ned Tijdschr Geneeskd*. 2016;160(0):D511.
2. Carman WF. The clinical significance of surface antigen variants of hepatitis B virus. *Journal of Viral Hepatitis*. 1997;4 Suppl 1:11–20.
3. Niesters HG, Rossen JW, van der Avoort H, Baas D, Benschop K, Claas EC et al. Laboratory-based surveillance in the molecular era: The TYPENED model, a joint data-sharing platform for clinical and public health laboratories. *Euro Surveillance: Bulletin Européen sur les Maladies Transmissibles [European Communicable Diseases Bulletin]*. 2013;18(4):20387.
4. European Centre for Disease Prevention and Control. Epidemiological assessment of hepatitis B and C among migrants in the EU/EEA. Stockholm: ECDC, 2016.
5. Fan L, Owusu-Edusei K, Jr, Schillie SF, Murphy TV. Cost-effectiveness of active-passive prophylaxis and antiviral prophylaxis during pregnancy to prevent perinatal hepatitis B virus infection. *Hepatology*. 2016;63(5):1471–80.



7.4 Human papillomavirus (HPV) infection

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

7.4.1 Key points

- Incidences of human papillomavirus (HPV)-associated cancers and death related to HPV-associated cancers has remained more or less stable in the past five years in the Netherlands.
- The bivalent vaccine has remained effective against HPV-16/-18 incident and persistent infections for at least five years post-vaccination, with significant cross-protection against HPV-31/-45 also being observed.
- The percentage of women positive for HPV-16 and/or -18 decreased from 23% in 2009, before vaccination was implemented, to 15% in 2015 among 16 to 24 year-old STI clinic attendees.
- The average annual disease burden of HPV-related disease over the period 1989–2014 was estimated at 11,427 DALYs (83% female), which is higher than has been estimated for any other infectious disease.
- The European Medicines Agency (EMA) concluded that evidence did not support a causal link between the currently available vaccines and either complex regional pain syndrome (CRPS) or postural orthostatic tachycardia syndrome (POTS).

7.4.2 Epidemiology

A persistent HPV infection with a high-risk HPV (hrHPV) type is a necessary cause in the development of cervical cancer. It can also cause vaginal, vulvar, penile, anal, mouth/oral and oropharyngeal cancer. In Europe, HPV prevalence was found to be 88% in anal cancers [1], 71% in vaginal cancers [2], 18% in vulvar cancers [3], 32% in penile cancers [4] and 22% in oropharynx cancers [5]. Figures 7.4.1 and 7.4.2 present the incidences of HPV-associated cancers and deaths related to HPV-associated cancers in the Netherlands, which have remained more or less stable in the past five years.

The non-oncogenic low-risk HPV (lrHPV) types 6 and 11 can cause genital warts (GW). In 2015, the number of GW diagnoses at STI clinics was 2,000 [6]. The number of diagnoses of GW by GPs was estimated at 37,826 in 2014, which was comparable to figures in 2013.

7.4.3 Pathogen

HPVs are highly conserved double stranded (ds) DNA viruses, using the replication machinery of, and co-evolving with, their host. HPV types differ from each other by at least 10% in the highly conserved L1 (major capsid protein) gene sequence. Within HPV types, variants are distinguished. Based on these criteria, HPV-16 can be divided into four and HPV-18 into three main variant lineages.

In 2015, HPV pathogen surveillance was mainly focused on HPV genotyping in two studies (HAVANA: HPV amongst vaccinated and unvaccinated adolescents; and PASSYON:

Papillomavirus surveillance among STI clinic youngsters) in order to determine the prevalence of HPV types in the (vaccinated) population. Changes in the occurrence of HPV types will be discussed below.

7.4.4 Research

7.4.4.1 Genetic diversity in the major capsid protein of HPV-16 and -18

Intratypic variants are being determined by molecular sequencing of the entire L1 gene for HPV-16 and -18 strains isolated in 2015. The genetic diversity in the L1 protein of HPV-16 and -18 strains was determined previously for 241 HPV-16 and 108 HPV-18 strains isolated in 2009 and 2011 in visitors to STI clinics in the Netherlands (PASSYON study) [7]. In this analysis a comparison with the variant used in the vaccine is included to enable close monitoring of an eventual shift in HPV-16 and -18 variants. HPV variants have been shown to differ in geographic origins and we found that European HPV-16 and -18 variants similar to the reference A lineage were identified most frequently in the Dutch isolates: 93% and 86% for HPV-16 and -18, respectively. Only a minority of our isolates concerned variant lineages, similar to the non-European variants similar to reference lineages B, C and D: 7% and 14% for HPV-16 and -18, respectively. 73% of the non-European variants of HPV-18 were found in people with a self-reported non-European ethnicity. L1 sequencing for strains collected in 2015 is still in progress. Preliminary results of our analyses of these strains show no indications for changes/differences in the intratypic HPV-16 and -18 variants collected in 2015.

7.4.4.2 HPV-16 and HPV-18 whole genome sequencing

In addition to identification of intratypic variants based on L1 sequencing, whole genome HPV-16 and -18 Sanger sequencing assays were developed at the RIVM. Here the whole genome genetic diversity of HPV16 and HPV18 strains circulating in the Dutch population was investigated in longitudinal samples obtained from the Chlamydia trachomatis Screening and Implementation (CSI) study. This study spanned four rounds, with on average one year between rounds. If sufficient diversity is found to occur in the study population, we could identify same-type reinfection events. Such HPV infections would falsely be identified as persisting infections based on conventional genotyping assays.

The developed assays allowed full forward and reverse sequencing of HPV-16 and HPV-18 genomes. Sequences were included only if coverage was >1 for all nucleotide positions across the genome.

So far, samples have been sequenced of 67 HPV-16 and 38 HPV-18 infections. Data analysis showed a strikingly high natural diversity of 63 unique HPV-16 variants and 40 unique HPV-18 variants. Among the sequenced infections were 43 HPV-16 and 21 HPV-18 persistent infections, of which sequence data has been obtained for at least one follow-up sample. In general, the longitudinal infections showed no sequence changes in up to three years after the initial sample, confirming strong conservation.

Additionally, sporadically for both HPV-16 and HPV-18, same-type reinfection events were found, where the follow-up samples had different sequences than the initial samples. However, considering we found only one occurrence for HPV-16 and one for HPV-18, we believe the incidence of same-type reinfections is rare.

7.4.4.3 HPV among vaccinated and unvaccinated adolescents (HAVANA)

A prospective cohort study which was initiated in 2009 among vaccinated and unvaccinated 14- to 16-year-old girls is still ongoing. In 2015, 1,113 young women participated in the study round. The primary aim is to monitor the effect of vaccination on HPV-type distribution amongst vaccinated and unvaccinated young women. Vaginal self-swabs collected in this cohort were tested for the presence of HPV DNA. Five years after vaccination, among vaccinated participants HPV-51, -56 and -58 were the most prevalent hrHPV types. Among unvaccinated participants HPV-51, -52 and -16 were the most prevalent hrHPV types. The cumulative persistence of vaccine types HPV-16 and -18 was lower in vaccinated participants up to five years post-vaccination (Figure 7.4.3). Vaccine effectiveness against incident and persistent infections was determined. The bivalent vaccine is effective against HPV-16/-18 incident and persistent infections at least five years post-vaccination, with substantial cross-protection observed against HPV-31/-45 (Table 7.4.1). In 2015, a small subset of the participants was asked to collect a cervical swab. With this swab, we aimed to improve insight into local immune cells and cytokines that are involved in HPV infection and clearance. Unfortunately, this kind of sampling was not suitable for future research on immune cells. Soon the possible detection of cytokines will be explored.

In 2016, girls born in 2001, who were the first eligible for a two-dose schedule in 2014, were invited to participate in the HAVANA2 study. They will be followed for at least five years. Invitations and the first sampling was initiated in August 2016.

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

To monitor possible changes in HPV dynamics over time, a biennial cross-sectional study among 16- to 24-year-old male and female STI clinic attendees was set up [8]. In 2009 (n=1,696), 2011 (n=1,905), 2013 (n=1,990) and 2015 (n=1,977), this study took place in STI clinics throughout the Netherlands. The genital samples collected were analysed for type-specific HPV DNA. The percentage of women positive for HPV-16 and/or -18 decreased from 23% in 2009, before vaccination was implemented, to 15% in 2015 ($p<0.01$). Among heterosexual men, there was also a decreasing trend in the percentage positive for HPV-16 and/or -18 (from 17% in 2009 to 11% in 2015, $p<0.01$), suggesting possible herd immunity from girls' vaccination. While the prevalence of HPV-16 and -18 decreased over time, the percentage of women positive for another hrHPV type increased from 50% in 2009 to 58% in 2015 ($p<0.01$). Overall, the percentage of women and heterosexual men positive for an hrHPV type remained stable over time ($p=0.15$ and 0.93 , respectively). Among MSM, there were no clear trends in HPV positivity. Potential confounding factors such as behavioural changes over time still need to be explored. This study is ongoing.

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

To monitor the effects on immunogenicity of the change from a three- to a two-dose vaccination schedule, a two-part study was set up. First, a retrospective cross-sectional serological evaluation among girls who had received three doses or two doses (at least five months apart) of the bivalent HPV vaccine was performed (birth cohorts 1997–2000). Results showed that GMCs for HPV-16/-18 were not non-inferior for two compared with three doses, except for HPV-18 (at 2–3 years after the first dose). However, antibody avidity for these types

showed non-inferiority of two compared with three doses, indicating a similar quality of response (submitted for publication).

Second, this study consists of a still ongoing cohort study, which started in 2014, among the first birth cohort that was eligible for vaccination with a two-dose schedule, i.e. birth cohort 2001. Just recently, medical ethics approval was given for a prolonged follow-up until five years post-vaccination. During this period, these girls will be followed yearly to assess the quality and quantity of the generated immune response.

7.4.4.6 *Cost-effectiveness of HPV vaccination against non-cervical diseases*

In a systematic review, we assessed the influence of non-cervical HPV-associated diseases on the incremental cost-effectiveness ratio (ICER) of pre-adolescent HPV vaccination. We identified 18 studies that included non-cervical diseases in the estimates of cost-effectiveness of HPV vaccination. The ICERs became substantially more favourable when HPV-related diseases other than cervix carcinoma were taken into account: compared with not including such other diseases, the mean ICERs were 2.85 times (girls only) to 3.89 times (gender-neutral versus girls only) more favourable. Including non-cervical diseases in the economic evaluation of HPV vaccination programmes makes it more likely that the ICER lies beneath accepted cost-effectiveness thresholds and therefore increases opportunities for gender-neutral vaccination (submitted for publication).

7.4.4.7 *Modelling*

Accurate estimates of the current and future burden of HPV infection in the Netherlands can support public health policy and priority setting within the NIP. The DALY measure is conveniently used to combine burden due to both morbidity and mortality associated with short- and long-term consequences of infection. Using this measure, the first national disease burden estimates for 32 infectious diseases in the Netherlands over the period 2007–2011 have recently been published [9], but this study did not consider HPV. The disease burden of HPV infection in the Netherlands was assessed separately. As a basis for estimation, annual cancer registrations during the period 1989–2014 for all anatomical sites with well established or possible etiological links to HPV infection were retrieved from the national cancer registry. The burden due to diagnoses of high-grade cervical lesions (detected through the cervical screening programme) or of anogenital warts (based on consultation data from a national GP surveillance network) was also included in estimation.

The average annual disease burden of HPV-related disease over the period 1989–2014 was estimated at 11,427 DALYs (9,536 female, 1,891 male), which is higher than has been estimated for any other infectious disease [9]. Moreover, there was a rising trend in the burden of HPV-related disease for all outcomes other than cervical cancer and laryngeal cancer in men. The disease burden was dominated by cervical cancer, although its share in the burden among women declined from 89% in 1989 to 78% in 2011–2014. The share of the total burden borne by men increased from 9.9% in 1989 to 25.7% in 2014. These findings represent the first comprehensive estimates of the disease burden caused by HPV infection in the Netherlands and may support decisions regarding vaccination policy.

To assess the cost-effectiveness of pre-adolescent male vaccination in the Netherlands, we expanded a Bayesian evidence synthesis framework previously used to estimate the direct

benefit of vaccinating 12-year-old boys along with girls [10]. The assessment considered the full spectrum of HPV-related cancers in males and females and accounted for herd immunity effects from vaccinating either girls or both sexes. The benefits to the heterosexual male population were distinguished from those to MSM, who derive little benefit from female vaccination yet are at increased risk of anal and oropharyngeal cancers. The base case analysis assumed lifelong vaccine efficacy and 40% HPV vaccine uptake among boys in addition to the current uptake of 60% among girls at the age of 12 years. This scenario resulted in incremental gains of 5.8 life years per 1,000 boys and 5.2 life years per 1,000 girls relative to girls-only vaccination. The prevention of cervical disease accounted for 73% of the gain in girls, whereas 68% of the gain in boys was due to prevention of oropharyngeal cancer. The ICER of vaccinating 12-year-old boys in the base case analysis was estimated at €24,782 per life-year gained, if we assumed a total vaccination cost of €250 per vaccinated boy and discounted future costs and benefits at 3% per year. Internationally, this represents 'good value for money' as the ICER under 3% discounting should be compared to a country's gross domestic product (GDP), which is €40,000 in the Netherlands. Sensitivity analyses showed dependency of the ICER on vaccine price, vaccine coverage (in girls as well as boys) and duration of vaccine efficacy. Boys' vaccination was cost-effective in all scenarios if the total vaccination cost per vaccinated boy was less than €150, assuming a separate tender for the vaccination of boys.

7.4.5 International developments

The RIVM summarised published data on the clinical efficacy, immunogenicity, safety and estimated impact of the HPV vaccines licensed for use in pre-adolescent girls as reported in the European public assessment reports (EPAR) published by the European Medicines Agency (EMA) [11]. The estimated health gain is about 10% larger for the nonavalent vaccine compared to the bivalent vaccine, while the bivalent vaccine was estimated to have about 10% more health gain compared to the quadrivalent vaccine. The latter is due to higher cross-protection. The authors assumed no difference in the duration of protection for the three vaccines.

7.4.5.1 Impact of HPV vaccination

Garland et al. reviewed the global impact and effectiveness of the quadrivalent vaccine [12]. The impact of HPV vaccination has become increasingly evident over the last decade, especially among girls who were vaccinated before exposure to HPV in countries with high vaccine uptake. After the introduction of the quadrivalent vaccine, rapid reductions up to ~90% in HPV types 6/11/16/18 and genital warts were demonstrated in Australia, Europe, North America and New Zealand. Decreases in prevalent HPV-6/11/16/18 infections became evident within four years after introduction of vaccination. In vaccinated birth cohorts who already began cervical screening, reductions of about 60% in low-grade cytological abnormalities and about 90% in high-grade histologically-confirmed cervical lesions were demonstrated.

Among 16–18-year-old sexually active women who undergo chlamydia screening across England, for which the estimated coverage of the bivalent HPV vaccine was 67%, the prevalence of HPV-16/18 infection decreased from 17.6% in 2008 to 6.1% in the post-vaccination period [13]. Smaller reductions were seen in women aged 19–21, who had lower estimated vaccine coverage.

7.4.5.2 *Reduced dose schedules*

An extensive overview of literature and estimates of the possible effects at population level of a two-dose schedule has been published [14]. It was concluded that a two-dose schedule has important benefits, such as easier logistics, reduced expenditure, potentially higher acceptance and fewer side-effects. It should be considered whether these benefits outweigh the likely differences on individual- and population-level impact between the two- and three-dose schedules, such as differences in humoral and cellular immune response and vaccine-effectiveness.

Puthanakit et al. showed in a randomised open trial that immunogenicity at one month after the last dose in girls aged 9–14 years who have received two doses of the bivalent HPV vaccine at 0 and 6 months or at 0 and 12 months is non-inferior to immunogenicity in women aged 15–25 years who have received three doses at 0, 1 and 6 months [15]. Romanowski et al. showed comparable antibody responses elicited by the two-dose schedule in girls aged 9–14 years and the three-dose schedule in women aged 15–25 years at 60 months after the first vaccination [16].

Evaluation of the immunogenicity of the quadrivalent vaccine by Hernandez-Avilla et al. showed that the two-dose schedule in girls aged 9–10 years was non-inferior to the three-dose schedule in girls of the same age and women aged 18–24 years at 21 months after the first vaccine dose [17]. Sankaranarayanan et al. found that the immune response in 10–18-year-old girls who had received two doses of the quadrivalent HPV vaccine was non-inferior to those having received three doses at 7 months. However, the immune response was inferior in the two-dose group (at 0 and 60 days) and in the one-dose group at 18 months after vaccination [18].

A review of the efficacy of less than three doses of the currently available HPV vaccines concluded that the immune response offered by two doses has been demonstrated to be comparable to that offered by three doses in clinical trials. However, studies embedded in the population-based screening programmes of different countries indicated reduced efficacy of two doses against virological and disease endpoints [19]. In the PATRICIA and Costa Rica Vaccine Trial, both phase III trials of the bivalent HPV vaccine, the efficacy of fewer than three doses was assessed in 15–25-year-old women after four years of follow-up [20]. The vaccine efficacy against incident HPV-16/18 infections for two doses was 76% (95% CI: 62–85%), which was similar to the protection provided by three doses (77%; 95% CI: 75–79%), and for one dose was 86% (95% CI: 71–94%). For women who had received the second of their two doses at 6 months some cross-protection was also observed against HPV-31/33/45 (68%; 95% CI: 27–87%). In a population-based setting in Scotland, VE against prevalent HPV-16/18 infection in 14–18-year-old girls was 55% (95% CI: 31–71%) for two doses and 48% (95% CI: 17–69%) for one dose [21]. VE against prevalent HPV-31/33/45 was 48% (95% CI: 8–72%) and -2% (95% CI: -85–45%) for two and one doses, respectively.

Blomberg et al. concluded that the risk of GW decreased significantly with each additional dose of quadrivalent vaccine [22]. However, for girls who received two doses, the incidence of GW reduced when the interval between doses was extended. With an interval of 6 months between the two doses, the incidence rate ratio (IRR) of two vs. three doses was close to 1.

7.4.5.3 Male vaccination

While pre-adolescent female vaccination programmes are common in most high-income countries, the vaccination of (pre-adolescent) males is still restricted to a few countries. Australia was the first to introduce a 'gender-neutral' or 'universal' HPV immunisation programme fully funded by the government. Formal cost-effectiveness analyses to support this decision were not made publicly available at the time [23]. The USA and several Canadian provinces soon followed with a recommendation to extend vaccination to boys. So far, Austria (and, by extension, Liechtenstein) is the only European country with a universal HPV immunisation programme. It should be noted that the health economic assessment of this programme was not performed in an incremental manner, i.e. the cost-effectiveness of vaccinating boys and girls was compared with 'no vaccination' only, not to 'girls only' vaccination [24].

In the UK, the Joint Committee on Vaccination and Immunisation advised on offering HPV vaccination to MSM up to 45 years old at genito-urinary medicine (GUM) and HIV clinics [25]. The Committee's advice followed cost-effectiveness analyses based on a mathematical model for HPV-6/11/16/18 transmission among MSM in England. The model was calibrated to local data on sexual behaviour, GUM attendance, HIV prevalence, warts and cancer incidence and HPV prevalence in anal samples obtained from 511 MSM in London, 2012. At a vaccine cost of £48 per dose, vaccinating all MSM aged 16–40 years regardless of HIV status was considered cost-effective in over 90% of model scenarios [26]. Meanwhile, a survey among sexual healthcare professionals on views and attitudes towards male HPV vaccination in the UK was performed, in which 83% recommended 'gender-neutral' HPV vaccination and 65% recommended selective vaccination of MSM. Half of the interviewed professionals expressed having poor knowledge about the use of HPV vaccine for MSM [27]. Thus, clear advice and guidelines will be required to ensure equitable opportunities for HPV vaccination.

7.4.5.4 Nonavalent vaccine

It has been estimated that worldwide the nonavalent vaccine could protect against ~90% of cervical cancers, 80–85% of vaginal cancers, 90–95% of anal cancers, 85–90% of vulvar cancers, ~86% of penile cancers, 93% of head and neck cancers, ~90% of genital warts cases and >90% of recurrent respiratory papillomatosis cases based on the prevalence of the vaccine types in the different HPV-associated cancers [28]. The nonavalent vaccine has been licensed in Europe since June 2015 according to a three-dose schedule [29]. In April 2016, the European Commission approved a two-dose schedule for girls and boys aged 9–14 years.

Castellsagué et al. evaluated the immunogenicity of the nonavalent vaccine in men 16–26 years of age compared with women 16–26 years of age. At month 7, the geometric mean titers (GMTs) for the nine vaccine types (i.e. HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58) in heterosexual men were non-inferior to those in women [30]. GMTs for MSM were numerically lower than for heterosexual men for all vaccine types. The immunogenicity of the nonavalent vaccine in females 12–26 years of age who had previously received the quadrivalent vaccine was assessed by Garland et al. [31]. Over 98% of the females who had received the nonavalent vaccine were seropositive for HPV types 31/33/45/52/58 at four weeks after the third dose.

However, GMTs for those HPV types were lower than in females who had not previously received quadrivalent vaccine, although the clinical significance of this difference is unknown.

Three studies assessed the economic impact of switching from the current vaccine to the nonavalent vaccine in the US. In the first study, the nonavalent vaccine was shown to be cost-effective compared with the bivalent and quadrivalent vaccines at any coverage rate, despite the greater per-dose cost of the new vaccine [32]. According to Chesson et al., the cost per quality-adjusted life year (QALY) gained by the nonavalent vaccine for both sexes (compared with the quadrivalent vaccine for both sexes) was cost-saving when assuming no cross-protection for quadrivalent vaccine and \$8,600 when assuming cross-protection against HPV-31, -33, -45, -52, and -58 for the quadrivalent vaccine [33]. Finally, in the third study, the nonavalent gender-neutral programme is estimated to be cost-saving irrespective of cross-protection assumptions [34]. However, according to this study the additional cost per dose of the nonavalent vaccine is less than \$13.

Laprise et al. found that if two doses of 9-valent vaccine protect for ≥ 20 years, the additional benefits in the US of a three-dose schedule are small compared to 2-dose schedules [35]. Moreover, vaccination with two-dose schedules is likely to be much more cost-effective than with three-dose schedules.

Using a dynamic transmission model, Boiron et al. evaluated the cost-effectiveness of replacing the current quadrivalent vaccine with the nonavalent vaccine in Austria [36]. In the base case, a two-dose schedule, lifelong vaccine type-specific protection and a vaccination coverage rate of 60% and 40% for girls and boys, respectively, for the 9-year-old cohorts were assumed. The ICER proved to be €16,441 per QALY gained, at an assumed nonavalent vaccine price of €135.

Chesson et al. evaluated the cost-effectiveness of providing three doses of nonavalent HPV vaccine to females aged 13–18 years who had previously completed a series of quadrivalent HPV vaccination [37]. When assuming no quadrivalent vaccine cross-protection, the ICER per QALY gained by additional nonavalent vaccination exceeded \$100,000. In conclusion, additional nonavalent vaccination is likely to be not as efficient as many other potential HPV vaccination strategies, such as increasing primary vaccine coverage.

7.4.5.5 Cost-effectiveness of screening programmes

HPV vaccination will also reduce cervical cancer risk in unvaccinated women. This (measurable) herd effect will be limited at first, but is expected to increase over time. Naber et al. therefore investigated at what level of herd immunity it is cost-effective to reduce screening intensity in partly vaccinated cohorts [38]. A simulation model was used in which the costs and effects of several screening strategies were assessed, assuming different levels of herd immunity between 0% to 100%. At first costs and QALYs gained of optimised screening compared to no screening in a pre-vaccinated cohort and in a vaccinated cohort were calculated. Furthermore, incremental cost-effectiveness of optimised screening in a pre-vaccinated cohort versus optimised screening in a vaccinated cohort was assessed. Primary HPV screening with cytology triage was the optimal strategy, with eight lifetime screens for the unvaccinated population

and three for vaccinated women. The ICER of screening unvaccinated women eight times instead of three was €28,085 in the absence of herd immunity. From a herd immunity level of 50% onwards, screening intensity based on the pre-vaccination risk level becomes cost-ineffective for unvaccinated women at a willingness to pay of €50,000/QALY. Reducing the intensity of uniform screening may then be considered.

Sander et al. performed a cost–utility analysis of integrated cervical cancer prevention programmes in Canada [39]. Combinations of vaccination and screening strategies were modelled with respect to the first vaccinated cohort (low herd immunity), and the steady state, i.e. all cohorts vaccinated (high herd immunity). Adding vaccination to the current screening schedule was cost-effective (<C\$10,000/QALY) across all scenarios. Delaying screening start age and/or extending screening intervals in vaccinated cohorts is likely to be cost-effective.

7.4.5.6 Safety

The EMA has reviewed data on complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS). This review concluded that the evidence does not support a causal link between the current available vaccines and CRPS or POTS [40].

A complete update on the safety of HPV vaccination is given in Section 5.3.1.5.

7.4.5.7 Screening uptake

Several studies were performed to measure participation in cervical screening among vaccinated cohorts. Palmer et al. concluded that at the age of 20 years unvaccinated Scottish women were less likely to attend screening than vaccinated women in the catch-up cohorts (RR: 0.65, 95% CI: 0.64–0.65) [41]. Boone et al. also found higher screening rates among vaccinated women in Missouri, USA (62% after first dose, 59% after second dose and 61% after third dose) than among unvaccinated women (53%) [42].

Hirth et al. found that 19–26-year-old women in the US who received one (OR: 0.60, 95% CI: 0.55–0.65) or two (OR: 0.80, 95% CI: 0.74–0.87) doses of the HPV vaccine were less likely to be screened in the three years following vaccine initiation than women who received three doses [43]. Results of a study by Paynter et al. suggest that women from Kansas City, Missouri, USA, who had received three doses of the HPV vaccine on or after 21 years of age were more likely to participate in cervical screening than women who had received three doses of the vaccine before 21 years of age (84% vs. 24%) [44].

7.4.6 Tables and figures

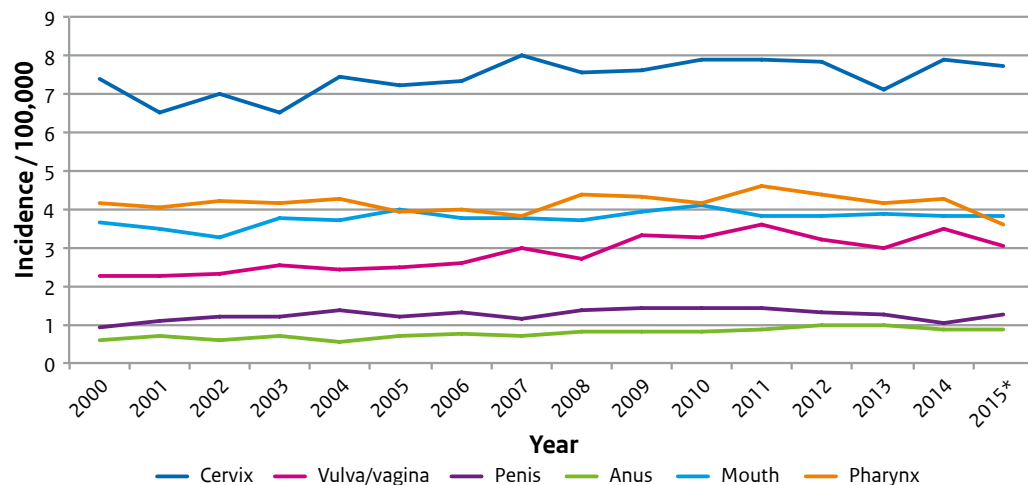


Figure 7.4.1 Incidence per 100,000 (standardised by the European standardised rate) of new cervical, anogenital, mouth/oral and pharynx/pharyngeal cancer cases in the Netherlands 2000–2015, by cancer type

*preliminary figures

Source: the Netherlands Cancer Registry (NKR)

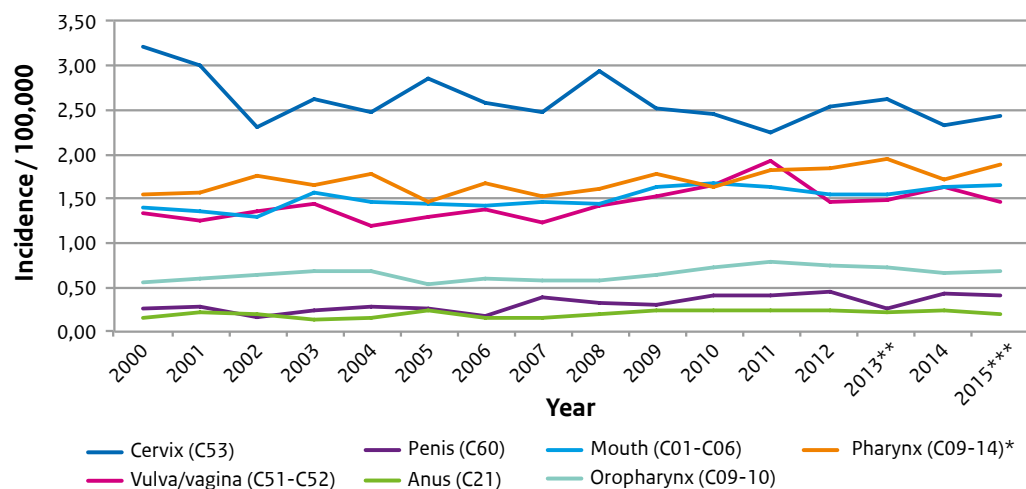


Figure 7.4.2 Incidence per 100,000 of deaths related to cervical, anogenital, mouth, oropharynx and pharynx cancer in the Netherlands 2000–2015 by cancer type

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

**In 2013, the 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, some significant shifts have been seen in the causes of death.

***preliminary figures

Source: CBS

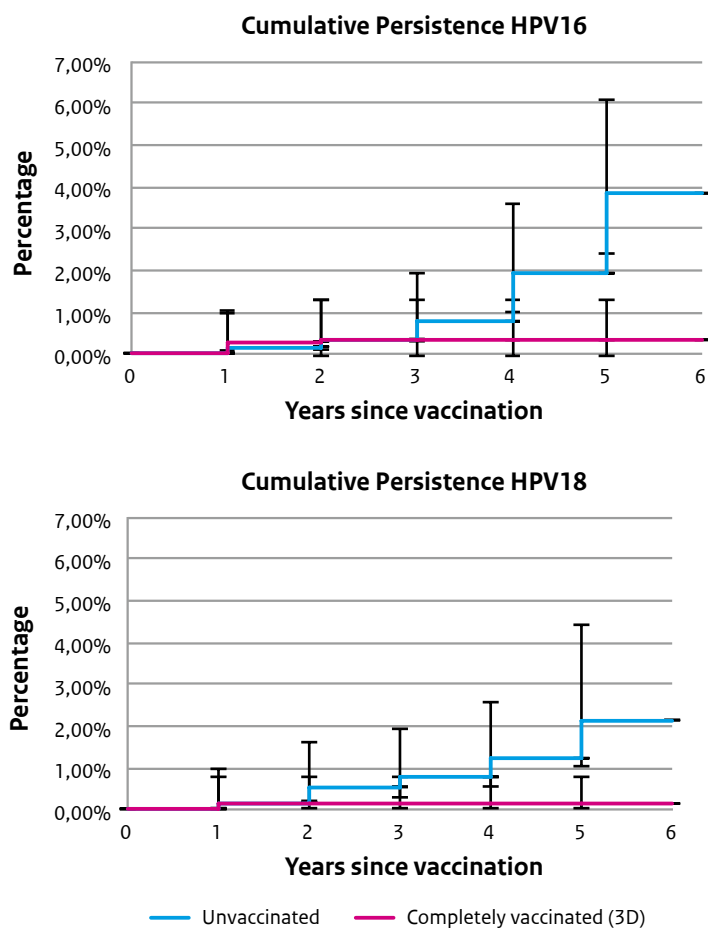


Figure 7.4.3 Cumulative persistence of HPV-16/18 in completely vaccinated (three-doses) and unvaccinated participants in the HAVANA study

Table 7.4.1 Vaccine effectiveness (VE) up to five years post-vaccination

	Crude VE	95% CI	Adjusted VE*	95% CI
Incident infections				
HPV-16 and -18	74%	(59%-83%)	78%	(61%-84%)
HPV-16,-18,-31,-45	77%	(67%-84%)	77%	(66%-84%)
Persistent infections				
HPV-16,-18 (#)	100%	##	100%	##
HPV-16,-18,-31,-45 (#)	88%	(71%-95%)	89%	(74%-96%)
HPV-16,-18	74%	(46%-87%)	79%	(57%-90%)
HPV-16,-18,-31,-45	71%	(57%-90%)	76%	(56%-87%)

* Adjusted for the following baseline characteristics: age, urbanisation degree, education, ethnicity, ever smoked, currently smoking, contraceptive use, ever had sexual intercourse, age of partner, lifetime number of sexual partners

Negative for one of these types at baseline

##Model does not converge

HPV=human papillomavirus

7.4.7 Literature

7.4.7.1 References

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7.5 Measles

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7.5.1 Key points

- Only 7 cases were reported from January 2015 until June 2016. All of them were reported between March 2015 and July 2015 and imported or import-related.

7.5.2 Epidemiology

Measles is a highly contagious infectious disease. High nationwide measles vaccination coverage is essential to sustain the elimination of measles, because below a certain fraction of susceptible individuals, only minor outbreaks occur [1]. Given the large epidemic in 2013/2014 in the Bible belt with 2,700 reported cases [2] and a high vaccination coverage (>95%) of the MMR-1 vaccination [3], a large outbreak of measles seemed very unlikely in 2015–2016, as the new susceptible individuals by birth in the orthodox Protestant community remained limited to only two birth cohorts. In 2015, seven cases were reported between March and July. Until June 2016 no more cases were reported. All seven cases were imported or import-related. Reported cases were between 27 and 58 years old. One case was a woman. One case reported having been vaccinated once; for one case vaccination status was unknown; all others were unvaccinated.

7.5.3 Pathogen

All seven cases were laboratory confirmed. Two were confirmed through the detection of measles IgM antibodies. Four cases were genotyped with D8, and one case was genotyped with B3.

7.5.4 Research

7.5.4.1 Air travel and measles transmission

Public health officials in the United Kingdom and the Netherlands conducted a joint measles outbreak investigation following detection of a measles cluster with a unique measles virus strain (B3). Through a combination of epidemiological investigation and sequence analysis, 33 measles cases were identified from February to April 2014. Nine secondary measles cases were epidemiologically linked to an infectious case travelling from the Philippines. Measles transmission was found to have occurred in flight, airport and household settings. This investigation highlighted the particular importance of measles genotyping in identifying transmission networks [4].

7.5.4.2 Correlates of protection

The correlate of measles immune protection (a plaque reduction neutralisation titer (NT) of 0.120 IU/ml) is based on a very limited set of data. During the latest measles epidemic, a substantial number of once vaccinated children were likely exposed to measles, which offered

a unique opportunity to study the immunological correlates of protection against measles virus infection and disease. These correlates are necessary for assessing the population's immunity, and guide the development of new measles vaccination strategies.

In a small observational study, we included 104 once-MMR vaccinated children aged 4–8 years attending schools with low MMR coverage to which measles was expected not yet to have spread, by taking a venous blood sample (pre-sample). A second serum sample (post-sample) was taken of 100 vaccinated and measles-exposed children after the outbreak had ended. We found that 19 children (18%) had evidence of measles virus infection, which is a relatively high attack rate (Figure 7.5.1). Only two of these children developed clinical measles (reported by the parents); both had pre-sample NT titers well below 0.120 IU/ml. These children could be considered cases of primary vaccine failure. The pre-sample NT GMT was significantly lower in children with evidence of measles virus infection during the follow-up period ($n=10$) than in those who were not infected ($n=74$) (0.56 and 1.83 IU/ml, respectively, $p<0.01$).

However, a considerable proportion of children with levels above 0.120 IU/ml had evidence of asymptomatic measles virus infection during the outbreak (presented at ECCMID 2016).

7.5.4.3 Evaluation of coverage, tolerability and effects of early MMR vaccination

During a large measles outbreak in the Netherlands among predominantly Orthodox Protestants in 2013/2014, a novel intervention was implemented by individually inviting all 6–14-month-olds for an early MMR vaccination in 29 municipalities with MMR-1 vaccination coverage below 90%. Routinely, infants receive their first dose of MMR at the age of 14 months. We estimated the coverage, the tolerability and the VE of this early MMR vaccination.

The uptake of early MMR vaccination was satisfactory, considering the low uptake in these municipalities. In total, 5,800 infants (57%) received an MMR vaccination before the age of 415 days. The uptake among DTaP-unvaccinated infants was extremely low: only 1% of infants without prior DTaP vaccinations received an early MMR.

Early MMR vaccination was well tolerated. Out of 962 infants who received an early MMR vaccine dose, the parents of 59 infants (6.1%) and 350 infants (36.4%) reported local and systemic adverse events, respectively [5].

The VE of this early MMR vaccination was also assessed. Early vaccinated and unvaccinated infants were followed during the measles epidemic. Infants vaccinated at 6–14 months of age had a lower risk of contracting measles than unvaccinated infants (94%, 95% CI: 79–98%).

Adjusted for religion and siblings' vaccination status, the VE decreased to 71% (95% CI: -72–95%), which suggests that part of the VE was caused by herd immunity being more prevalent among vaccinated infants (presented at ESCAIDE 2015).

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

Children who received an early measles immunisation between 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 reducing the age of first immunisation, taking all three components of the MMR vaccine (measles, mumps, rubella) into consideration. A negative correlation between reducing the age and the humoral (antibody) response for measles has been reported in the literature. Multiplex (MIA/Luminex) technology was performed to determine IgG antibody titers against measles, mumps and rubella up to 2 years of age.

A blunted antibody response was indeed observed when reducing the age of first immunisation, most significantly for children who received immunisation below 9 months of age. This blunting was strongest for measles, and somewhat less for rubella, while for mumps, there were hardly any differences noted in comparison with children who received the regular MMR immunisation at 14 months of age. Current studies are ongoing into the functional properties of the antibodies (virus neutralisation, avidity, memory repertoire), as well as into the cellular correlates of immune protection, up to 4 years of age.

7.5.4.5 Measles virus epitope presentation by HLA

In 2015 an immuno-biochemical study to characterise the role of host factors in so-called epitope presentation of measles virus peptides to host immune cells was finalised [6]. A large number of natural measles virus epitopes were identified, indicating that all measles virus proteins can in principle be targeted by the host response. This knowledge is of use in follow-up studies regarding T cell immunity against measles.

7.5.4.6 Measles vaccination below 9 months of age: Systematic literature review and meta-analyses of effects and safety.

In order to inform the discussion about an optimal age for the first dose of a measles-containing vaccine (MCV), the RIVM performed a systematic review commissioned by the World Health Organization Department of Immunization and Biologicals on the effects and safety of MMR vaccination below 9 months of age. In summary, the available evidence suggests that an MCV below 9 months of age is immunogenic, effective and safe. The humoral immunogenicity and VE of MCV administered <9 months of age were somewhat lower than reference values for MCV administered at 9–11 and >12 months of age. Limited evidence suggested that the age of administration did not differ on cellular immunity. No severe adverse events were found among 2,000 infants receiving an MCV <9 months of age. A preliminary version has been published [7] and findings were presented at the Strategic Advisory Group of Experts (SAGE) on Immunisation meeting in October 2015.

7.5.5 International developments

As to surveillance at European level: in 2015, 3,969 cases of measles were reported [8]. Most cases were reported in Germany (62.1%), including one measles-related death in a 19-month-old child. The measles notification rate was lower than the elimination target (one case per million population) in 14 of the 30 reporting countries. The highest notification rate was in infants under 1 year of age (55.6 cases per million population).

Worldwide, the total number of measles cases reported to the WHO was 224,540 in 2015 [9]. During 2000–2014 the annual reported incidence declined by 73%, from 146 to 40 cases per million population [10]. However, in the last five years, this decline has slowed considerably. To resume progress towards measles elimination, the performance of national immunisation programmes needs to be improved and it should be emphasised that measles elimination is an important public health goal.

7.5.6 Tables and figures

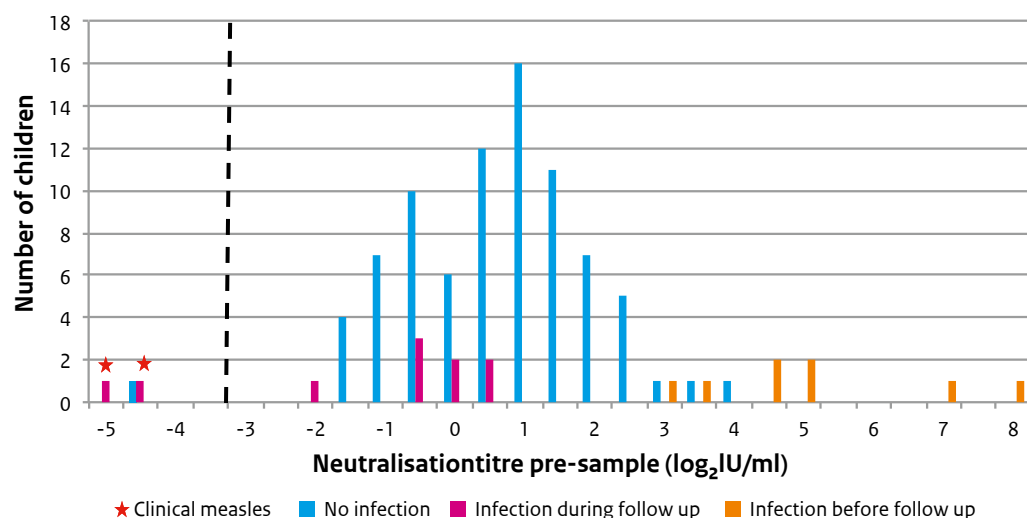


Figure 7.5.1 Distribution of pre-sample NT titre by infection status

Note: The vertical dotted line indicates the correlate of protection against measles (0.120 IU/ml).

7.5.7 Literature

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*RIVM publication



7.6 Meningococcal serogroup C (MenC) disease

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7.6.1 Key points

- In 2015, 8 cases of meningococcal serogroup C (MenC) disease were reported, including one vaccine failure (22-year-old male).
- Two MenC cases were reported in 2016 (up to August).

7.6.2 Epidemiology

Since the introduction of the conjugated MenC vaccine in 2002 at 14 months of age with a catch-up for 1–18-year-olds, the incidence of meningococcal serogroup C (MenC) disease has decreased enormously from 1.38 per 100,000 in 2002 to 0.05 per 100,000 in 2015 (Figure 7.6.1). In 2015, eight cases of MenC were reported (Table 7.6.1): six males of 2 months, 8 months, and 22, 37, 68 and 71 years, and two females of 35 and 75 years. The 75-year-old female died; it is unknown whether she had an underlying disease. The male aged 22 years had been vaccinated with NeisVac-C when he was 9 years old and is therefore a vaccine failure. He did not have an underlying disease. This is the fourth case of vaccine failure since the introduction of the conjugated MenC vaccine in 2002. Of two of the other vaccine failures, it is known that they had an immune deficiency.

Up to August 2016, two MenC cases were reported: an 80-year-old female and a 17-year-old female. Both had no underlying disease and did not die. The 17-year-old female was vaccinated according to the Polish vaccination programme, but the type of MenC vaccine or the dates of vaccination are unknown.

7.6.3 Pathogen

All MenC cases in 2015 and 2016 had the same finetype (P1.5,2:F3-3), except for the 17-year-old female in 2016 (P1.18-1,3:F3-9).

7.6.4 Research

In a follow-up of the phase IV Men C booster study (TIM study) the persistence of serologic responses three years after a second MenC-TT vaccination administered to healthy 10-, 12- and 15-year-old children nine years after their single primary vaccination with the MenC-TT vaccine was determined. The rate of meningococcal antibody decay clearly decreased during the first and third year compared to the first year after the second MenC-TT vaccination. Furthermore, a bi-exponential decay model estimated a very long-term persistence of elevated protective antibody levels after the second MenC-TT vaccination.

A phase IV trial was conducted to demonstrate non-inferiority of the quadrivalent MenACWY-TT vaccine to the monovalent MenC vaccine (JIM study). A total of 410 healthy children aged 10, 12 and 15 years, who had been primed once with the single MenC-TT vaccine between the ages of 14 months and 3 years, were randomised to receive either MenC-TT or MenACWY-TT

vaccine. As a first result, the MenACWY-TT vaccine showed similar protection as the MenC-TT vaccine in terms of MenC rSBA responses at one month after the study vaccination. Further analyses of the serology, saliva and cellular results are in progress.

To explore the effects of immunosenescence in the older population, a cohort of 200 adults between 50 and 65 years of age were enrolled in the Stimulage study. They were vaccinated with the quadrivalent MenACWY vaccine and blood samples were obtained just before (T₀) and 7 days (T₁), 28 days (T₂) and 1 year (T₃) after vaccination. Larger blood volumes were obtained from a subset of this cohort to investigate the cellular immune responses and possible immunosenescence markers. The first results are expected next year.

7.6.5 International developments

In the UK, the MenC booster vaccination at 13–14 years has been replaced by the quadrivalent MenACWY vaccine because of an increase in MenW disease [1], and the MenC vaccination at three months has been removed from the vaccination programme (for more details see Section 8.2 on Meningococcal non-serogroup C disease).

Stefanelli and colleagues report on an increase of invasive meningococcal disease serogroup C in Tuscany, Italy [2]. From January 2015 to the end of February 2016, 43 cases were reported, of which 10 died, compared with two cases in 2014 and three in 2013. The age group 20–29 years was most affected (n=15; IR: 3.9/100,000), followed by the age group 9–19 years (n=10; IR: 2.6/100,000). Five of 42 patients had been vaccinated with a meningococcal C conjugate vaccine. Thirty-five of the 40 strains analysed belonged to C:P1.5-1,10-8:F3-6:ST-11(cc11), which is the same type associated with several outbreaks among MSM in past years in various countries. In response to the outbreak, a single dose of meningococcal (ACYW) polysaccharide-protein conjugate vaccine has been actively offered free-of-charge to the age group 11–19 years. In addition, the vaccine has been offered to individuals aged 20–44 years residing in the area of the local health units that have reported at least one case of serogroup C *N. meningitidis* since 2015. In 2016, due to the increasing number of cases in age groups not previously included in the vaccination target groups, the immunisation campaign was extended to the whole Tuscany region and to older people, maintaining the active offer only to the 11–20 years age group.

Koch and colleagues evaluated a temporary vaccination recommendation in response to an outbreak of invasive meningococcal serogroup C disease in MSM in Berlin in 2012–2013 [3]. Vaccination was offered to HIV-infected MSM free of charge; others had to request reimbursement or pay out of pocket. Among online survey respondents, 60% were aware of the recommendation. Of these, 39% had obtained vaccination (70% of HIV-infected, 13% of HIV-negative/non-tested MSM). Physicians considered concerns regarding reimbursement, vaccine safety and lack of perceived disease risk as primary barriers. After the recommendation, no further outbreak-related cases occurred.

7.6.6 Tables and figures

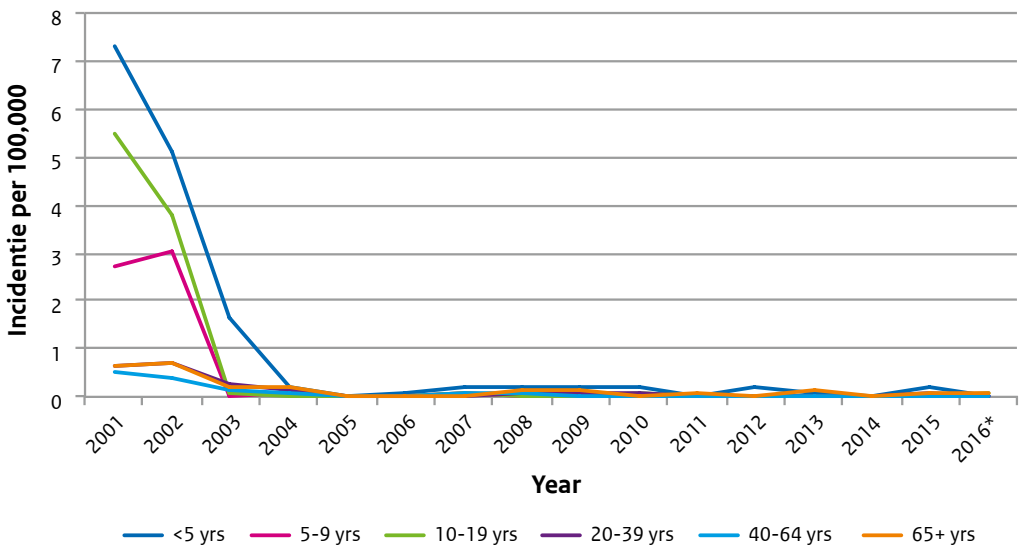


Figure 7.6.1 Age-specific incidence of meningococcal serogroup C disease, 2001–2016*
(*up to August)

Source: NRBM

Table 7.6.1 Absolute numbers of meningococcal serogroup C disease, 2001–2016*
(*up to August)

Age in yrs	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016*
<5	73	52	17	2	0	1	2	2	2	2	0	2	1	0	2	0
5-9	27	30	0	1	0	0	1	0	0	0	0	0	0	0	0	0
10-19	105	73	1	0	0	0	1	0	0	2	0	0	0	0	0	1
20-39	31	32	12	6	1	1	1	3	2	2	1	0	1	1	3	0
40-64	27	20	7	4	2	1	5	3	1	0	0	1	0	1	0	0
65+	14	15	5	4	1	1	0	3	4	0	2	0	4	1	3	1
Total	277	222	42	17	4	4	10	11	9	6	3	3	6	3	8	0

Source: NRBM

7.6.7 Literature

7.6.7.1 References

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7.6.7.2 Recent RIVM publications

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2. Stoof SP, Buisman AM, van Rooijen DM, Boonacker R, van der Klis FR, Sanders EA, Berbers GA. Different Dynamics for IgG and IgA memory B cells in adolescents following a meningococcal serogroup C tetanus toxoid conjugate booster vaccination nine years after priming: A role for priming age? *PLoS One.* 2015 Oct 12;10(10):e0138665.
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7.7 Mumps

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7.7.1 Key points

- The incidence of mumps in 2015 was low but higher than in 2014.
- In 2015 and the first six months of 2016, indication of mumps endemic transmission was found.
- Most of the mumps cases in the Netherlands were caused by genotype G.

7.7.2 Epidemiology

Following the introduction of mumps vaccination within the NIP in 1987, there was a large decline in the incidence of mumps in the Netherlands. The first signs of an increase were observed in 2004 with an outbreak among (mainly vaccinated) students [1]. Subsequently, an outbreak occurred among unvaccinated schoolchildren in the Bible Belt (2007–2009) [2]. From late 2009 until 2012, a countrywide epidemic with over 1,500 cases occurred, which again in particular affected (vaccinated) student populations (Figure 7.7.1) [3]. Since 2012, the number of reported mumps cases among students has declined in the Netherlands. Conversely, there has been an increase in the number of mumps cases among non-students (>25 years of age) from non-university cities. In 2014, only 40 mumps cases were reported. Most of these were sporadic cases or small clusters, which did not cause major outbreaks. This was confirmed by the genotyping of the laboratory-confirmed cases, because a high genotypic diversity was found among the cases tested.

In 2015 the incidence of mumps increased and 89 cases were reported (Figure 7.7.1). About half were male (53%) and the mean age was 26 years (range 7–65). Sixty per cent were twice vaccinated, 11% once vaccinated, 18% were unvaccinated and the vaccination status was unknown for 11%. Forty per cent of cases were students. Four patients were hospitalised, of which one had orchitis. Another two patients reported orchitis but were not hospitalised. In 2015, two outbreak clusters were identified (Figure 7.7.2). The first cluster at a hockey club in the west of the Netherlands (Zuid-Holland) comprised 13 reported mumps cases (cluster 1). The second cluster was linked to a pub and MBO college in the same area and comprised seven cases (cluster 2). New and more discriminative molecular typing tools based on the mumps haemagglutinin-neuraminidase (HN) and fusion (F) genes indicated that the two clusters were caused by an identical mumps virus genotype G (molecular cluster A), indicating a resurgence of mumps and the endemic transmission of the mumps virus between March and May 2015.

In 2016, until 30th June, 45 mumps cases were reported. Two outbreak clusters were reported, both in the province of Brabant. The first cluster included eight cases and was linked to carnival celebrations (cluster 3) and the second cluster (seven cases) to a football club (cluster 4). As in 2015, the sequence analyses demonstrated that cases from both epidemiological clusters belonged to a unique genotype G molecular cluster (molecular cluster C).

7.7.3 Pathogen

Since 2010, most of the mumps cases in the Netherlands have been caused by mumps virus genotype G. Besides genotyping based on the mumps virus small hydrophobic (SH) gene, we have expanded the typing tools for the mumps virus and sequenced the HN gene and F gene of a subset of samples. Unlike the SH gene sequence, which shows only minor variation within genotype G, the nucleotide variation in the HN gene and F gene sequences is more divergent and allows the investigation of transmission pathways.

7.7.4 Research

7.7.4.1 *Molecular surveillance*

Mumps virus international genotype classification is currently based on sequence analysis of the SH gene. However, the molecular resolution of the SH gene is too small and, though internationally acknowledged as the first genotype standard for mumps, has proved inadequate to distinguish outbreak clusters from new virus introductions of the same genotype. Expansion of our genetic analysis to other structural mumps genes (HN and F) has increased our ability to track mumps virus transmission in the absence of an epidemiological link [4]. In this way, ongoing virus transmission can be detected in the population, which provides an early warning signal for emerging mumps outbreaks. Furthermore, the size and duration of ongoing mumps outbreak clusters can be estimated more precisely.

7.7.4.2 *Strain-specific differences in mumps proteins*

Mumps virus surface proteins are currently being analysed to identify structural differences between the mumps virus genotype G strains causing mumps outbreaks that were circulating during the recent mumps outbreaks and other mumps virus genotypes, including the Jeryl Lynn vaccine strain, which belongs to genotype A. Using homology models and B cell epitope mapping, we have identified multiple variable sites in the mumps virus surface proteins of the Jeryl Lynn vaccine strain and genotype G strains which could affect mumps virus immunity and pathogenesis, and therefore may contribute to the occurrence of mumps virus genotype G outbreaks among MMR-vaccinated people. This investigation was carried out in collaboration with the Belgian Scientific Institute of Public Health (WIV).

Apart from B cell epitopes, efforts are being made to identify mumps-specific T cell epitopes. Bioinformatic analyses and prediction models using HLA supermotifs have been used to select potential mumps-specific T cell epitopes. Special attention is given to variable sequences (vaccine strain versus circulating genotype(s)) containing potential T cell epitopes in order to be able to identify possible differences in T cell immunity between these genotypes. A set of (overlapping) peptides of the mumps nucleoprotein has been made and is being used to identify the first mumps virus epitopes that are naturally processed, presented and recognised by T cells. The identification of T cell epitopes of the mumps virus provides a tool to measure mumps-specific T cell responses.

7.7.4.3 *Correlates of protection*

Data from a serological study carried out among mumps-exposed vaccinated students showed that pre-outbreak mumps-specific IgG concentrations were generally lower in infected people than they were in non-infected people [5]. Vaccine-induced humoral immune responses in this cohort were further studied in 2015 by investigating the neutralisation capacity of antibodies induced by mumps vaccination assay [6]. The results indicate that strain-specific neutralisation differs between pre-outbreak samples from infected and non-infected people. The neutralisation of wild type mumps virus genotype G and D strains is reduced in the infected group compared with the non-infected group. Furthermore, within the infected group, the neutralisation titres against mumps virus genotype G were lower than those against the Jeryl Lynn (genotype A) vaccine strain. These results suggest that genotype G-specific neutralisation assays are preferred as a tool for the surveillance of protection against mumps virus infection.

7.7.4.4 *Cellular immunity*

Using clinical samples from the BofTrans cellular study, collected in 2011 at the end of the mumps outbreak, a sensitive Interferon- γ -ELISpot assay to study cellular immunity against mumps was developed [7]. It was found that not only T cells but also NK cells contributed to the production of Interferon- γ after stimulation by the mumps virus. This assay can further be used in follow-up studies to investigate whether mumps vaccination induces cellular immunity that is cross-protective against circulating mumps viruses.

7.7.4.5 *Mumps virus pathogenesis*

The understanding of mumps virus pathogenesis and the role of immunity is limited. Analysis of saliva and urine samples from unvaccinated and twice-MMR-vaccinated mumps patients in relation to clinical data shows that vaccinated patients less often shed mumps virus in their urine. It also shows that mumps virus shedding in urine is positively associated with high salivary viral loads on the day of onset of disease and with the occurrence of bilateral parotitis and orchitis. Immunological factors seem to play an important role in the severity of the disease, since MMR vaccination has a protective effect on the development of bilateral parotitis and orchitis and on the shedding of mumps virus in urine [8]. However, further studies are needed, as it is not clear which immune responses are most at play and essential for protection against mumps virus infection.

7.7.4.6 *Clinical MMR-3 study*

A third dose of MMR could be an effective intervention to control outbreaks among vaccinated people, but sufficient evidence regarding immunogenicity, safety and effectiveness is currently lacking. For this purpose, a clinical study will be initiated in 2016 to study the safety and the short- and long-term mumps-specific humoral and cellular immunity of a third dose of MMR vaccine in young adults. In June 2016, this clinical study, which is a collaboration between the RIVM and Spaarne Gasthuis, was approved by the Medical Ethical Committee.

7.7.5 International developments

Mumps outbreaks have occurred in many countries around the world in recent years, often in highly vaccinated populations in school and student settings [9–13]. The waning of vaccine-induced immunity and strain differences are proposed as explanations for vaccine failure.

During an outbreak of mumps in a high school in Spain a reduced VE following one dose of mumps vaccine compared to two doses was found [14]. A study from the Czech Republic analysing almost 10,000 mumps cases, of which 82% were vaccinated, showed that the risk of complications was lower in vaccinated patients but increased with the time since vaccination in twice-vaccinated patients [15]. Fiebelkorn et al. found slightly increased mumps virus neutralising antibodies one month and one year after a third MMR dose, which could decrease susceptibility during an outbreak [16]. Although a third dose of MMR has been suggested as an outbreak control measure in specific populations, the effectiveness of a third dose has not been established [10].

7.7.6 Tables and figures

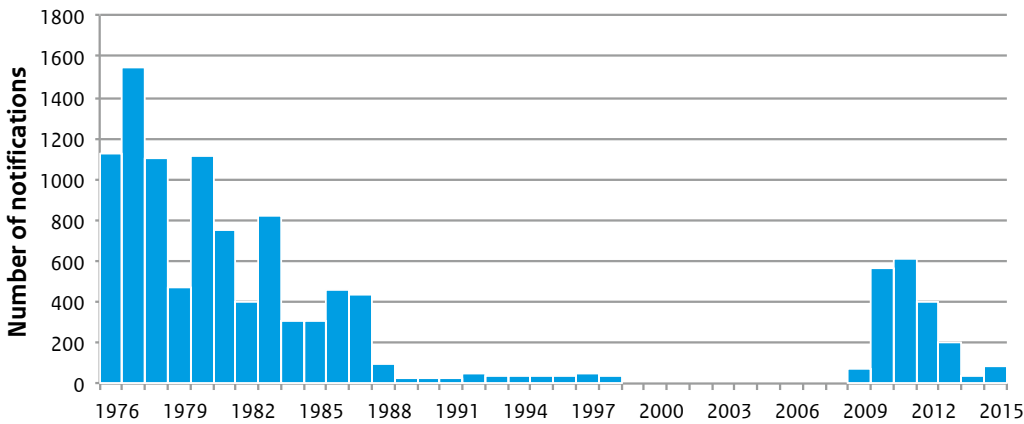


Figure 7.7.1 Number of notified mumps cases in the period 1976–2015
Source: Osiris

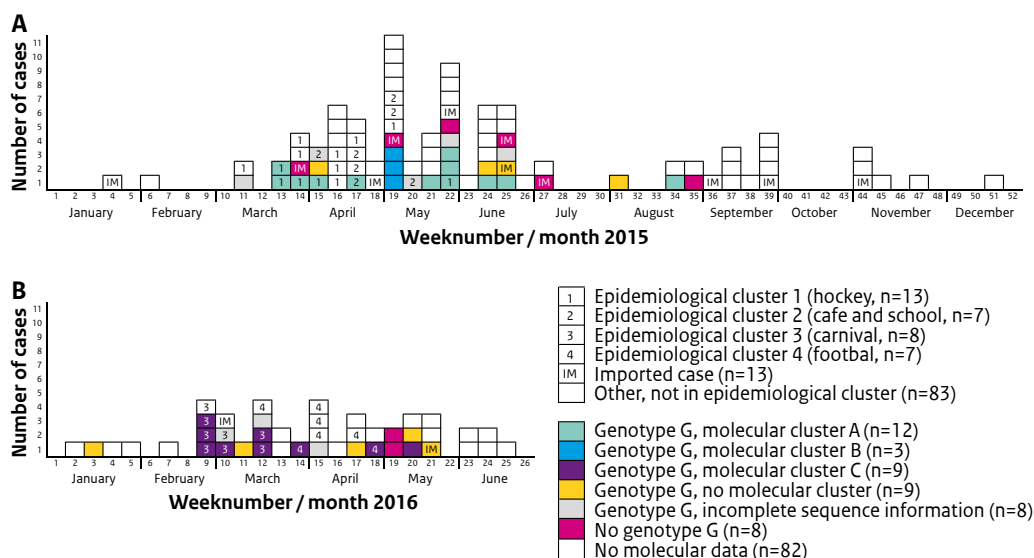


Figure 7.7.2 Number of mumps cases reported per week in 2015 (A) and 2016 (B) including epidemiological and molecular cluster and genotype information

Source: Osiris

7.7.7 Literature

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*RIVM publication



7.8 Pertussis

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7.8.1 Key points

- The incidence of pertussis notifications in 2015 (39 per 100,000) was lower than in 2014 (55 per 100,000), an epidemic year.
- Since the introduction of acellular pertussis within the primary series (2005), VE of infant vaccinations remained high until the preschool booster dose.
- Estimated VE of the pre-school booster dose has remained high for about 4–5 years. Thereafter, vaccinated children more often contract pertussis.
- In December 2015, the Health Council recommended offering all pregnant women a pertussis vaccination in the third trimester of pregnancy for better protection of their newborns.
- The prevalence of pertactin-deficient (i.e. a component of acellular vaccines) strains was 16% in 2015 compared with 10% in 2014.

7.8.2 Epidemiology

7.8.2.1 Disease

In 2015, the incidence rate (IR) of pertussis notifications was lower than in 2014, not only overall but also age specific (Figures 7.8.1 and 7.8.2). A slight decrease in notifications was observed in the first quarter of 2016 compared with 2015. However, for the age groups up to 4 years of age, IRs in the first quarter of 2016 were higher than IRs in 2015.

Hospitalisation data for 2015 are not available yet. In July 2015, a pertussis outbreak in a neonatal intensive care unit (NICU) was reported [1]. The index case was a nurse, fully vaccinated during childhood, working at the NICU. She infected one infant. Subsequently, this infant infected three other infants. No other employees or parents were infected. All contacts received antibiotic prophylaxis.

Among notified cases, in 2015 one death, of an unvaccinated young infant, was reported; in 2016, up to 1st July, three deaths were reported: two young, unvaccinated infants and one female of about 60 years of age. According to Statistics Netherlands, in 2015, one 0-year-old infant is reported to have died from pertussis. It is unsure if this is the same infant as reported to have died within the notifications.

The Health Council (HC) advised the Ministry of VWS to offer all pregnant women a pertussis vaccination in the third trimester for better protection of newborns. The mean number of pertussis cases in infants below 6 months would decrease from 128 before the implementation to 26 after implementation of maternal vaccination. Hereby, vaccine-effectiveness was set at 92% and coverage at 63%. The HC stated that monitoring of the effectiveness and safety of maternal vaccination is essential. Furthermore, the HC urged that the determinants of acceptance should be studied and the results used during implementation. See Chapter 4 for more details.

7.8.2.2 Vaccine effectiveness

VE, estimated through the 'screening method' for the infant vaccination series, is shown in Figure 7.8.3. We would like to emphasise that the VE as presented should not be interpreted as 'true' absolute efficacy, but are used to study trends in VE estimations. In 2005, an infant combination vaccine with an acellular pertussis component was introduced into the NIP, resulting in an increase of VE of the primary series for 1–3-year-olds [2]. In the first years after introduction, the VE of 2- and 3-year-olds was lower than current estimates, because these children had received whole-cell vaccine during infancy. From 2007 onwards, the VE of 1- to 3-year-olds remained well above 80%.

The VE of the booster dose at 4 years of age seems to decrease when children have reached the age of 8 years, i.e. 4–5 years after the booster vaccination, especially in epidemic years (Table 7.8.1).

7.8.3 Pathogen

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

The first shift we have found compared with previous years (2010–2015) is the emergence of strains that are deficient in vaccine components Prn and FHA. Prn-deficient strains were first observed in 2010, and their prevalence increased from 1% to 16% in the years 2010–2015. In 2016 (up to July), one Prn-deficient strain has been found among the 20 strains so far. *B. pertussis* can use different mutations to inactivate Prn [3]. For example, a transposon can be inserted into the Prn gene or a single nucleotide polymorphism can lead to a stop codon, resulting in a truncated protein. 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 and 5% in 2016 so far.

A second shift concerned the serotypes. Since 2010, an increase of Fim3 strains has been observed. This is probably due to the high level of antibodies against Fim2 strains followed by an increase of strains with Fim3. No other major shifts were found compared with previous years.

7.8.4 Research

7.8.4.1 Epidemiology

We assessed the under-reporting of pertussis-related hospitalisations and deaths using capture-recapture analysis for two sources [4]. For hospitalisations we used the Notifiable Disease Registry (Osiris) and the National Registration Hospital Care (LBZ) as sources. The under-reporting was estimated to range between 30% and 50% for infants below 2 years of age, and to be much higher (~80%) for those 2 years and older. For deaths we used Osiris and the death registry of Statistics Netherlands (CBS) as sources. The under-reporting ranged from 50% to 30% in infants <2 years, increasing to 70–90% for those ≥2 years.

We also conducted a study on the medical records of 0–2-year-old infants hospitalised for pertussis during 2005–2014. The results are expected next year.

7.8.4.2 Pathogen

In collaboration with the Radboud UMC in Nijmegen (Dr D Diavatopoulos), a mouse model was used to study whether acellular vaccines were less effective against Prn-deficient strains than against Prn-producing strains. In this study, the efficacy of the two- and three-component acellular vaccine and the whole-cell vaccine against Prn-deficient strains was compared. The results showed lower efficacy of the three-component vaccine against Prn-deficient strains. In theory, a five-component vaccine should be more effective against Prn-deficient strains than two- or three-component vaccines. Currently in progress is an analysis of whole genome sequence data obtained from *B. pertussis* strains (Prn-producing and Prn-deficient) after mouse passage.

7.8.4.3 Immunology

In 2015 and 2016, pertussis-related immunological research further underpinned the notion that the resurgence of pertussis in vaccinated populations has a multifactorial etiology: adaptation of the pathogen, suboptimal immunity and genetic host factors were all found to play a role. First, using an in vitro model of human innate immune cells, certain circulating strains of *B. pertussis* were found to be able to evade innate immune recognition, due to genetic changes in the Lipo-Poly-Saccharide molecule that undermine its normal TLR-4 activating capacity [5]. Also, as was published in a review article, the whooping cough bacterium has developed different strategies to evade bacterial killing by the human complement system [6]. Second, results from our cumulative immunological studies in pre-clinical mouse models [7, 8] and in various vaccinated [9] and infected [10] cohorts confirmed the fundamental importance of the presence of TLR-4 ligation for priming of optimal Th1/Th17 type immunity. This is elicited, for example, by vaccines based on whole cells or by natural infection, but not by acellular vaccines. Immunological insights from cumulative human clinical [11] and experimental studies [12] were meta-analysed in two review articles, to advance conceptual thinking about the improvement of current pertussis vaccination. Finally, it was discovered that the clinical outcome of pertussis may partly be influenced by host genetic factors [13]. A study on immunological responses after infant vaccinations following maternal pertussis vaccination (MIKI) started in 2013. Infants received a reduced NIP schedule with vaccinations at 3 and 5 months of age. Half of the mothers were vaccinated in their third trimester of pregnancy, half directly after birth. The inclusion for the study is finished and the follow-up of infants is ongoing. This follow-up period is extended with additional visits at 2 and 4 years of age. The first results are expected in 2017.

7.8.5 International developments

In 2015, a €30 million European subsidy, in the framework of a Horizon2020/IMI2 programme on pertussis immunological research, was granted to the PERISCOPE consortium. The RIVM participates in this network of 22 European knowledge institutes and industrial partners. It is a principal task of the RIVM to conduct clinical immunological studies in the field of pertussis vaccination and infection and to develop and use innovative pertussis immune assays. The five-year PERISCOPE project started on 1st March 2016.

7.8.6 Tables and figures

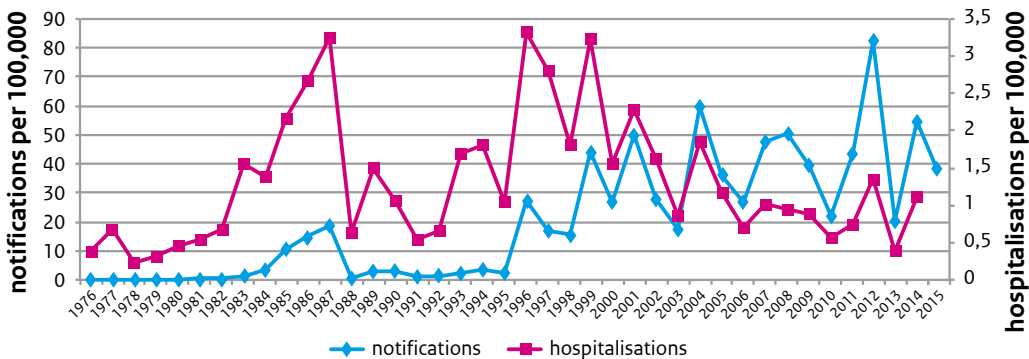


Figure 7.8.1 Pertussis notifications (left Y-axis) and hospitalisations (right Y-axis) per 100,000 for 1976–2015

Sources: Osiris, DHD

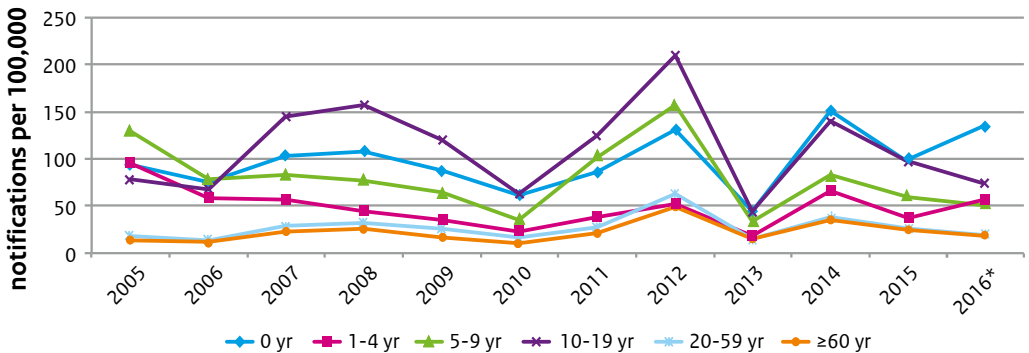


Figure 7.8.2 Pertussis notifications per 100,000 per age category for 2005–2016

* For 2016 only notifications with a first day of symptoms in the first quarter of the year are included.

Source: Osiris

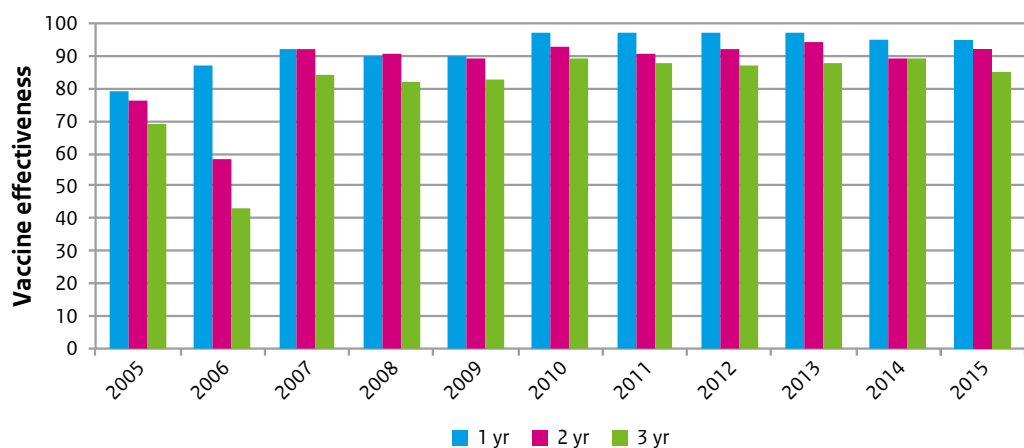


Figure 7.8.3 Vaccine effectiveness estimated for 1-, 2- and 3-year-olds for 2005–2015

Table 7.8.1 Estimation of vaccine effectiveness of the pre-school booster by the ‘screening method’ for 5–15-year-olds per birth cohort (%)

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

7.8.7 Literature

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*RIVM publication



7.9 Pneumococcal disease

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7.9.1 Key points

- The introduction of pneumococcal conjugate vaccination (PCV) led to a significant decrease in overall invasive pneumococcal disease (IPD) in children under 5 years of age and in elderly aged 65 years and older.
- The incidence of PCV7-type IPD remained very low in 2015–2016, with an incidence of 0.9 per 100,000.
- The incidence of IPD caused by the additional serotypes in PCV10 (serotype 1, 5 and 7F) was 0.5 per 100,000 in children under 5 years old in 2015–2016. In other age groups, the incidence of PCV10-7 type IPD further decreased (although not significantly) in 2015–2016, due to herd protection.
- Non-PCV10-type IPD incidence remained stable in 2015–2016 in all age groups.
- The incidence of PCV13-10-type IPD, including serotype 19A, seemed to decrease after PCV10 introduction in 2011–2013 but increased slightly (in <5- and 50–64-year-olds) or stabilised (in 5–49- and >65-year-olds) in 2014–2015 and 2015–2016, indicating absence of cross-protection of PCV10 against serotype 19A.
- The VE of at least two doses of PCV10 was 87% (95% CI: 33–97%) against vaccine type IPD and 92% (35–99%) against serotype 7F.

7.9.2 Epidemiology

7.9.2.1 Overall invasive pneumococcal disease (IPD) incidence

In the epidemiological year 2015–2016, 636 IPD cases were reported by the nine sentinel laboratories (covering 25% of the Dutch population). This resulted in an overall IPD incidence of 15.1 per 100,000 in 2015–2016 (Figure 7.9.1). The incidence in 2015–2016 was significantly lower than before introduction of the 7-valent pneumococcal conjugate vaccine (PCV7) in <5-year-olds (75% reduction) and >65-year-olds (19% reduction). There was no significant change in incidence in 2015–2016 compared with 2014–2015 (15.2 per 100,000).

7.9.2.2 Vaccine type IPD incidence

In 2015–2016, 33 (5.2%) reported IPD cases were caused by a PCV7 serotype, resulting in an incidence of 0.8 per 100,000 (Figure 7.9.2). The incidence of PCV7-type IPD in 2015–2016 was significantly lower than before the introduction of PCV7 in all age groups (overall reduction of 89%). In 2015–2016, PCV7-type IPD incidence was similar to that in 2014–2015 (0.6 per 100,000) in all age groups.

In 2015–2016, 76 (11.9%) reported IPD cases were caused by the three additional serotypes included in PCV10 (serotypes 1, 5 and 7F), resulting in an incidence of 1.8 per 100,000 for PCV10-7 type IPD (Figure 7.9.2). The incidence of PCV10-7 type IPD in 2015–2016 was significantly lower than in the two years before PCV10 introduction in all age groups (overall reduction of 40%). Compared with 2014–2015 (2.4/100,000) there was a further decrease of PCV10-7 type IPD incidence in 2015–2016 of 26%.

7.9.2.3 Non-vaccine-type IPD incidence

In 2015–2016, 527 (82.9%) reported IPD cases were caused by serotypes not included in PCV10, resulting in an incidence of 12.5 per 100,000 (Figure 7.9.2). The incidence of non-PCV10-type IPD in 2015–2016 was significantly higher than before the introduction of PCV7 and PCV10 in all age groups, except for <5-year-olds (overall increase compared with pre-PCV7 period was 121%). There were no significant differences between 2015–2016 and 2014–2015 (12.1/100,000) in the incidence of non-PCV10-type IPD.

Of special interest is the group of non-PCV10-type IPD caused by the three additional serotypes included in PCV13: serotypes 3, 6A and 19A. In 2015–2016, these serotypes caused 21.1% (n=134) 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 2015–2016 was significantly higher than before the introduction of PCV7 in 5–49-year-olds (144% increase), 50–64-year-olds (67% increase) and >65-year-olds (41% increase). The incidence of PCV13-10-type IPD, and specifically serotype 19A, seemed to decrease after the introduction of PCV10 in 2011–2013 but increased slightly (<5- and 50–64-year-olds) or stabilised (5–49- and >65-year-olds) in 2014–2015 and 2015–2016, suggesting no cross-protection of PCV10 against serotype 19A.

In 2015–2016, 180 (46.9%) of the IPD cases among >65-year-olds were caused by serotypes included in the 23-valent pneumococcal polysaccharide vaccine (PPV23) but not in PCV13 (PPV23-PCV13). The incidence of PPV23-PCV13-type IPD in >65-year-olds has increased steadily in recent years from 10.6 per 100,000 in 2004–2005 to 23.9 per 100,000 in 2015–2016.

7.9.2.4 Vaccine failure

Since the introduction of PCV7, 35 cases of vaccine-type IPD have been reported among vaccine-eligible children (born from 1st April 2006 and at least 2 months old) in the nationwide surveillance. Of these, 17 children (49%) had been vaccinated with at least two doses (with the second dose given at least two weeks before diagnosis) and were therefore considered vaccine failures (Table 7.9.1). Most vaccine failure cases had serotype 19F (n=7, 41%). There were three vaccine failure cases in 2015 and one in 2016 (up to May), all of them having been vaccinated with PCV10.

7.9.2.5 Vaccine effectiveness against IPD

The VE of PCV7 and PCV10 was calculated using the indirect cohort (or Broome) method [1], 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 PCV7 or PCV10 vaccination aged at least 2 months and with known serotype and vaccination status. For PCV7, 11 of the 19 (58%) vaccine-type IPD cases and 269 of the 282 (95%) non-vaccine type IPD cases had been vaccinated with at least two doses. This resulted in a VE of 93% (95% CI: 81–98%) for at least two doses of PCV7 compared with zero doses. Serotype-specific VE could be calculated for serotypes with at least one vaccinated and one unvaccinated case. VE was 98% (83–100%) for serotype 9V, 98% (83–100%) for serotype 18C and 71% (-159–97%) for serotype 19F.

For PCV10, five of the eight (63%) vaccine-type IPD cases and 99 of the 107 (93%) non-vaccine-type IPD cases had been vaccinated with at least two doses. This resulted in a VE of 87% (95% CI: 33–97%) for at least two doses of PCV10 compared with zero doses. Serotype-specific VE

was 92% (35–99%) for serotype 7F. VE against PCV10-related IPD was 28% (-23–84%) and, specifically, VE against serotype 19A was 57% (-99–91%). From these results, cross-protection of PCV10 against vaccine-related IPD including serotype 19A cannot be deduced.

7.9.2.6 IPD mortality

From 2014 to 2016, 132 IPD cases among children under 5 years of age were reported nationally. For 79 cases (60%), the mortality status was known. Five of the 79 (6%) cases died. These five cases had non-vaccine type IPD (serotypes 3, 15C, 23A, 22F, 24F) and two had known comorbidity.

7.9.3 Pathogen

Molecular genetic analysis of pneumococcal strains isolated from IPD patients in 2013–2015 (post-PCV10 period) is ongoing. Preliminary results show no obvious changes in the genetic diversity of these isolates compared with previous years. Two potential capsular switch events were detected in 2013–2015, both concerned a switch between non-vaccine capsules.

7.9.4 Research

7.9.4.1 Sex differences in IPD incidence

Age-specific IPD incidences in the pre-PCV7 (June 2004–May 2006), post-PCV7 (June 2008–May 2011) and post-PCV10 (June 2013–May 2015) periods were compared between females and males. Changes in IPD incidence, comparing post-PCV7 to pre-PCV7 and post-PCV10 to post-PCV7, were also compared between females and males. IPD incidence within the pre- and post-PCV7/10 periods was higher in males for all age groups, except for 20–39-year-olds in the post-PCV7 and post-PCV10 period (males: 4.7 and 2.6/100,000; females: 5.0 and 4.0/100,000, respectively). Within this age group, comparing post-PCV7 with pre-PCV7, IPD incidence decreased in males whereas it increased in females due to a significant increase of non-PCV7 serotypes in females, which was not observed in males. After PCV10 introduction, PCV10 herd protection became apparent in all age groups and in both sexes. However, only in women aged ≥40 years did PCV10 herd effects coincide with a significant increase in non-PCV10 serotype IPD, which precluded a decrease in overall IPD incidence. In conclusion, IPD incidence is higher in males than females. PCV7/10 introduction caused a higher non-vaccine-type IPD incidence in women aged 20–39 years than in males in the same age group, probably due to more contact with PCV7/10-vaccinated children.

7.9.4.2 Pneumococcal carriage

Nasopharyngeal carriage of *S. pneumoniae*, *H. influenzae*, *S. aureus* and *M. catarrhalis* was determined by conventional culture in 329 24-month-old children in 2015–2016 (OKIDOKI-4 study). Pneumococcal serotyping was performed by Quellung. Overall pneumococcal carriage rates were significantly lower in 2015–2016 (48%) than in 2013 (56%; $p=0.04$). Carriage of PCV10 serotypes was lower in 2015–2016 (1.2%) than in 2013 (2.4%; $p=0.56$). 19A carriage was also lower in 2015–2016 (4.0%) than in 2013 (8.4%; $p=0.03$), making it no longer the dominant serotype. Serotype 6C (6.7%) and 23B (6.7%) became the new dominant serotypes in 2015–2016.

A similar decreasing trend as for pneumococcal carriage was seen for *H. influenzae* (61% compared with 69%; $p=0.04$) and *Moraxella catarrhalis* (73% compared with 76%; $p=0.37$). In contrast, carriage rates of *Staphylococcus aureus* were higher in 2015–2016 (11%) than in 2013 (7%; $p=0.06$).

Molecular versus conventional diagnostic methods were compared for detecting serotype-specific carriage in two cross-sectional studies in vaccinated infants (OKIDOKI-2 and OKIDOKI-3 studies) [2]. Nasopharyngeal samples from 1,169 11- and 24-month-old children were tested by conventional culture for *S. pneumoniae* and qPCR for selected serotypes (including PCV13 serotypes). Compared to culture, qPCR significantly increased the number of pneumococcal carriers (69% vs. 57%, $p<0.0001$). For serotypes reliably targeted by qPCR, the number of serotype-carriage events detected by qPCR ($n=709$) was 1.68× higher compared to culture ($n=422$). There was no evidence of a hidden circulation of vaccine-targeted serotypes, despite vaccine serotypes still significantly contributing to IPD in unvaccinated individuals, supporting the presence of a substantial *S. pneumoniae* reservoir outside vaccinated children.

7.9.4.3 Immunogenicity of PCV10 and PCV13

A comparative study in infants was performed (PIEN) in 2012 to compare the immunogenicity of PCV10 versus PCV13. Serological and cellular immune responses were measured in blood samples from the infants before and after the 11-month booster vaccination. Subtle differences in immunogenicity between the vaccines were found, related to different antigen content per vaccine or intrinsic serotype immunogenicity, yet all serotypes in the two vaccines induced protective antibody levels [3] and immunological B cell memory [4]. Using data from the PIEN study [3] and the PIM study [5], pneumococcal-specific serum IgG levels after primary immunisation with PCV10 or PCV13 were compared at 5, 8, and 11 months of age. PCV10- and PCV13-induced antibody concentrations against shared serotypes remained above the seroprotective level throughout the entire period between primary series and booster dose, except for serotypes 4 and 19F for PCV10 and 4 and 6B for PCV13. Antibody levels of serotype 19F in the PCV10 group and serotype 6B in both groups did not decline, suggesting exposure to these serotypes or cross-reaction. PCV13 responses were in general somewhat lower than for PCV10 and declined faster for 5 out of the 10 shared serotypes. Both vaccines are highly immunogenic, inducing protective antibody levels in the period between the primary series and the booster dose. But some difference in the kinetics of the induced specific antibody responses were found, depending on serotype and vaccine.

7.9.4.4 Etiology of pneumonia at the GP's

In 2015, a pilot study was performed in the sentinel GPs (proportion of the GPs participating in NIVEL Primary Care Database) in which the etiology of community-acquired pneumonia in patients aged 65 years and above was assessed through urinary antigen tests for *Streptococcus pneumoniae* and *Legionella pneumophila*. A total of 52 specimens were collected, but none of these urine samples tested positive. The median age of the sampled patients was 70 years. Based on the results of the pilot study on the etiology of pneumonia, it does not seem useful to implement routine diagnostics for community-acquired pneumonia in primary care using urine antigen tests. The focus in establishing etiology should be on hospitalised pneumonia patients.

7.9.5 (Inter)national developments

7.9.5.1 Sex-dependent immune responses to PCV vaccination

Voysey et al. performed a meta-analysis of clinical vaccination studies conducted by a single centre in the UK, in which vaccines were administered to children under 3 years of age and immunological parameters measured [6]. They found significantly higher pneumococcal serotype-specific IgG-levels following pneumococcal conjugate vaccination in girls than in boys. This higher level among girls was present following the primary series, just before the booster, one month after the booster, and one year after the booster. However, the difference one month after the booster was less pronounced than at the other time points and statistically significant for only one serotype.

7.9.5.2 Vaccine effectiveness of PCV10

Verani et al. applied the indirect cohort method to estimate the effectiveness of PCV10 in young children in Brazil [7]. The adjusted effectiveness of one dose or more was 72.8% (95% CI: 44.1–86.7%) against vaccine-type IPD and 61.3% (95% CI: 14.5–82.5%) against vaccine-related IPD. They also found significant protection from one dose or more against individual vaccine serotypes (14, 6B, 23F, 18C) and against vaccine-related serotype 19A, suggesting cross-protection of PCV10 against serotype 19A, in contrast to our results.

Deceuninck et al. assessed the effectiveness of PCV7, PCV10 and PCV13, which were sequentially used to prevent IPD in Quebec [8]. A case-control study was performed, including IPD cases of 2–59 months diagnosed during the years 2005–2013. Against vaccine-type IPD, VE (≥ 1 dose) was 90% (82–95%) for PCV7, 97% (84–99%) for PCV10 and 86% (62–95%) for PCV13. Against 19A IPD, VE was 42% (-9%–69%) for PCV7, 71% (24–89%) for PCV10, and 74% (11–92%) for PCV13. All three PCV vaccines showed a high level of protection against IPD caused by serotypes included in their formulation and there was a high level of cross-protection against 19A for PCV10.

7.9.5.3 Impact of PCV on pneumococcal pneumonia

Van Werkhoven et al. assessed herd protection from infant pneumococcal conjugate vaccination on non-IPD pneumococcal community-acquired pneumonia (PCAP) in adults 65 years and older in the period 2008–2013 in the Netherlands [9]. Serotype-specific urinary antigen detection was used to categorise episodes of PCAP caused by PCV7, PCV10-7, PCV13-10 and non-PCV13 serotypes. Of 270 non-IPD PCAP episodes with known serotype, PCV7 serotypes decreased from 28% in 2008–2009 to 7% in 2012–2013 (p-value for trend < 0.001). No change in PCV10-7 (19% overall) and PCV13-10 (29% overall) serotypes was observed yet. Non-PCV13 serotypes increased from 30% in 2008–2009 to 37% in 2012–2013 (p-value for trend 0.048). These trends correspond with national IPD data.

Pletz et al. compared the distribution of the vaccine-serotypes covered by PCV7 and PCV13 in adult patients with pneumococcal community-acquired pneumonia in Germany between the periods 2002–2006 and 2007–2011 [10]. In Germany, the vaccination of children started in 2007 with PCV7, which was replaced by PCV13 in 2010. In 391 patients with pneumococcal pneumonia, serotype was determined using a new serotype-specific multiplex urinary antigen detection

assay. The proportion of PCV7-serotypes significantly decreased in patients with non-invasive pneumococcal pneumonia from 30.6% (2002–2006) to 13.3% (2007–2011, $p < 0.001$). Conversely, PCV13 serotypes remained stable during the study period with a coverage of 61.5% (2002–2006) and 59.7% (2007–2011) in non-invasive pneumococcal pneumonia, mainly due to an increase in pneumococcal serotypes 1, 3 and 7F during the second period.

7.9.5.4 Efficacy/effectiveness of PPV23

In 2016, four meta-analyses were published on the VE of PPV23. Falkenhorst et al. assessed the evidence for the VE of PPV23 against IPD and pneumococcal pneumonia in people aged 60 years and over, including RCTs and observational studies [11]. VE against pneumococcal pneumonia was 64% (35–80%) in RCTs ($n=2$, after excluding two studies with a high risk of bias) and 48% (25–63%) in cohort studies ($n=2$). VE against all-type IPD was 45% (15–65%) in cohort studies ($n=3$) and 59% (35–74%) in case-control studies ($n=3$). Pooling four studies using the indirect cohort method resulted in a VE of 37% (27–45%) against vaccine-type IPD.

Kraicer-Melamed et al. summarised the results of studies reporting on the VE of PPV23 in preventing IPD and CAP in individuals over the age of 50 years [12, 13]. The VE for PPV23 in preventing IPD was 50% (21–69%) for cohort studies ($n=8$) and 54% (32–69%) for case-control studies ($n=4$). The VE estimates for CAP were -10% (-36–12%) for RCTs ($n=3$), 17% (-26–45%) for cohort studies ($n=9$), and 7% (-10–21%) for case-control studies ($n=7$).

Schiffner-Rohe et al. from Pfizer performed a meta-analysis of RCTs to investigate the effect of PPV23 for preventing pneumococcal CAP in adults of 60 years and over [14]. They included four studies, of which three did not demonstrate efficacy of PPV23. The only study that showed efficacy of PPV23 was performed in nursing homes in Japan. The pooled VE estimate for pneumococcal CAP was 28% (-58%–67%). There was significant heterogeneity between the studies, which could be explained by study setting, continent of trial and method of pneumococcal diagnostics.

Diao et al. conducted a meta-analysis of RCTs to assess the VE of PPV23 in an immunocompetent population [15]. PPV23 was weakly associated with the prevention of all-cause pneumonia (VE of 13% (2–24%), $n=7$). The VE of PPV23 against pneumococcal pneumonia was 46% (-65–82%) ($n=3$).

7.9.5.5 Cost-effectiveness

In several studies, the cost-effectiveness of vaccinating adults over 50 has been explored. Blommaert et al. assessed the cost-effectiveness of vaccinating healthy adults over 50 in Belgium with either PCV13 or PPV23 alone or with a combined strategy using both PCV13 and PPV23 [16]. Using a static multi-cohort model incorporating Dutch CAPITA trial data, the consequences of pneumococcal vaccination in adults over 50 were evaluated. Pneumococcal vaccination programmes either with PCV13 or PPV23 in healthy adults >50 proved to be cost-ineffective at a willingness to pay of €35,000 per QALY. At a vaccine price of €75 per dose, PCV13 vaccination of healthy adults over 50 is unlikely to be cost-effective in combination with PPV23 versus PPV23 only.

Stoecker et al. examined the cost-effectiveness of adding PCV13 to the US' adult immunisation schedule [17]. In the base case scenario, adding PCV13 at age 65 or replacing PPV23 with PCV13 at age 65 provided more value for money than adding PCV13 at ages 50 or 60. For a cohort of 65-year-olds in 2013, the ICER of adding PCV13 at age 65 to the schedule was \$62,065 per QALY gained, which rose to \$272,621 after six years of projected herd protection from the childhood immunisation programme. The authors conclude that the addition of one dose of PCV13 for adults appears to have an ICER comparable to other vaccination interventions in the short run, though anticipated herd protection from the childhood immunisation programme may dramatically increase the ICER after only a few years.

In England, the cost-effectiveness of vaccinating immunocompetent 65 year olds with PCV13 was assessed by van Hoek and Miller [18]. Vaccination of a cohort of immunocompetent 65-year-olds with PCV13 would directly prevent 26 cases of IPD, 69 cases of CAP and 15 deaths. The associated ICER is £257,771 per QALY gained and is therefore considered not cost-effective. To obtain a cost-effective programme, the price per dose would need to be negative. The absolute incidence of vaccine-type disease among the elderly is likely to become very low due to wider benefits of the childhood PCV13 vaccination programme (introduced in 2010), such that a specific PCV13 vaccination programme targeting the immunocompetent elderly would not be cost-effective.

Treskova et al. assessed the cost-effectiveness of three strategies (PCV13 only, PPV23 only, and PCV13 and PPV23 sequentially) in the context of PCV13 use in children and PPV23 use in elderly in Germany [19], using a dynamic model. In the base case scenario PPV23 only was cost-effective (ICER=€14,113 per QALY gained) as compared with no vaccination, even when PPV23 was considered ineffective against pneumococcal pneumonia (ICER=€37,813 per QALY gained). PCV13 alone versus PPV23 alone was dominated by PPV23 and sequential vaccination versus PPV23 alone was not cost-effective (ICER=€366,103 per QALY gained).

Rodríguez-González-Moro et al. estimated the ICER of vaccinating chronic obstructive pulmonary disease (COPD) patients ≥50 years old with PCV13 compared with the current PPV23 vaccination policy in Spain [20]. Over a lifetime horizon and for a 629,747 COPD total population, PCV13 would prevent 2,224 cases of inpatient non-bacteremic pneumonia (NBP), 3,134 cases of outpatient NBP, and 210 IPD cases in comparison with PPV23. Additionally, 398 related deaths would be averted. The ICER was €1,518 per QALY gained for PCV13 versus PPV23. PCV13 among older COPD patients was found to be cost-effective.

Kuhlmann and von Schulenburg evaluated the cost-effectiveness of universal vaccination with PCV10 or PCV13 in Germany [21]. A population-based Markov model was developed including indirect herd effects and replacement disease. In the base case analysis, the ICER of PCV13 versus PCV10 infant vaccination was €9,826 per QALY gained. For that reason, PCV13 is likely to be a cost-effective intervention compared with PCV10 within the German health care system.

7.9.5.6 Future vaccines

Strategies for the development of novel serotype-specific conjugate vaccines are mainly directed at reducing cost and increasing coverage. Examples include a 'PCV10' variant in India, adapted to endemic serotypes (PCV13 minus 3, 4, and 18C; Serum Institute of India), a variant of PCV13 that lacks 6A but includes 22F and 33F (Biological E), and PCV15 (Merck), which consists of PCV13 serotypes supplemented with 22F and 33F. For all of these formulations, non-inferiority to licensed vaccines (with a cut-off for anticapsular polysaccharide antibody concentration of 0.35 µg/mL aggregated across all serotypes) will have to be established, which may prove difficult, as the inclusion of more serotypes may decrease immunogenicity. Alternative pneumococcal vaccine strategies involve the use of pneumococcal proteins that contribute to pathogenesis and are common to all serotypes, thus potentially providing serotype-independent protection. Protein-based vaccines are likely to be simpler and therefore more affordable. Furthermore, an efficacious protein antigen could be used as a carrier in a capsular polysaccharide (CP) protein conjugate vaccine formulation.

One example of the latter is the MAPS platform (multiple antigen presenting system [22], in which various antigen components, including polysaccharides and proteins, are integrated in the same construct. MAPS was shown to elicit broad protective antibody and Th17 responses against CP and protein in animal models [23]. Another example is described by LimmaTech Biologics, which uses a proprietary bioconjugation platform to couple detoxified pneumolysin to CP4. When used in a guinea-pig model, both CP4-specific opsonophagocytic responses and pneumolysin-specific neutralising antibodies were observed. Clinical proof-of-concept trials for this bioconjugate vaccine are planned [24].

A phase II randomised trial in the Gambia in which two protein-based pneumococcal vaccine formulations (pneumolysin toxoid and PhtD; GSK) were combined with PCV10, showed no impact on carriage or acquisition of *S. pneumonia* beyond that provided by PCV10 [25].

The GEN-004 vaccine (Genocea), containing three conserved pneumococcal proteins, is designed to protect against colonisation through a Th17 mechanism. It was shown to be protective in animal models [26] and was recently tested in the experimental human challenge model established in Liverpool [27]. The vaccine was well tolerated and immunogenic.

Acquisition of carriage was consistently lower in vaccinated than control subjects, but these differences were not statistically significant [28].

Another serotype-independent vaccine in development, PbuBioVax, is produced from genetically modified pneumococci and contains multiple proteins including detoxified pneumolysin and PspA. In a phase I study, this vaccine was shown to be well tolerated and immunogenic, generating antibody responses to a variety of pneumococcal antigens [29].

The PATH whole-cell vaccine, produced from an unencapsulated strain, confers Th17-mediated protection against colonisation and antibody-mediated protection against invasive disease [30]. A phase I/II study in healthy toddlers in Kenya is ongoing to assess safety and tolerability, and explore whether a measurable immune response is elicited.

7.9.6 Tables and figures

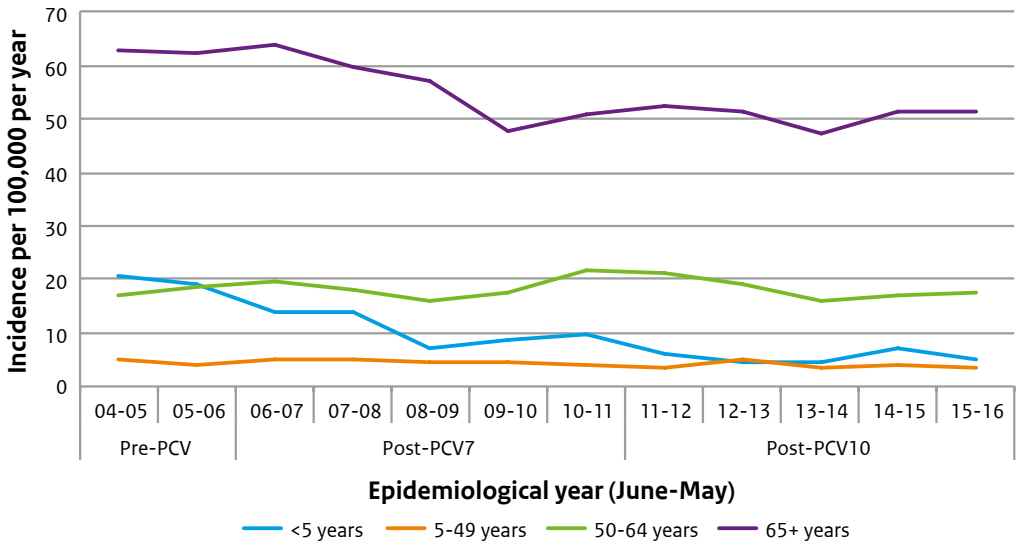


Figure 7.9.1 Incidence of IPD caused by all serotypes, presented by epidemiological year (e.g. 04-05 = June 2004–May 2005)

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

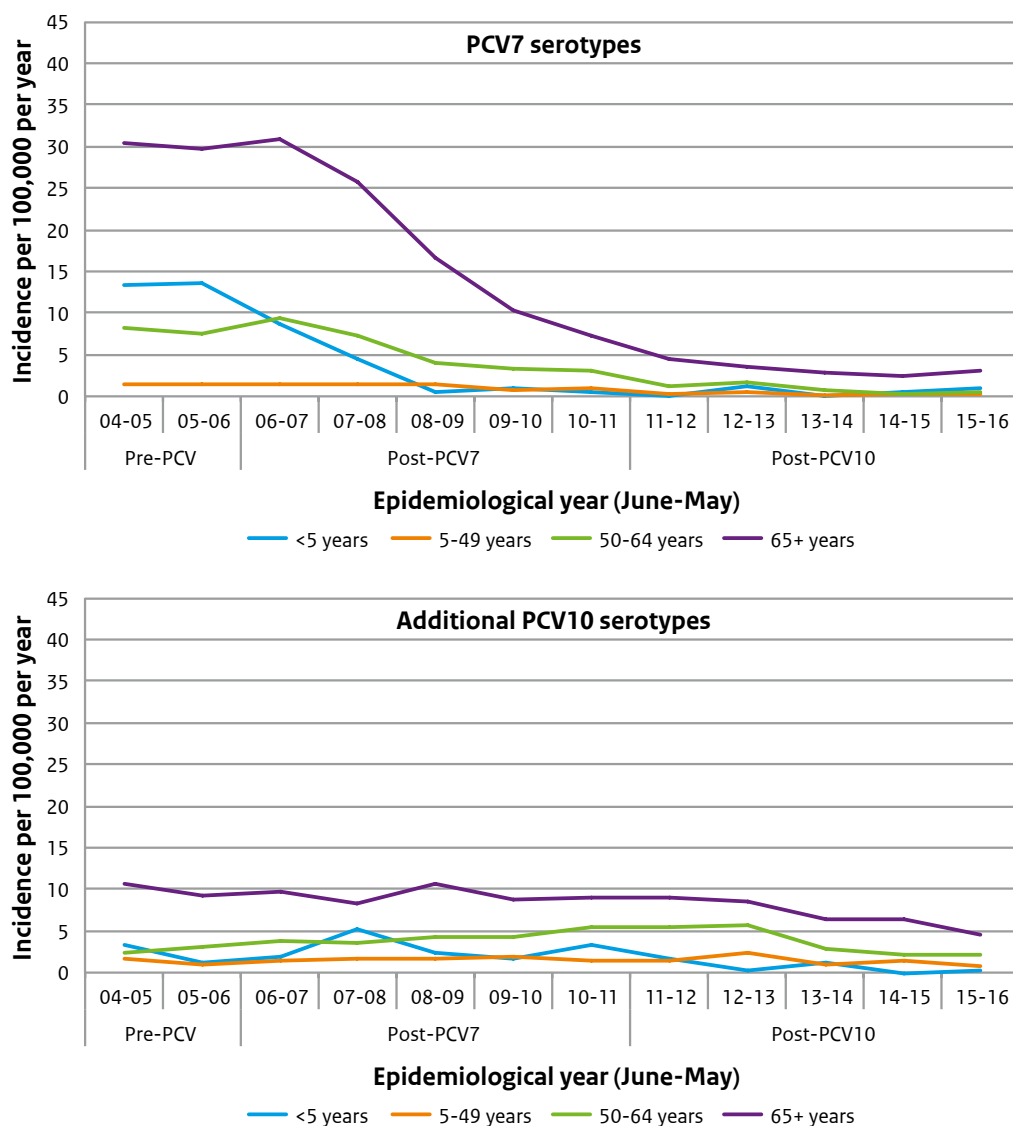


Figure 7.9.2a Incidence of IPD caused by PCV7 serotypes and PCV10-7 serotypes, presented by epidemiological year (e.g. 04–05 = June 2004–May 2005)

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

Source: NRBM

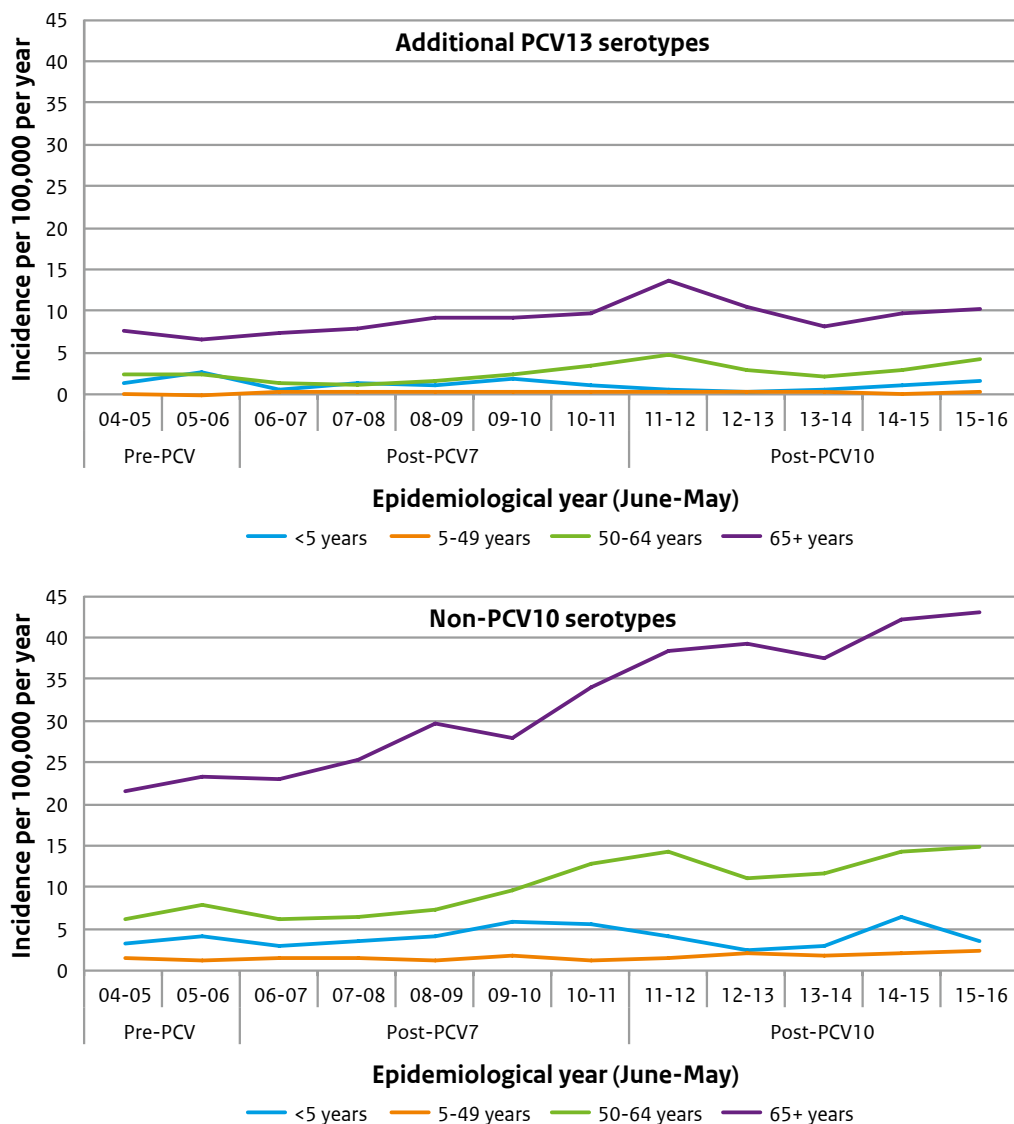


Figure 7.9.2b Incidence of IPD caused by PCV13-10 serotypes and non-PCV10 serotypes, presented by epidemiological year (e.g. 04-05 = June 2004–May 2005)

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

Source: NRBM

Table 7.9.1 Children with vaccine-type IPD having received at least two vaccinations (with at least two weeks between the second dose and diagnosis) based on nationwide surveillance 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

Sources: NRBM, Praeventis, Osiris

7.9.7 Literature

7.9.7.1 References

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*RIVM publication

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7.10 Poliomyelitis

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

7.10.1 Key points

- In 2015 and in 2016, up to 1st July, no cases of poliomyelitis were reported.
- In July 2015, a vaccine-derived poliovirus (VDPV) type 3 was found in a young Syrian refugee without clinical symptoms.
- In December 2015 Sabin 1 and 2 strains were detected in a child returning from Pakistan.
- In the two polio-endemic countries (Afghanistan and Pakistan), reports of wild poliovirus type 1 have decreased substantially.
- By the end of May 2016 all countries had made the big shift from tOPV to bOPV and included IPV in their vaccination programmes.

7.10.2 Epidemiology

In 2015 and in 2016, up to 1st July, no cases of poliomyelitis were reported in the Netherlands (Figure 7.10.1).

7.10.3 Pathogen

In one sample collected on 29th January 2015, at the primary refugee entry point in Ter Apel, the Netherlands, a Sabin vaccine strain poliovirus type 1 was found. Furthermore, through routine enterovirus surveillance, in July 2015 an ambiguous vaccine-derived poliovirus (VDPV) type 3 was found in a young Syrian refugee. He had no clinical symptoms of polio. Follow-up of the case and surrounding contacts revealed no circulation of poliovirus. Also through routine enterovirus surveillance, in December 2015, Sabin 1 and 2 strains were detected in a child returning from Pakistan. The first follow-up sample was positive for poliovirus Sabin 2 only. Two follow-up samples were negative for poliovirus and it was concluded that the oral polio vaccine (OPV) shedding had stopped.

7.10.4 Research

A recent paper by Dunn et al. described an immunodeficient case who excreted type 2 VDPV for 28 years, as estimated by the molecular clock established with VP1 capsid gene nucleotide sequences of serial isolates [1].

This indicates that VDPV isolated from immunodeficient cases represents a real risk of polio re-emergence in the post-eradication era.

Currently, large amounts of highly virulent polioviruses must be grown for IPV manufacturing. A release from these production facilities would be disastrous. Knowlson et al. have designed extremely genetically stable and hyper-attenuated viruses for IPV production with negligible risk to the human population should they escape. These attributes allow safe vaccine production in the post-eradication world [2].

7.10.5 International developments

In 2015–2016, polio remained endemic in two countries – Afghanistan and Pakistan. Although most parts of both countries are polio-free, areas with ongoing transmission within the country itself and to neighbouring countries remain. In 2016, up to 19th June, no importation of polio into non-endemic countries was observed.

Of the three strains of wild poliovirus (types 1, 2 and 3), wild poliovirus type 2 was eradicated in 1999. This was officially declared by the Global Commission for the Certification of Poliomyelitis Eradication on 20th September 2015 [3]. No wild poliovirus type 3 cases have been reported since 2014. Case numbers of wild poliovirus type 1, which circulates in Pakistan and Afghanistan only, are at their lowest level ever.

The number of circulating VDPV decreased in 2015 (n=32) compared with 2014 (n=55). Three VDPVs have been reported in 2016, up to 17th May. To boost a further reduction in VDPVs, all countries with OPV in their immunisation programmes 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 essential facilities. In the Netherlands, the inventory of facilities maintaining poliovirus materials is currently ongoing.

To strengthen protection through vaccination, all countries included at least one dose of IPV in their immunisation programme in 2015.

7.10.6 Tables and figures

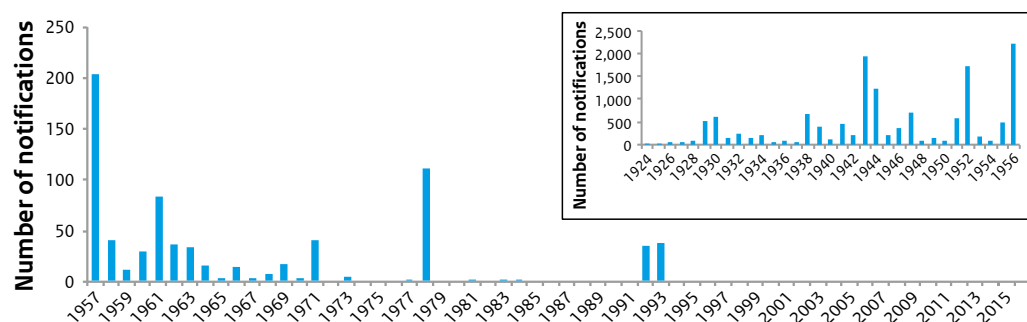


Figure 7.10.1 Notifications of poliomyelitis in the Netherlands 1924–1956 and 1957–2016. For 2016, reports up to 1st July are included.

Source: Osiris

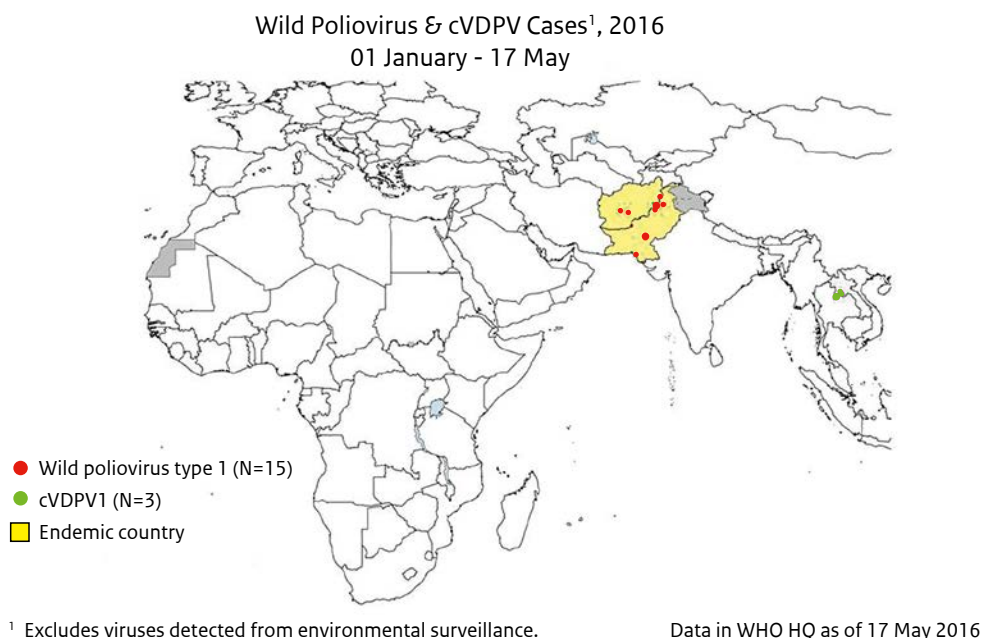


Figure 7.10.2 Wild poliovirus cases worldwide

Source: <http://www.polioeradication.org/portals/0/Image/Data&Monitoring/currentyear.jpg>

7.10.7 Literature

7.10.7.1 References

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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 calendar year 2015, one rubella case was reported. In 2016, up to July, no cases of rubella were reported.
- In 2013, a large rubella outbreak started in Poland. In 2015 this outbreak still continues, although reported numbers are decreasing.

7.11.2 Epidemiology

In the calendar year 2015, one rubella case was reported. The patient was an unvaccinated 31-year-old male who contracted rubella visiting relatives in Namibia. The most likely source of infection of the adult case was a relative in Namibia. In 2016, up to July, no cases of rubella were reported.

7.11.3 Pathogen

The disease was confirmed by IgM serology; no genotyping results are available.

7.11.4 Research

A multidisciplinary Dutch expert group was convened to prepare a national guideline on rubella screening during pregnancy. In the Netherlands, there is no uniform policy on rubella screening. Some midwives screen all pregnant women, some screen only risk groups and others do not screen at all. Given the high vaccination coverage and low incidence of rubella, the screening of all pregnant women is not cost-effective [1]. The guideline is expected in the second half of 2016.

7.11.5 International developments

In 2013, a large rubella outbreak started in Poland, with more than 38,000 cases reported. This outbreak reflects the historical immunisation policy, where selective vaccination of adolescent girls since 1989 and universal vaccination since 2004 led to an immunity gap among adolescent males and young adults [2]. In the period 1st July 2015 – 30th June 2016, Poland reported over 1,553 cases, accounting for 91% of all cases reported in the EU/EEA [3]. However, as only 1% of reported cases from Poland are laboratory-confirmed, these numbers should be interpreted with caution [3, 4]. Other countries reporting significant numbers of rubella cases in 2015 were Germany (90 cases) and Italy (38 cases) [5].

The WHO initiated a rubella IgG standardisation workgroup in 2013/2014, to provide a guideline for appropriate rubella IgG screening during pregnancy. Standardisation of rubella virus IgG assays is required as many women currently gain immunity from MMR immunisation and not from natural infection, which results in different IgG levels [6]. Follow-up studies and recommendations for usage of serological tests for rubella are expected from this

international group after 2016, and will be incorporated in a revised version of the International Laboratory Manual for measles and rubella [4].

According to a press release, Public Health England ended screening for rubella in pregnancy in April 2016 [5].

7.11.6 Literature

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*RIVM publication



7.12 Tetanus

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

7.12.1 Key points

- In 2015, one case of tetanus was reported. No cases were reported in 2016, up to 1st July.

7.12.2 Epidemiology

In 2015, an unvaccinated 18-year-old male with signs of tetanus was reported. He had a critical attitude towards vaccination. He probably contracted the bacterium after being wounded by firework. He recovered. In 2016, up to 1st July, no tetanus cases were reported.

7.12.3 Pathogen

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

7.12.4 Tables and figures

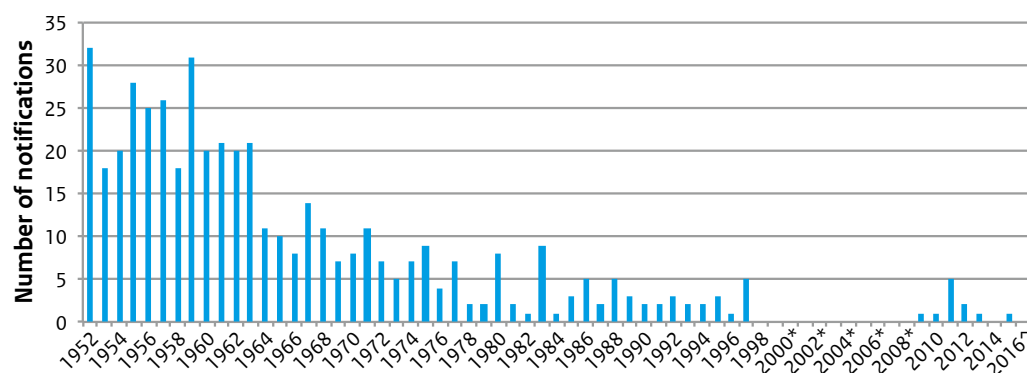


Figure 7.12.1 Reported cases of tetanus in the Netherlands by year, 1952–2016

* Between 1999 and 2009 tetanus was not notifiable.

^ For 2016 notifications up to 1st July were counted.

Source: Osiris

8

Future NIP candidates

8.1 Hepatitis A

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

8.1.1 Key points

- In 2015, the number of reported hepatitis A patients (80 cases) remained low compared with previous years.
- More than half of the cases were younger than 20 years, and older cases were more likely to be hospitalised.
- Fifty-nine per cent of the Dutch cases were reported to be travel-related, with Morocco reported most frequently.

8.1.2 Epidemiology

In 2015, 80 cases of hepatitis A were reported in the Netherlands, corresponding to 0.5 cases per 100,000 inhabitants. This is lower than 2014 (105 cases) and 2013 (110 cases), and the lowest since hepatitis A became notifiable in 1999 (Figure 8.1.1 / Appendix 2). No mortality due to hepatitis A was reported. The age distribution over the years 2006–2015 is given in Figure 8.3.2. In line with 2006 and 2014, more than half of the cases in 2015 were aged below 20 years. In total, 23 patients were hospitalised (29%); of those aged below 20 years this percentage was 19% (8/42), compared with 39% of the cases aged 20 years or older (15/38). Based on the reports, 14 epidemiologically linked clusters with a total of 29 cases could be deduced. A further four cases could be linked to cases in 2014.

The percentage of travel-related cases was 59% in 2015 (Figure 8.1.1). This is higher than in previous years: 43–51% (2006–2009), 31% (2010), 40–45% (2011–2012), and 53–55% (2013–2014). Morocco (13/47; 28%) was reported most frequently; all other countries were reported a maximum of five times. Half of the clusters (11/18) were at least partly travel-related, mostly from Morocco (5 clusters) or Syria and/or Lebanon (4 clusters). Consumption of food or water was reported as the source of the infection in 36% of the cases, of which 25/29 (86%) consumed food or water in an endemic country.

8.1.3 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 the hepatitis A virus. From contacts of cases, faecal samples can be sent for virus detection and typing if taking a serum sample is not preferred. In 2015, of 50 (60%) cases samples were submitted for virus typing and the samples of 49 cases were positive by PCR and could be sequenced. Thirty-two cases (40%) reported in Osiris were not accompanied by a sample for sequence analysis. The lab or Municipal Health Service (GGD) probably reasoned 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 121 serum and faecal samples from the cases and their contacts were tested. HAV RNA was detected in 56

(46%) and 55 could be typed, which resulted in 43 unique sequences, of which 13 were detected in clusters of 2–8 cases. Since 2011, there seems to have been a slight but steady increase in the fraction of HAV 1A strains (Figure 8.1.3), mostly originating from Morocco. In 2015, eight cases were reported among refugees or contacts of refugees from Syria. Several of the refugees were young adults, suggesting that in Syria this age group was not protected by childhood infection. Sequences from Syria cannot be distinguished from those from Turkey and Lebanon, so it is not possible to tell from strain typing information where refugees were infected. More than half of the samples sent to the IDS are negative for HAV in PCR. Most of these are from elderly patients with weak IgM response, high total Ig or IgG and frequently no indication for hepatitis. These positive IgM reactions obtained through screening usually do not represent acute HAV infections and do not require source and contact tracing. If hepatitis is indicated in this patient group, then we recommend testing for hepatitis E virus by serology or PCR.

8.1.4 Research

The hepatitis A virus used to be the only species in the genus *Hepatovirus*, family *Picornaviridae*. HAV is a ubiquitous human pathogen, also recovered from primates, but its origins are unknown. The discovery of nonprimate HAV-related viruses may provide new insights into the origin and evolution of HAV. Since 2015, at least 13 new species in the *Hepatovirus* genus have been described. The new species were discovered in harbour seals [1], woodchucks [2], bats, rodents, hedgehogs and shrews [3]. These new species share a number of features with human and simian HAV that are unique to the genus *Hepatovirus* distinct from other genera within the family. One of these features, codon usage, was analysed for seal and woodchuck hepatitis A viruses and showed similar bias for rare codons to that seen in the human viruses. In hepatitis A, virus codon usage bias is governed by a strong purifying selection against CG-dinucleotides, which was also observed in the small mammal viruses. Antibodies against bat viruses in some bat sera reacted with human HAV in immunofluorescence, immunoprecipitation and even in neutralisation assays. This research provides important insights into the origins of the hepatitis A virus. The viral phylogeny suggests an ancient origin of HAV within small insectivorous mammals. There is no reason to suspect that these recently discovered hepatitis A virus species form new zoonotic threats.

8.1.5 International developments

Since 2006, routine vaccination has been recommended for all children aged 12 to 23 months in the United States. Dhankhar et al. [4] assessed the cost-effectiveness of two hepatitis A vaccination strategies from a societal perspective, taking productivity losses into account. Using a dynamic transmission model, thus including herd immunity effects, universal vaccination and vaccination of children in regions with high hepatitis A incidence was evaluated. The reported hepatitis A incidence (between 1980 and 1995) obtained from the National Notifiable Diseases Surveillance System was used as input data for the model. On average, universal routine hepatitis A vaccination prevented 259,776 additional infections, 167,094 outpatient visits, 4,781 hospitalisations, and 228 deaths annually. Compared with the regional vaccination policy, universal routine hepatitis A vaccination was cost-saving. This research was sponsored by MSD. Incidence data used were rather old, while in most Western

countries hepatitis A incidence has declined over the last years. No cost-effectiveness comparison was made between a vaccination programme and no vaccination programme, which is usually common practice. An economic evaluation that compares a vaccination programme with no vaccination programme would most likely result in less favourable ICERs.

In the US the cost-effectiveness of a one-time catch-up hepatitis A vaccination to reduce the number of unvaccinated children was evaluated [5]. In this study, a catch-up vaccination for children at target ages from 2 to 17 years was compared with the current routine vaccination at 1 year with no catch-up intervention. Given the low baseline of HAV disease incidence in the US, a catch-up vaccination recommendation would be less cost-effective than many other vaccine interventions. Hepatitis A catch-up vaccination would become cost-effective at a threshold of \$50,000 per QALY only if the incidence of HAV rose above 5.0 cases per 100,000 population.

In Catalonia, Spain, a universal programme of HAV A+B vaccination of children aged 12 years has existed since 1998 [6]. The effect of this on the incidence of hepatitis A outbreaks was evaluated. A reduction in person-to-person outbreaks related to schools was seen. Advancing the vaccination to the second year of life would probably lead to a higher benefit of the universal vaccination. Hospitalisation rates increased after introduction of the vaccination, which can be explained by a shift of HAV infection to older people, who are susceptible to more serious illness and are not vaccinated. Outbreaks related to MSM and immigrants were more common in the post-vaccination period than in the pre-vaccination period, as vaccination is not optimal in these groups.

In 2004, 143 Indian children received a single dose of live attenuated HAV vaccine [7]. After 10 years of follow-up, 121 subjects were available for assessment. Immunogenicity was 87.6% in this group. When the 13 subjects who had received additional vaccinations due to vaccine failure or low titres after the first vaccination are excluded, the seroprotection rate was 98.1% (95% CI: 93.5–99.8%).

Liu et al. [8] report a randomised clinical trial among 239 young adults aged 16–21 years in Nanchang City, China. In the study, the seroprotection of one or two doses of inactivated vaccine (Healive) is compared with one dose of live attenuated vaccine (Biovac). At the start of the study in 2008, 37 subjects had to be excluded due to testing positive for anti-HAV IgG. The remaining subjects were randomly assigned to one of the three vaccine groups. At 12, 24 and 36 months, seroprotection rates and GMCs of anti-HAV IgG were significantly higher in the two-dose inactivated vaccine group than in both one-dose groups. Furthermore, the rates and GMCs were higher in the one-dose inactivated vaccine group than in the attenuated vaccine group. At 36 months of follow-up, seroprotection rates were 100% (95% CI: 89.8–100%), 93% (95% CI 79.9–99.2%) and 65% (95% CI 48.3–79.4%) for the two-dose inactivated vaccine group, one-dose inactivated vaccine group and the attenuated vaccine group, respectively. The GMCs at 36 months were, respectively, 805.7 (565.9–1147.0), 93.9 (61.2–144.1) and 42.1 (26.1–67.8).

The impact of vaccination was evaluated three years after the introduction of HAV vaccination in Panama [9]. Since 2007, children have been offered a two-dose HAV vaccination (Havrix®) through a Universal Mass Vaccination programme. Although a decline had already been seen before the start of the programme, a greater decline was seen afterwards. In the post-vaccination period, a 90% and 87% reduction in hepatitis A incidence was seen in the vaccinated population and the general population, respectively.

Based on data on the follow-up of Argentinean children up to the age of 14–15 years after a two-dose HAV vaccination (Avaxim), the long-term persistence of antibodies was modelled [10]. Eight models were tested, using the information from 54 children with complete follow-up. Extrapolation of the data showed a predicted seroprotection of 88% of the vaccinated subjects for at least 30 years post-vaccination.

8.1.6 Tables and figures

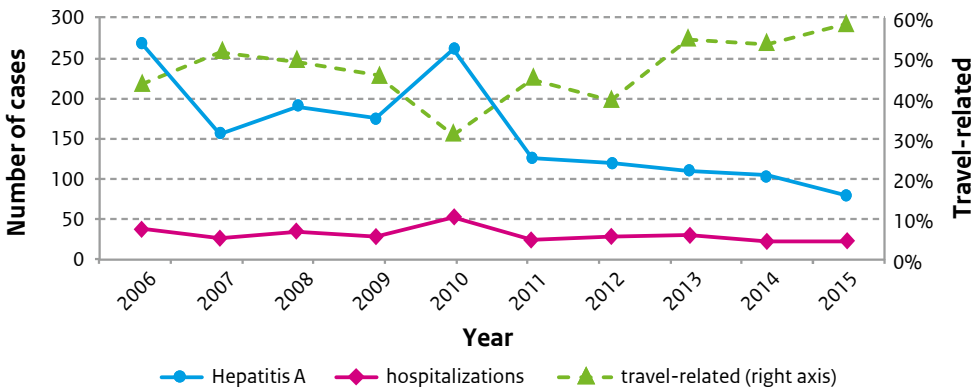


Figure 8.1.1 Number of reported and hospitalised cases of hepatitis A, and the percentage travel-related cases, 2006–2015

Source: Osiris

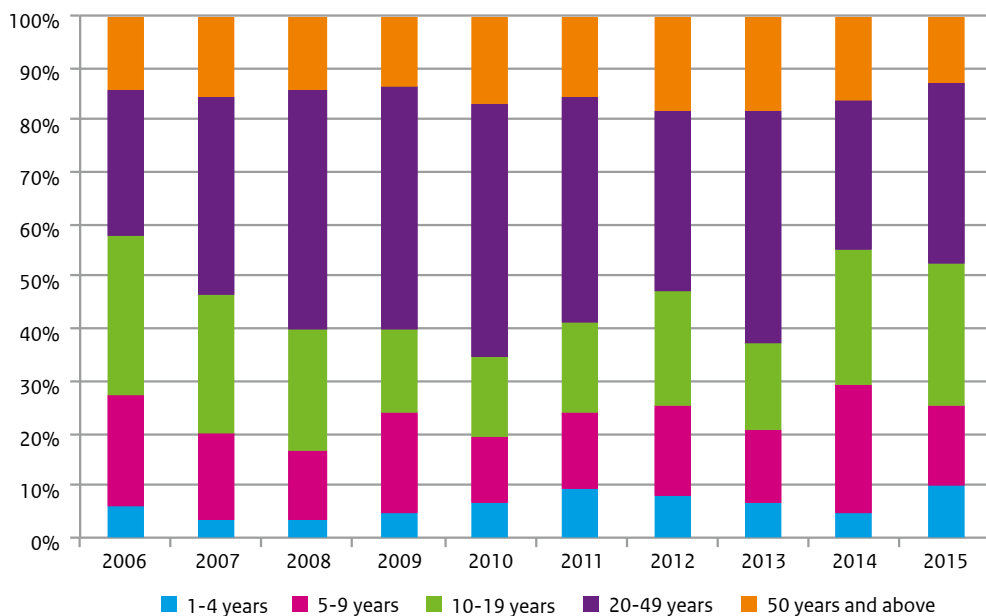


Figure 8.1.2 Age distribution of hepatitis A cases, 2006–2015

Source: Osiris

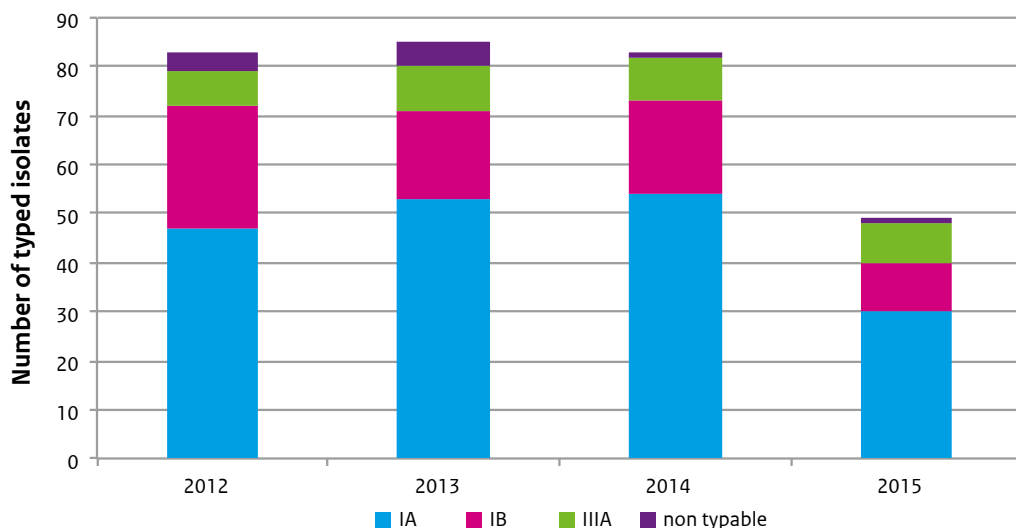


Figure 8.1.3 HAV genotype distribution of HAV strains detected in the Netherlands in 2012–2015

8.1.7 Literature

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8.2 Meningococcal disease caused by non-serogroup C types

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

8.2.1 Key points

- In 2015, 64 cases of meningococcal serogroup B (MenB) disease were reported, a similar number as in 2014 (n=60). In 2016, up to August, 54 cases of MenB were reported, which was 1.4 times higher than in the same period in 2015. The incidence of MenB was highest in children under five years in 2015 and 2016 (2.1 and 3.4 per 100,000, respectively).
- In 2015 and 2016, a large increase in the number of cases with meningococcal serogroup W (MenW) disease was observed (26 cases in 2016 up to August compared with 9 cases in 2015 and one to seven cases per year during 2005–2014).
- The recent MenW cases are mainly elderly aged 65 years or older (42%), and the increase is due to an increase in finetype P1.5,2:F1-1, which is associated with the hypervirulent clonal complex 11.
- In 2015, 7 cases of meningococcal serogroup Y (MenY) disease were reported, which was somewhat lower than in the previous five years (12–15 cases annually). In 2016, up to August, 11 cases of MenY were reported.

8.2.2 Epidemiology

8.2.2.1 Meningococcal serogroup B

In 2015, 72% of all meningococcal cases were serogroup B. In total, 64 cases of meningococcal serogroup B (MenB) disease were reported (Figure 8.2.1), a similar number as in 2014 (n=60). In 2016, up to August, 54 MenB cases were reported, which was 1.4 times higher than in the same period in 2015. The incidence of MenB was still highest in children under five years in 2015 (2.1 per 100,000, n=19). The incidence in this age groups showed a gradual decrease up to 2015 (Figure 8.2.2) but increased again in 2016 to 3.4 per 100,000 (20 cases up to August). Mortality data are available for 90–95% of cases. Mortality was 3.1% (2/64) in 2015 and 4.9% (69/1,408) from 2004 to 2016.

8.2.2.2 Meningococcal serogroup W

In 2015, nine cases of meningococcal serogroup W (MenW) disease were reported and in 2016, up to August, 26 MenW cases were reported (Figure 8.2.3). During 2005–2014, there were on average only four MenW cases per year (range: 1–7; IR=0.022 per 100,000 population per year). The incidence rate (IR) increased significantly in 2015 (0.053 per 100,000 per year) compared with 2005–2014 (IRR=2.3 [95% CI: 1.1–4.8]). In 2016, the IR (0.231/100,000/year) increased significantly compared with 2015 (IRR=4.3 [2.0–9.2]). In 2016, up to August, 27% of all meningococcal cases were MenW (26/95); this was 10% (9/90) in 2015 and 3% (38/1,454) in 2005–2014.

Of the 31 MenW cases since October 2015, two were <5 years (6%), three were 10–19 years (10%), six were 20–49 years (19%), seven were 50–64 years (23%) and 13 were ≥65 years (42%).

Two of 26 cases for which mortality data were available (n=26) died (8%). The vast majority of cases had finetype P1.5,2:F1-1 (26/30; 87%), which is associated with the hypervirulent clonal complex 11.

8.2.2.3 Meningococcal serogroup Y

In 2015, seven cases of meningococcal serogroup Y (MenY) disease were reported (Figure 8.2.1), which was somewhat lower than in the previous five years (12–15 cases per year). In 2016, up to August, 11 MenY cases were reported. In 2015, most cases were 65 years or older (6/7 cases) and in 2016 five cases were 65 year or older (Table 8.2.1).

8.2.2.4 Other meningococcal serogroups

In 2015, no cases of meningococcal disease due to other serogroups were reported, and in 2016, up to August, one case of meningococcal serogroup X disease was reported in an 83-year-old woman.

8.2.3 Pathogen

We observed a sudden increase in the number of MenW cases with finetype P1.5,2:F1-1 in 2015 and 2016, when this finetype caused the vast majority of the cases.

8.2.4 Research

A large carriage study was conducted in the Netherlands during the epidemiological years 2013 and 2014 (the so-called Carmen study). Oropharyngeal swabs and questionnaires were collected from 1,715 Dutch adolescents and young adults aged 13–23 years. A meningococcal isolate was identified in 270 subjects (16%) by culture. The most prevalent serogroups identified by whole-genome sequencing were MenB (4%), MenX (2%) and MenY (2%). Carriage was age-dependent with a sharp increase before the age of 15 years and related to lifestyle rather than age.

In the JIM study (described in Section 7.6), the quadrivalent MenACWY-TT vaccine induced a robust and mainly primary response to serogroup A, W and Y with 95% of the participants showing protective functional antibody levels up to one year.

8.2.5 International developments

8.2.5.1 MenB vaccination

The UK introduced a universal vaccination programme against MenB for infants in the autumn of 2015 [1]. Infants are offered the 4CMenB vaccine at 2, 4 and 12 months of age. As fever occurs in 50–60% of infants receiving 4CMenB vaccination, parents are advised to give prophylactic paracetamol. The first reliable evaluations of the programme are expected around two years after implementation.

8.2.5.2 MenW outbreak in the United Kingdom

The UK is currently experiencing a national outbreak of MenW disease. The number of MenW cases in England have increased from 19 cases in the epidemiological year 2008/2009 to 176 cases in 2014/2015, and its contribution to total meningococcal cases increased from 1.7% to 24% of all confirmed cases, respectively [2]. This increase has resulted from a rapid expansion

of a single endemic hypervirulent strain belonging to the hypervirulent clonal complex 11 (cc11), which was also responsible for the ongoing group W IMD outbreak in Chile and other South American countries [3]. In August 2015, the UK introduced an adolescent MenACWY conjugate vaccination programme targeting 14–18-year-olds and new undergraduate university entrants [4]. The regular MenC booster vaccination at 13–14 years has been replaced by the quadrivalent MenACWY vaccine. Adolescents are the target group for vaccination because this age group experiences a high attack rate, and, as with MenC, teenagers and young adults have the highest carriage rates and are considered to be responsible for driving transmission. Following anecdotal reports of teenagers with MenW disease presenting predominantly gastrointestinal symptoms, Campbell and colleagues performed a case review of 15 MenW cases in 15–19-year-olds diagnosed in England between July 2015 and January 2016 [5]. Seven of the 15 cases presented with a short history of nausea, vomiting and diarrhoea; five of these seven cases died within 24 hours of presentation to hospital. The unusual gastrointestinal presentation has also been reported in the ongoing MenW outbreak in Chile, where 14 of 58 group W IMD cases (24%) were initially diagnosed as gastroenteritis and 8 of these 14 died [6]. Ladhani and colleagues assessed the effectiveness of meningococcal B vaccine against the currently circulating MenW:cc11 strain [7]. Although the MenB vaccine has been licensed for prevention of MenB disease, the vaccine antigens are also found among non-MenB meningococci, independently of the capsule. Therefore, antibodies raised by the MenB vaccine could induce complement-mediated killing of other meningococcal groups, including the endemic MenW:cc11 strain. They found that MenW:cc11 isolates causing invasive disease in England and Wales possessed alleles for NadA-2/3 peptide variants that are predicted to be highly cross-protective with the 4CMenB NadA variant. The isolates also possessed alleles for NHBA peptide 29, which, although different from peptide two in 4CMenB, has the potential to induce cross-protection. Therefore, it might be expected that the implementation of this MenB vaccine will also induce protection against these MenW strains.

8.2.5.3 Cost-effectiveness

Several European countries have evaluated the cost-effectiveness of a multicomponent serogroup B meningococcal vaccine for use in individuals aged two months or older. Gasparini et al. assessed the cost-effectiveness of vaccinating Italian infants less than one year old with four doses (at 2, 4, 6 and 12 months of age) as opposed to non-vaccination [8]. Using a static cohort simulation model, the ICER per QALY was €109,762 in the base case and €26,599 if underestimated cases were taken into account. However, Tirani et al. found that universal vaccination would not be cost-effective, based on epidemiological data from the most populated Italian regions (Lombardy and Piemonte) [9].

A previously developed model for England was adapted to the German setting to predict the potential health impact and cost-effectiveness of universal vaccination against MenB disease [10]. Vaccination strategies included infant and adolescent vaccination, alone or in combination, and with one-off catch-up programmes. Sixty-five per cent vaccine uptake and 82% strain coverage were assumed. Under base case assumptions with a vaccine list price of €96.96 the ICER was >€500,000 per QALY for all considered strategies. Given the current very low incidence of MenB disease in Germany, universal vaccination would prevent only a small absolute number of cases, at a high overall cost.

Lecocq et al. assessed the cost-effectiveness of five vaccination strategies in France: infants at 3, 5, 6 and 13 months, toddlers at 13, 15 and 27 months and adolescents at 15 years given two doses one month apart [11]. A booster dose at 15 years old and a catch-up for 15-year-old subjects during the first 15 years of the programme were added to the infant and toddler strategies. Under the assumption of herd immunity, the adolescent vaccination would provide the lowest costs per QALY gained (€135,902), preventing 24% of cases. In conclusion, given current meningococcal epidemiology in France and the available data on the efficacy of the vaccine, routine vaccination against serogroup B meningococcal disease is not cost-effective.

8.2.6 Tables and figures

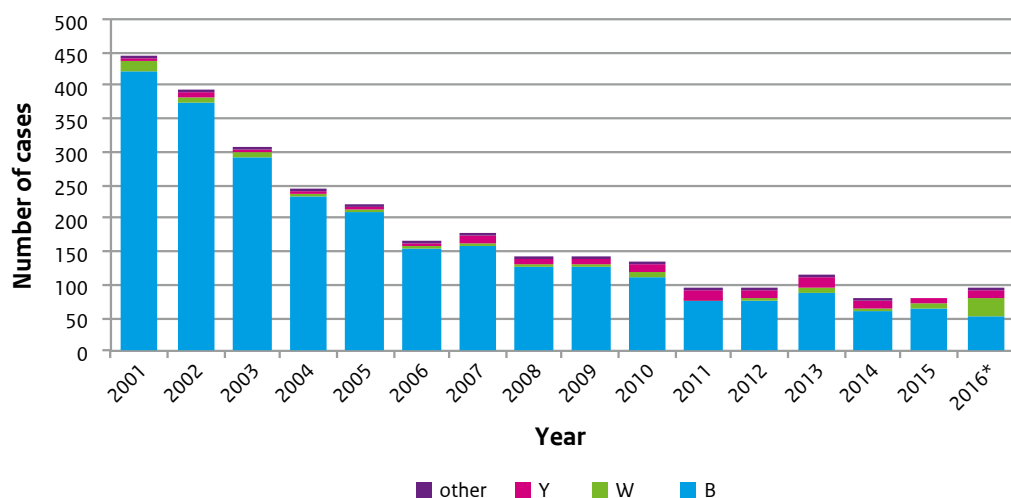


Figure 8.2.1 Number of cases of meningococcal non-serogroup C disease per serogroup, 2001–2016* (*up to August)

Source: NRBM

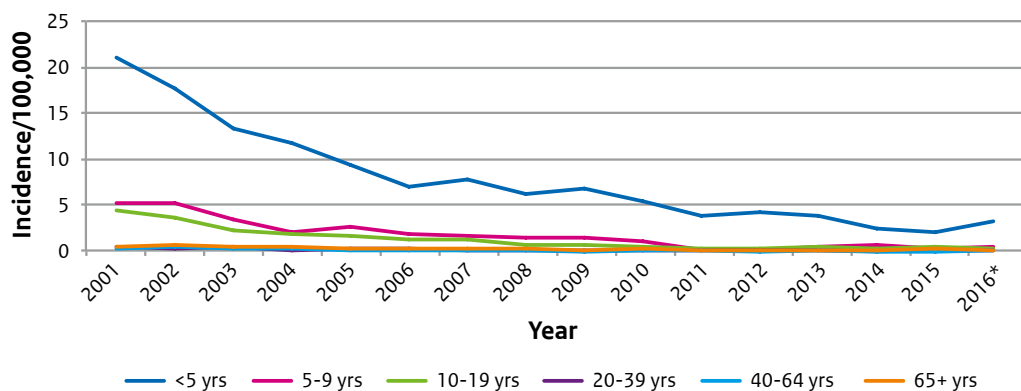


Figure 8.2.2 Age-specific incidence of meningococcal serogroup B disease, 2001–2016*
(*up to August)

Source: NRBM

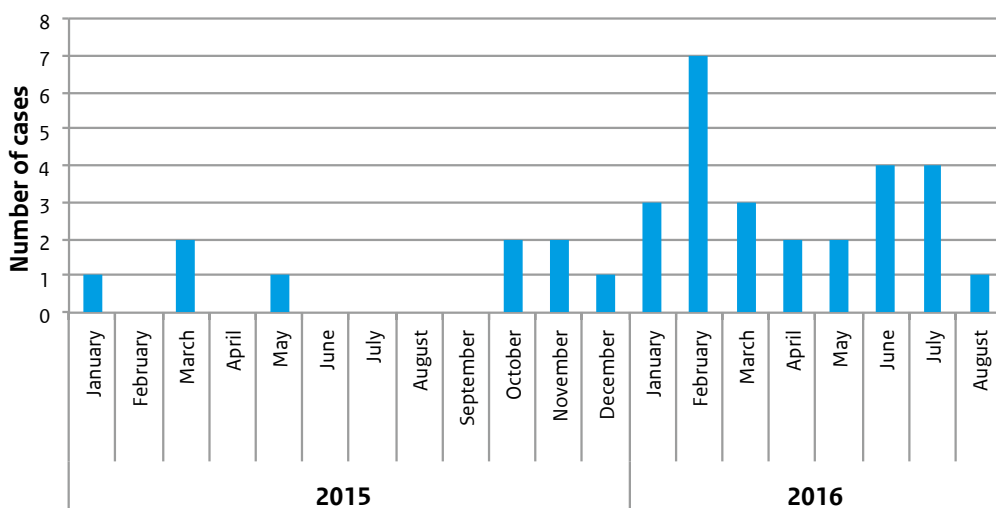


Figure 8.2.3 Number of cases of meningococcal serogroup W disease, 2015–2016*
(*up to August)

Source: NRBM

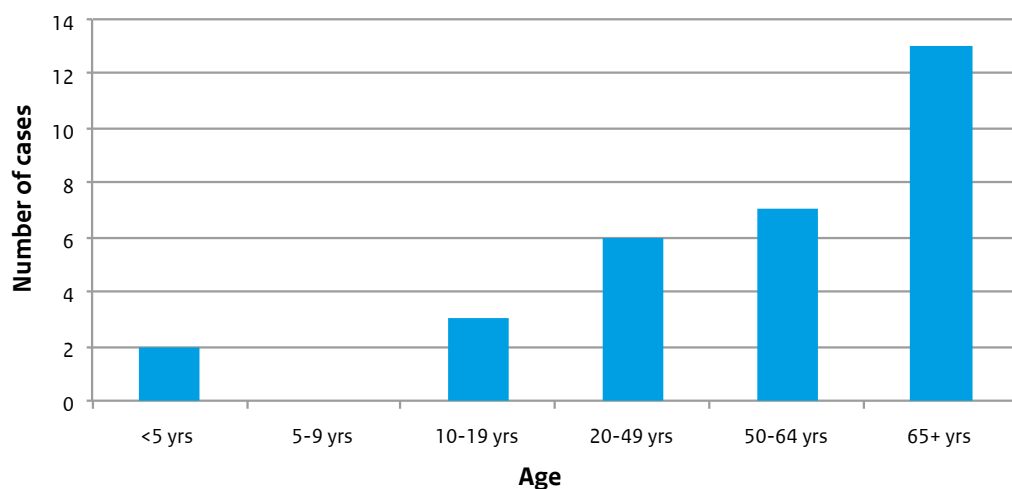


Figure 8.2.4 Age distribution of 22 cases of meningococcal serogroup W disease that were reported from October 2015 up to August 2016

Source: NRBHM

Table 8.2.1 Number of cases of meningococcal serogroup Y disease per age category, 2001–2016* (*up to August)

Age in yrs	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016*	Total
0–4	0	0	1	0	0	0	0	0	1	1	0	2	2	1	0	0	8
5–9	0	0	0	1	0	0	1	0	0	0	1	3	0	1	0	0	7
10–19	0	1	1	2	0	0	1	0	0	2	5	0	2	2	0	2	18
20–39	1	2	1	0	0	0	1	1	1	3	2	2	0	2	0	1	17
40–64	1	0	1	1	2	0	2	2	2	3	3	3	3	1	1	3	28
65+	2	4	1	2	3	4	6	4	3	3	4	2	8	5	6	5	62
Total	4	7	5	6	5	4	11	7	7	12	15	12	15	12	7	11	140

Source: NRBHM

8.2.7 Literature

8.2.7.1 References

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8.3 Respiratory syncytial virus infection

A.C. Teirlinck, A. Meijer, W. van der Hoek, A. Suijkerbuijk, A. Lugner, H.de Melker, N.A.T. van der Maas

8.3.1 Key points

- RSV infection has a high morbidity and mortality rate in infants and the elderly.
- Currently 16 candidate vaccines are in pre-registration trials.
- A maternal RSV vaccine to protect newborns is in phase III clinical trial. No adverse pregnancy outcomes were reported and active transplacental transport of antibodies against F-protein occurred, indicating protection of the newborn against RSV.

8.3.2 Epidemiology

The respiratory syncytial virus (RSV) is the most common cause of acute lower respiratory infections in children <5 years of age worldwide (33.8 million new RSV episodes in 2005). In Western countries, it is the most frequent reason for hospitalisation among infants (3.4 million episodes in 2005) [1]. In a prospective study among elderly and high-risk adults, RSV and influenza A resulted in similar lengths of stay, rates of use of intensive care units (15% and 12%, respectively) and mortality (8% and 7%, respectively). RSV infection accounted for 10.6% of hospitalisations for pneumonia, 11.4% for chronic obstructive pulmonary disease, 5.4% for congestive heart failure and 7.2% for asthma [2].

8.3.2.1 Disease

Current Dutch RSV surveillance is primarily based on GP surveillance of patients with influenza-like illness (ILI) and other acute respiratory infections (ARI). This involves collecting nose and throat swabs from a subset of patients and testing them for influenza virus, RSV, rhinovirus and enterovirus. The weekly reporting of virological laboratory surveillance by 20 virologic laboratories provides further insight into numbers of RSV.

In the season 2015/2016, a total of 107 RSVs were detected in 1,238 nose swabs and throat swabs (8.6%) from ILI and ARI patients, collected by sentinel GPs [3]. The percentage of positive specimens from the GP sentinel surveillance was highest in the age group below two years old (ILI 28%, ARI 42%) (Figure 8.3.1).

The percentages were lower in older children (5–14 years; ILI 3%, ARI 7%) and young adults (15–44 years; 5% ILI, 3% ARI) and then increased again, starting in the age groups above 45 years (5% ILI, 9% ARI) and in the age group above 65 years (10% ILI, 7% ARI).

The number of positive RSV diagnoses reported by 20 virologic laboratories in the Netherlands (virological laboratory surveillance) in 2015/2016 (n=1,348; through week 20) was lower than in previous seasons [3]. Since the respiratory season 2011/2012, a clear drop can be observed in the number of detections compared to the previous year, which is probably the result of changes in the testing policy of hospitals, which have requested less laboratory diagnosis for RSV-suspect patients.

8.3.2.2 Cost-effectiveness

Using English hospital data, the possible net benefits of an RSV immunisation programme of infants were estimated. An immunisation programme may decrease RSV infections and would then save the direct and indirect medical care costs from hospitalisation, morbidity and mortality [4]. The results show that the immunisation programme has a beneficial cost–benefit ratio, due to its positive effects on life expectancy and quality of life.

Meijboom et al. assessed the cost-effectiveness of a hypothetical RSV vaccine for the elderly in the Netherlands [5]. Using base case assumptions, it was estimated that the vaccination of everyone 60 years and older would prevent 3,402 GP visits, 2,989 antibiotic prescriptions, 535 hospitalisations and 249 deaths and would cost €73,261 per QALY gained, for a vaccine effectiveness of 70%. As expected, vaccinating only the high-risk population of 60 years and older would reduce the cost per QALY gained to €34,796. According to the authors there is potential to develop a vaccine that might be considered cost-effective in the Netherlands.

8.3.3 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 Netherlands, in the season 2015/2016 more RSV-B than RSV-A was detected in GP specimens, except in the ILI patients below four years of age, where the number of RSV-A detections was higher than the number of RSV-B detections. 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 they are relatively stable, monitoring of their evolution is important [6].

8.3.4 Research

RSV surveillance and estimating the burden of disease from RSV have recently been listed as priority topics by the WHO and ECDC. This is because vaccines are expected to become available in the coming years (see Section 8.3.5) and establishing an epidemiological and virological baseline is essential for monitoring the impact of RSV vaccines. Currently, the ECDC is developing a joint protocol for activities related to the burden of RSV disease. Furthermore, the RIVM is a partner in a consortium that has been provisionally granted a proposal by the IMI that aims to develop a detailed understanding of the clinical, economic and social impacts of RSV infection in infants, the elderly and other high-risk populations. Strengthening RSV surveillance and strengthening European or international collaboration on RSV surveillance is one of the goals of this project.

8.3.5 International developments

Currently, no RSV vaccines are licensed, but there are 60 candidate vaccines targeting the paediatric and elderly population. Sixteen of these are in pre-registration clinical trials (Figure 8.3.2) [7].

A recombinant RSV F protein nano-particle vaccine has reached phase III clinical trials in pregnant women and the elderly. Among more than 8,000 pregnant women, no adverse pregnancy outcomes were reported and active transplacental transport of antibodies against F-protein occurred, indicating protection of the newborn against RSV [8]. Furthermore, subunit vaccines, based on the F-protein, are in phase II clinical trials for administration in the elderly and pregnant women.

8.3.6 Tables and figures

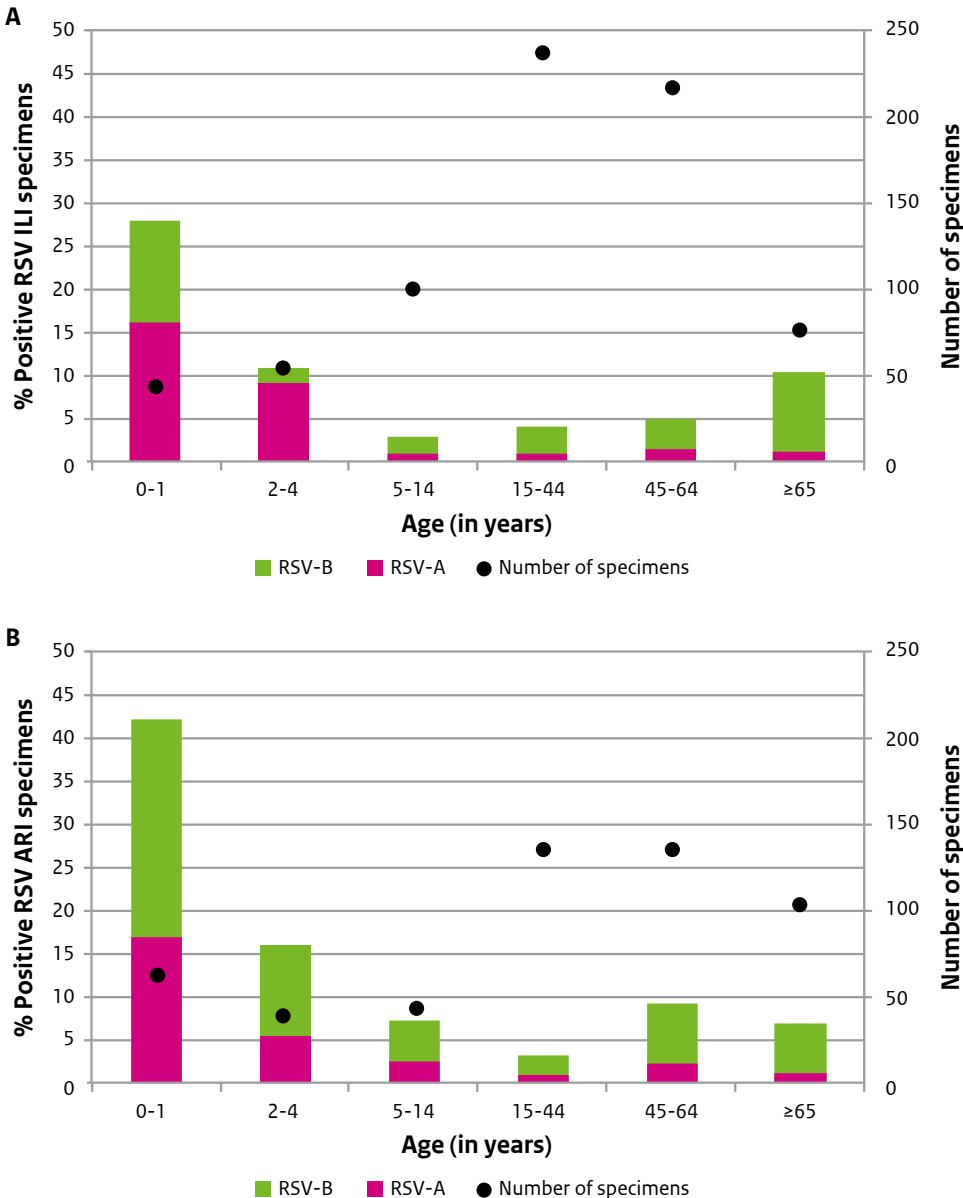


Figure 8.3.1 Percentage of RSV-A and RSV-B positive ILI specimens (A) and ARI specimens (B), and the number of tested specimens, taken by sentinel GPs during the respiratory season of 2015/2016 (week 40 of 2015–week 20 2016), displayed for six age categories

Sources: NIVEL Primary Care Database, NIC location RIVM

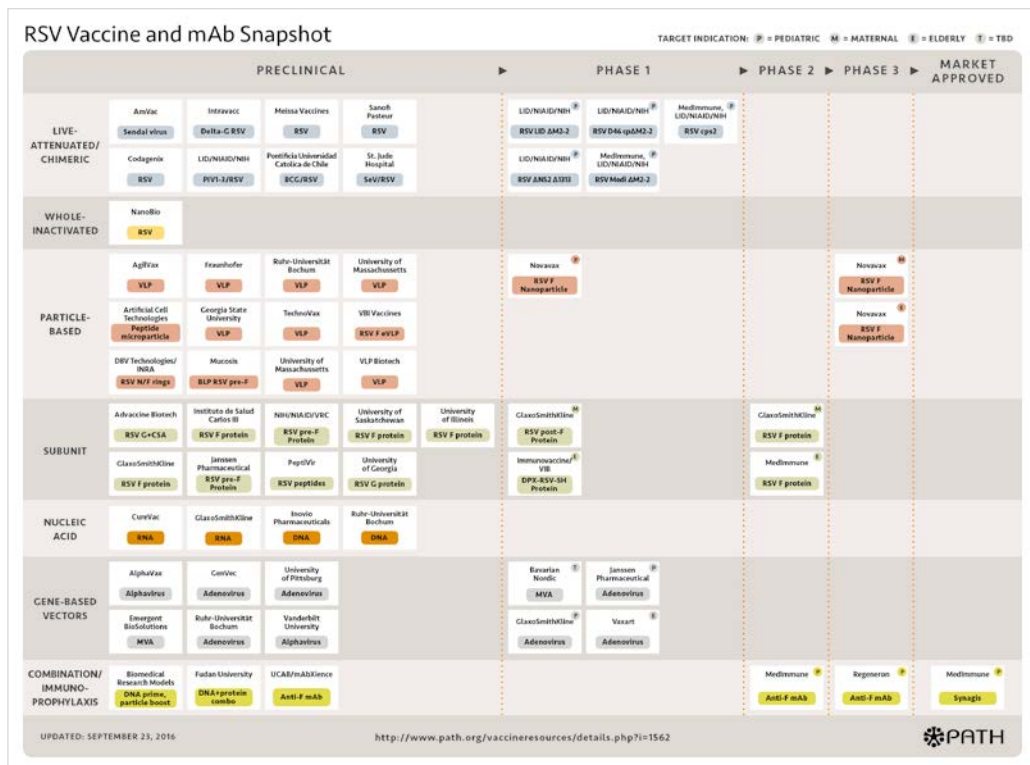


Figure 8.3.2 RSV vaccine technology landscape snapshot, updated till June 2016

Source: <http://sites.path.org/vaccine-development/respiratory-syncytial-virus-rsv/>

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8.4 Rotavirus infection

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8.4.1 Key points

- In 2015, an average rotavirus season was observed, although a hyperendemic season had been anticipated after the exceptionally low numbers in 2014.
- G4P[8] was the most prevalent genotype in 2015.

8.4.2 Epidemiology

Weekly rotavirus-positive test results are reported by the Working Group Clinical Virology. Because of the exceptionally low and delayed season in 2014 (absolute number of rotavirus-positive detections $n=607$, epidemic peak in mid-April and beginning of May), a hyperendemic season was anticipated for the 2015 season. However, the 2015 season ($n=1,323$) appeared average, comparable to the 2012 season ($n=1,288$) and followed the usual pattern with the epidemic peak in March. It should be noted that observations for the 2016 season up to 10th July again show remarkably low numbers ($n=487$) of reported rotavirus cases and a delayed start, suggesting a similar pattern as observed during the 2014 season (Figure 8.4.1). A repeated low-endemic 2016 season could indicate a transition to a biannual rotavirus epidemic pattern in the Netherlands, as observed in some countries with moderate to high rotavirus vaccine coverage rates. Future years will show whether this pattern is sustained. The origin of such a change in epidemic pattern in the Netherlands is currently unknown and a focus of research (see Section 8.4.4).

GP consultations for all-cause gastroenteritis (GE) in children under the age of 5 years confirm the pattern observed by the laboratory rotavirus detections in 2015 (Figure 8.4.2) [1]. The mean weekly GE consultation rate in the calendar year 2015 was 97 per 100,000 persons in under 5-year-olds. The number of weekly laboratory rotavirus-positive test results 1996–2014 show a correlation of 0.95 with data on the number of hospital admissions for acute gastroenteritis, ICD-9: 86–93, 5859 for children <5 years. Using regression analysis as previously described [2], the number hospitalisations for gastroenteritis attributable to rotavirus in children under 5 was estimated at 3,508 in 2015, 1,613 in 2014 and 3,952 in 2013. It was estimated that the proportion of rotavirus hospital admissions that occurred in patients 60 years and older increased from 4% at the beginning of this century to about 21% in the last four years.

8.4.3 Pathogen

For the 2015 rotavirus season, the IDS/RIVM received 289 faeces samples that tested positive for rotavirus from laboratories participating in the Working Group Clinical Virology, and 272 of these samples could be typed (Table 8.4.1). The most prevalent genotype in 2015 was G4P[8], which accounted for half of the typed strains ($n=137$, 50%) (Figure 8.4.3). The proportion of G1P[8] further decreased to 10% of the strains that were typed and the proportion of G2P[4]

was similar to recent years. Preliminary observations for 2016 indicate similarity to 2014, both in numbers and in dominance of G9P[8] (data not shown).

8.4.4 Research

The IDS/RIVM has been using sequence analysis for rotavirus typing since May 2013. This allows more in-depth analysis of the circulating strains; within genotypes different strains can be sequenced and distinguished, which was not possible before. Phylogenetic analysis of sequenced G9P[8] strains from recent years revealed two main strains that co-circulated in recent years, but the ratio between the two main strains varied over the years (Figure 8.4.4).

EuroRotaNet is a European rotavirus surveillance network established in January 2007. The IDS/RIVM participates, together with 14 other countries, in this network. Within this project, Dutch microbiological laboratories can send rotavirus-positive faeces samples to the IDS for typing using sequencing. The results for the Netherlands are described in Section 8.4.3. EuroRotaNet combines the results of the participating countries into an overview of circulating genotypes of rotavirus in consecutive rotavirus seasons in Europe and produces annual reports. In its last report it concluded that there is no evidence for the emergence of rotavirus vaccine escape strains due to rotavirus vaccination programmes in Europe [3]. No new emerging strains have been detected in any of the countries participating in EuroRotaNet. The genotype distribution varies by European country and there is a higher variability in circulating strains during the peak season than out of season [4].

Following the unusual rotavirus epidemiology in 2014 in the Netherlands, several research activities were executed aimed at unravelling the mechanisms that led to the exceptional 2014 season. Faeces samples that had been collected as part of two population-based studies were tested for rotavirus. These samples were collected randomly between February 2010 and September 2014 from healthy young children, irrespective of symptoms. Results confirmed less circulation of rotavirus, both symptomatic and asymptomatic, among young children in 2014 than in 2013 or 2012 [5]. This finding confirms that the drop in rotavirus detections in 2014 was associated with reduced circulation of rotavirus in the population, rather than a shift in disease severity to mild or asymptomatic infections [5].

Furthermore, a study was executed to investigate the effect of some potential contributing mechanisms on rotavirus transmission in the Netherlands and their impact on rotavirus transmission in 2014 [6]. The main goal was to investigate how temperature, humidity and the proportion of susceptible individuals are associated with rotavirus transmission in the Netherlands. The results showed that higher proportions of susceptible individuals and lower temperatures are associated with increases in rotavirus transmission. For 2014, the findings suggest that relatively mild temperatures combined with the low proportion of susceptible individuals contributed to lower rotavirus transmission in the Netherlands. However, the model, which overestimated the magnitude of the peak, suggested that other factors were likely to have been instrumental in reducing the incidence that year.

Studies that are currently running include the RIVAR study and the RotaFam study. The RIVAR project (Risk-Group Infant Vaccination Against Rotavirus) is a combined multicentre study and implementation project on rotavirus vaccination in high-risk infants. High-risk infants are children with congenital pathology, prematurity or low birth weight. Primary objectives include an assessment of the feasibility and impact of a rotavirus vaccination programme for high-risk infants implemented in paediatric hospitals/secondary care units in the Netherlands and determination of rotavirus vaccine effectiveness among high-risk infant populations, where there is currently a lack of such data. Rotavirus vaccination is implemented in a stepped-wedge manner across 13 participating hospitals. As of May 2016, the first three hospitals started rotavirus vaccination. Implementation will be completed in all participating hospitals by June 2017. An observational study accompanying both the pre- (one year) and post-implementation (2.5 years) periods in participating hospitals will assess vaccine effectiveness, programme impact, rotavirus epidemiology within hospitals, vaccine coverage rates and timeliness of vaccination among rotavirus vaccine-eligible high-risk infants. To study VE, high-risk infants are being recruited to participate in an observational study measuring occurrence of (rotavirus) gastroenteritis until 18 months of age. Recruitment covers both pre- (unvaccinated) and post-implementation (vaccinated) periods. Enrolment started in December 2014. Measurements include parental reporting of gastroenteritis, symptom and severity scoring and collection of stool samples.

The RotaFam study is a prospective cohort study that started in January 2016, assessing rotavirus transmission in an unvaccinated cohort of young households (with children <2 years old). Three hundred and five households are being monitored intensively for the occurrence of gastroenteritis during 10 consecutive weeks. Both symptomatic and asymptomatic rotavirus infections are being assessed. The longitudinal household data is being used to quantify rotavirus transmission and its key determinants. The project intends to elucidate the mechanisms driving rotavirus transmission, epidemiology and vaccination impact by generating household transmission data and its application to population dynamic models. As a spin-off, this project is studying the incidence and household transmission of other major enteric viruses, including norovirus, adenovirus and astrovirus.

The RIVM has set up the initiative to further investigate the impact of rotavirus vaccination in several European regions, and the possible herd effects caused by vaccination in surrounding countries. The distribution of rotavirus genotypes that are circulating in the Netherlands and those circulating in surrounding countries will also be investigated.

8.4.5 International developments

As of 1st May, 2016, 81 countries added rotavirus vaccination to their national immunisation programmes. Some countries, such as Canada, Italy and Sweden introduced rotavirus vaccination in phases or region by region. European countries with a national, publicly funded rotavirus programme include Armenia, Austria, Belgium, Estonia, Finland, Georgia, Germany, Israel, Latvia, Luxembourg, Moldova, Norway, Tajikistan, United Kingdom and Uzbekistan [7]. In France, rotavirus vaccines are no longer recommended for routine children immunisation, because of three infant deaths and many serious side effects as described previously in detail in the NIP report of 2014–2015 [8, 9]. In the Netherlands, rotavirus vaccination is not included in the NIP.

The Health Council is currently preparing an advice about introducing rotavirus in the NIP or not. Recently, no new economic evaluations of RV vaccination in a Western country have been published. The last two cost-effectiveness analyses performed for the Netherlands in four hospitals in 2005-2011 concluded that targeted RV vaccination of high-risk infants was highly cost-effective [10]. Universal vaccination could be cost-effective when taking into account herd immunity effects and QALY losses of caretakers and with a vaccine price below €60. In the other Dutch study, Tu et al. concluded that universal RV vaccination was economically favourable, even at higher vaccine prices [11].

8.4.6 Tables and figures

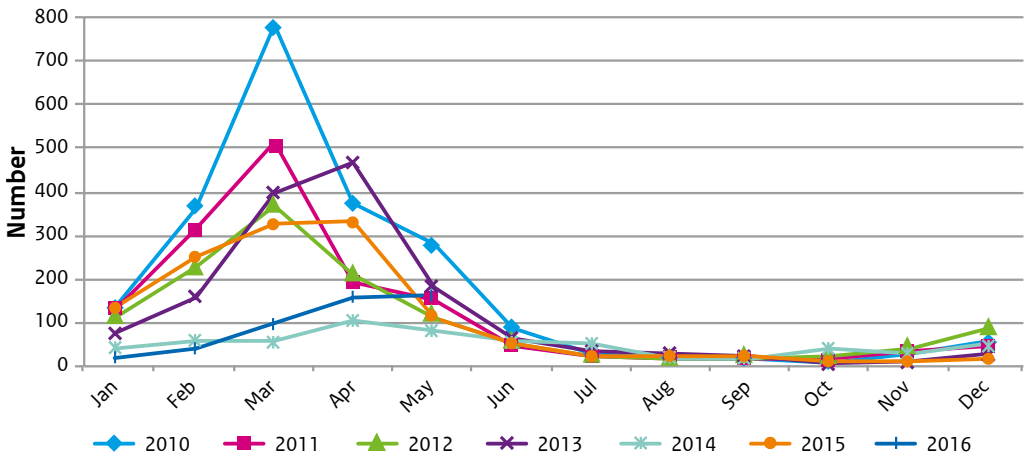


Figure 8.4.1 Reported laboratory diagnoses of rotavirus per month, 2010–2015

Source: Working Group Clinical Virology

Table 8.4.1 Number of positive rotavirus samples sent to and typed at the RIVM per year, 2011–2015

Type	2011	2012	2013	2014	2015	Total
G12P8	41	4	1	6	2	54
G1P8	224	48	83	20	25	400
G2P4	15	23	41	29	34	142
G3P8	6	50	51	7	14	128
G4P8	13	39	35	12	137	236
G9P8	40	71	23	49	32	215
Other	51	36	53	16	28	184
Total	390	271	287	139	272	

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

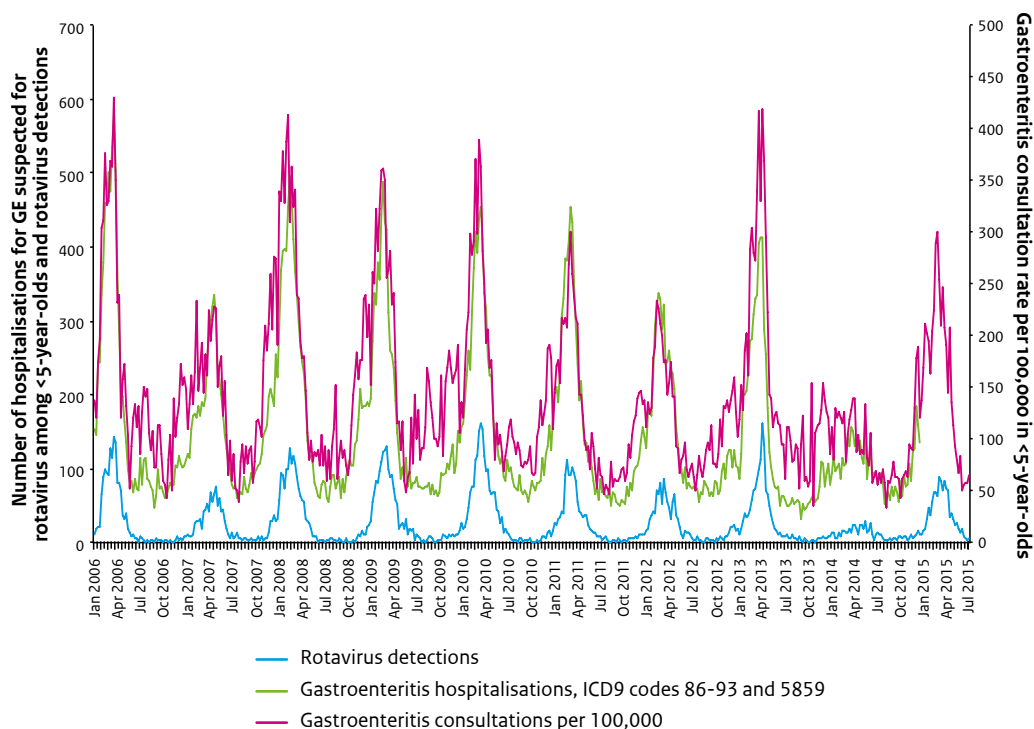


Figure 8.4.2 Laboratory rotavirus diagnoses, general practice gastroenteritis consultation rates in <5-year-old children, and gastroenteritis hospitalisations suspected of rotavirus among <5-year-old children (estimated with ICD-codes 86-93 and 5859), 2006–2015

Sources: Working Group Clinical Virology, DHD, NIVEL [1]

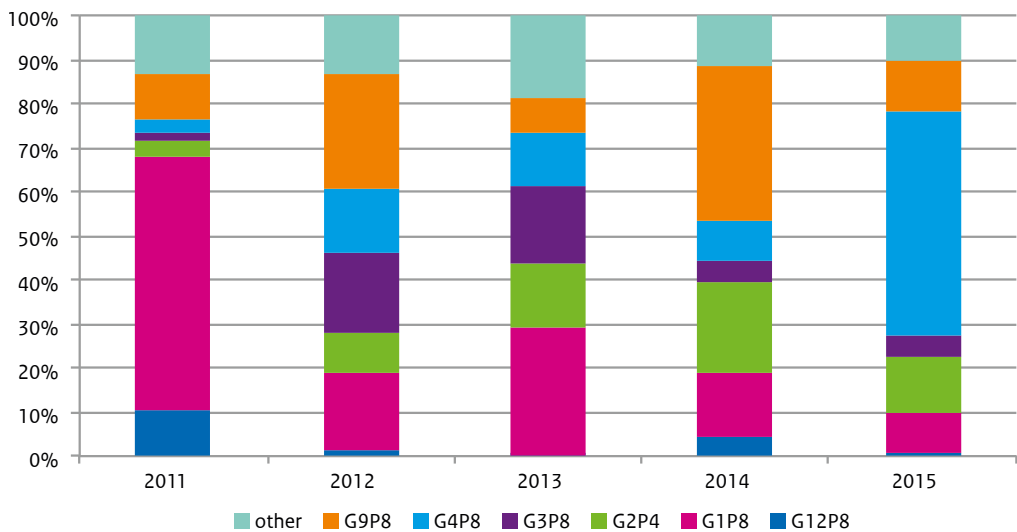


Figure 8.4.3 Distribution of rotavirus types per year as genotyped at the RIVM, 2011–2015

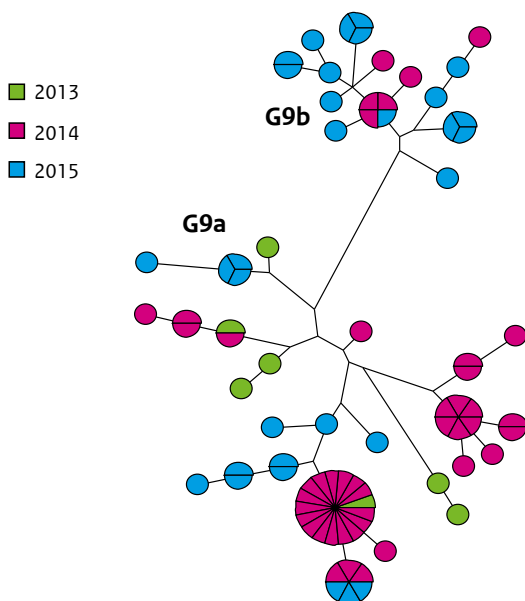


Figure 8.4.4 Maximum parsimony tree of G9 sequences from several years. The two main strains (G9a and G9b) can be distinguished with unequal distribution over the years

8.4.7 Literature

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*RIVM publication

8.5 Varicella zoster virus (VZV) infection

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8.5.1 Key points

- The VZV epidemiology (incidence of GP consultations, hospitalisations and deaths) is comparable to previous years.
- Countries that have implemented varicella vaccination showed a rapid decrease in the incidence of varicella and hospitalisation rates due to varicella but it is too early to evaluate the overall benefits of varicella vaccination.
- The Health Council of the Netherlands concluded that vaccination against herpes zoster should not be included in a public programme such as the NIP.

8.5.2 Epidemiology

According to a new, more precise method for estimating morbidity rates used by NIVEL from 2012 onwards, the incidence of herpes zoster is higher than it was according to the old method (Table 8.5.1) [1, 2]. The new method uses constructed episodes of illness (episodes are closed after 4 and 16 weeks without a reconsultation of the GP for varicella and herpes zoster, respectively), based on an algorithm instead of the recorded 'raw' episodes of care in the old method. Because of these changes, the incidence for 2010–2012 was recalculated. In the period 2010–2013, 2.2% of patients with a new varicella episode had more than one new episode in the same year; for herpes zoster the figure was 2.5%.

The incidence of varicella episodes per 100,000 of population is highest in the age groups below five years, whereas the incidence of herpes zoster episodes is highest in the age groups above 50 years (Figure 8.5.1). The incidence of hospitalisations due to varicella is highest among newborns, while the incidence of hospitalisations due to herpes zoster is highest among the oldest age groups (Figure 8.5.2 and Table 8.5.2).

Mahamud et al. found that national death certificate data tend to overestimate the number of deaths in which herpes zoster is the underlying or contributing cause of death [3]. If we apply their rate of deaths in which herpes zoster was validated as the underlying cause of death (0.25 (range 0.10–0.38) per 1 million population) on the Dutch population in 2015, we would expect 4.2 deaths (range 1.7–6.4) instead of the 33 deaths (preliminary data) that were reported in 2015 (Table 8.5.3).

8.5.3 Pathogen

Weinert et al. showed that the attenuated VZV vaccine virus evolves rapidly (~10–6 substitutions/site/day) but that, when the virus undergoes latency, rates decrease dramatically. They stated that the data are best explained by a model in which viral populations evolve for around 13 days before becoming latent, but then undergo no replication during latency, implying that viral evolution rates depend strongly on transmission patterns [4].

8.5.4 Research

Immunity against VZV decreases over time. There are two ways in which immunity can be boosted: (1) exogenous boosting by contact with a person experiencing varicella, and (2) endogenous boosting by a reactivation attempt of the virus. Using previous data [5], transmission modelling was used to estimate age-specific rates of reactivation and exogenous as well as endogenous boosting. Models with high levels of exogenous boosting and low or zero endogenous boosting, constant rate of loss of immunity, and reactivation rate increasing with age give the best fit to the data. To robustly predict the impact of varicella vaccination on the incidence of herpes zoster, evidence on rates of immune boosting and reactivation in individuals with waned immunity are needed [6]. A modelling study by Ogunjimi et al. estimated the duration of exogenous boosting after re-exposure to VZV to be limited to one or two years and that endogenous boosting has no significant effect [7].

8.5.5 International developments

8.5.5.1 Varicella

Helmuth et al. reviewed the epidemiological studies regarding varicella conducted in Europe in the period 2004–2014. They concluded that, although varicella is mainly a disease of childhood, sero-epidemiological studies show regional differences in the proportion of susceptible adults. Seroconversion happened at a younger age in Northern and Western Europe than in Eastern and Southern Europe. These differences are most likely a reflection of differences in childcare patterns and urbanisation. Countries that have implemented varicella vaccination showed a rapid decrease in incidence and hospitalisation rates due to varicella, but it is too early to evaluate the overall benefits of varicella vaccination [8]. This is mainly because the vaccination period has been too short to draw conclusions on the possible impact on herpes zoster incidence.

Starting from 2003, eight Italian regions introduced universal varicella vaccination with different schedules. Following the significant decrease in incidence and hospitalisations achieved in regions that had introduced varicella vaccination, such as Sicily, Veneto, Apulia, and Puglia [9–11], the National Immunization Plan 2012–2014 scheduled the introduction of universal varicella vaccination nationwide in Italy in 2015 [12]. After the introduction of varicella vaccination in Germany (one dose since 2004 and two doses since 2009), the burden of varicella-related disease has been reduced by about 40% overall, and by about 60% in children <5 years of age [13]. The overall estimate of the VE of one dose of varicella vaccine was 86.6% (95% CI: 85.2–87.9%), and of two doses 97.3% (95% CI: 97.0–97.6%) in the period 2009–2014 [14]. Siedler et al. also stated that an increase in herpes zoster began before varicella vaccination was introduced and was not affected by vaccination [13].

Some regions in Spain have included universal varicella vaccination in their programme since 2006. Gil-Prieto et al. showed that in these regions varicella-related hospitalisations were significantly lower than in regions without universal vaccination [15].

A modelling study predicted that the varicella incidence in France will decrease by 57%, and related complications by 76% over time, when routine varicella vaccination is introduced (replacing both MMR with MMRV vaccines at current coverage levels) [16].

A Belgian study showed a substantial burden of disease due to varicella, especially among

young and previously healthy children, which is known from the literature [17]. In Australia, vaccination against varicella (one dose at 18 months of age) was included in the NIP in 2005. All catch-up for children aged 10–13 years without a history of infection or vaccination was funded until 2015. Ceasing this catch-up programme in 2015 was projected to increase varicella-associated morbidity between 2035 and 2050 by 39%. This modelling study also showed that the incremental benefit of a second dose fell by 70% if the coverage of the first dose was high (95% instead of 83%) [18].

8.5.5.2 Herpes zoster

A post-licensure community-based study in southeastern Minnesota showed that vaccination against herpes zoster was associated with a reduction of 54% (95% CI: 32–69%) in herpes zoster incidence, and 61% (95% CI: 22–80%) in postherpetic neuralgia in persons aged ≥ 60 years (average follow-up time three years). This is consistent with the results of the original clinical trial and other post-licensure effectiveness studies. They also found a reduction of 58% (95% CI: 31–75%) in prodromal symptoms and 70% (95% CI: 33–87%) in medically attended prodrome [19]. Tseng et al. found that prior herpes zoster vaccination is associated with a lower risk of postherpetic neuralgia in women (adjusted relative risk 0.41 (95% CI: 0.26–0.64) but not in men (adjusted relative risk 1.06 (95% CI: 0.58–1.94). The differences between men and women need to be investigated further and might reflect different healthcare-seeking behaviour [20]. Another study by Tseng et al. showed that the VE of Zostavax[®] decreased from 68.7% (95% CI: 66.3–70.9%) in the first year to 4.2% (95% CI: -24.0–25.9%) in the eighth year, suggesting that revaccination might be needed [21]. A study conducted by Levin et al. showed persistence of increased VZV-specific CMI ≥ 10 years after vaccination in individuals ≥ 70 years of age, and they had similar responses to a booster dose of the same magnitude as 60–69-year-old individuals vaccinated for the first time [22].

Diez-Domingo et al. found that in adults ≥ 50 years the intramuscular administration of Zostavax[®] elicited similar immune responses to subcutaneous administration and was well tolerated, with fewer injection-site reactions than with subcutaneous administration [23]. In addition to glycoprotein E or open reading frame (ORF) 68, Laing et al. identified ORF9 and ORF18, which maybe useful components of subunit vaccines. Zoster vaccination increased the median magnitude (2.3-fold) and breadth (4.2-fold) of VZV-specific CD4⁺ T cells one month post-vaccination, while both measures declined by six months [24].

Terada et al. showed that to identify potential non-responders to VZV vaccination and to predict the risk of clinical VZV infection it might be important to measure post-vaccination cell-mediated immunity (CMI) and to know the history of natural infection [25].

Association studies suggest an increased risk of an acute cardiovascular event following a herpes zoster episode. Using a self-controlled case series study design, Minassian et al. found a 2.4-fold (95% CI: 2.2–2.6) increased rate of ischemic stroke and a 1.7-fold (95% CI: 1.5–1.9) increased rate of myocardial infarction in the first week after zoster, followed by a gradual resolution. Vaccination against herpes zoster did not seem to affect these associations [26].

The Health Council of the Netherlands concluded that vaccination against herpes zoster should not be included in a public programme such as the NIP [27]. This is because herpes zoster does not spread in a way that might pose a threat to the health of the population or that might be

an impediment to the fabric of society, and it is not an epidemic disease. Furthermore, the effectiveness and duration of the protection of Zostavax® is considered to be limited, and the vaccine is not safe for immunocompromised people.

8.5.5.3 Cost-effectiveness

Since 2011, the licensure of the live attenuated vaccine against herpes zoster has been extended to adults between 50 and 59 years. Using a Markov model, Le and Rothberg have evaluated cost-effectiveness for people aged 50 to 59 years versus no vaccination [28]. For every 1,000 people receiving the vaccine at age 50 years, 25 zoster cases and one post-herpetic neuralgia case could be prevented. The ICER for herpes zoster vaccine versus no vaccine was \$323,456 per QALY gained. The findings support the decision of the US Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) not to recommend the vaccine for adults in this age group.

Lopez-Belmonte et al. evaluated the cost-effectiveness of vaccination against herpes zoster among people aged 50 years and older compared to the current situation where no vaccination is being administered [29]. Vaccinating 30% of the Spanish population aged 50 years and older resulted in €16,577 per QALY gained. Sensitivity analyses showed that the model was most sensitive to the herpes zoster and post-herpetic neuralgia epidemiological data, the health state utilities values, and vaccine price used. In contrast with the study of Le et al., this study proved vaccination of the 50+ population in Spain against herpes zoster to be economically attractive.

Gabutti et al. proposed offering herpes zoster vaccination to people aged 60–70 years in Italy to reduce the herpes zoster burden, which would be cost-effective according to a national economic evaluation study [30].

Baracco et al. evaluated the cost-effectiveness of practices related to screening for immunity and immunisation against varicella among health care workers (HCW) in the United States [31]. Following universal varicella vaccination, the ACIP recommends that all HCW have evidence of varicella immunity. In this study, eight different strategies of varicella screening and vaccination of HCW were assessed: no intervention programme; clinical screening only; clinical screening and selective vaccination; serologic screening only; clinical screening and selective serologic screening; clinical screening and selective serologic screening and selective vaccination; serologic testing and selective vaccination; and universal vaccination. The outcomes were presented in terms of the probability of acquiring varicella, the economic impact of varicella per employee per year, and the cost of preventing additional cases of varicella. The most favourable strategy was vaccinating HCW with negative clinical screening and serologic test, resulting in an ICER of \$50,000 per case of varicella prevented.

Based on a hypothesis that infection by VZV may lead to the delayed onset of asthma in children/adolescents (conversely, vaccination would lead to the earlier onset of asthma), Ditkowsky et al. assessed the cost-effectiveness of the US' VZV vaccination programme, taking the onset and incidence of asthma into account [32]. The VZV vaccination programme proved to be less costly than the 'no vaccination' scenario, despite the delayed onset of asthma post-VZV infection. However, vaccination resulted in increased asthma morbidity and mortality. According to the authors, VZV's effect on asthma symptoms needs further evaluation before firm conclusions can be reached.

8.5.6 Tables and Figures

Table 8.5.1 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 (2010–2014) (rounded off to tens)

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

*Dutch Sentinel General Practice Network (CMR) [33]; since 2008, this network has changed from registration on paper to electronic reporting, which may have resulted in under-reporting of the weekly number of varicella patients. We therefore used data from NIVEL-PCD from 2008 onwards.

**NIVEL-PCD, old method [34].

***NIVEL-PCD, new method from 2012 onwards [1]; 2010–2012 recalculated.

Source: NIVEL

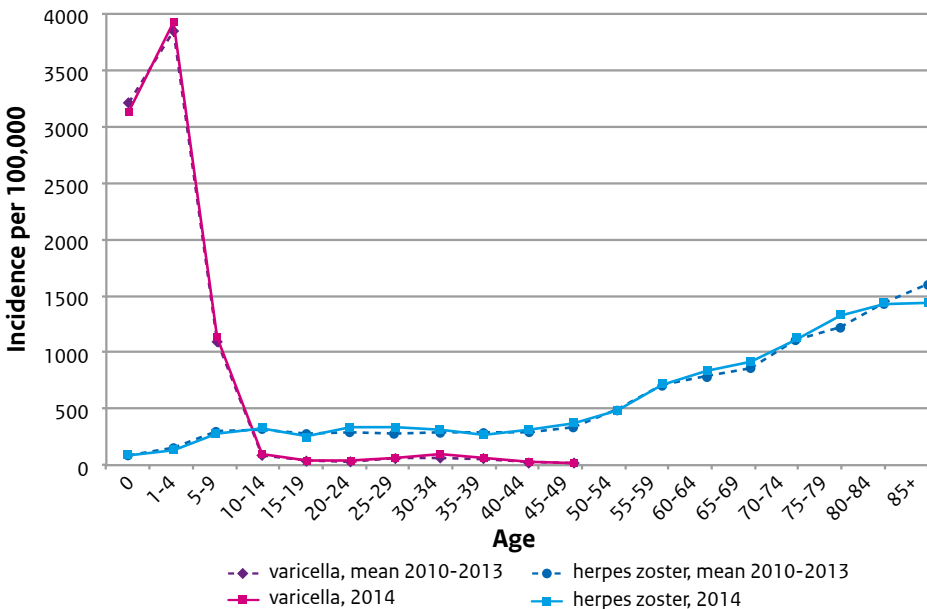


Figure 8.5.1 Estimated incidence per 100,000 of population of episodes of varicella (ICPC code A72) and herpes zoster (ICPC code S70) in 2014 versus mean 2010–2013 by age group [1]

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

Source: NIVEL

Table 8.5.2 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 [35]

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.

Source: DHD

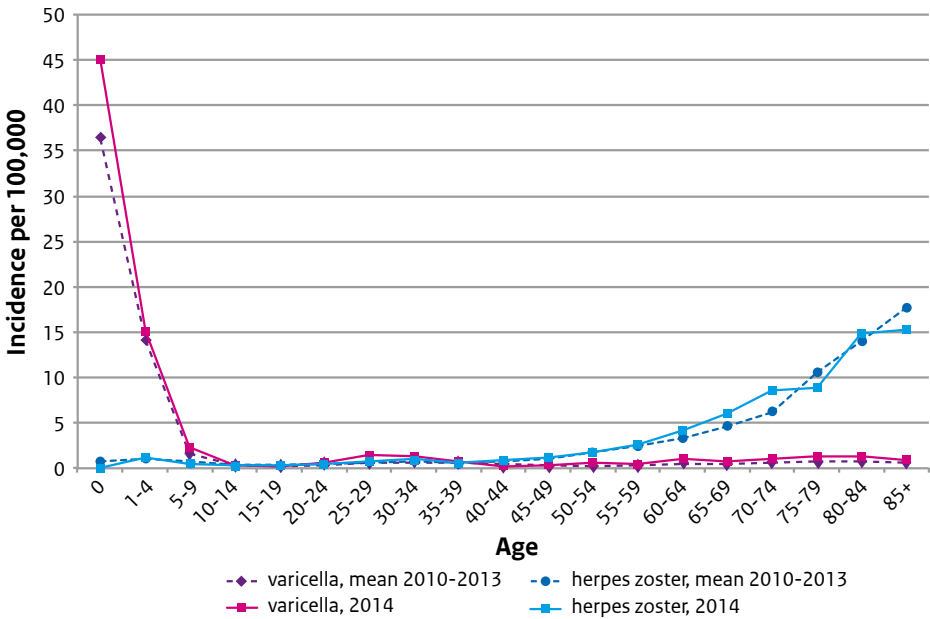


Figure 8.5.2 Incidence per 100,000 of population of hospitalisations due to main diagnosis of varicella (ICD-10 code B01) and herpes zoster (ICD-10 code B02) in 2014 versus mean incidence in 2000–2013 by age group [35]

Source: DHD

Table 8.5.3 Absolute number of deaths with main cause varicella (ICD-10 code B01) and herpes zoster (ICD-10 code B02), 2005–2015 [36]

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

*Preliminary data

Source: CBS

8.5.7 Literature

8.5.7.1 References

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9

Other potential future
NIP target diseases

9.1 Vaccines under development

An update of information on vaccines for infectious diseases in development that have reached the clinical testing phase and are relevant for the Netherlands is given in the table below. Vaccine development takes 10–15 years, and only a small percentage of vaccines tested in phase I achieve marketing authorisation. Relevant developments in combination vaccines are described in earlier chapters.

9.2 Tables and figures

Pathogen	Vaccine	Status
Bacteria		
<i>Chlamydia</i>	Adjuvanted chlamydia vaccine CTH522 (SSI)	Phase I
<i>Clostridium difficile</i>	Toxoid	Phase II and III, FDA fast track (Pfizer, Sanofi Pasteur)
<i>Helicobacter pylori</i>	HP3 (Chiron/Novartis)	Phase I completed, limited protective immunity
<i>Shigella</i>	Live attenuated single-strain, Inactivated trivalent whole cell, Chemical glycoconjugate recombinant glycoconjugate (biconjugate)	Phase II Phase I Phase III Phase II
<i>Staphylococcus aureus</i>	Conjugate (SA4Ag, 4 antigen), fast track FDA Protein	Phase II Previous phase I–III with different single antigen vaccine candidates all failed, safety concerns and low efficacy Phase I

Pathogen	Vaccine	Status
Bacteria		
<i>Streptococcus group A & B</i>	Group A:	Phase II
	N-terminal M protein-based multivalent vaccines (26-valent and 30-valent vaccines)	
	Conserved M protein vaccines (the J8 vaccine and the StreptInCor vaccine)	Phase I
	Group B:	Phase II
	CPS-protein conjugate (mono and trivalent)	Proof of concept in pregnant women
	Protein	Phase I
<i>Tuberculosis</i> (all forms all ages)	2, 3 or 4 antigen adjuvanted fusion protein	Phase II
	Live attenuated vaccine BCG	On market but low efficacy
	Modified recombinant BCG	Phase II
	recombinant subunit	Phase II
	Lysate of neurotrimin (NTM)	Phase III
Viruses		
Chikungunya	Live recombinant measles virus based Virus-like particle (NIAID)	Phase II, Immunogenic and safe in adults
Cytomegalo (CMV)	Glycoprotein B DNA eVLP	Phase I and II
Dengue	Live recombinant (tetraivalent)	Phase II–III
	Inactivated (tetraivalent)	Phase I
	Recombinant subunit (tetraivalent)	Phase I
	Monovalent subunit DNA	Phase I
		Dengvaxia Sanofi registration approved for 9–45-year-olds
Ebola	rVSV-ZEBOV (Merck/ NewLink Genetics)	Phase II–III
	ChAd3-EBOZ (GSK/NIH/NIAID)	Phase III ready to start but insufficient patients
		Phase II
	Ad26-EBOV and MVA-EBOV (Johnson & Johnson and Bavarian Nordic)	
	Recombinant nanoparticle based (Novavax)	Phase I

Pathogen	Vaccine	Status
Viruses		
Enterovirus 71	Inactivated whole virus	Phase III
Epstein–Barr	Recombinant gp350 Glycoprotein subunit	Phase II
Hepatitis E	Recombinant protein	Phase II, (Hecolin®, Xiamen China Approved in China; not registered in EU)
Herpes simplex	HSV-2 replication defective (preventive)	Phase I
	Glycoprotein subunit (therapeutic)	Phase I–II
Noro	Virus-like particles (bivalent)	Proof of concept in human challenge
Marburg	DNA	Phase I
MERS-CoV	MVA-MERS-S DNA	Phase I
Parainfluenza type I	Live attenuated	Phase I–II
SARS	Recombinant DNA plasmid	Phase I
West Nile	Inactivated	Phase I
	Live attenuated	Phase I

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

List of abbreviations

4CMenB	multicomponent meningococcal B vaccine
ACIP	Advisory Committee on Immunisation Practices
AE	adverse events
AEFI	adverse events following immunisation
AFP	acute flaccid paralysis
aP	acellular pertussis
ARI	acute respiratory infections
AS	adjuvant system
BCG	Bacillus Calmette-Guérin
BES	Bonaire, Sint Eustatius and Saba, the Dutch Caribbean
bOPV	bivalent oral polio vaccine
CAP	community-acquired pneumonia
CAPITA	Community-Acquired Pneumonia immunisation Trial in Adults
CBS	Statistics Netherlands
CC	clonal complex
CDC	Centres for Disease Control and Prevention
CI	confidence interval
CIb	Centre for Infectious Disease Control
CIN	cervical intraepithelial neoplasia
CMI	cell-mediated immunity
CMV	cytomegalovirus
COPD	chronic obstructive pulmonary disease
CRM	CRM conjugate
CRPS	complex regional pain syndrome
CSF	cerebrospinal fluid
CSI	Chlamydia trachomatis Screening and Implementation study
CVP	child vaccine provider
DALY	disability-adjusted life year
DHD	Dutch Hospital Data
DNA	deoxyribonucleic acid
DTaP	combination of diphtheria, tetanus and acellular pertussis vaccines
DTaP-IPV	combination of diphtheria, tetanus, acellular pertussis and inactivated polio vaccines
DT-IPV	combination of diphtheria, tetanus and inactivated polio vaccines
DTP	combination of diphtheria, tetanus and pertussis vaccines
DTpa	combined reduced-antigen-content diphtheria-tetanus-acellular pertussis vaccine
DTwP	combination of diphtheria, tetanus and whole-cell pertussis vaccines
ECDC	European Centre for Disease Control and Prevention
ELS	extensive limb swelling
EMA	European Medicines Agency
EPAR	European public assessment reports
EPIS	Epidemic Intelligence Information System
F	fusion

FDA	Food and Drug Administration
FHA	filamentous haemagglutinin
Fim2	serotype 2 fimbriae
Fim3	serotype 3 fimbriae
GAPIII	WHO global action plan to minimise poliovirus facility-associated risk
GDP	gross domestic product
GGD	Municipal Health Service
GMC	geometric mean concentrations
GMT	geometric mean titers
GP	general practitioner
GSK	GlaxoSmithKline
GUM	genitourinary medicine
GW	genital warts
HAV	hepatitis A virus
HAVANA	study of HPV prevalence among young girls
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HC	Health Council
HCW	health care workers
HepB	hepatitis B virus
HepB-HPY	recombinant hepatitis B vaccine
Hib	<i>Haemophilus influenzae</i> type b
Hie	<i>Haemophilus influenzae</i> type e
Hif	<i>Haemophilus influenzae</i> type f
Hib-MenC-TT	combined <i>Haemophilus influenzae</i> type b and <i>Neisseria meningitidis</i> serogroup C tetanus toxoid conjugate vaccine
HIV	human immunodeficiency virus
HN	haemagglutinin-neuraminidase
HPV	human papillomavirus
HPV2	bivalent HPV vaccine
HPV4	quadrivalent HPV vaccine
HPV9	nonavalent HPV vaccine
hrHPV	high-risk human papillomavirus
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
IDS	Centre for Infectious Disease Research, Diagnostics and Screening
IDU	injecting drug use
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
IU/ml	international units per milliliter
JCVI	Joint Committee on Vaccination and Immunisation
JIM	Juvenile Immunisatie Meningokokken ACWY
LBZ	National Register Hospital care
LINH	Netherlands Information Network of General Practice
LMR	National Medical Registration
IrHPV	low-risk human papillomavirus
MBO	intermediate vocational education
MCV	measles-containing vaccine
MENA	Middle East and North Africa
MenACWY-CRM	quadrivalent meningococcal CRM conjugate vaccine
MenACWY-D	quadrivalent meningococcal diphtheria toxoid conjugate vaccine
MenACWY-PS	quadrivalent meningococcal polysaccharide vaccine
MenACWY-TT	quadrivalent meningococcal tetanus toxoid conjugate vaccine
MenB	Meningococcal serogroup B
MenC	Meningococcal serogroup C
MenC-TT	Meningococcal serogroup C polysaccharide-tetanus toxoid
MenW	Meningococcal serogroup W
MenX	Meningococcal serogroup X
MenY	Meningococcal serogroup Y
MERS-CoV	Middle East Respiratory Syndrome-coronavirus
MF	multiplication factor
MHS	Municipal Health Service
MIA	multiplexed immuno assays based on Luminex technology
MLST	multilocus sequence typing
MMR	combination of measles, mumps and rubella vaccines
MMRV	combination of measles, mumps, rubella and varicella vaccines
MSM	men who have sex with men
MSW	men who have sex only with women
NBP	non-bacteremic pneumonia
NIAID	National Institute of Allergy and Infectious Diseases
NICU	neonatal intensive care unit
NIP	National Immunisation Programme
NIVEL	Netherlands Institute for Health Services Research
NIVEL-PCD	NIVEL Primary Care Database
NK	natural killer
NKR	Netherlands Cancer Registry
NPG	National Influenza Prevention Programme
NRBM	Netherlands Reference laboratory for Bacterial Meningitis
NT	neutralisation titer

NTHi	nontypeable <i>Haemophilus influenzae</i> strains
NTM	neurotrimin
NVI	Netherlands Vaccine Institute
OPV	oral polio vaccine
OR	odds ratio
ORF	open reading frame
PASSYON	Papillomavirus Surveillance among STI clinic Youngsters
PCAP	pneumococcal community-acquired pneumonia
PCR	polymerase chain reaction
PCV	pneumococcal conjugate vaccine
PCV7	heptavalent pneumococcal conjugate vaccine
PCV10-7	additional serotypes in PCV10 compared to 2007 (serotype 1, 5 and 7F)
PCV13	13-valent pneumococcal conjugate vaccine
PCV13-10	additional serotypes in PCV13 compared to PCV10 (serotype 3, 6A and 19A)
PCV7-TT	heptavalent pneumococcal conjugate tetanus toxoid conjugate vaccine
PCV15	15-valent pneumococcal conjugate vaccine
PHiD-CV	10-valent pneumococcal nontypeable <i>Haemophilus influenza</i> protein D conjugate vaccine
PhtD	pneumococcal histidine triad D
PIENTER	Study assessing immunisation effect to evaluate the NIP
PIM	Pneumokokken Iets Minder
Pneu	pneumococcal vaccination
POTS	postural orthostatic tachycardia syndrome
PPV	proportion of population vaccinated
PPV23	23-valent pneumococcal polysaccharide vaccine
Prn	pertactin
PRP	polyribosyl-ribitol-phosphate
Ptx	pertussis toxin
QALY	quality-adjusted life year
RCT	randomised controlled trial
RIVAR	multicentre study Risk-Group Infant Vaccination Against Rotavirus
RIVM	National Institute for Public Health and the Environment, the Netherlands
RNA	ribonucleic acid
RR	relative risk
rSBA	rabbit serum bactericidal activity
RSV	respiratory syncytial virus
RV	rotavirus
SAGE	Strategic Advisory Group of Experts
SARS	severe acute respiratory syndrome
SD	standard deviation
SH	small hydrophobic
SP-MSD	Sanofi Pasteur MSD
SPR	RIVM strategic programme
STI	sexually transmitted infections

SUR	Surinam, Netherlands Antilles and Aruba
Tdap	tetanus, diphtheria and pertussis vaccine
TLR	toll-like receptor
TT	tetanus toxoid
UA	under-ascertainment
UE	underestimation
UR	under-reporting
VAERS	Vaccine Adverse Event Reporting System, United States
VDPV	vaccine-derived polio virus
VE	vaccine effectiveness
VLP	virus-like particle
VP	viral protein
VPD	vaccine-preventable disease
VTE	venous thromboembolism
VZV	varicella zoster virus
VWS	Ministry of Health, Welfare and Sports
WHO	World Health Organization
WIV	Belgian Scientific Institute of Public Health
YLD	years lived with disability
YLL	years of life lost

Appendix

Appendix 1 Surveillance methodology

Disease surveillance

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

Mortality data

Statistics Netherlands (CBS) registers mortality data from death certificates on a statutory basis. The registration specifies whether it concerns a natural death, a non-natural death or a stillborn child. In the event of a natural death, the physician should report the following data: 1. the illness or disease that has led to death (primary cause); 2. a. any complication, directly related to the primary cause, that has led to death (secondary cause); b. 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 data has been using the IRIS programme for automatically coding the causes of death [1]. One of the advantages of this is the increase of international comparability of the figures. The change in coding caused (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. See Table A1.1 for the period of notification for each disease [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)). Since that time, physicians, laboratories and heads of institutions have had to report 42 notifiable infectious diseases, instead of 36, to the Public Health Services. There are four categories of notifiable disease. Diseases in category A have to be reported directly by telephone following a laboratory-confirmed diagnosis. Diseases in categories B1, B2 and C must be reported within 24 hours or one working day after laboratory confirmation. However, for several diseases there is under-reporting and 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 <i>Haemophilus influenzae</i> type b	C	from December 2008 onwards
Hepatitis B disease	B2	from 1950 onwards
Invasive pneumococcal disease ^a	C	from December 2008 onwards
Mumps	C	1975-1999, 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 Prisma in the National Medical Register (LMR); since 2011, DHD has managed the LMR. Since 2013, the National Register Hospital Care (LBZ), managed by Dutch Hospital Data (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 (see 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 is also susceptible to under-reporting, as shown by De Greeff et al. in a paper on meningococcal disease incidence [4]. Hospitalisation data for 2015 is not yet available.

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

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

*These numbers are an approximation of the exact percentpercentage

Sources: Statistics Netherlands (CBS) up to 2009 and Dutch Hospital Data (DHD) from 2010 onwards

Data on mortality and hospitalisation is 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 [5]. 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 is 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) is more reliable for these diseases. Data on mortality of IPD is 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 and elsewhere, as more general ICD categories are felt to suffice. Moreover, gastroenteritis hospitalisations are often not tested in general or 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. [6]. By using this method, the proportion of hospitalisations for gastroenteritis attributable to RV is estimated, by comparing the weekly laboratory surveillance reports (virological laboratories) of RV 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 samples. The number of hospital admissions attributable to RV infection was the scaling factor times the number of positive laboratory results per week. For this report, the constant and scaling factor were estimated by fitting the model on hospitalisation data and weekly laboratory surveillance reports of 2010-2014 (5 years). The scaling factor estimated by this model was used for estimating the RV-attributed hospital admissions for the years 2015 and 2016 by multiplying it with the RV-positive laboratory numbers of 2015 and 2016.

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 [7]. However, limited information on patients is registered and, in many cases, laboratory confirmation is not sought for self-limiting VPDs. The different laboratory surveillance systems for diseases targeted by the NIP are outlined below.

Netherlands Reference Laboratory Bacterial Meningitis

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

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

Virological laboratories

Each week, virological laboratories, which are part of the Dutch Working Group for Clinical Virology, send positive results of virological diagnostics to the RIVM. Approximately 22 laboratories send information regularly. Aggregated results are shown on the RIVM website. It is important to bear in mind that the presence of a virus does not automatically imply the presence of disease. Since 1st 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 the routine electronic health records of GPs participating in Netherlands Institute for Health Services Research (NIVEL) Primary Care Database (NIVEL-PCD), which incorporates the former LINH (Landelijk Informatie Netwerk Huisartsenzorg), now maintained at the NIVEL. NIVEL-PCD uses routinely recorded data from health care providers to monitor health and the utilisation of health services in a representative sample of the Dutch population. All complaints and illnesses are recorded using the International Classification of Primary Care (ICPC-1). Annual incidence estimates of the total number of new episodes appearing in general practice in the Netherlands were made by extrapolating the reporting rates in these practices to the total number of Dutch residents, as obtained from CBS.

In 2012, there was a fourfold increase in the number of general practices participating in NIVEL-PCD compared with the previous group of LINH practices, resulting in a representative sample of 386 participating general practices with approximately 1.2 million registered patients (<http://www.nivel.nl/NZR/zorgregistraties-eerstelijn>). From 2012, incidence rates from NIVEL-PCD were calculated using an adjusted procedure: there were changes in the definitions of episodes and in calculations of incidence, which caused an increase in the incidence for many diseases. Episode duration is defined by the time between the first and last consultation registered with the same code 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 [8]. Because of these changes, we decided to report previously published incidence rates until 2011 based on the old method [9] and incidence rates from 2012 using the new method [10]. 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 into the number of years of life lost (i.e. premature mortality) and the number of years lived at less than full health (i.e. morbidity). The result is a single measurement unit that quantifies the years of healthy life lost due to a certain disease or infection. The full methodology used to estimate the disease burden of infectious diseases in the Netherlands expressed in DALYs is described in the State of Infectious Diseases in the Netherlands, 2013 [11, 12].

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 [12]. A specific type of a case-control design to estimate VE is the indirect cohort design or Broome method [14]. 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 controls for biases in ascertainment between cases and controls, as both cases and controls are actually diseased. An assumption for this design is that vaccinated people are at the same risk of non-vaccine-type infection as unvaccinated people. This means that the VE is underestimated in the case of cross-protection of the vaccine against non-vaccine-type disease. Conversely, if a replacement disease occurs only in vaccinated people, the VE is overestimated.

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. To this end, a random selection 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) [15] and in 2006–2007 (Nblood=7,904) [16]. 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) [17].

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 [18].

As from 1st 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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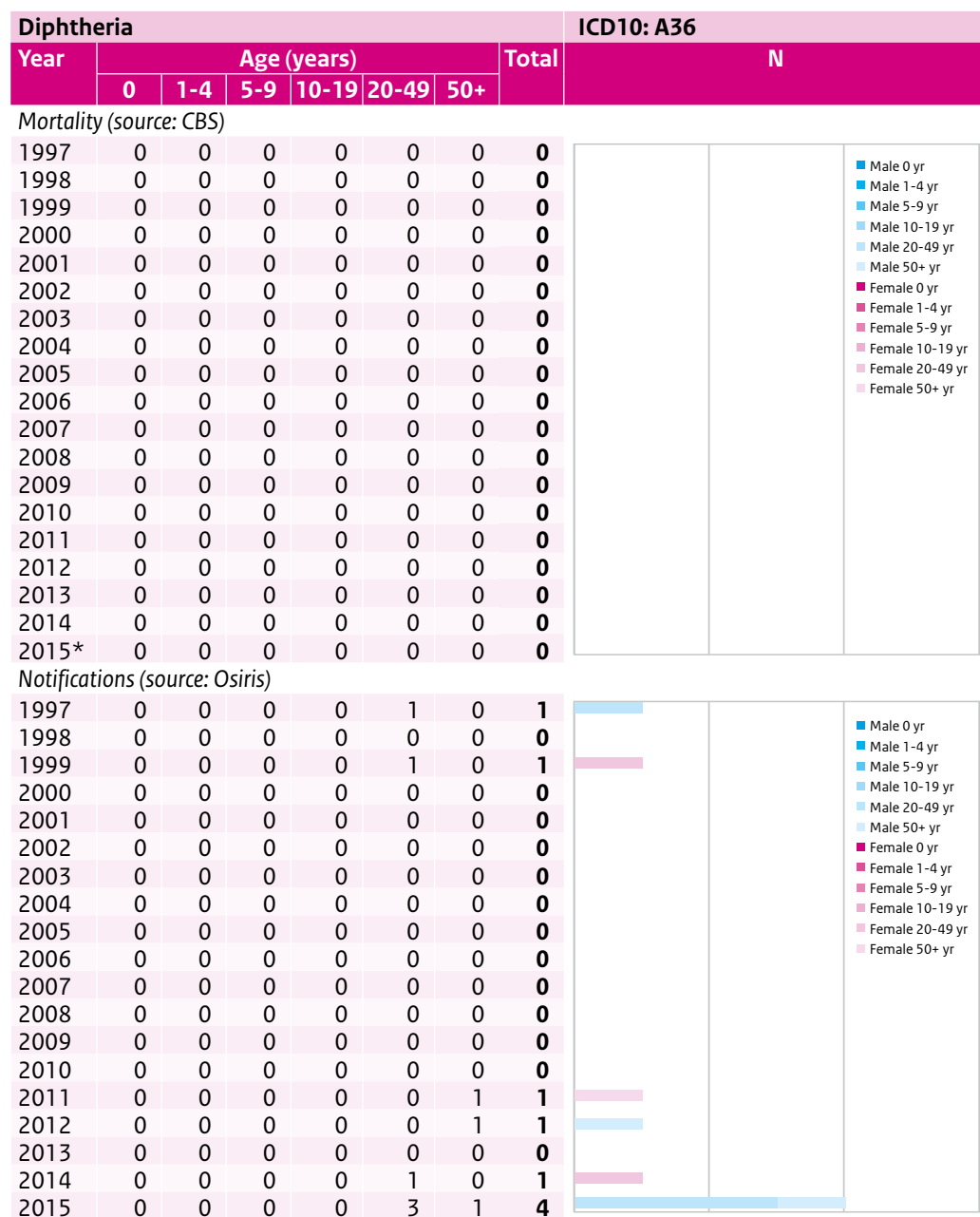
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Appendix 2 Morbidity and mortality figures

Diseases included in the current NIP



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

Diphtheria							ICD9: 032 ICD10: A36
Year	Age (years)						N
	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	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	

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

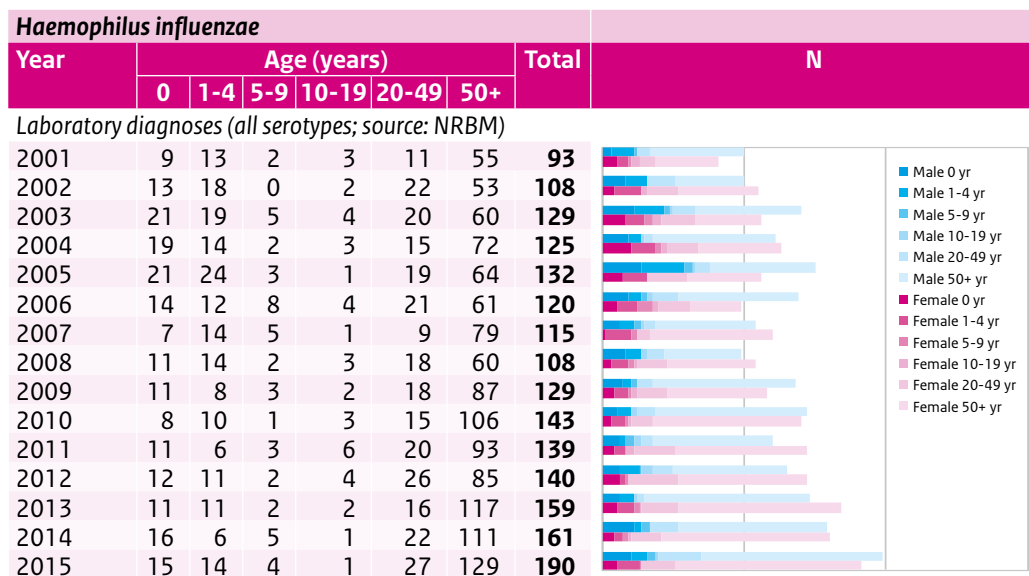
2000	0	0	0	0	0	1	1	
2001	0	0	0	0	0	2	2	
2002	0	0	0	0	0	1	1	
2003	0	0	0	0	0	1	1	
2004	0	0	0	0	0	0	0	
2005	0	0	0	0	0	1	1	
2006	0	0	0	0	0	0	0	
2007	0	0	0	0	1	2	3	
2008	0	0	0	1	0	1	2	
2009	0	0	0	0	0	0	0	
2010	0	0	0	0	1	1	2	
2011	0	0	0	0	3	2	5	
2012	0	0	0	0	2	2	4	
2013	0	0	0	1	3	1	5	
2014	0	0	0	1	4	5	10	
2015	0	0	0	0	6	5	11	

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

** Number of diphtheria isolates.

Haemophilus influenzae											
Year	Age (years)						Total	N			
	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	21	7	19				
2014	4	3	2	1	3	6	19				
2015	3	4	0	0	5	2	14				
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				

*Notifiable since 2009



Hepatitis B							ICD9: 070.2-3 ICD10: B16, B17.0, B18.0, B18.1
Year	Age (years)						N
	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	

Hospitalisations** (source: Prisma/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 causes of death is partly automatic.

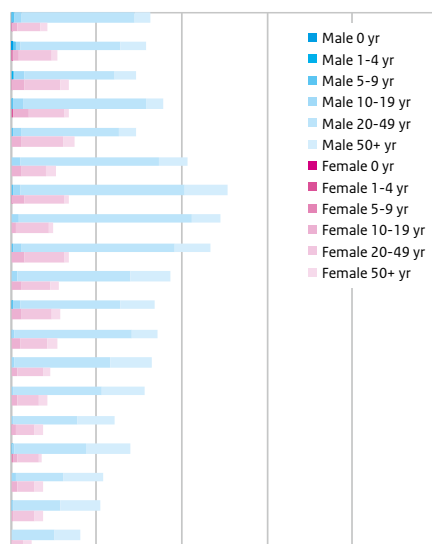
** Up to 2012, diseases are coded according to the ICD-9 coding system. From 2013, diseases are coded according to the ICD-10 coding system.

** For 18 patients, age is unknown.

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

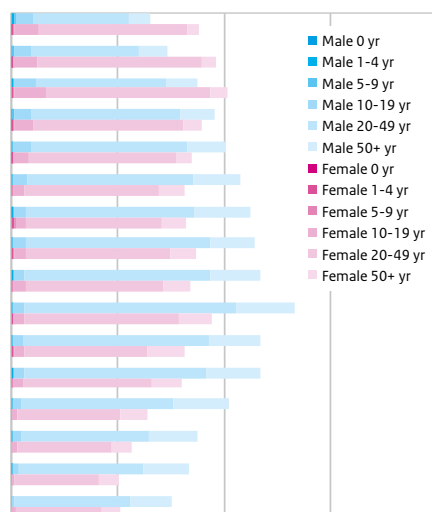
Notifications (Acute; source: Osiris)

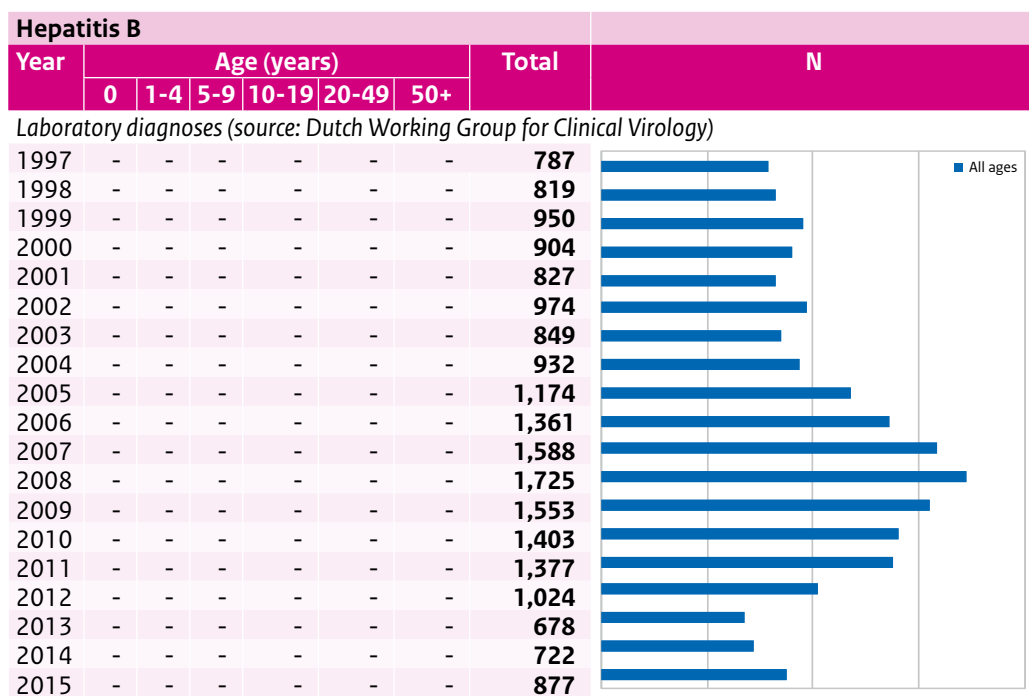
1997	1	1	3	15	158	28	206
1998	3	1	5	10	157	37	213
1999	0	4	1	26	148	35	214
2000	0	3	1	31	186	26	247
2001	0	0	2	23	163	33	221
2002	0	0	0	22	193	44	259
2003	0	1	3	22	240	56	322
2004	0	1	0	15	240	40	296
2005	0	0	2	26	227	46	301
2006	0	0	0	20	166	56	242
2007	0	1	1	20	154	50	226
2008	0	0	1	13	170	41	225
2009	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



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	787	247	1,074
2015	0	1	1	31	755	226	1,014

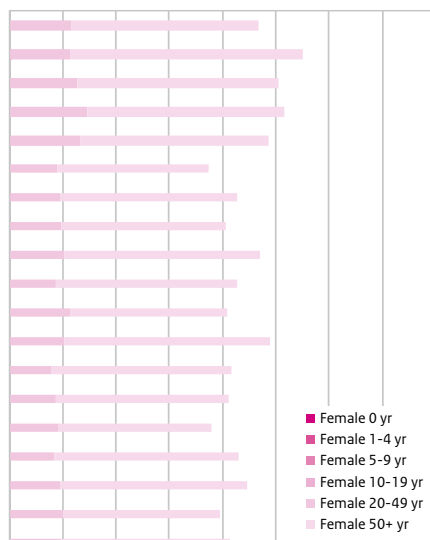




Human papillomavirus							ICD10: C53
Year	Age (years)						N
	0	1-4	5-9	10-19	20-49	50+	

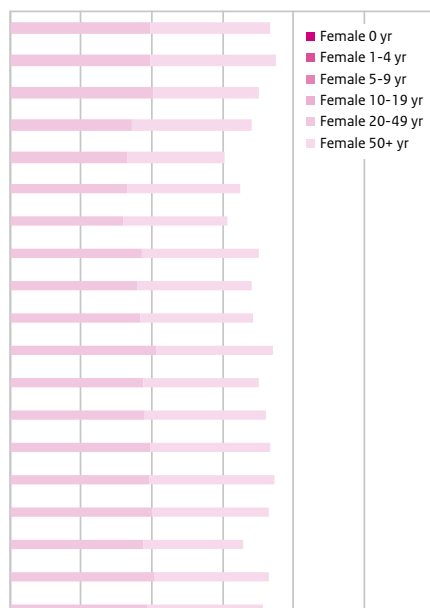
Mortality (cervical cancer; source: CBS)

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



Registrations (cervical cancer; source NKR)

1997	0	0	0	1	395	336	732
1998	0	0	0	0	396	352	748
1999	0	0	0	1	402	299	702
2000	0	0	0	0	344	338	682
2001	0	0	0	0	332	272	604
2002	0	0	0	0	332	316	648
2003	0	0	0	0	319	292	611
2004	0	0	0	1	371	328	700
2005	0	0	0	0	358	322	680
2006	0	0	0	0	368	319	687
2007	0	0	0	0	412	328	740
2008	0	0	0	0	374	326	700
2009	0	0	0	0	381	340	721
2010	0	0	0	0	397	338	735
2011	0	0	0	0	390	356	746
2012	0	0	0	1	400	330	736
2013	0	0	0	0	377	281	658
2014	0	0	0	0	408	321	729
2015**	0	0	0	0	386	329	715



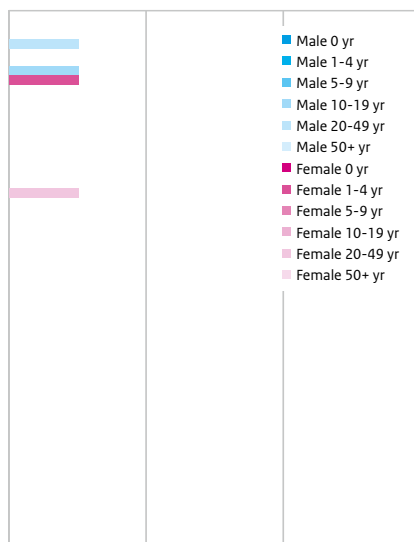
* Preliminary figures. From the statistical year 2013, the coding of causes of death is partly automatic.

** Preliminary figures

Measles							ICD10: B05
Year	Age (years)						N
	0	1-4	5-9	10-19	20-49	50+	

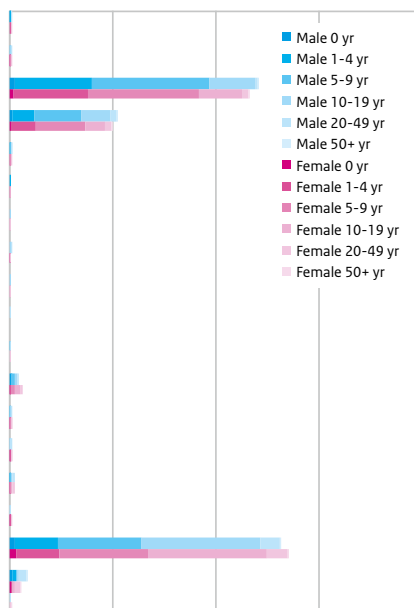
Mortality (source: CBS)

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



Notifications (source: Osiris)

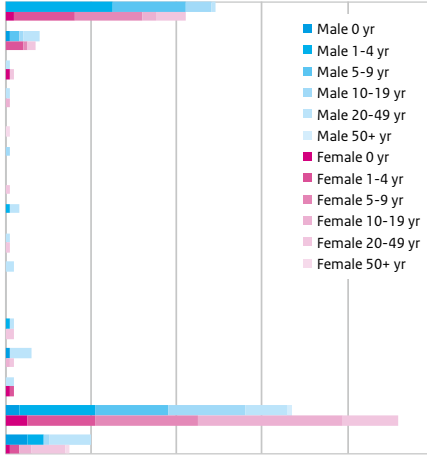
1997	1	9	0	0	11	0	21
1998	1	1	2	2	3	0	9
1999	41	738	1,112	427	44	2	2,364
2000	19	225	469	237	64	3	1,017
2001	0	3	4	3	7	0	17
2002	0	2	0	1	0	0	3
2003	0	0	1	2	1	0	4
2004	1	1	0	3	6	0	11
2005	0	0	1	1	1	0	3
2006	0	0	0	0	1	0	1
2007	0	1	0	0	8	0	9
2008	4	8	38	39	21	0	110
2009	1	2	2	3	7	0	15
2010	1	2	2	1	9	0	15
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



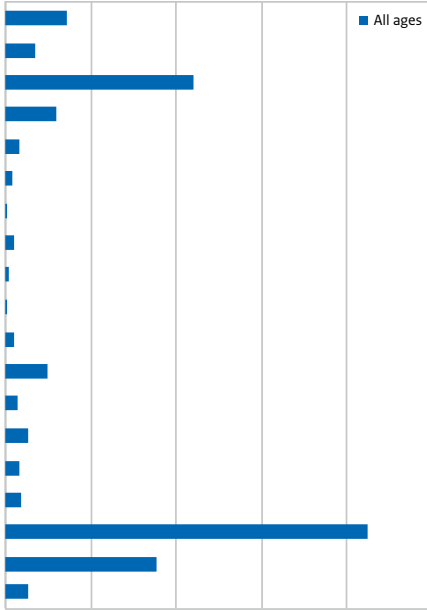
*Preliminary figures. From the statistical year 2013, the coding of causes of death is partly automatic.

Measles							ICD9: 055 ICD10: B05
Year	Age (years)						N
	0	1-4	5-9	10-19	20-49	50+	

Hospitalisations* (source: Prismant/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)

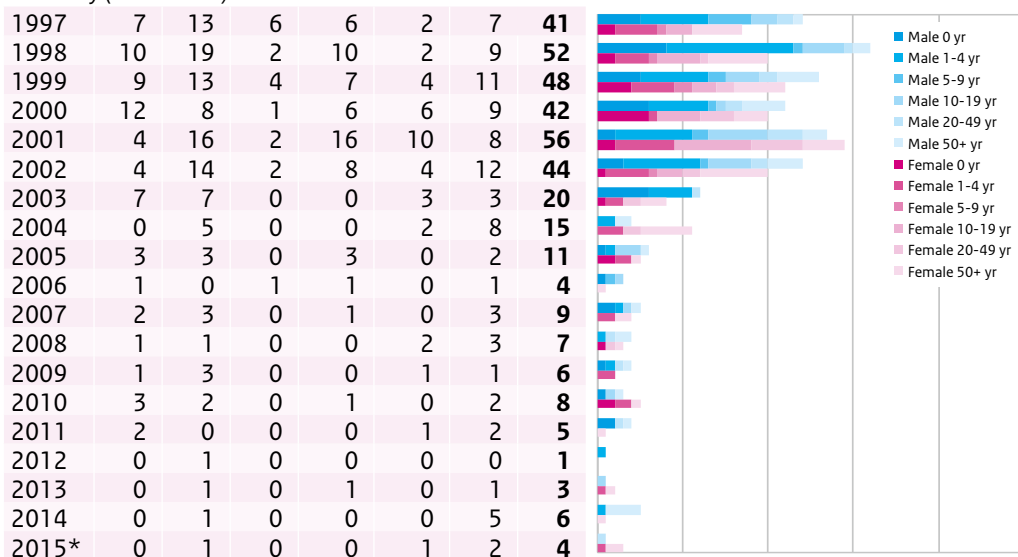
1997	-	-	-	-	-	-	36	
1998	-	-	-	-	-	-	17	
1999	-	-	-	-	-	-	110	
2000	-	-	-	-	-	-	30	
2001	-	-	-	-	-	-	8	
2002	-	-	-	-	-	-	4	
2003	-	-	-	-	-	-	1	
2004	-	-	-	-	-	-	5	
2005	-	-	-	-	-	-	2	
2006	-	-	-	-	-	-	1	
2007	-	-	-	-	-	-	5	
2008	-	-	-	-	-	-	24	
2009	-	-	-	-	-	-	7	
2010	-	-	-	-	-	-	13	
2011	-	-	-	-	-	-	8	
2012	-	-	-	-	-	-	9	
2013	-	-	-	-	-	-	212	
2014	-	-	-	-	-	-	91	
2015	-	-	-	-	-	-	13	

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

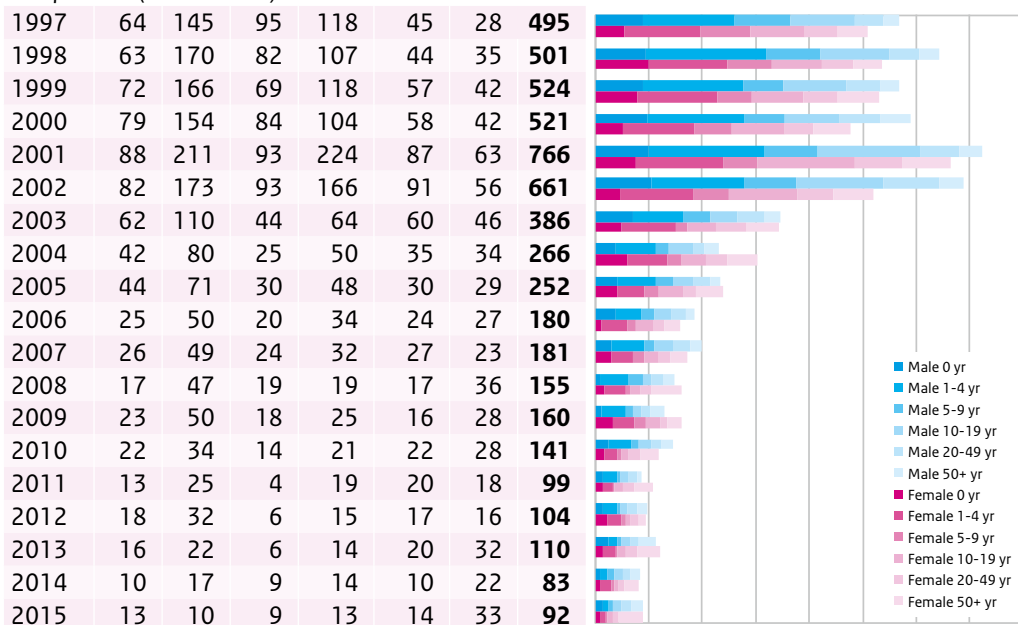
*For six patients, age is unknown.

Meningococcal disease							ICD10: A39
Year	Age (years)						N
	0	1-4	5-9	10-19	20-49	50+	

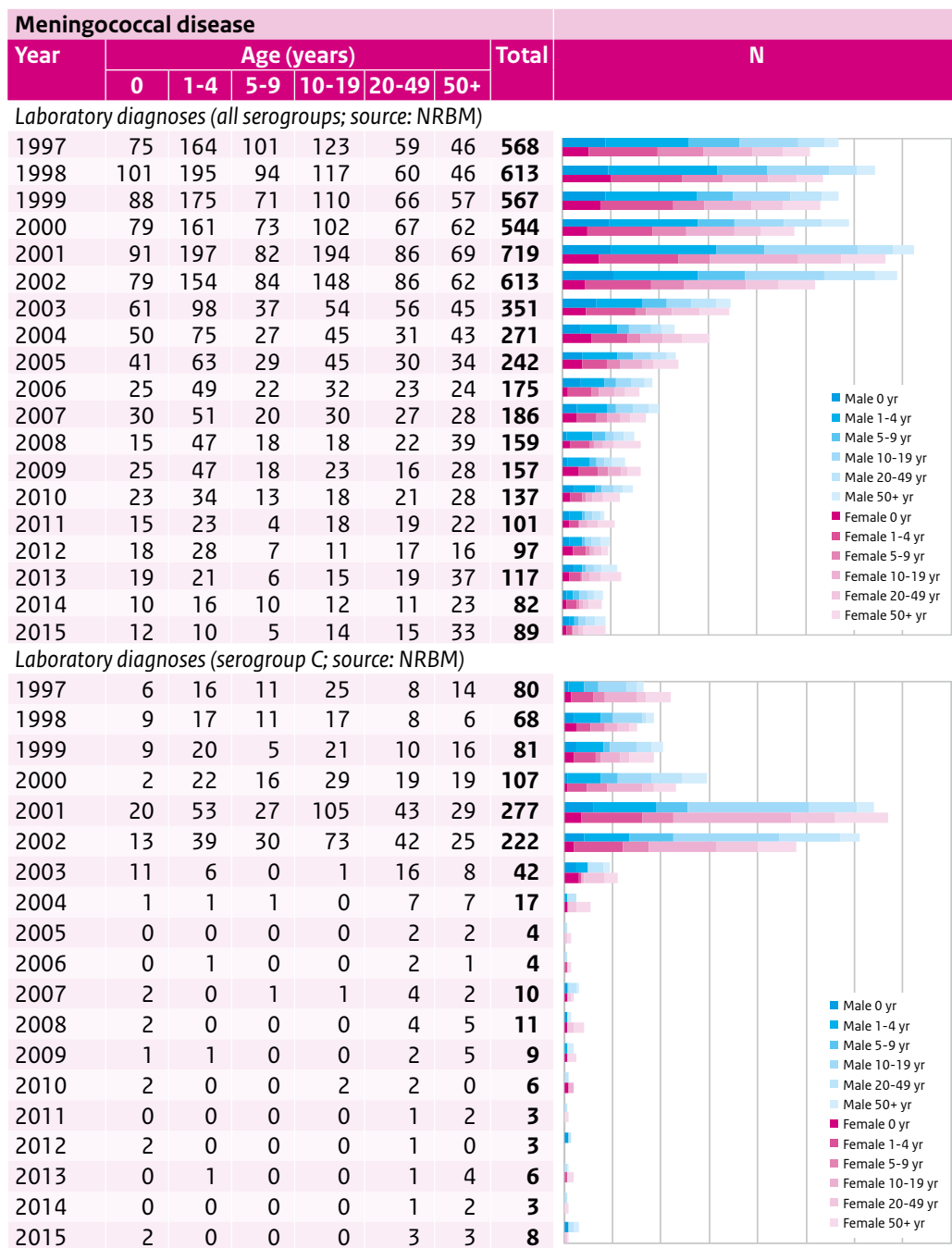
Mortality (source: CBS)



Notifications (source: Osiris)

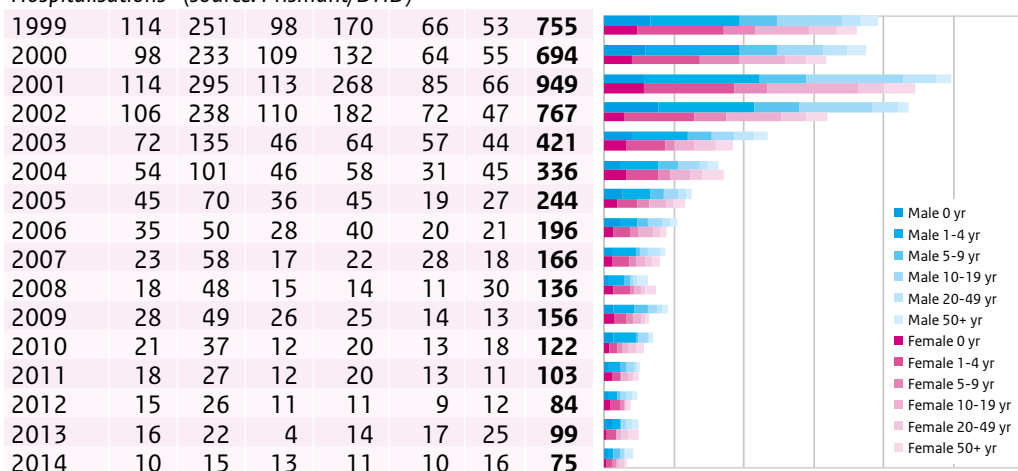


*Preliminary figures. From the statistical year 2013, the coding of causes of death is partly automatic.



Meningococcal disease							ICD9: 036.0-4, 036.8-9 ICD10: A39	
Year	Age (years)						Total	N
	0	1-4	5-9	10-19	20-49	50+		

Hospitalisations* (source: Prismant/DHD)



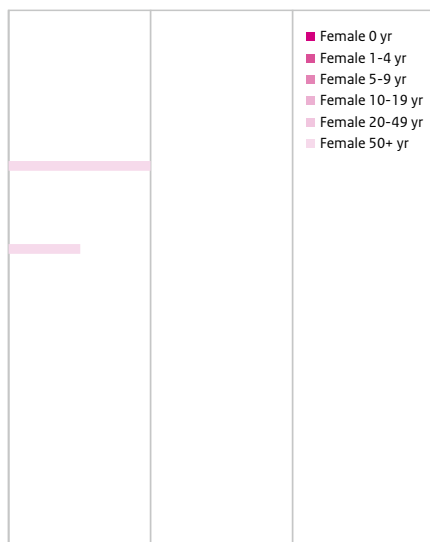
*Up to 2012, diseases are coded according to the ICD-9 coding system. From 2013, diseases are coded according to the ICD-10 coding system.

*For 12 patients age is unknown.

Mumps							ICD10: B26
Year	Age (years)						N
	0	1-4	5-9	10-19	20-49	50+	

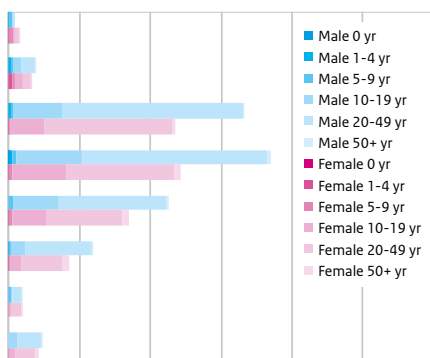
Mortality (source: CBS)

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



Notifications (source: Osiris)

2008**	0	2	10	5	7	1	25
2009	0	9	8	22	30	2	71
2010	0	4	5	119	435	6	569
2011	1	6	10	169	412	15	613
2012	0	2	12	110	260	13	397
2013	0	3	2	37	152	11	205
2014	0	0	4	5	28	2	39
2015	0	0	2	21	61	5	89



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

**Notifiable from 1st December 2008 onwards.

Mumps							ICD9: 072 ICD10: B26
Year	Age (years)						N
	0	1-4	5-9	10-19	20-49	50+	

Hospitalisations* (source: Prisma/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	

Male 0 yr
Male 1-4 yr
Male 5-9 yr
Male 10-19 yr
Male 20-49 yr
Male 50+ yr
Female 0 yr
Female 1-4 yr
Female 5-9 yr
Female 10-19 yr
Female 20-49 yr
Female 50+ yr

Laboratory diagnoses (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	-	-	-	-	-	-	29	
2015	-	-	-	-	-	-	64	

All ages

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

*For one patient, age is unknown.

Pertussis							ICD10: A37
Year	Age (years)						N
	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	

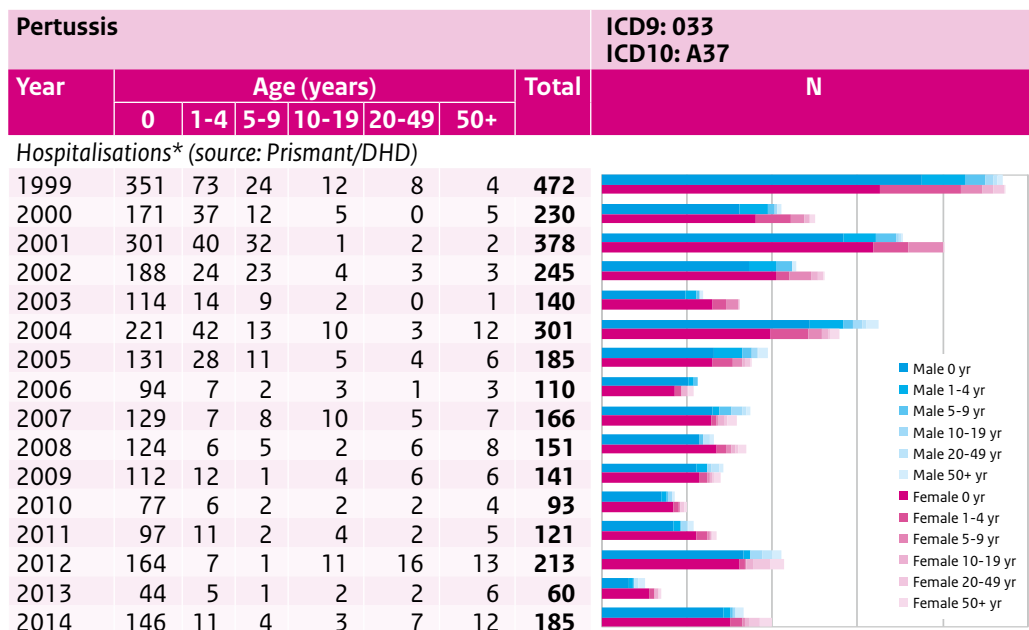
■ Male 0 yr
 ■ Male 1-4 yr
 ■ Male 5-9 yr
 ■ Male 10-19 yr
 ■ Male 20-49 yr
 ■ Male 50+ yr
 ■ Female 0 yr
 ■ Female 1-4 yr
 ■ Female 5-9 yr
 ■ Female 10-19 yr
 ■ Female 20-49 yr
 ■ Female 50+ yr

Notifications (source: Osiris)

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	

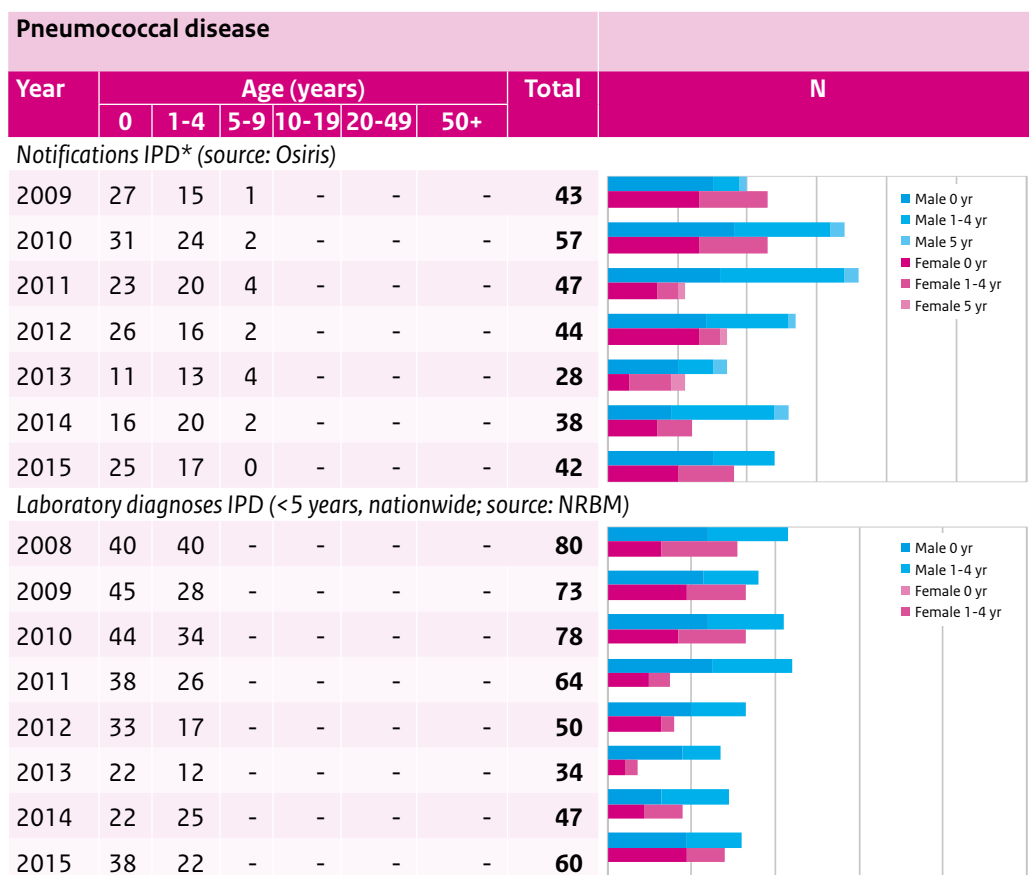
■ Male 0 yr
 ■ Male 1-4 yr
 ■ Male 5-9 yr
 ■ Male 10-19 yr
 ■ Male 20-49 yr
 ■ Male 50+ yr
 ■ Female 0 yr
 ■ Female 1-4 yr
 ■ Female 5-9 yr
 ■ Female 10-19 yr
 ■ Female 20-49 yr
 ■ Female 50+ yr

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



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

*For three patients, age is unknown.



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

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

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	

Mortality IPD (all ages, sentinel labs (covering 25% of Dutch population); source: NRBM)

2004	-	-	-	-	-	-	-	
2005	3	0	0	0	1	101	105	
2006	0	1	0	0	3	91	95	
2007	0	0	0	0	7	82	89	
2008	0	1	0	0	7	82	90	
2009	1	1	1	0	4	75	82	
2010	0	0	0	0	6	52	58	
2011	0	0	0	0	3	65	68	
2012	-	-	-	-	-	-	-	
2013	-	-	-	-	-	-	-	
2014	-	-	-	-	-	-	-	
2015	-	-	-	-	-	-	-	

Pneumococcal disease							ICD9: 481 ICD10: J13
Year	Age (years)						N
	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	



*Hospitalisations pneumococcal pneumonia** (source: Prisma/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 causes of death is partly automatic.

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

**For 16 patients age is unknown.

Poliomyelitis								ICD10: A80
Year	Age (years)						Total	N
	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	

■ Male 0 yr
 ■ Male 1-4 yr
 ■ Male 5-9 yr
 ■ Male 10-19 yr
 ■ Male 20-49 yr
 ■ Male 50+ yr
 ■ Female 0 yr
 ■ Female 1-4 yr
 ■ Female 5-9 yr
 ■ Female 10-19 yr
 ■ Female 20-49 yr
 ■ Female 50+ yr

Notifications (source: Osiris)

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	

■ 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

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

Poliomyelitis								ICD9: 045 ICD10: A80		
Year	Age (years)						Total	N		
	0	1-4	5-9	10-19	20-49	50+				
Hospitalisations* (source: Prismant/DHD)										
1999	0	0	0	0	0	0	0	<div><div></div>Male 0 yr</div> <div><div></div>Male 1-4 yr</div> <div><div></div>Male 5-9 yr</div> <div><div></div>Male 10-19 yr</div> <div><div></div>Male 20-49 yr</div> <div><div></div>Male 50+ yr</div> <div><div></div>Female 0 yr</div> <div><div></div>Female 1-4 yr</div> <div><div></div>Female 5-9 yr</div> <div><div></div>Female 10-19 yr</div> <div><div></div>Female 20-49 yr</div> <div><div></div>Female 50+ yr</div>		
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, diseases are coded according to the ICD-10 coding system.

Rubella (acquired)							ICD10: B06
Year	Age (years)						N
	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	

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	

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

Rubella (acquired)							ICD9: 056 ICD10: B06
Year	Age (years)						N
	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	

■ Male 0 yr
 ■ Male 1-4 yr
 ■ Male 5-9 yr
 ■ Male 10-19 yr
 ■ Male 20-49 yr
 ■ Male 50+ yr
 ■ Female 0 yr
 ■ Female 1-4 yr
 ■ Female 5-9 yr
 ■ Female 10-19 yr
 ■ Female 20-49 yr
 ■ Female 50+ yr

Laboratory diagnoses (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	-	-	-	-	-	-	32	
2015	-	-	-	-	-	-	18	

■ All ages

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

Tetanus								ID10: A33-35
Year	Age (years)						Total	N
	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	

■ Male 0 yr
 ■ Male 1-4 yr
 ■ Male 5-9 yr
 ■ Male 10-19 yr
 ■ Male 20-49 yr
 ■ Male 50+ yr
 ■ Female 0 yr
 ■ Female 1-4 yr
 ■ Female 5-9 yr
 ■ Female 10-19 yr
 ■ Female 20-49 yr
 ■ Female 50+ yr

Notifications (source: Osiris)

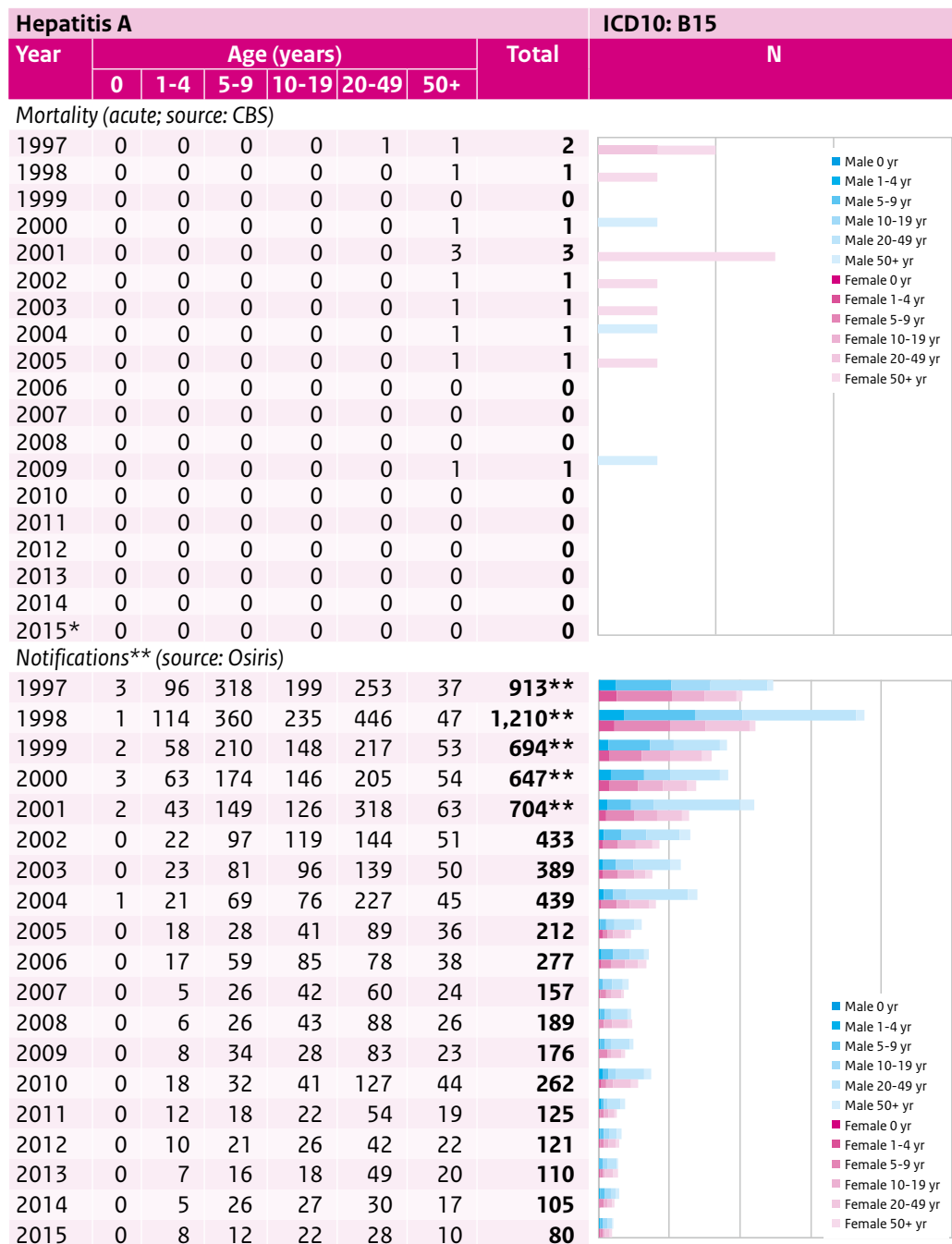
1997	0	0	0	0	1	3	4	
1998	0	0	0	0	0	0	0	
1999**	-	-	-	-	-	-	-	
2000**	-	-	-	-	-	-	-	
2001**	-	-	-	-	-	-	-	
2002**	-	-	-	-	-	-	-	
2003**	-	-	-	-	-	-	-	
2004**	-	-	-	-	-	-	-	
2005**	-	-	-	-	-	-	-	
2006**	-	-	-	-	-	-	-	
2007**	-	-	-	-	-	-	-	
2008**	-	-	-	-	-	-	-	
2009	0	0	0	0	0	1	1	
2010	0	0	0	0	0	2	2	
2011	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	

■ 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

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

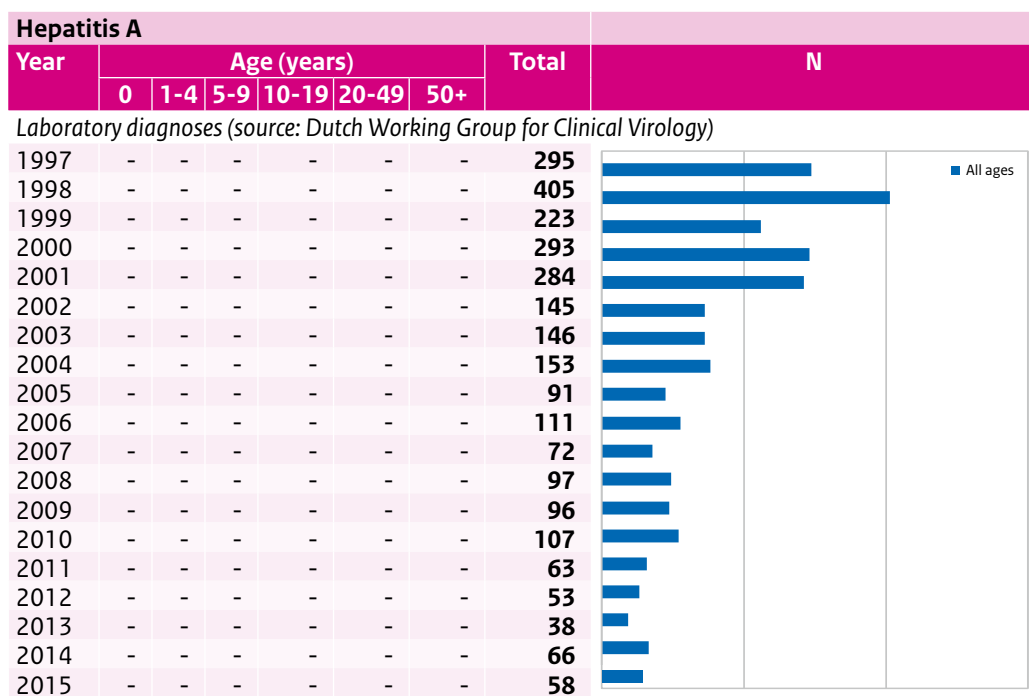
**No notifications in 1999-2008

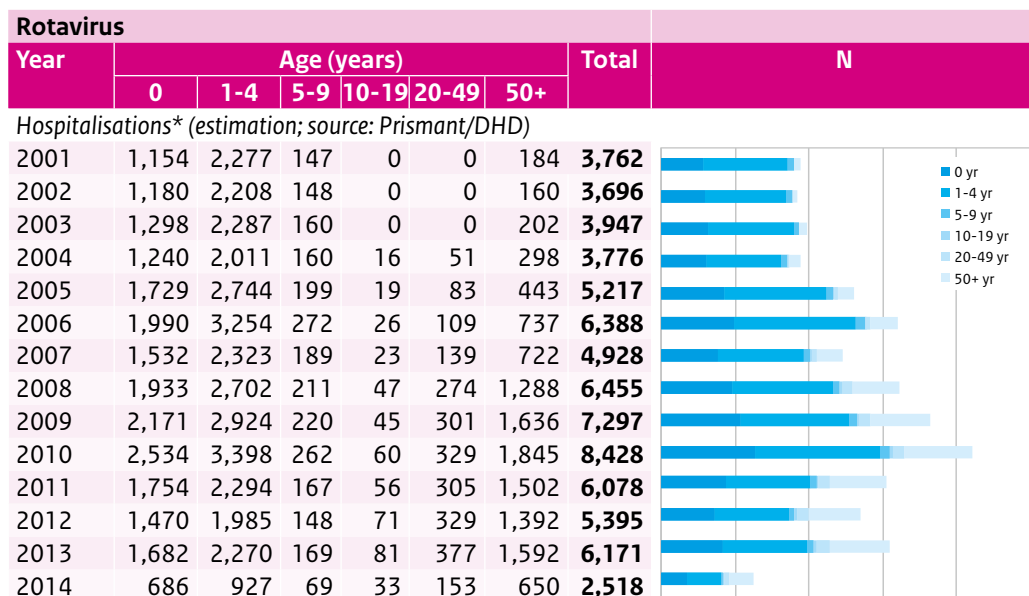
Potential NIP target diseases



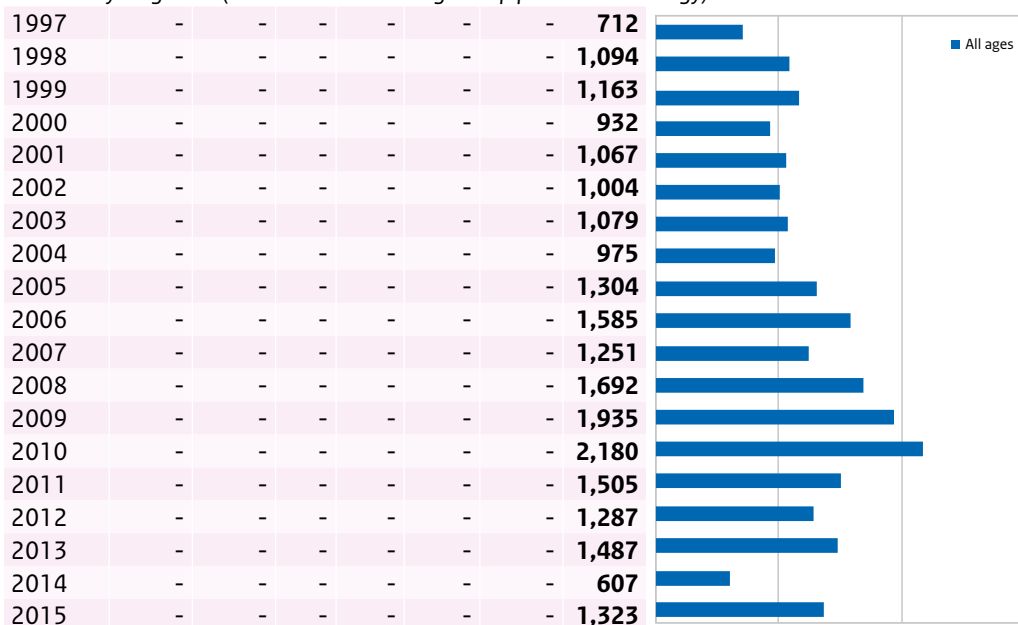
*Preliminary figures. From the statistical year 2013, the coding of causes of death is partly automatic.

**In the period 1997-2001 for 25 patients, age is unknown.





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



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

Varicella (chickenpox)							ICD9: 052 ICD10: B01
Year	Age (years)						N
	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	

■ Male 0 yr
 ■ Male 1-4 yr
 ■ Male 5-9 yr
 ■ Male 10-19 yr
 ■ Male 20-49 yr
 ■ Male 50+ yr
 ■ Female 0 yr
 ■ Female 1-4 yr
 ■ Female 5-9 yr
 ■ Female 10-19 yr
 ■ Female 20-49 yr
 ■ Female 50+ yr

Hospitalisations** (source: Prisma/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	

■ 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

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

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

Herpes zoster (shingles)							ICD9: 053 ICD10: B02
Year	Age (years)						N
	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	

Hospitalisations** (source: Prisma/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 causes of death is partly automatic.

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



Vaccin changes in the NIP after 2000

Legend

- [1] Only children at least one of whose parents was born in a country where hepatitis B is moderately or highly endemic and children whose mother had tested positive for HBsAg.
- [2] Only for children whose mother tested positive for HBsAg.
- [3] Only for children whose mother tested positive for HBsAg and children with Down syndrome.
- [4] Used until March 2008.
- [5] Only girls were vaccinated and received three doses of HPV vaccine: at 0, 1 and 6 months.
- [6] Only girls were vaccinated and received two doses of HPV vaccine: at 0 and 6 months.

July 2001

- Acellular pertussis vaccine (GSK)
4 years of age
Children born on or after 1 January 1998

September 2002

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

March 2003

- ← DTwP-IPV vaccine (NVI) and Hib vaccine (NVI)
→ DTwP-IPV/Hib vaccine (NVI)
2, 3, 4 and 11 months of age
Children born on or after 1 April 2002
- HBVAXPRO (SP MSD)
2, 3, 4 and 11 months of age
Children born on or after 1 January 2003
(specific risk groups [1])

January 2005

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

January 2006

- HBVAXPRO (SP MSD)
birth
Children born on or after 1 January 2006
(specific risk groups [2])
- ← Infanrix IPV+Hib (GSK)
→ Pediacel (SP MSD)
2, 3, 4 and 11 months of age
Children born on or after 1 February 2005

June 2006

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

June 2006

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

July 2006

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

September 2006

- ← MMR vaccine (NVI)
- MMR-VaxPro (SP MSD) and Priorix (GSK)
- 14 months of age
- Children born on or after July/August 2005

January 2008

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

October 2008

- ← Priorix (GSK)
- MMR-VaxPro (SP MSD) and Priorix (GSK)
- 9 years of age
- Children born on or after 1 October 1999

January 2010

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

January 2010

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

February 2008

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

May 2011

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

July-December 15th 2008

- ← Pediacel (SP MSD)
- Infanrix IPV+Hib (GSK)
- 2, 3, 4 and 11 months of age
- Children born on or after 1 August 2007

October 2011

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

September 2008

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

December 2013

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

September 2008

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

January 2014

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

Appendix 4 Composition of vaccines used in the NIP

Vaccine	Composition
M-M-R VaxPro / SP MSD EU/1/06/337 Mumps, measles and rubella vaccine 0.5 ml	Mumps virus (Jeryl Lynn) > 12,500 TCID ₅₀ (tissue culture infectious doses) Measles virus (Enders' Edmonston) > 1000 TCID ₅₀ Rubella virus (Wistar RA 27/3) > 1000 TCID ₅₀
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 Adsorbed 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
Infanrix Hexa / GSK RVG17641 Diphtheria, tetanus, pertussis (acellular component), hepatitis B (rdNA), inactivated poliomyelitis vaccine and conjugated <i>Haemophilus influenzae</i> 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
DT-IPV vaccine / NVI 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 Al ³⁺

Vaccine	Composition
REVAXIS / SP MSD 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 (<i>Saccharomyces cerevisiae</i>)
HBVAXPRO / SP 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 <i>Saccharomyces cerevisiae</i> (strain 2150-2-3) yeast by recombinant DNA technology
Act-HIB / SP MSD <i>Haemophilus influenzae</i> type b Conjugate Vaccine (Tetanus Protein - Conjugate) 0.5 ml	Purified polyribose ribitol phosphate capsular polysaccharide (PRP) of <i>Haemophilus influenzae</i> type b ¹ 10 µg ¹ covalently bound to tetanus protein 20 µg
Cervarix / GSK EU/1/07/419	Human papillomavirus type 16 L1 protein ^{2,3,4} 20 µg Human papillomavirus type 18 L1 protein ^{2,3,4} 20 µg ¹ adjuvanted by AS04 containing 3-O-desacyl-4'-monophosphoryl lipid A (MPL) ³ 50 µg ² absorbed on aluminium hydroxide, hydrated (Al(OH) ₃) 0.5 mg AL ³⁺ in total ³ L1 protein in the form of non-infectious virus-like particles (VLPs) produced by recombinant DNA technology using a Baculovirus expression system which uses Hi-5 Rix4446 cells derived from <i>Trichoplusia ni</i> .

Vaccine	Composition
NeisVac-C / Baxter RVG 26343 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 <i>Haemophilus influenzae</i>) 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.europa.eu.

Appendix 5 Overview of recent RIVM publications 2015-mid 2016

Vaccination coverage

1. van Lier EA, Oomen PJ, Giesbers H, van Vliet JA, Drijfhout IH, Zonnenberg-Hoff IF et al. Immunisation coverage National Immunisation Programme in the Netherlands: Year of report 2016. Bilthoven: RIVM, 2016 RIVM report 2016-0064.
2. Klomp JH, van Lier A, Ruijs WL. Vaccination coverage for measles, mumps and rubella in anthroposophical schools in Gelderland, The Netherlands. *Eur J Public Health*. 2015;25:501–5.

Burden of disease

1. van Lier A, McDonald SA, Bouwknegt M, group EPI, Kretzschmar ME, Havelaar AH et al. Disease burden of 32 infectious diseases in the Netherlands, 2007–2011. *PLoS One*. 2016;11(4):e0153106.
2. Kristensen M, van Lier A, Eilers R, McDonald SA, Opstelten W, van der Maas N et al. Burden of four vaccine-preventable diseases in older adults. *Vaccine*. 2016;34(7):942–9.

Acceptance of vaccination

1. Visser O, Hautvast JLA, van der Velden K, Hulscher MEJL. Intention to accept pertussis vaccination for cocooning: A qualitative study of the determinants. *PLoS ONE* 2016;11(6):e0155861.
2. Van Lier A, Tostmann A, Harmsen IA, de Melker HE, Hautvast JL, Ruijs WL. Negative attitude and low intention to vaccinate universally against varicella among public health professionals and parents in the Netherlands: Two internet surveys. *BMC Infect Dis*. 2016 Mar 15;16(1):127.
3. Harmsen IA, Bos H, Ruiter RA, Paulussen TG, Kok G, de Melker HE, Mollema L. Vaccination decision-making of immigrant parents in the Netherlands; A focus group study. *BMC Public Health*. 2015 Dec 10;15:1229.
4. Eilers R, Krabbe PF, de Melker HE. Attitudes of Dutch general practitioners towards vaccinating the elderly: Less is more? *BMC Fam Pract*. 2015 Oct 28;16:158.
5. 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 Aug 11. pii: S0264-410X(16)30607-7.

Adverse events

1. van der Maas NA, Woudenberg T, Hahné SJ, de Melker HE. Tolerability of early measles-mumps-rubella vaccination in infants aged 6–14 months during a measles outbreak in the Netherlands in 2013–2014. *J Infect Dis*. 2016 May 1;213(9):1466–71.
2. van der Maas NA, Godefrooij S, Vermeer-de Bondt PE, de Melker HE, Kemmeren JM. Tolerability of 2 doses of pandemic influenza vaccine (Focetria(R)) and of a prior dose of seasonal 2009–2010 influenza vaccination in the Netherlands. *Hum Vaccin Immunother*. 2016;1–6.

3. Verbeek NE, van der Maas NA, Sonsma AC, Ippel E, Vermeer-de Bondt PE, Hagebeuk E et al. Effect of vaccinations on seizure risk and disease course in Dravet syndrome. *Neurology*, 2015;85(7):596–603.
4. van der Maas N, Dijs-Elsinga J, Kemmeren J, van Lier A, Knol M, de Melker H. Safety of vaccination against influenza A (H1N1) during pregnancy in the Netherlands: Results on pregnancy outcomes and infant's health: Cross-sectional linkage study. *BJOG*, 2015.

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

1. van Wijhe M, McDonald SA, de Melker HE, Postma MJ, Wallinga J. Effect of vaccination programmes on mortality burden among children and young adults in the Netherlands during the 20th century: A historical analysis. *The Lancet Infectious Diseases*. 2016 Feb 9.
2. Donken R, de Melker HE, Rots N, Berbers G, Knol MJ. The use of the non-inferiority margin for comparing vaccines in vaccine trials: A systematic review. *Vaccine*, 2015;33:1426–32.
3. van der Maas NA, van Aerde K, Bont LJ, Bekker MN, Rots N, de Melker HE. [Infection prevention in newborns through maternal vaccination: Current insights and developments]. *Ned Tijdschr Geneeskd*, 2016;160:D411.

Current NIP

Diphtheria

1. Swart EM, van Gageldonk PG, de Melker HE, van der Klis FR, Berbers GA, Mollema L. Long-term protection against diphtheria in the Netherlands after 50 years of vaccination: Results from a seroepidemiological study. *PLoS One*. 2016 Feb 10;11(2):e0148605.

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

None

Hepatitis B

1. Soetens LC, van Benthem BH, Urbanus A, Cremer J, Benschop KS, Rietveld A et al. Ongoing transmission of hepatitis B virus in rural parts of the Netherlands, 2009–2013. *PloS one*. 2015;10(2):e0117703.

Human papillomavirus (HPV) infection

1. Bogaards JA, Wallinga J, Brakenhoff RH, Meijer CJ, Berkhof J. Direct benefit of vaccinating boys along with girls against oncogenic human papillomavirus: Bayesian evidence synthesis. *BMJ*. 2015 May 12;350:h2016.
2. van den Broek IVF, van Aar F, van Oeffelen AAM, Woestenberg PJ, Heijne JCM, den Daas C et al. Sexually transmitted infections in the Netherlands in 2015. *Bilthoven: RIVM*, 2016 2016-0027.
3. Donken R, Bogaards JA, van der Klis FR, Meijer CJ, de Melker HE. An exploration of individual- and population-level impact of the 2-dose HPV vaccination schedule in pre-adolescent girls. *Hum Vaccin Immunother*. 2016 Jun 2;12(6):1381–93.

4. Donken R, Knol MJ, Bogaards JA, van der Klis FR, Meijer CJ, de Melker HE. Inconclusive evidence for non-inferior immunogenicity of two- compared with three-dose HPV immunization schedules in preadolescent girls: A systematic review and meta-analysis. *J Infect.* 2015 Jul;71(1):61–73.
5. Donken R, de Melker HE, Rots NY, Berbers G, Knol MJ. Comparing vaccines: A systematic review of the use of the non-inferiority margin in vaccine trials. *Vaccine.* 2015 Mar 17;33(12):1426–32.
6. King AJ, Sonsma JA, Vriend HJ, van der Sande MA, Feltkamp MC, Boot HJ et al. Genetic Diversity in the Major Capsid L1 Protein of HPV-16 and HPV-18 in the Netherlands. *PLoS one.* 2016;11(4):e0152782.
7. Luttmer R, Dijkstra MG, Snijders PJ, Jordanova ES, King AJ, Pronk DT et al. Presence of human papillomavirus in semen of healthy men is firmly associated with HPV infections of the penile epithelium. *Fertil Steril.* 2015 Oct;104(4): 838–44.e8.
8. Mollers M, King AJ, Knol MJ, Scherpenisse M, Meijer CJ, van der Klis FR et al. Effectiveness of human papillomavirus vaccine against incident and persistent infections among young girls: Results from a longitudinal Dutch cohort study. *Vaccine.* 2015 May 28; 33(23):2678–83.
9. Mooij SH, van Santen DK, Geskus RB, van der Sande MA, Coutinho RA, Stolte IG et al. The effect of HIV infection on anal and penile human papillomavirus incidence and clearance: A cohort study among MSM. *AIDS.* 2016 Jan 2;30(1):121–32.
10. Vink MA, Bogaards JA, Meijer CJ, Berkhof J. Primary human papillomavirus DNA screening for cervical cancer prevention: Can the screening interval be safely extended? *Int J Cancer.* 2015 Jul 15; 137(2):420–7.
11. Vink MA, van de Kasstelee J, Wallinga J, Teunis PF, Bogaards JA. Estimating seroprevalence of human papillomavirus type 16 using a mixture model with smoothed age-dependent mixing proportions. *Epidemiology.* 2015 Jan;26(1):8–16.
12. Vink MA, Berkhof J, van de Kasstelee J, van Boven M, Bogaards JA. A bivariate mixture model for natural antibody levels to human papillomavirus types 16 and 18: Baseline estimates for monitoring the herd effects of immunization. *PLoS One.* 2016 Aug 18;11(8):e0161109.
13. Vriend HJ, Bogaards JA, van Bergen JE, Brink AA, van den Broek IV, Hoebe CJ et al. Medical microbiological laboratories and the CSI group. Incidence and persistence of carcinogenic genital human papillomavirus infections in young women with or without Chlamydia trachomatis co-infection. *Cancer Med.* 2015 Oct;4(10):1589–98.
14. van der Weele P, van Logchem E, Wolffs P, van den Broek I, Feltkamp M, de Melker H et al. Correlation between viral load, multiplicity of infection, and persistence of HPV16 and HPV18 infection in a Dutch cohort of young women. *J Clin Virol.* 2016 Aug 4;83:6–11.
15. Welling CA, Mooij SH, van der Sande MA, van Rooijen MS, Vermeulen-Oost WF, King AJ et al. Association of HIV infection with anal and penile low-risk human papillomavirus infections among men who have sex with men in Amsterdam: The HIV & HPV in MSM Study. *Sex Transm Dis.* 2015 Jun;42(6):297–304.

Measles

1. Nic Lochlainn L, Mandal S, de Sousa R, Paranthaman K, van Binnendijk R, Ramsay M et al. A unique measles B3 cluster in the United Kingdom and the Netherlands linked to air travel and transit at a large international airport, February to April 2014. *Euro Surveillance*. 2016;21(13).
2. Schellens IM, Meiring HD, Hoof I, Spijkers SN, Poelen MC, van Gaans-van den Brink JA et al. Measles virus epitope presentation by HLA: Novel insights into epitope selection, dominance, and microvariation. *Frontiers in Immunology*. 2015;6:546.
3. van der Maas NA, Woudenberg T, Hahné SJ, de Melker HE. Tolerability of early measles-mumps-rubella vaccination in infants aged 6-14 months during a measles outbreak in the Netherlands in 2013-2014. *J Infect Dis*. 2016 May 1;213(9):1466-71.
4. Schellens IM, Meiring HD, Hoof I, Spijkers SN, Poelen MC, van Gaans-van den Brink JA, Costa AI, Vennema H, Keşmir C, van Baarle D, van Els CA. Measles virus epitope presentation by HLA: Novel insights into epitope selection, dominance and microvariation. *Frontiers Immunology* 2015 Nov 2;6:546.

Meningococcal serogroup C (MenC) disease

1. Stoof SP, Rodenburg GD, Knol MJ, Rümke LW, Bovenkerk S, Berbers GA et al. Disease burden of invasive meningococcal disease in the Netherlands between June 1999 and June 2011: A subjective role for serogroup and clonal complex. *Clin Infect Dis*. 2015 Oct 15;61(8):1281-92.
2. Stoof SP, Buisman AM, van Rooijen DM, Boonacker R, van der Klis FR, Sanders EA et al. Different dynamics for IgG and IgA memory B cells in adolescents following a meningococcal serogroup C tetanus toxoid conjugate booster vaccination nine years after priming: A role for priming age? *PLoS One*. 2015 Oct 12;10(10):e0138665.
3. Stoof SP, van der Klis FR, van Rooijen DM, Bogaert D, Trzciński K, Sanders EA et al. Salivary antibody levels in adolescents in response to a meningococcal serogroup C conjugate booster vaccination nine years after priming: Systemically induced local immunity and saliva as potential surveillance tool. *Vaccine*. 2015 Jul 31;33(32):3933-9.
4. Stoof S. Invasive meningococcal disease and prevention through vaccination. Towards an optimal meningococcal serogroup C vaccination schedule. Thesis (12 November 2015).

Mumps

1. Gouma S, Hahne SJ, Gijselaar DB, Koopmans MP, van Binnendijk RS. Severity of mumps disease is related to MMR vaccination status and viral shedding. *Vaccine*. 2016;34(16):1868-73.
2. Gouma S, Ten Hulscher HI, Schurink-van 't Klooster TM, de Melker HE, Boland GJ, Kaaijk P et al. Mumps-specific cross-neutralization by MMR vaccine-induced antibodies predicts protection against mumps virus infection. *Vaccine*. 2016;34(35):4166-71.
3. Gouma S, Cremer J, Parkkali S, Veldhuijzen I, van Binnendijk RS, Koopmans MPG. Mumps virus F gene and HN gene sequencing as a molecular tool to study mumps virus transmission. *Infect Genet Evol*. 2016;in press.

4. Han WG, Emmelot ME, Jaadar H, Ten Hulscher HI, van Els CA, Kaaijk P. Development of an IFN γ ELISPOT for the analysis of the human T cell response against mumps virus. *J Immunol Methods*. 2016;431:52–9.
5. Kaaijk P, Gouma S, Ten Hulscher HI, Han WG, Kleijne DE, van Binnendijk RS et al. Dynamics of the serologic response in vaccinated and unvaccinated mumps cases during an epidemic. *Hum Vaccin Immunother*. 2015;11(7):1754–61.

Pertussis

1. Brummelman J, Veerman RE, Hamstra HJ, Deuss AJ, Schuijt TJ, Sloots A et al. Bordetella pertussis naturally occurring isolates with altered lipooligosaccharide structure fail to fully mature human dendritic cells. *Infection and immunity*. 2015;83(1):227–38.
2. Jongerius I, Schuijt TJ, Mooi FR, Pinelli E. Complement evasion by Bordetella pertussis: Implications for improving current vaccines. *Journal of molecular medicine (Berlin, Germany)*. 2015;93(4):395–402.
3. Brummelman J, Helm K, Hamstra HJ, van der Ley P, Boog CJ, Han WG et al. Modulation of the CD4(+) T cell response after acellular pertussis vaccination in the presence of TLR4 ligation. *Vaccine*. 2015;33(12):1483–91.
4. Brummelman J, Raeven RH, Helm K, Pennings JL, Metz B, van Eden W et al. Transcriptome signature for dampened Th2 dominance in acellular pertussis vaccine-induced CD4(+) T cell responses through TLR4 ligation. *Scientific reports*. 2016;6:25064.
5. de Rond L, Schure RM, Ozturk K, Berbers G, Sanders E, van Twillert I et al. Identification of pertussis-specific effector memory T cells in preschool children. *Clinical and vaccine immunology: CVI*. 2015;22(5):561–9.
6. van Twillert I, Bonacic Marinovic AA, van Gaans-van den Brink JA, Kuipers B, Berbers GA, van der Maas NA et al. The use of innovative two-component cluster analysis and serodiagnostic cut-off methods to estimate prevalence of pertussis reinfections. *PloS one*. 2016;11(2):e0148507.
7. van Twillert I, Han WG, van Els CA. Waning and aging of cellular immunity to Bordetella pertussis. *Pathogens and disease*. 2015;73(8):ftv071.
8. Brummelman J, Wilk MM, Han WG, van Els CA, Mills KH. Roads to the development of improved pertussis vaccines paved by immunology. *Pathogens and disease*. 2015;73(8):ftv067.
9. Brummelman J. Improving pertussis vaccination: Central role of CD4 T cell programming [PhD thesis]: University Utrecht; 28th April 2016.
10. Han WG, Hodemaekers HM, Nagarajah B, Poelen MM, Helm K, Janssen R et al. Association of vitamin D receptor polymorphism with susceptibility to symptomatic pertussis. *PloS one*. 2016;11(2):e0149576.
11. McDonald SA, Teunis P, van der Maas N, de Greeff S, De Melker H, Kretzschmar ME. An evidence synthesis approach to estimating the incidence of symptomatic pertussis infection in the Netherlands, 2005–2011. *BMC Infect Dis*. 2015;15:588.
12. van Gent M, Heuvelman CJ, van der Heide HG, Hallander HO, Advani A, Guiso N et al. Analysis of Bordetella pertussis clinical isolates circulating in European countries during the period 1998–2012. *Eur J Clin Microbiol Infect Dis*. 2015 Apr;34 (4): 821–30.

13. Mooi FR, Zeddeman A, Gent MV. The pertussis problem: Classical epidemiology and strain characterization should go hand in hand. *J Pediatr (Rio J)*. 2015 Jul–Aug; 91 (4):315–7.
14. Bart MJ, van der Heide HG, Zeddeman A, Heuvelman K, van Gent M, Mooi FR. Complete genome sequences of 11 *Bordetella pertussis* strains representing the pandemic ptxP3 lineage. *Genome Announc*. 2015 Nov 25; 3(6).

Pneumococcal disease

1. Wyllie AL, Wijmenga-Monsuur AJ, van Houten MA, Bosch AA, Groot JA, van Engelsdorp Gastelaars J et al. Molecular surveillance of nasopharyngeal carriage of *Streptococcus pneumoniae* in children vaccinated with conjugated polysaccharide pneumococcal vaccines. *Scientific reports*. 2016;6:23809.
2. Wijmenga-Monsuur AJ, van Westen E, Knol MJ, Jongerius RM, Zancolli M, Goldblatt D et al. Direct comparison of immunogenicity induced by 10- or 13-valent pneumococcal conjugate vaccine around the 11-month booster in Dutch infants. *PLoS one*. 2015;10(12):e0144739.
3. Wijmenga-Monsuur AJ, van Westen E, Knol MJ, Jongerius RMC, Zancolli M, Goldblatt D et al. Correction: Direct comparison of immunogenicity induced by a booster dose of pneumococcal conjugate vaccines Synflorix® or Prevenar-13® in infants. *PLoS One*. 2016 May 11;11(5):e0155088.
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5. Bosch AA, van Houten MA, Bruin JP, Wijmenga-Monsuur AJ, Trzciński K, Bogaert D et al. Nasopharyngeal carriage of *Streptococcus pneumoniae* and other bacteria in the 7th year after implementation of the pneumococcal conjugate vaccine in the Netherlands. *Vaccine*. 2016 Jan 20;34(4):531–9.
6. Prins-van Ginkel AC, Berbers GA, Grundeken LH, Tcherniaeva I, Wittenberns JJ, Elberse K, Mollema L, de Melker HE, Knol MJ. Dynamics and determinants of pneumococcal antibodies specific against 13 vaccine serotypes in the pre-vaccination era. *PLoS One*. 2016 Jan 21;11(1):e0147437.
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14. Verhagen LM, Rivera-Olivero IA, Hermesen M, Sisco MC, Maes M, del Nogal B, Bogaert D et al. Immunogenicity of the 13-valent pneumococcal conjugate vaccine and nasopharyngeal colonization in Warao Amerindian children in Venezuela. Accepted by *European Respiratory Journal*.

Poliomyelitis

1. Duizer E, Rutjes S, de Roda Husman AM, Schijven J. Risk assessment, risk management and risk-based monitoring following a reported accidental release of poliovirus in Belgium, September to November 2014. *Euro Surveill*. 2016;21(11).
2. Benschop KS, van der Avoort HG, Duizer E, Koopmans MP. Antivirals against enteroviruses: A critical review from a public-health perspective. *Antivir Ther*. 2015;20(2):121–30.

Rubella

None

Tetanus

1. van der Maas NAT, Donken R, te Wierik MJM, Swaan CM, Hahne SJM, 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. Accepted for publication in *Emergency Medicine Journal*.

Potential NIP target diseases

Hepatitis A

None

Meningococcal non-serogroup C disease

1. Stoof SP, Rodenburg GD, Knol MJ, Rümke LW, Bovenkerk S, Berbers GA, Spanjaard L, van der Ende A, Sanders EA. Disease burden of invasive meningococcal disease in the Netherlands between June 1999 and June 2011: A subjective role for serogroup and clonal complex. *Clin Infect Dis*. 2015 Oct 15;61(8):1281–92.

Respiratory syncytial virus

None

Rotavirus

1. Pijnacker R, Mughini-Gras L, Vennema H, Duizer E, Pelt Wv. Marked decrease in rotavirus detections among preschool children unvaccinated for rotavirus in the Netherlands, 2014. *Pediatr Infect Dis J*. 2016 Jul;35(7):809–11.

Varicella zoster virus (VZV) infection

1. van Lier A, Lugnér A, Opstelten W, Jochemsen P, Wallinga J, Schellevis F et al. Distribution of health effects and cost-effectiveness of varicella vaccination are shaped by the impact on herpes zoster. *EBioMedicine*. 2015;2(10):1494–9.
2. van Lier A, de Melker H. Nieuw gordelroosvaccin voor ouderen. *Ned Tijdschr Geneeskd*. 2015;159:A9369.
3. van Lier A, Tostmann A, Harmsen IA, de Melker HE, Hautvast JLA, Ruijs WLM. Negative attitude and low intention to vaccinate universally against varicella among public health professionals and parents in the Netherlands: Two internet surveys. *BMC Infect Dis*. 2016;16(1):127.

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

Volksgezondheidszorg.info:

<https://www.volksgezondheidszorg.info/>

Cervical cancer screening programme:

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

Other NIP-related RIVM reports

Vaccinatiegraad Rijksvaccinatieprogramma Nederland, Verslagjaar 2016:

<http://www.rivm.nl/bibliotheek/rapporten/2016-0064.pdf>

Terugblik Rijksvaccinatieprogramma 2015:

<http://www.rivm.nl/bibliotheek/rapporten/2016-0029.pdf>

Adverse events in the Netherlands Vaccination Programme, reports in 2010 and Review 1994–2010: <http://www.rivm.nl/bibliotheek/rapporten/2015051004.pdf>

Product information

M-M-RVAXPRO (MMR):

<http://www.rivm.nl/dsresource?objectid=rivmp:183945&type=org&disposition=inline>

Infanrix-IPV (DKTP):

<http://www.rivm.nl/dsresource?objectid=rivmp:60726&type=org&disposition=inline>

Infanrix Hexa (DKTP-Hib-HepB):

<http://www.rivm.nl/dsresource?objectid=rivmp:116776&type=org&disposition=inline>

DTP (DTP):

<http://www.rivm.nl/dsresource?objectid=rivmp:119441&type=org&disposition=inline>

REVAXIS (DTP):

<http://www.rivm.nl/dsresource?objectid=rivmp:315770&type=org&disposition=inline>

Engerix-B Junior (HepB):

<http://www.rivm.nl/dsresource?objectid=rivmp:60837&type=org&disposition=inline>

HBVAXPRO (HepB adults):

<http://www.rivm.nl/dsresource?objectid=rivmp:60857&type=org&disposition=inline>

Act-HIB (Hib):

<http://www.rivm.nl/dsresource?objectid=rivmp:60910&type=org&disposition=inline>

Cervarix (HPV):

<http://www.rivm.nl/dsresource?objectid=rivmp:116768&type=org&disposition=inline>

NeisVac-C (MenC):

<http://www.rivm.nl/dsresource?objectid=rivmp:60983&type=org&disposition=inline>

Synflorix (Pneumokokken):

<http://www.rivm.nl/dsresource?objectid=rivmp:116782&type=org&disposition=inline>

National organisations

General

Ministry of Health, Welfare and Sports:

<http://www.rijksoverheid.nl/onderwerpen/vaccinaties>

Health Council:

<http://www.gezondheidsraad.nl/>

GGD GHOR:

<http://www.ggdghorkennisnet.nl/>

Safety of vaccines

Netherlands Pharmacovigilance Centre Lareb:

<http://www.lareb.nl/>

College ter Beoordeling van Geneesmiddelen (CBG):

<http://www.cbg-meb.nl/>

Data sources

Statistics Netherlands (CBS):

<http://www.cbs.nl/>

Dutch Hospital Data (DHD):

<https://www.dhd.nl/>

Nederlands instituut voor onderzoek van de gezondheidszorg (NIVEL):

<http://www.nivel.nl/>

Nederlands Referentielaboratorium voor Bacteriële Meningitis (NRBM):

<https://www.amc.nl/web/Het-AMC/Afdelingen/Medische-afdelingen/Medische-Microbiologie/Onderafdelingen/Het-Nederlands-Referentielaboratorium-voor-Bacteriele-Meningitis.htm>

Integrated Primary Care Information (IPCI):

<http://www.ipci.nl/>

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/nwkv>

International organisations

World Health Organization (WHO):

<http://www.who.int/en/>

World Health Organization (WHO) Europe:

<http://www.euro.who.int/en/home>

European Centre for Disease Prevention and Control (ECDC):

<http://ecdc.europa.eu/en/>

Centers for Disease Control and Prevention (CDC):

<http://www.cdc.gov/>

ClinicalTrials.gov:

<https://clinicaltrials.gov/>

Advisory Committees

Joint Committee on Vaccination and Immunisation (JCVI):

<https://www.gov.uk/government/groups/joint-committee-on-vaccination-and-immunisation>

Advisory Committee on Immunization Practices (ACIP):

<http://www.cdc.gov/vaccines/acip/>

Standing Committee on Vaccination (STIKO):

http://www.rki.de/EN/Content/Prevention/Vaccination/Vaccination_node.html

Safety of vaccines

European Medicines Agency (EMA):

<http://www.ema.europa.eu/ema/>

U.S. Food and Drug Administration (FDA):

<http://www.fda.gov/>

International 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/>

Communication platforms

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

Vaccination of risk groups

Influenza vaccination

RIVM website on Influenza vaccination:
<http://www.rivm.nl/Onderwerpen/G/Griep/Griep prik>

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

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

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

Tuberculosis

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

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

Nationaal plan tuberculosebestrijding 2011–2015:
<http://www.rivm.nl/bibliotheek/rapporten/215081001.pdf>

Traveller vaccination

Landelijk Coördinatiecentrum Reizigersadviesing:
<http://www.lcr.nl/Vaccinaties>

Erratum

Datum: 06-12-2016
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Surveillance and developments in 2015-2016

Fouten:

In de Publiekssamenvatting staat in de eerste zin een onjuist aantal vaccinaties vermeld, namelijk 1.547.000. Dit moet zijn 2.160.000.

The first sentence of the Synopsis contains an incorrect total number of vaccinations, namely 1,547,000. This should be 2,160,000.

Chapter 1 paragraph 1.1.2 contains an incorrect total number of vaccine doses, namely 1,547,000. This should be 2,160,000.

Projectleider:

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