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The National Immunisation Programme in the Netherlands

Developments in 2009

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Abstract

The National Immunisation Programme in the Netherlands
Developments in 2009

This report gives an update of data on pathogen, epidemiology and adverse events after vaccination in 2008 and the first part of 2009 with regard to diseases included in the current National Immunisation Programme (NIP) and for (potential) new target diseases for which a vaccine is available.

As a result of the high national vaccination coverage in general, the number of cases of many of the diseases currently covered by the NIP were low in 2008 and 2009. A substantial reduction of severe pneumococcal disease was observed among age groups targeted for pneumococcal vaccination. Despite a somewhat lower incidence of hepatitis B in 2008 compared to 2007, circulation among man having sex with man (MSM) is ongoing. Pertussis occurs regularly with every three years an epidemic. The incidence among adults is increasing but the morbidity remains highest among unvaccinated infants. The measles epidemic of 2008 affecting mostly unvaccinated antroposofic people ended by 2009. In the catch-up campaign for HPV vaccination (starting in March 2009 for girls born in 1993-1996), coverage amounted to 50% for the first dose.

The incidence of rotavirus among young children was highest in 2008 since 2000, while the incidence of chickenpox in 2008 was rather low. Furthermore, vaccination of elderly (70+) against herpes zoster may be cost-effective. These data should be used in the advice to the minister regarding potential inclusion into the NIP.

Key words:
National Immunisation Programme, rotavirus, varicella zoster, HPV, meningococcal B disease

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Rapport in het kort

Het Rijksvaccinatieprogramma in Nederland
Ontwikkelingen in 2009

Dit rapport geeft een overzicht van het voorkomen van verwekkers van ziekten uit het Rijksvaccinatieprogramma (RVP), de epidemiologie en bijwerkingen na vaccinatie in 2009. Hetzelfde geldt voor ontwikkelingen over nieuwe vaccins die in de toekomst eventueel in het RVP worden opgenomen.

Net als in voorgaande jaren is in 2008 en 2009 het aantal gevallen van de meeste ziekten uit het RVP laag. Dat komt door de hoge vaccinatiegraad in Nederland. In deze jaren nam het aantal gevallen van ernstige aandoeningen door pneumokokken die zijn waargenomen bij kinderen die voor vaccinatie in aanmerking kwamen in belangrijke mate af. In 2008 nam hepatitis B licht af, wel komt deze aandoening veelvuldig voor bij mannen die sex hebben met mannen. Kinkhoest komt regelmatig voor, met om ongeveer iedere drie jaar een epidemie. Kinkhoest neemt toe onder volwassenen, maar verloopt het ernstigst bij ongevaccineerde kinderen. De mazelenepidemie van 2008, voornamelijk onder ongevaccineerde antroposofen, eindigde begin 2009. Het opkomstpercentage tijdens de eerste ronde van de inhaalcampagne van de vaccinatie tegen baarmoederhalskanker (HPV, gestart in maart 2009 voor meisjes die in de jaren 1993 tot en met 1996 zijn geboren) was 50 procent.

Het aantal gevallen rotavirus was in 2008 het hoogst sinds 2000. Voor waterpokken was het aantal gevallen in 2008 laag. Tot slot is vaccinatie van ouderen (70-plus) tegen gordelroos mogelijk kosteneffectief. Deze gegevens zullen meegenomen kunnen worden in het advies aan de minister om vaccinatie tegen deze drie ziekten eventueel op te nemen in het RVP.

Trefwoorden:
Rijksvaccinatieprogramma, rotavirus, varicella zoster, HPV, meningokokken B

Preface

This report gives an overview of the developments in 2009 for the diseases included in the current National Immunisation Programme (NIP): diphtheria, pertussis, tetanus, poliomyelitis, *Haemophilus influenzae* serotype b (Hib) disease, mumps, measles, rubella, meningococcal serogroup C disease, hepatitis B (risk groups only), pneumococcal disease and Human papillomavirus (HPV) infection. Furthermore, surveillance data with regard to (potential) new target diseases for which a vaccine is available, are described: rotavirus infection and varicella zoster virus (VZV) infection. In addition meningococcal serogroup B disease is included in the report because of the close relationship of data collected for meningococcal serogroup C disease.

The report is structured as follows. In chapter 1 a brief introduction is provided on the changes in the NIP during 2009 and recent measurements of vaccine coverage. Chapter 2 focuses on current target diseases of the NIP. For each disease, surveillance data on pathogen, epidemiology and adverse events after vaccination are presented. The amount of new surveillance data that has become available in 2009 with respect to a certain disease is reflected in the size of the section concerned. The NIP could be extended in the future with new target diseases, which are discussed in chapter 3. In the extensive summary the disease-specific highlights are described since the previous report in 2008. The information provided in this report may inform the Health Council and Ministry of Health, Welfare and Sport on relevant developments with respect to vaccine preventable diseases.

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List of abbreviations

ACA	Acute Cerebellar Ataxia
ACIP	Advisory Committee on Immunisation Practices
AEFI	Adverse Events Following Immunisation
AFP	Acute Flaccid Paralysis
aP	acellular Pertussis
CI	Confidence Interval
CIb	Centre for Infectious Disease Control, the Netherlands
c-VDPV	circulating Vaccine-Derived Polio viruses
DTP	Combination of Diphtheria, Tetanus, and Pertussis vaccines
ECDC	European Centre for Disease Control and Prevention
ELEK	
ELISA	Enzyme-Linked ImmunoSorbent Assay
FHA	Filamentous Haemagglutinin
GP	General Practitioner
GSK	Glaxo Smith Kline
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
Hib	*Haemophilus influenzae* type b
HPV	Human Papillomavirus
ICD	International Classification of Diseases
IPCI	Integrated Primary Care Information
IPD	Invasive Pneumococcal Disease
IPV	Inactivated Polio Vaccine
iVDPV	VDPVs that can be attributed to an immunocompromised person
Men C	Meningococcal C
MMR	Combination of Measles, Mumps, and Rubella vaccines
MMRV	Combination of Measles, Mumps, Rubella, and Varicella vaccines
mOPV	monovalent Oral Polio Vaccine
MS	Multiple Sclerosis
MSM	Men having Sex with Men
NID	National Immunisation Day
NIP	National Immunisation Programme
NIVEL	Netherlands Institute for Health Services Research
NPL	National Polio Laboratory
NPG	National Influenza Prevention Programme
NRBM	Netherlands Reference laboratory for Bacterial Meningitis
NVI	Netherlands Vaccine Institute
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccine
PIENTER	Assessing Immunisation Effect To Evaluate the NIP
Pneumo	Pneumococcal vaccination
Prn	Pertactin
QALY	Quality Adjusted Life Years
OPV	Oral Polio Vaccine
RIVM	National Institute for Public Health and the Environment, the Netherlands
SP-MSD	Sanofi Pasteur MSD

STI	Sexually Transmitted Infections
tOPV	trivalent oral polio vaccine
VDPV	Vaccine Derived-Polio Virus
VZV	Varicella Zoster Virus
WHO	World Health Organisation
WPV	Wild Polio virus

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Executive summary

In the present report, we describe surveillance data with respect to vaccine-preventable diseases in the period 2000 to 2008/2009 that are included in the National Immunisation Programme (NIP) in the Netherlands. Furthermore, surveillance data with regard to (potential) new target diseases for which a vaccine is available, are described: rotavirus infection and varicella zoster virus (VZV) infection. In addition, meningococcal serogroup B disease is included in the report because of the close relationship of data collected for meningococcal serogroup C disease. At present children in the Netherlands are vaccinated at 2, 3, 4 and 11 months with DTaP-IPV-Hib (combination of diphteria, tetanus, acellular pertussis, inactivated polio, and *Haemophilus Influenzae* type b vaccines) in one limb and 7-valent conjugated pneumococcal vaccine in the other limb. Furthermore, children for whom at least one of the parents originates from a hepatitis B endemic country are vaccinated with a hexavalent combination vaccine including DTaP-IPV-Hib and Hepatitis B. At 14 months of age children are offered meningococcal C conjugate vaccine and measles-mumps-rubella-vaccine (MMR). Furthermore, at 4 and 9 years vaccination is offered against DTaP-IPV and DT-IPV and MMR, respectively. In 2009, a catch-up programme for Human papillomavirus-vaccination (HPV) has started for girls born in 1993 to 1996. Vaccination of the first NIP cohort (i.e. girls born between 1 January 1997 and 31 August 1997) will start in April 2010.

At national level, the average vaccination percentages in 2009 for all vaccinations included in the NIP were around 95%. In spite of the extra vaccination against pneumococcal disease, the average vaccination percentages were in general somewhat higher than in 2008. For infants, the percentage for MMR, Hib and meningococcal C disease vaccinations was 96%, for DTaP-IPV, 95% and for pneumococcal disease, 94%. The vaccination coverage for hepatitis B offered to children of whom at least one parent was born in a country where hepatitis B is moderately or highly endemic, was somewhat lower and amounted to 92.9%.
A short summary or highlights in 2009 are presented below for each of the diseases included in the report.

Diphteria
No diphtheria cases were observed in 2009.

Pertussis
The emergence of more virulent strains and of escape variants which do not produce two important components of pertussis vaccines, pertussis toxin and pertactin, are worrying developments and underline the importance of strain surveillance and the need to improve pertussis vaccines.
The highest morbidity and mortality due to pertussis is found in 0-6 month old infants who are too young to be fully vaccinated. A study on the direct costs of pertussis carried out by the National Institute for Public Health and the Environment (RIVM) suggests that cocooning will be more attractive from an economical point of view than repetitive adolescent and adult vaccination.
Higher frequency of (severe) local reactions after the booster vaccination with a combined diphtheria, tetanus, and acellular pertussis vaccine (dTaP) at 4 years of age was observed for those cohorts that received acellular pertussis vaccine in the primary series.

Tetanus
One case of tetanus was notified in 2009 (data until week 48) who was incompletely vaccinated. The national seroprevalence study Pienter 2 showed that overall the Dutch population is very well protected

against tetanus. However, individuals born before the NIP introduction, first generation migrants from non-Western countries and individuals from protestant denominations remained at risk.

Poliomyelitis
The last case of poliomyelitis in the Netherlands was observed in 1993. In 2009 finally successes in fighting poliovirus circulation in Nigeria: effective nationwide NIDs with tOPV and localized use of mOPV 1 have reduced circulation of all three serotype viruses (WPV1 and WPV3, as well as VDPV 2) dramatically. Especially for polio 1, for the first time in history, a period of at least 4 months without cases was reported, with good surveillance indicators.

***Haemophilus influenzae* serotype b (Hib) disease**
The incidence of Hib disease remained at a low level in 2009.

Measles
In 2008 an outbreak of around 100 cases of measles occurred mainly in unvaccinated individuals with anthroposophic beliefs. In 2009, the incidence of measles was low, but included a fatal case in a 38 year old unvaccinated man.

Mumps
The genotype D mumps outbreak that started in 2007 mainly among unvaccinated orthodox reformed individuals stopped in the beginning of 2009.

Rubella
The incidence of rubella in 2008 and 2009 was very low.

Meningococcal serogroup C and B disease
Only very few meningococcal serogroup C disease cases were observed in 2009. Since the introduction of meningococcal C vaccination in 2002 no vaccine failures have been observed. One of the first remarkable results from the Pienter 2 project is that the large-scale introduction of meningococcal C conjugate vaccine has led to improved protection on the long-term in adolescents showing a gradual increase in the meningococcal C polysaccharide-specific antibody levels with age. However, but antibody persistence after vaccination of infants with a single-dose schedule at 14 months may be insufficient to ensure long term protection in the future.
In 2009 the incidence of serogroup B disease further declined.

Hepatitis B
The incidence of HBV infection in 2008 was lower than in 2007. However, transmission among MSM is ongoing.

Pneumococcal disease
Three years after introduction of PCV-7 a substantial reduction of vaccine-type IPD was observed in vaccinated cohorts, however the number of cases with IPD due to non-vaccine type pneumococci increased. Although only little time has passed, there is evidence for some herd-immunity in unvaccinated cohorts.

HPV
In 2009 50% of 13-16 year olds girls were vaccinated in the catch-up mass campaign of HPV 16/18 vaccination. Introduction of routine HPV-vaccination in the NIP for 12-year olds were postponed because of the H1N1 epidemic. The monitoring programme of HPV vaccination started alongside introduction. During intensive surveillance of safety of the HPV campaign, no unexpected or serious

side effects with a causal relationship with the vaccination occurred following administration of 192,119 doses. In accordance with data from foreign studies, side effects may be common, but are in general mild and short-lived.

Rotavirus
In 2008, rotavirus with genotype G1P[8] was the most detected rotavirus type in the Netherlands. Furthermore, although children aged younger than 5 years remained most vulnerable for rotavirus, an increase was observed in the proportion of elderly becoming infected.

VZV infection
The estimated incidence of general practitioner consultations for chickenpox was somewhat lower in 2008 which is in accordance with inter-epidemic cycle between 2 and 5 years. In 2009 the potential effects of programmatic herpes zoster vaccination of elderly was assessed by using an evaluation model for introducing a new vaccine in the Dutch National Immunisation Programme. The cost-effectiveness ratio for introduction of the vaccine for 70-year olds was estimated to be just above the socially accepted threshold in the Netherlands of €20,000 per QALY. The prevented disease burden is in particular related to a decrease in postherpetic neuralgia. Due to limited vaccine efficacy a considerable part of the disease burden caused by herpes zoster will remain, even with optimal acceptance of programmatic vaccination.

Conclusion
Most of the target diseases are under control as a result of the high vaccination uptake for many years. For the new introduced HPV vaccine it will be a challenge to increase coverage over the years to come. For pertussis other vaccination strategies including cocooning are important to reduce the disease burden among young infants. Data on cost effectiveness (herpes zoster) and disease burden (VZV infection) and disease incidence and circulation of strains (rotavirus) that became available in 2009 need consideration in the decision-making process with regard to desirability of routine vaccination.

1 Introduction

1.1 Background

Vaccination of a large part of the population in the Netherlands against diphtheria, tetanus and pertussis (DTP) was introduced in 1952. The National Immunisation Programme (NIP) was started in 1957 offering DTP and inactivated polio vaccination (IPV) in a programmatic approach to all children born from 1945 onwards. Nowadays also vaccination against measles, mumps, rubella (MMR), *Haemophilus influenzae* type b (Hib), meningococcal C disease (Men C), pneumococcal disease and hepatitis B (for high-risk groups only) is included in the programme. The vaccines that are currently administered and the age of administration are specified in Table 1. Vaccinations within the NIP in the Netherlands are administered to the target population free of charge and on a voluntary basis. In addition to diseases included in the NIP, influenza vaccination is offered through the National Influenza Prevention Programme (NPG) currently to individuals aged 60 years and over (65 years and over before October 2008), and individuals otherwise considered at increased risk of morbidity and mortality following an influenza infection in the Dutch population. Furthermore, vaccination against tuberculosis is offered to children of immigrants from high prevalence countries. For developments on influenza and tuberculosis we refer to reports of the Health Council and the KNCV Tuberculosis Foundation.[1-3]

Table 1 Vaccination schedule of the NIP from 2006 to 2009*

Age	Injection 1	Injection 1 (risk groups only)[a]	Injection 2
At birth (<48 hours)		HBV [b]	
2 months	DTaP-IPV/Hib	DTaP-HBV-IPV/Hib	Pneumo
3 months	DTaP-IPV/Hib	DTaP-HBV-IPV/Hib	Pneumo
4 months	DTaP-IPV/Hib	DTaP-HBV-IPV/Hib	Pneumo
11 months	DTaP-IPV/Hib	DTaP-HBV-IPV/Hib	Pneumo
14 months	MMR	MMR	Men C
4 years	DTaP-IPV	DTaP-IPV	
9 years	DT-IPV	DT-IPV	MMR

* Introduction of Human papillomavirus (HPV) vaccination within the NIP will start in 2010 (see section 1.2)

[a] Only for children of whom at least one parent was born in a country where hepatitis B is moderately or highly endemic and children of whom the mother tested positive for Hepatitis B surface Antigen (HBsAg).

[b] Only for children of whom the mother tested positive for HBsAg.

Source: http://www.rivm.nl/rvp/rijks_vp/vac_schema/

1.2 Changes in the NIP in 2009

On the 1st of April 2008, the Health Council advised the minister of Health, Welfare and Sports to include Human papillomavirus (HPV) vaccination for 12-year old girls in the NIP and to conduct a catch-up programme for girls aged 13-16 years.[4] The minister decided, based on the results of the tender of the two vaccines, to include HPV vaccination in the NIP and a catch-up programme for those

born in 1993 to 1996, which started in March 2009. The first NIP cohort (i.e. those born between 1 January 1997 and 31 August 1997) was originally planned to be offered vaccination after the summer holidays of 2009. However, due to the deterrent effect of the new pandemic Influenza A (H1N1), and the foreseen logistic pressure by the Municipal Health Services when vaccination against this flue was performed, the regular HPV vaccination campaign will start not earlier than spring 2010.

1.3 Vaccination coverage

The national immunisation coverage in the Netherlands has been excellent since the start of the NIP. For 2009, the average vaccination percentages for all vaccinations included in the NIP were considerably above the lower limit of 90% for 2009.[5] In spite of the extra vaccination against pneumococcal disease, the average vaccination percentages were in general somewhat higher than in 2008 (see Table 2). For babies, the percentage for MMR, Hib and meningococcal C disease vaccinations was 96 percent, for DTaP-IPV, 95% and for pneumococcal disease, 94%. The vaccination coverage for hepatitis B still requires extra attention because it is relatively low. Children who are infected with this virus at a young age have a higher risk of becoming a carrier of this virus and of contracting liver disorders at long term. This vaccination is only offered to children in risk groups.

Table 2 Vaccination coverage per vaccine for age cohorts of newborns, toddlers, and school-children in 2006-2009

Vaccination coverage (%)											
		Newborns*					Toddlers*		School-children*		
Report-year	Cohort	DTaP-IPV	Hib	Pneu **	Men C	MMR	Cohort	DTaP-IPV	Cohort	DT-IPV	MMR ***
2006	2003	94.3	95.4		94.8	95.4	2000	92.5	1995	93.0	92.9
2007	2004	94.0	95.0		95.6	95.9	2001	92.1	1996	92.5	92.5
2008	2005	94.5	95.1		95.9	96.0	2002	91.5	1997	92.6	92.5
2009	2006	**95.2**	**95.9**	**94.4**	**96.0**	**96.2**	2003	**91.9**	1998	**93.5**	**93.0**

Vaccination coverage (%)			
		Newborns*	
Report-year	Cohort	HBV	HBV[a]
2006	2003	86.7	90.3
2007	2004	88.7	92.3
2008	2005	90.7	97.4
2009	2006	**92.9**	**95.6**

* Vaccination coverage is assessed on age of two years (newborns), five years (toddlers), and ten years (school-children)

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

*** Two MMR vaccination (in the past 'at least one MMR vaccination' was reported)

[a] Children of whom the mother tested positive for HBsAg.

2 Current National Immunisation Programme

2.1 Diphtheria

F. Reubsaet, G. Berbers, F.R. Mooi, N.A.T. van der Maas

Pathogen and disease

Epidemiology

In the period 2008 to week 32 in 2009 no cases of diphtheria have been notified.[6 7] In the same period two isolates were send for to the National Institute for Public Health and the Environment. In a nose isolate *C. diphtheriae* Belphanti was identified and *Corynebacterium diphtheriae* Mitis/Intermedius (together with *Staphylococcus aureus* and *Streptococcus pyogenes*) was isolated from erysipelas on a patient's leg, who had visited Australia an the Philippines. Both strains were negative in the toxin PCR and ELEK-test. These results are comparable with earlier years (see Table 3)

Table 3 Diphteria strains reported in the Netherlands

Year	Age (years)	Sex	Source	Diagnosis	Tox-PCR	Elek-test
2000	68	f	Nose	*Corynebacterium diphtheriae* Belfanti	neg	neg
2001	49	m	Nose	*Corynebacterium diphtheriae* Belfanti	neg	neg
2001	58	m	Throat	*Corynebacterium ulcerans*	+	+
2002	78	m	Bronchial wash	*Corynebacterium diphtheriae*	neg	neg
2003	69	m	Throat	*Corynebacterium diphtheriae*	neg	neg
2004	-	f	Rhesus-monkey	*Corynebacterium ulcerans*	+	+
2005	53	f	Sputum	*Corynebacterium diptheriae* Belfanti	neg	neg
2007	26	f	lymphangitis Digit	*Corynebacterium ulcerans*	+	+
2008	13	m	Nose	*Corynebacterium diphtheriae* Belfanti	neg	neg
2008	67	f	Erysipelas	*Corynebacterium diphtheriae* Mitis/Intermedius	neg	neg

Adverse events

See section 2.2.

2.2 Pertussis

F.R. Mooi, S.C. de Greeff, G.A.M. Berbers, N.A.T. van der Maas

Recent changes in the NIP

In 2009 the following pertussis vaccines were used (T. de Graaf, NVI, personal communication): Infants: Pediacel (SPMSD), Infanrix-IPV-Hib (GSK). Infanrix Hexa (GSK) was used for infants at risk for Hepatitis B) and for the preschool booster Infanrix-IPV (GSK).

Pathogen

Strain variation

As observed in previous years, P3 strains predominated in 2009. These strains were found in a frequency of 90% (range 72% to 100%) in the period 2004-2008 and in a frequency of 96% in the period January-July 2009. There is evidence that P3 strains are more virulent than the P1 strains, which predominated in the 1990s, due to a higher production of pertussis toxin.[8] Like the P1 strains, P3 strains show (small) differences in antigenic make up in pertussis toxin and pertactin compared to pertussis vaccines.[9] A notable trend observed in the last two years is the replacement of serotype 3 by serotype 2 strains. Serotype 2 strains increased in frequency from 4% in 2007 to 67% in 2009. Finally, the increase in non-B. pertussis clinical isolates from patients suspected of pertussis should be mentioned. In the period 2004-2008, *B. parapertussis* and *B. holmesii* comprised 3% (range 0-7%) of all clinical Bordetella isolates and this increased six fold to 18% in 2009. The reasons for these changes are not clear. The changes may be an artifact due to increased awareness of non-B. pertussis infections. Or these changes may be related to the replacement of the whole cell pertussis vaccine by an acellular vaccine in 2005. In particular, the less broad immunity induced by acellular vaccines compared to whole cell vaccines may give non-B. pertussis Bordetella species a competitive advantage.[10]

Disease

Epidemiology

Since the sudden upsurge in 1996-1997, the incidence of reported and hospitalised pertussis cases has remained high. Peaks in reported cases were observed every 2-3 years (i.e. in 1999, 2001, 2004 and 2008) (see Figure 1). The largest increase in pertussis was observed in adolescents and adults. Based on notifications until June, the extrapolated incidence in 2009 is lower than in 2007 and 2008.

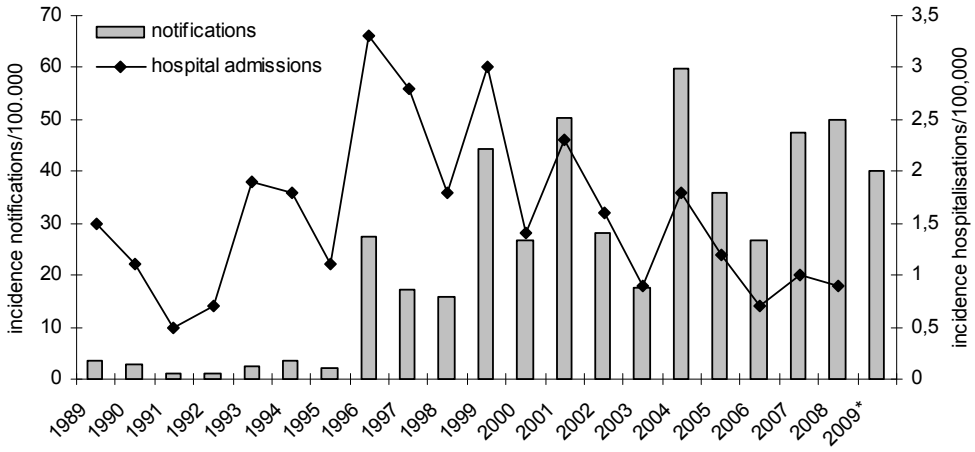

Figure 1 Incidence of pertussis notifications (grey bars) and hospitalisations (line) by year in 1989-July 2009

*** Notifications in 2009 were extrapolated to a whole year. Data for hospitalizations are not yet available for 2009**

The introduction of the preschool booster-vaccination for 4-year-olds with an acellular vaccine in the autumn of 2001 caused a significant decrease in the incidence of pertussis among the targeted population (see Figure 2).

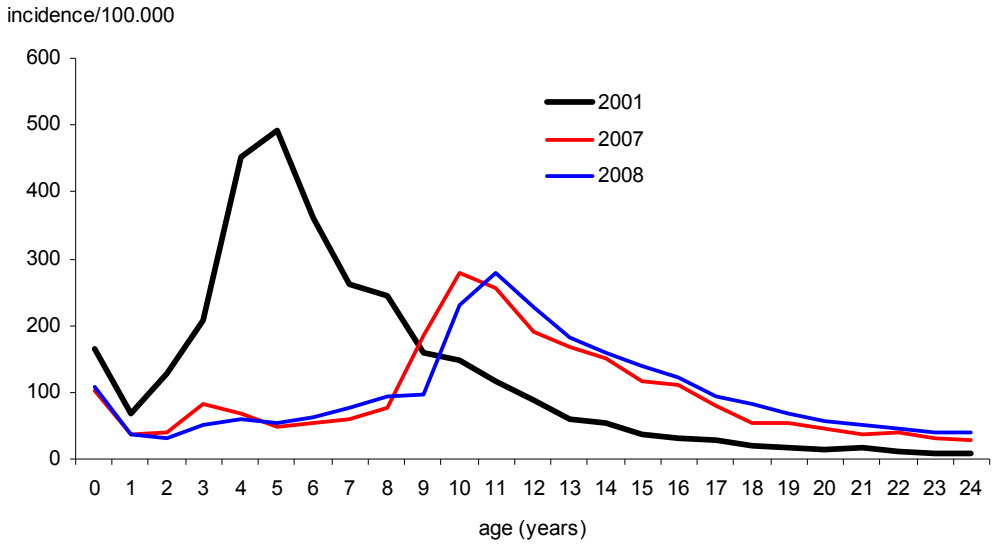

Figure 2 **Age-specific incidence of notified cases in 2001 (before introduction of the preschool booster) and in 2007-2008 (after introduction of the preschool booster)**

Since the replacement of the whole cell vaccine by an acellular vaccine in 2005, the average annual incidence in recently vaccinated children aged 1-3 years (not yet eligible for the preschool booster) is lower than in the beginning of this century when the whole cell vaccine was used (see Figure 3), suggesting an increase in vaccine efficacy. In the same period, the incidence of notifications for pertussis among adolescents and adults increased (see Figure 3).

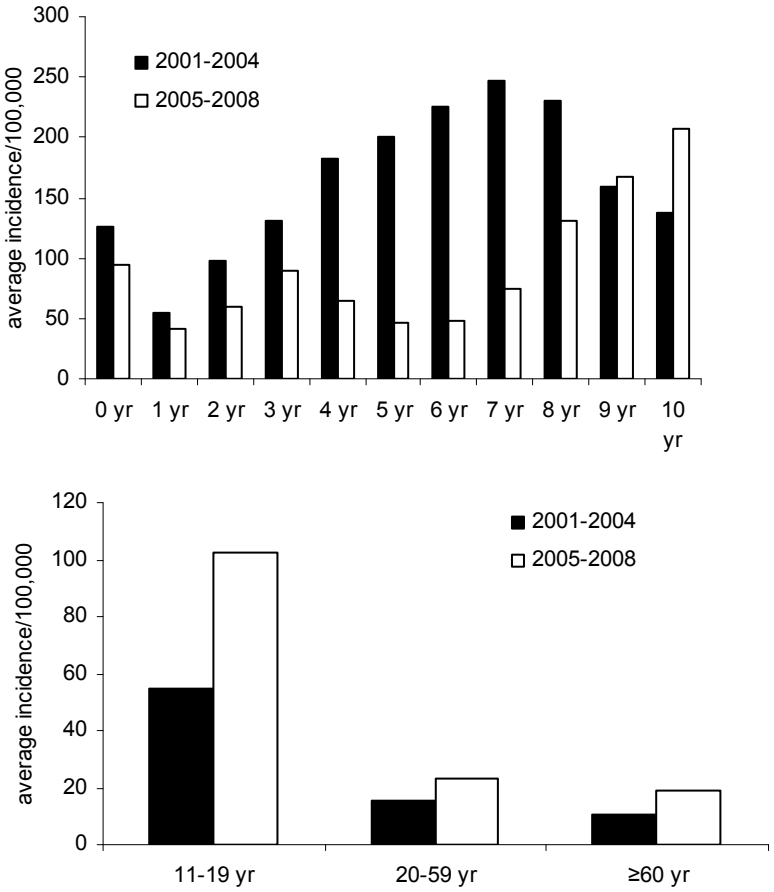

Figure 3 Incidence of notifications for pertussis in children 0-10 years of age (left) and adolescents and adults (right). Average annual incidences in 2001-2004 compared to 2005-2008

Burden of disease
Since 1996, 10 children have died from pertussis: 2 in 1996, 2 in 1997, 1 in 1998, 3 in 1999, 1 in 2004 and 1 in 2006. In 2008 one elderly woman (aged 75-80) died. All deceased children were less than 3 months of age, except for a girl in 2006 who was 11 years old. The girl was asthmatic and mentally and physically handicapped. These conditions may have contributed to the severity of pertussis and her death.

Since 1997 the number of infants <6 months hospitalized for pertussis shows a decreasing trend (Figure 4). Presumably, the transmission from siblings to susceptible infants has been reduced as a result of the preschool booster given since 2001. Since the replacement of the whole cell vaccine by the acellular vaccine in 2005, the incidence of hospitalisations in children aged 6-11 months and 1-3 years reduced with almost 60%. However, in infants less than 6 months of age, a less strong reduction (30%) was observed (see Figure 4; NB logarithmic scale).

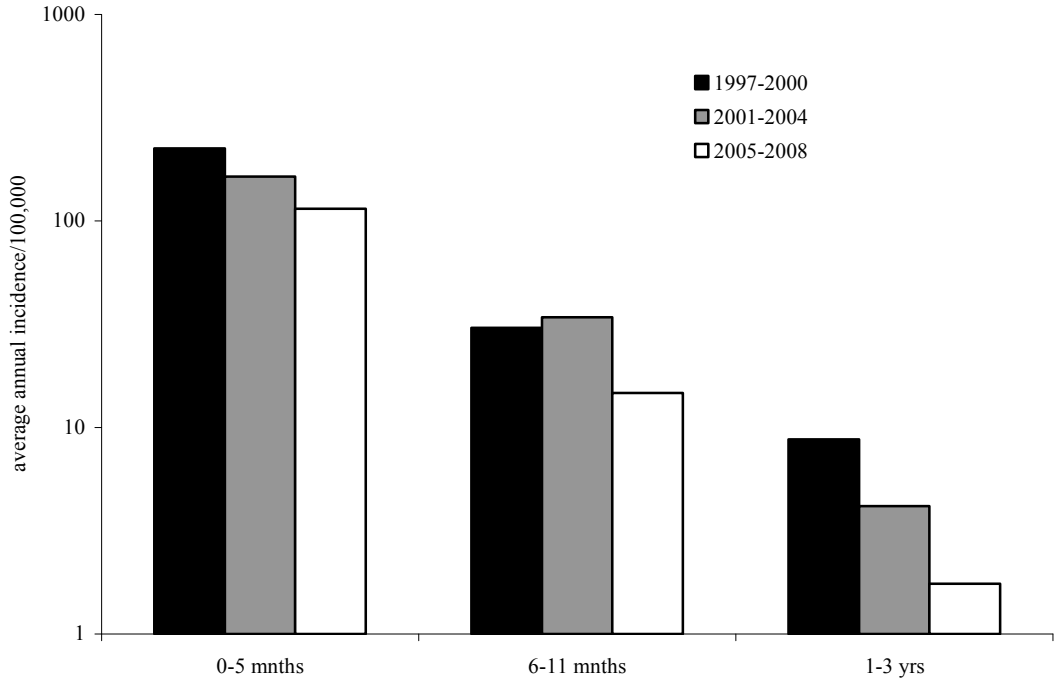

Figure 4 Average annual incidence (on a logscale) of children hospitalized for pertussis by age-group, and per period 1997-2000 (no preschool booster), 2001-2004 (preschool booster given to 4 year olds) and 2005-2008 (acellular vaccine in use)

In 2006-2008 we conducted a population-based, nationwide, prospective study (BINKI-study) to identify which household members infected an infant hospitalized for pertussis. Based on 164 households, we found that after household exposure 53% of 560 household contacts were infected with *B. pertussis* and half of them reported typical pertussis symptoms. Furthermore, we found that the most likely source of infection of the infant was a sibling (41%), mother (38%) or father (17%). Interestingly, within 1-3 years after vaccination with whole-cell or acellular vaccine, a significant percentage of children was again susceptible for typical pertussis. These results show that a considerable part (35-55%) of infant cases with pertussis can be prevented by protection of young parents against pertussis. Furthermore, it emphasizes that current vaccines are not effective enough to prevent typical pertussis in household situations. To reduce the disease burden of pertussis and to prevent transmission, new vaccines that induce longer protection are needed.

Adverse events

The number of reported adverse events following immunisation (AEFI) with dTaP-IPV/Hib in 2008 was 687, which is comparable to the numbers of reports in 2007 and 2006 (664 and 719, respectively).[11 12] However, there was a sharp increase of the amount of reports following dTP-IPV at four years of age (i.e 71 in 2007 versus 298 in 2008) , which are now the most prevalent (24.2%; 95% CI 17.7-34.7) among all reports. The reporting rate for (severe) local reactions after the booster vaccination at this age increased from 0.12 per 1000 vaccinated children in 2007, to 3 per 1000 in the second half year of 2008.[13] Almost all of the children of 2008 had primary series with acellular dTP-IPV-/Hib vaccine, introduced in 2005 in contrast to previous cohorts that had been vaccinated with dT-IPV. Reports following other doses are more or less stable. No new categories of adverse events were revealed.

2.3 Tetanus

S.J.M. Hahné, N.A.T. van der Maas

Pathogen
Strain variation
Tetanus is very rare in the Netherlands, and systematic typing is not performed.

Disease
Epidemiology
Since 2009, tetanus is a notifiable disease in the Netherlands. Up to week 48 of 2009, one person with tetanus meeting the case definition was notified. This concerned a 60 year old man who was incompletely vaccinated (two doses, the last in 2001).
Hospital episode statistics show that during 2008, three individuals were admitted to hospital with a main and/or side diagnosis of tetanus and 24 with a main and/or side diagnosis of neonatal tetanus. In 2005, 2006 and 2007, respectively three, seven and one individuals were admitted with a main and/or side diagnosis of tetanus. In the period of 2000-2004, between 3 and 9 hospital admissions were coded as tetanus. However, these data are not specific, as the clinical symptom of tetany (e.g. due to low calcium) can be reported as tetanus.

During 2009, the results of the national seroprevalence study Pienter 2 became available. Results suggest that overall the Dutch population is very well protected against tetanus: 94.2% (95% C.I. 93.5-94.8) had a tetanus anti-toxin level above the minimal protective value (≥0.01 IU/ml). However, individuals born before the NIP introduction, first generation migrants from non-Western countries above 23 years and individuals from protestant denominations remain at risk for tetanus. Implications for post-exposure prophylaxis remain to be determined.

Adverse events
See section 2.2.

2.4 Poliomyelitis

H.G.A.M. van der Avoort, N.A.T. van der Maas

Pathogen
Since 1996 two surveillance systems are in place in the Netherlands to document the absence of poliovirus circulation in the Netherlands. In close co-operation with 20 virological laboratories covering the whole nation, an enterovirus surveillance system has been set up.
These laboratories report the results from all cell culture tests from stool samples on cell lines on which poliovirus will grow, if present. Isolates and stool samples for which the presence of polio virus is suspected, either because of the clinical picture of the patient or because of properties of isolates found in the laboratory are immediately sent to the National Polio Laboratory (NLP) at RIVM, for further analysis and characterization. Furthermore untyped and untypable enteroviruses are sent to RIVM on a regular basis to exclude the presence of poliovirus. Yearly about 10.000 stool samples are proven to be poliovirus negative. In about 7% of the samples a non-polio-enterovirus is reported.

At 15 locations in the bible belt, at schools with a high percentage of non-vaccinated children and in villages with polio patients during the 1992/3 epidemic, seven times per year a sewage sample is taken and analyzed in the NPL for the presence of poliovirus. This environmental surveillance system allows systematic, anonymous screening for poliovirus circulation among the risk group where the effect of poliovirus infection is most dramatic. Experience around the 1992/3 outbreak has shown that environmental surveillance can herald an upcoming epidemic and can be used to measure its extent.

In a country like the Netherlands that uses IPV for regular vaccination of children in the National Vaccination Programme, detection of polioviruses by enterovirus or environmental surveillance activities is unexpected: Figures 5 and 6 show however that the systems in place in the Netherlands are so sensitive that almost every year one or more Sabin OPV viruses are detected by these systems. The origin of these polioviruses is for most of the cases vaccination of children (adopted or seeking health care in the Netherlands) in a country that still uses OPV for vaccination. As more and more countries are changing to IPV, the number of imported OPV isolations is getting smaller in recent years. On two occasions the isolation of OPV viruses is linked to incidental use of OPV in the Netherlands. In 2000 OPV was given to the Cape Verdian community in the Rotterdam area, in response to a polio 1 outbreak in their home country. Polioviruses were shown to be present in stool samples from five children in Rotterdam hospitalized for non-poliovirus infection related diseases. Furthermore an OPV virus was found in the sewage system one week after OPV vaccination of IPV production staff. In three sewage samples taken at schools in the risk area, OPV virus was proven to be present. The origin of these viruses could not be determined.

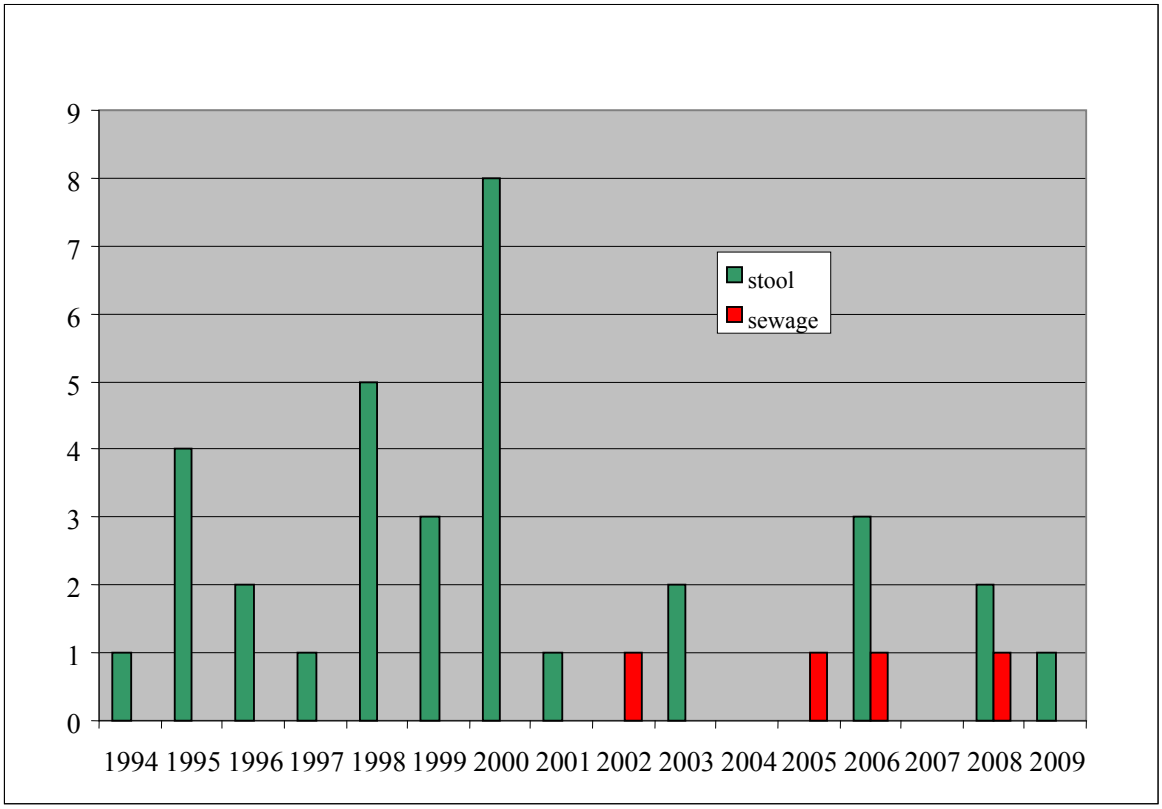

Figure 5 Poliovirus isolates reported in the Netherlands

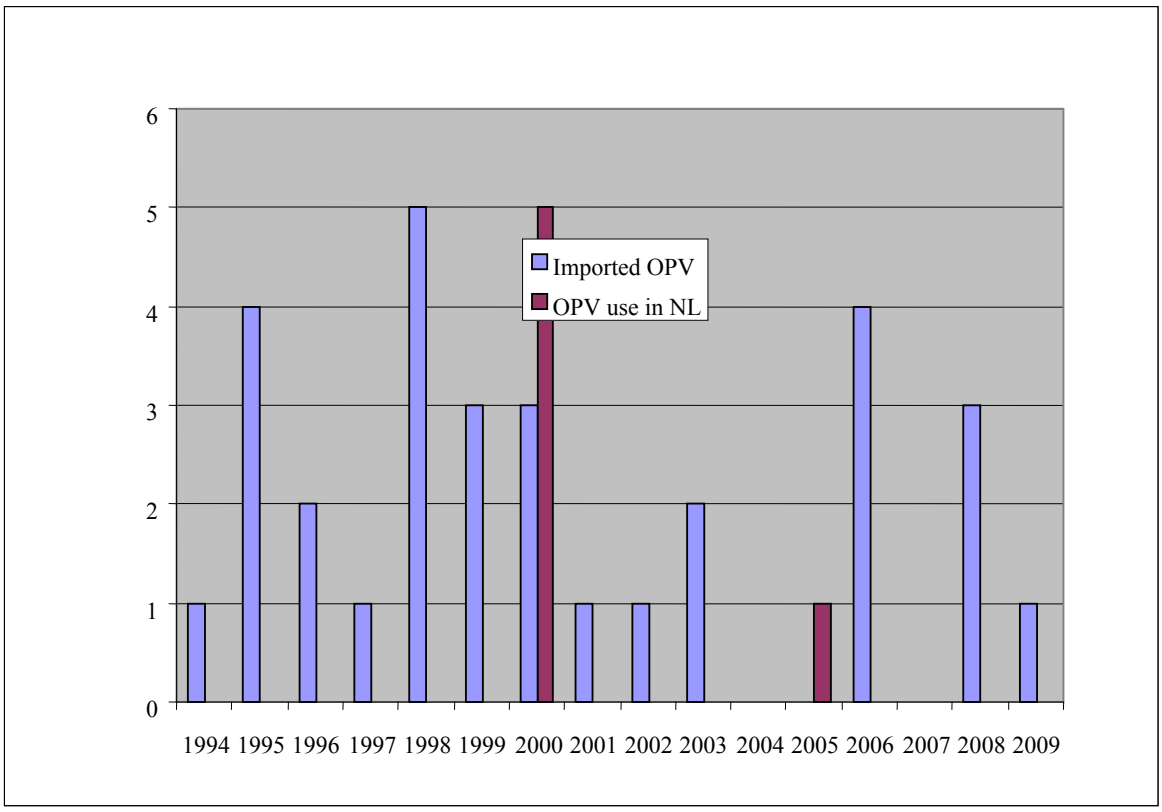

Figure 6 Origin of polioviruses isolated in the Netherlands

In 2009 the polio situation (see Figure 7) has improved dramatically in Nigeria. Good quality national wide NIDs with various vaccines (tOPV, and mOPV1) have lead to a period of more than three months without AFP cases caused by polio 1, and dramatic lower numbers on isolations for type 3 wild polio virus and type 2 cVDPV. Synchronized interventions have stopped or most likely will stop poliovirus circulation in neighbouring countries in 2009.
The situation in the other three polio endemic countries has improved only marginally; political unrest being the most disturbing factor in Pakistan and Afghanistan. Key to success in India is to sustain the intense efforts to close immunisation gaps in young children and migrants - the groups which are currently sustained WPV transmission - particularly in the 100 ‘high-risk’ blocks of western Uttar Pradesh and Bihar.

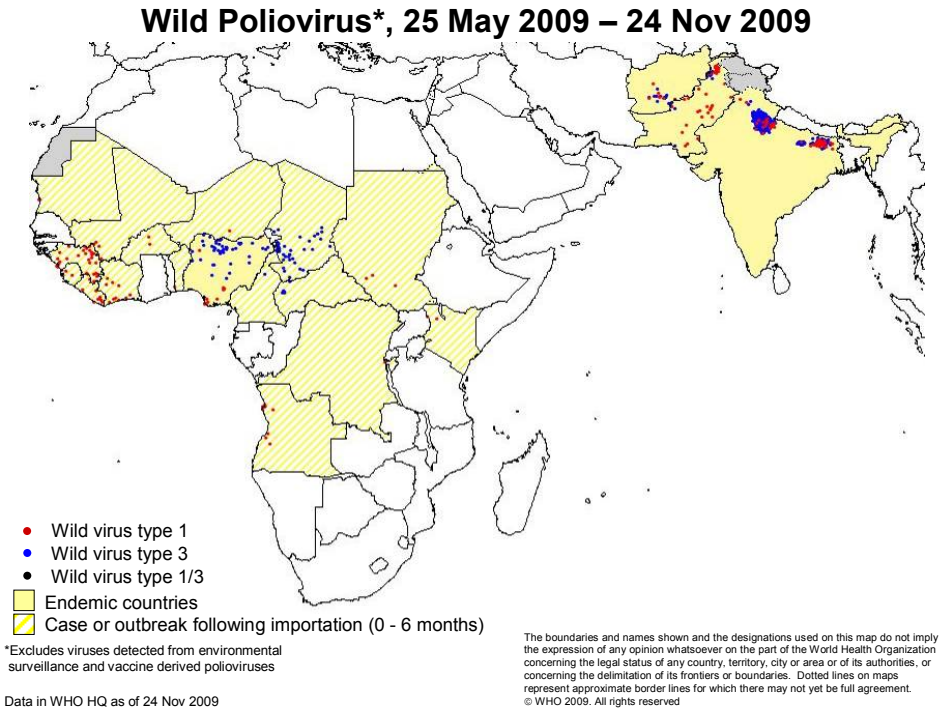

Figure 7 Wild poliovirus infected districts, 25 May 2009 – 24 Nov 2009

Disease
Epidemiology in the Netherlands
The last case of poliomyelitis in the Netherlands occurred in February 1993. This case was the last case of the polio 3 epidemic that struck the unvaccinated community in the Netherlands since September 1992, with 71 cases, two of which died.

Adverse events
See section 2.2.

2.5 *Haemophilus influenzae* serotype b (Hib) disease

L.M. Schouls, S.C. de Greeff, N.A.T. van der Maas

Pathogen
No changes in the composition of the circulating *H. influenzae* population have been observed (see Figure 8).

Disease
Epidemiology
Since the introduction of vaccination in 1993, the number of patients with Hib disease has decreased from 250 cases in 1993 to 12 cases in 1999 (see Figures 8 and 9). However, in 2002-2005 the number of patients with Hib disease increased significantly with a peak of 48 cases in 2004. Since then the

annual number of cases decreased again to approximately 25 cases annually (see Figure 8). In 2008 the number of cases amounted to 27. The reason for the upsurge of cases of invasive Hib disease has remained enigmatic.

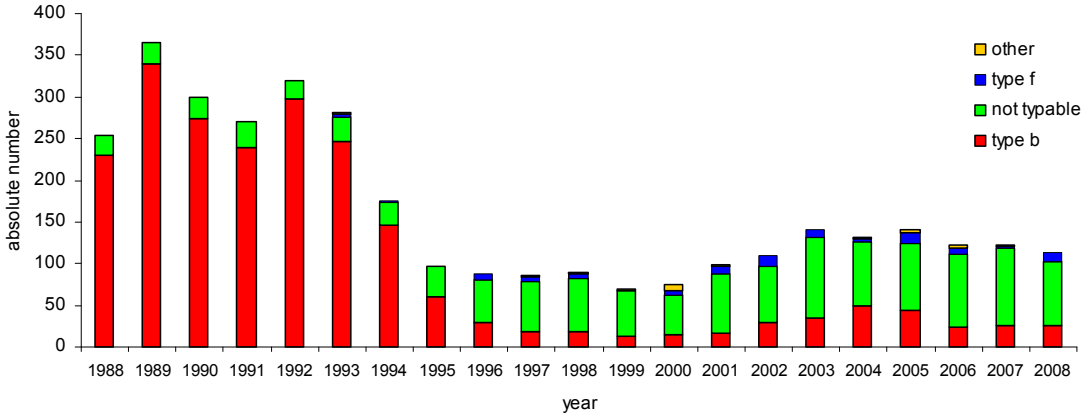

Figure 8 Absolute number of *H. influenzae* isolates by type, 1988-2008

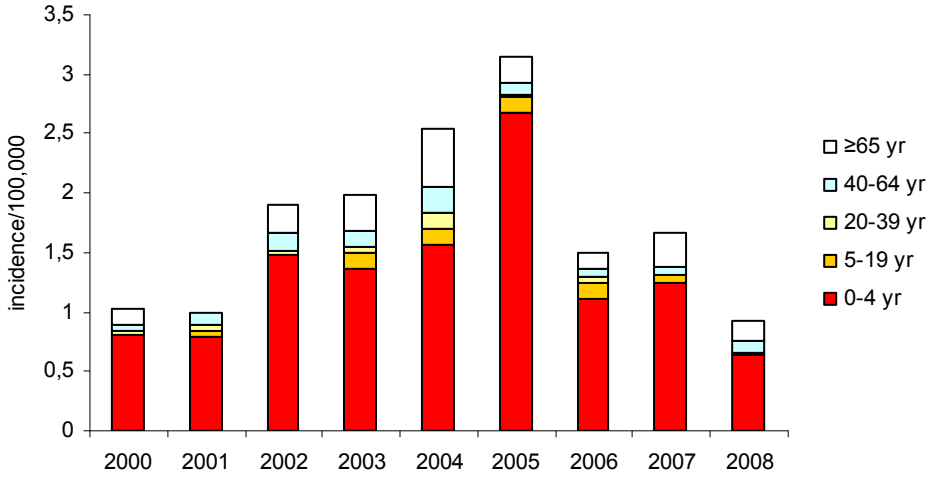

Figure 9 Age specific incidence of patients with invasive Hib disease by year

In the vaccinated cohorts the number of infections due to Hib and the number of vaccine failures showed a peak in 2005 but decreased again the following years (see Figure 10; the annual incidence per 100,000 is shown in Figure 11).

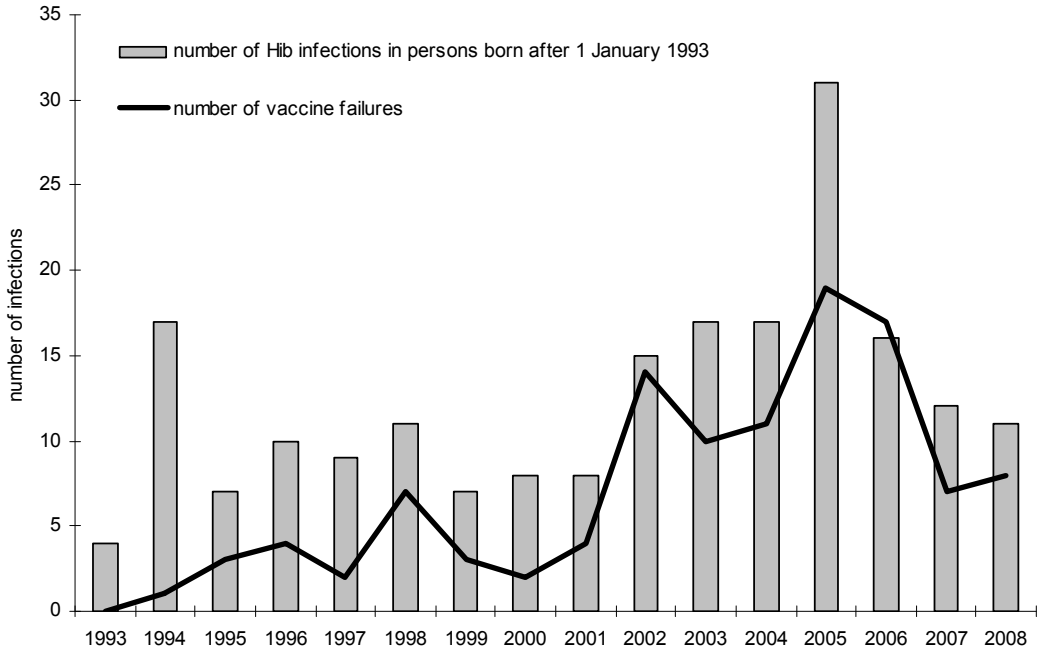

Figure 10 Annual number of Hib infections in persons targetted for vaccination (i.e. born after 1 January 1993) and number of vaccine failures

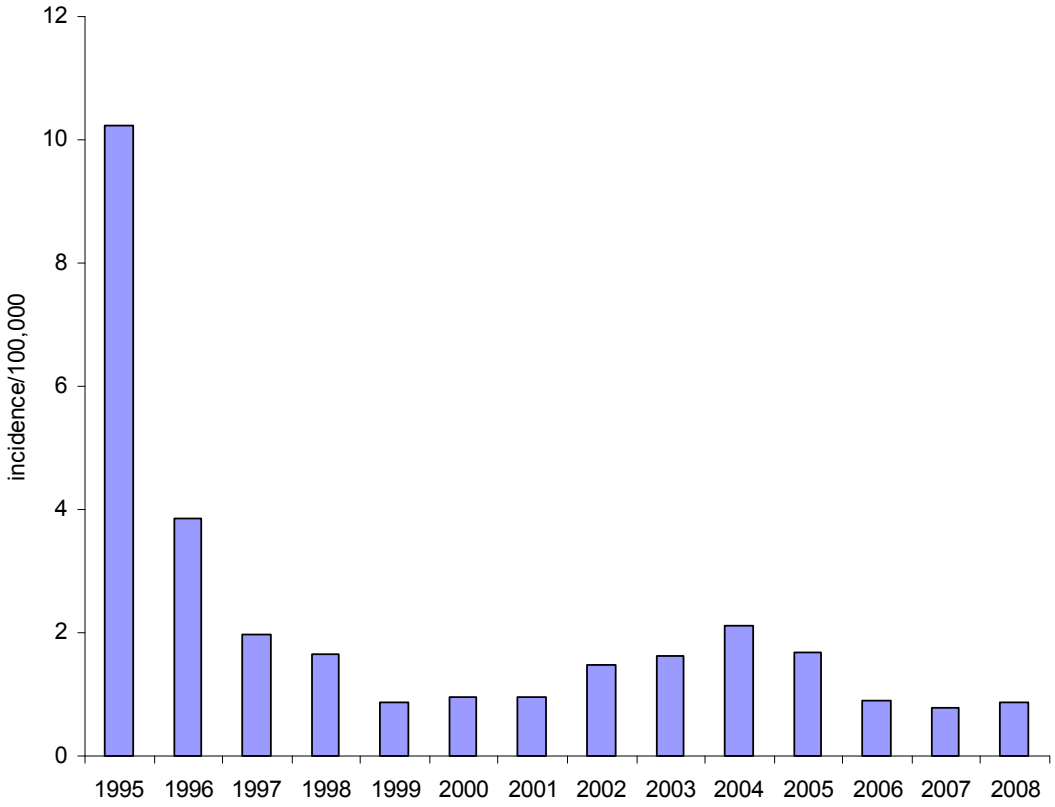

Figure 11 Annual incidence of invasive Hib infections in persons targetted for vaccination (i.e. born after 1 January 1993)

Adverse events
See section 2.2.

2.6 Mumps

S.J.M. Hahné, R van Binnendijk, J.M. Kemmeren

Pathogen
Strain variation
The mumps outbreak that started in the Netherlands in August 2007 was caused by genotype D.[14] During 2008, strains from 129 cases of mumps could be genotyped, of which 95% were genotype D, 4% were genotype G and 1% was the vaccine strain (JL). During 2009 (up to week 48), 24 cases were genotyped: 42% was genotype D and 58% genotype G. The most recent genotype D strain was detected in May 2009.

Disease

Epidemiology

Since 2009, mumps is again a notifiable disease in the Netherlands (notification of mumps was ceased between 1999 and 2008, inclusive). Up to week 48, 37 cases were notified with a date of onset in 2009 (see Table 4). Of these, 31 were laboratory confirmed; 6 were not confirmed but had an epidemiological link to a laboratory confirmed case. The cases were equally distributed in time, with in each month less than 10 cases. In the most recent two years when mumps was notifiable (1997 and 1998), 47 and 34 cases were notified, respectively.

The outbreak of mumps that started in August 2007 seems to have ceased in the beginning of 2009. The outbreak strain was not detected after May 2009, and the number of notified cases in 2009 is similar to that in 1997 and 1998.

For 33 of the 37 notified cases in 2009, the vaccination status was reported. Of these, 21 were unvaccinated and 12 were vaccinated. Of these 12, five had received one dose, five two doses and two an unknown number of doses of vaccine. During 2010, results of a cohort study into mumps vaccine effectiveness, carried out during the outbreak, will become available.

Hospital episode statistics show that during 2008, 50 individuals were admitted to hospital with a main and/or side diagnosis of mumps, reflecting the clinical impact of the outbreak (see Table 4). The majority of these concerned a diagnosis of ‘mumps without complications’ (16 admissions) and mumps meningitis (14 admissions).

Table 4 Number hospital admissions for mumps

Year	Hospital admissions
2000	4
2001	2
2002	7
2003	4
2004	8
2005	8
2006	9
2007	10
2008	50
2009 (up to week 48)	37

Adverse events

In 2007, reports following MMR and MenC vaccination have decreased significantly, not explained by the decreasing birth cohort, but in 2008 an increase was seen. Compared to 2007 in which the vaccine was delivered by one manufacturer, more than 90% of the MMR vaccine used in 2008 came from four different manufacturers. A difference in risk of convulsions and aseptic meningitis is seen when different vaccine virus strains were used, but overall, reactogenicity of the currently used MMR vaccines is comparable.[15, 16 17] Therefore, the fluctuation in number of reports after MMR and/or MenC vaccination can not be explained up till now, but it may be random variation.

In a study on the association of acute cerebellar ataxia with vaccinations, no association was found with MMR.[18]

2.7 Measles

S.J.M. Hahné, R van Binnendijk, J.M.Kemmeren

Pathogen

Strain variation

During part of 2008 an outbreak of measles occurred among individuals of whom most were unvaccinated based on antroposophical beliefs.[19] From all subclusters in this outbreak at least one measles virus strain for typing was available, and all typed isolates were indistinguishable (genotype D8, reference strain MVi/Den Haag.NL D/25.08, EU878303). Of the nine cases that occurred in 2009 (up to week 48) an isolate was available for four (one D8, three D9 strains).

Disease

Epidemiology

During 2008, 109 cases of measles were reported, most of whom belonged to the above mentioned outbreak (see Table 5). During 2009 (up to week 48), nine cases occurred. Six of these were laboratory confirmed and three were reported based on an epidemiological link to a laboratory confirmed case. One of the laboratory confirmed cases died. This concerned a 38 year old, previously healthy man, who was a Scottish resident who temporarily lived in the Netherlands. He most likely acquired measles during his travel in Thailand. He was reportedly unvaccinated. Two other laboratory confirmed cases were also in non-Dutch residents: they were crew on a cruise ship that was visiting Groningen. The Municipal Health Service Groningen advised vaccination of all persons on board. Four of the other cases in 2009 were clustered in one, unvaccinated family.

Hospital episode statistics show that during 2008, four individuals were admitted to hospital with a main and/or side diagnosis of measles (see Table 5).

Table 5 Number of notifications and hospital admissions for measles

Year	Notifications	Hospital admissions
2000	1017	19
2001	17	4
2002	3	3
2003	4	7
2004	9	1
2005	3	1
2006	1	3
2007	10	2
2008	109	4
2009 (up to week 48)	9	n.a.

n.a.= not available

Adverse events

See section 2.6.

2.8 Rubella

S.J.M. Hahné, R. van Binnendijk, J.M. Kemmeren

Pathogen
Strain variation
For none of the eight cases notified during 2009 a genotype was available.

Disease
Epidemiology
During 2008, two cases of rubella were notified (see Table 6). During 2009, up to week 48, eight cases of rubella were notified, none in pregnant women. Of the eight cases, none was vaccinated. Five cases were linked. This concerned children of two separate families who were attending a low vaccine coverage school in the region 'South Limburg'.
For four of the eight cases, samples were received at RIVM. Three cases were PCR positive and one PCR negative. However, for none of the cases genotyping was successful.
Hospital episode statistics show that during 2008, five individuals were admitted to hospital with a main or side diagnosis of rubella (see Table 6).

Table 6 Number of notifications and hospital admissions for rubella

Year	Notifications	Hospital admissions
2000	12	7
2001	4	6
2002	3	5
2003	1	5
2004	70	7
2005	345	17
2006	5	9
2007	1	5
2008	2	5
2009 (up to week 48)	8	n.a.

n.a. = not available

Adverse events
See section 2.6.

2.9 Meningococcal serogroup C (MenC) disease

L.M. Schouls, S.C. de Greeff, G.A.M. Berbers, R. de Voer, J.M. Kemmeren

Pathogen
No changes in the composition of the population of circulating *Neisseria meningitidis* have been observed. The majority of cases of meningococcal disease are caused by type B (85%). 5-10 Cases are

caused by serogroup Y (2-5%), and also by serogroup C. Serogroup W135 is found in 1-5 cases and serogroup X in 0-3 cases.

Disease

Epidemiology

Since the introduction of the conjugated meningococcal C vaccine the incidence of serogroup C disease has strongly decreased (see Figure 12). In 2008 only 11 cases of invasive meningococcal group C disease were reported. Two were unvaccinated children aged 6 and 11 months, respectively. All other cases were in unvaccinated adults (see Table 7). Since the introduction of MenC vaccination in the Dutch NIP no cases of meningococcal group C disease in previously vaccinated persons have been reported.

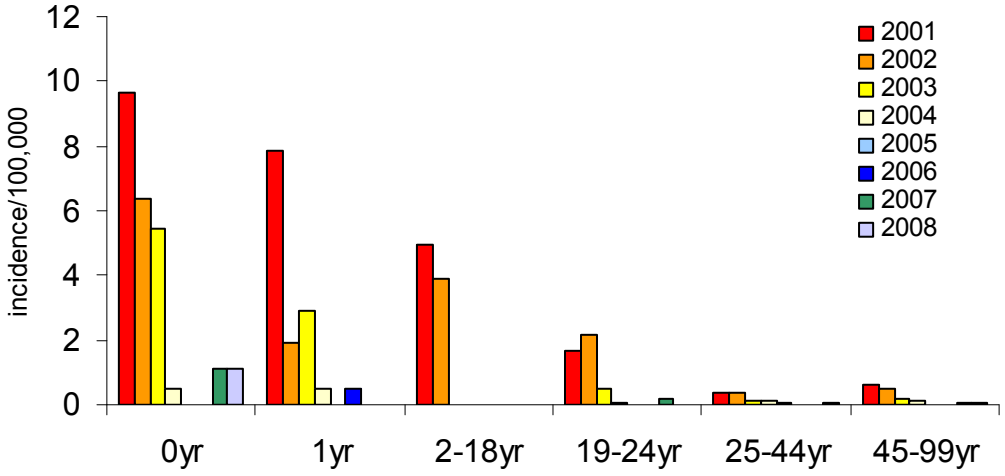

Figure 12 Age-specific incidence of meningococcal C disease by year, 2000-2008

Table 7 Absolute number of patients with meningococcal C disease

	2000	2001	2002	2003	2004	2005	2006	2007	2008
0 yr	2	20	13	11	1	0	0	2	2
1 yr	5	16	4	6	1	0	1	0	0
2-18 yr	60	164	131	1	1	0	0	1	0
19-24 yr	10	19	25	6	1	0	0	2	0
25-44 yr	7	18	17	7	6	2	1	1	3
44-99 yr	21	39	31	11	7	2	2	3	6
total	**105**	**276**	**221**	**42**	**17**	**4**	**4**	**9**	**11**

Meningococcal serogroup C conjugate (MenCC) vaccine was included in the National Immunisation Programme in 2002. Next to a single vaccination for all 14-month-old children, a catch-up campaign was conducted between June and November 2002 for all children and adolescents between 1 and 19 years of age (overall vaccine coverage 94%). Following introduction of the vaccine the incidence of MenC disease decreased dramatically in all immunized age cohorts as well as in the non-immunized cohorts, indicating a large herd-effect.

In the serum collections collected in 1995-1996 (Pienter-project) and 2006/2007 (Pienter 2-project) MenC polysaccharide-specific IgG as well as the seroprevalence of (functional) bactericidal antibodies

were measured. Remarkably, we observed a gradual increase in the persistence of MenC polysaccharide-specific antibodies with age in the immunized cohorts (see Figure 13a, b).

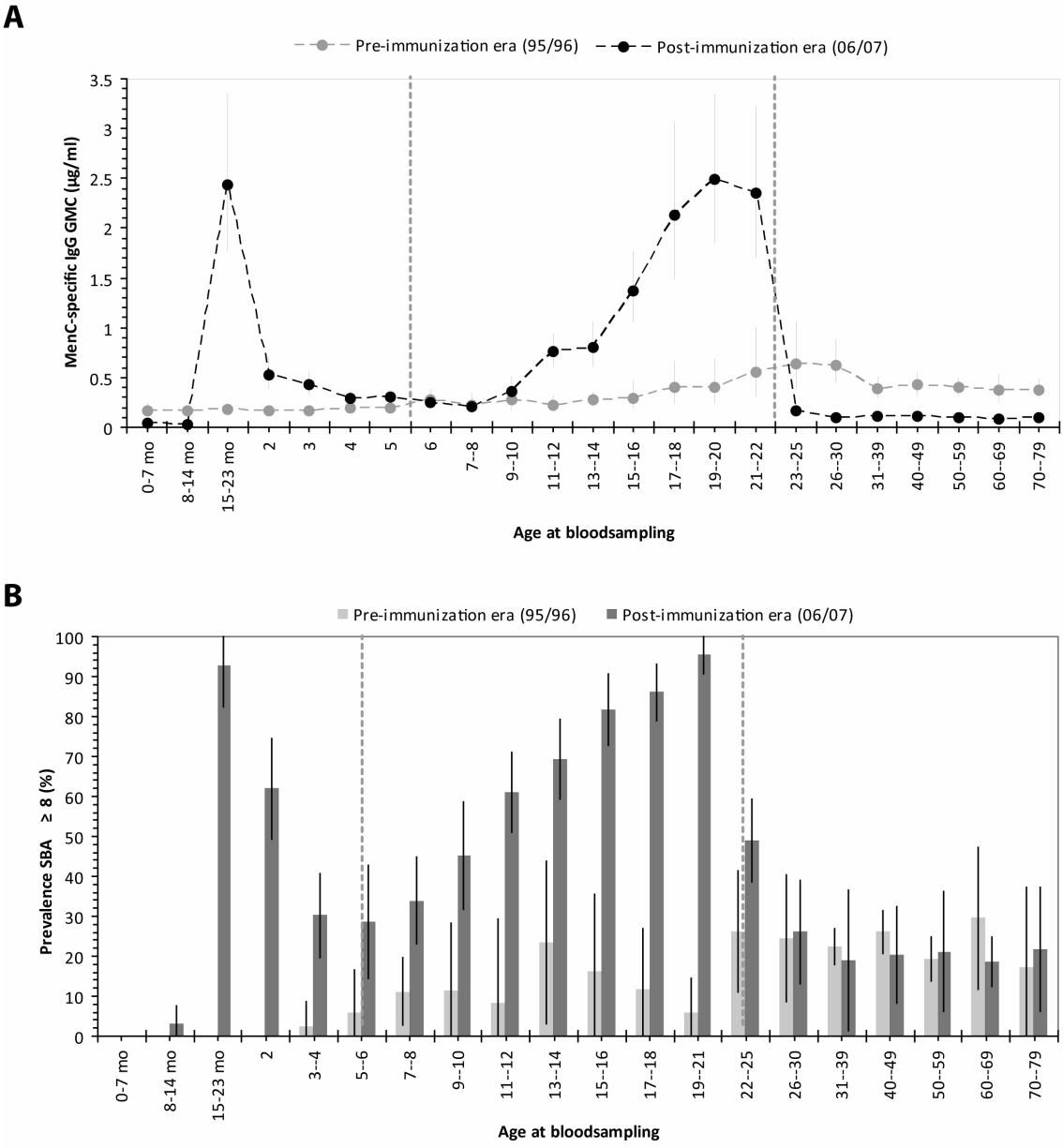

Figure 13 MenC PS-specific IgG (A) and seroprevalence of serum bactericidal antibody (SBA) titers ≥8 (B) within each age-cohort, pre- and post-introduction of the MenC conjugate vaccine. Error bars indicate 95% confidence intervals, vertical lines indicate cohorts immunized in catch-up campaign. Age at bloodsampling is indicated in years or as stated otherwise (mo = age in months).

This increase was not limited towards the polysaccharide moiety of the vaccine, but interestingly also antibodies towards the carrier protein (tetanus) were persisting in an age-related manner in the oldest immunized adolescents of the catch-up campaign. Furthermore, in non-immunized age-cohorts (>25 years of age at the time of sampling for the second serum bank) MenC polysaccharide-specific

antibodies declined compared to the pre-MenCC immunisation era (see Figure 13a). At present this has not yet resulted in a lower protection in the ages above 25 years of age (see Figure 13b). So far, large-scale introduction of a MenC conjugate vaccine has led to improved long-term protection in adolescents, but in infants a single-dose schedule at 14 months may not provide sufficient protection on the long-term.

Adverse events
For the reported adverse events in the passive surveillance system we refer to section 2.6. Furthermore, several clinical trials are performed to the reactogenicity of the quadrivalent ACYW135 polysaccharide vaccine in which vaccines with different amount of polysaccharide antigens and/or the conjugation method were compared. A phase II study showed that MenACWY-CRM and MPSV4 vaccines were well tolerated (local reactions 67% vs. 60%; systemic reactions, 50% vs. 49%, respectively).[20] None of the 13 serious adverse events were assessed as related to study vaccine. A phase III trial reports also a similar reactogenicity, with 64% of the MenACWY-CRM recipients and 70% of the Menactra recipients reporting mild and/or moderate solicited reactions.[21] Neither vaccine was associated with a serious adverse event. Two studies that evaluated the immunogenicity and reactogenicity of five formulations of a novel, combined MenACWY conjugate candidate vaccine that varied both in the amount of polysaccharide and the conjugation method demonstrated that the MenACWY-TT formulations tested were well tolerated and had reactogenicity profiles that resembled that of the licensed polysaccharide control vaccine, although one serious adverse event occurred in the MenACWY-TT group. Eight days after vaccination this subject developed urticaria considered to be causally related to vaccination by the investigator.[22]

2.10 Hepatitis B

S.J.M. Hahné, H.J. Boot, J.M.Kemmeren

Pathogen
Strain variation
Since 2004, blood samples for genotyping are collected from all cases of acute HBV infection that are notified. Results of the molecular epidemiological analyses are summarised in two recent publications.[23, 24] These suggest that although the incidence of acute HBV infection in the Netherlands has decreased, transmission among men who have sex with men is ongoing.

Disease
Epidemiology
In 2008, 219 cases of acute hepatitis B were notified in the Netherlands (incidence: 1,3/100.000 population), a decrease of 4% compared to 2007. The annual number of notified acute HBV infections was in 2008 similar to that in the late 1990s, after an increase in the early 2000s (see Table 8 and Figure 14). The number of notified chronic infections increased since 2000 (see Table 8). Explanations for this include an increase in notification compliance and increased testing.

Table 8 Number of notifications for acute and chronic HBV infections

Year	Notifications (acute HBV infection)	Notifications (chronic HBV infection)
2000	284	1242
2001	197	1219
2002	247	1448
2003	319	1445
2004	296	1471
2005	302	1460
2006	242	1512
2007	227	1582
2008	219	1576

In both men and women, unsafe sexual contact remains the most frequently reported risk factor for acute hepatitis B (see Figure 14).[24]

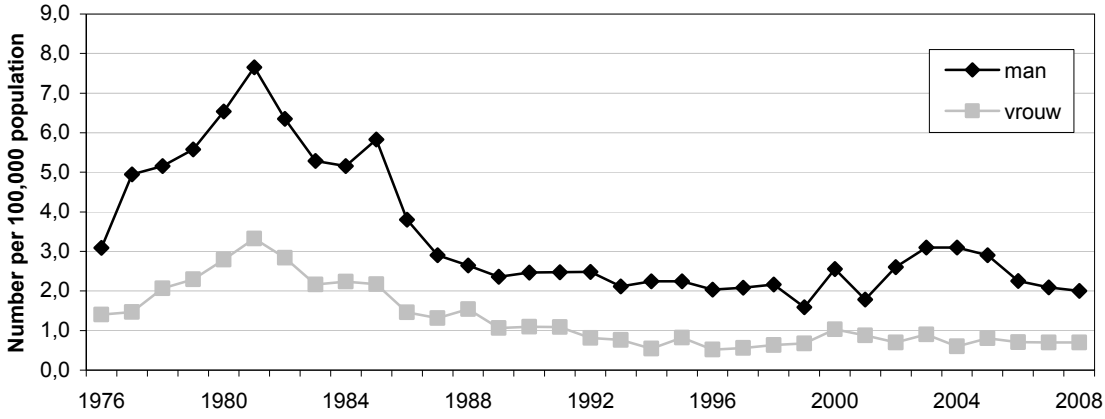

Figure 14 Notified cases of acute hepatitis B per 100,000 population by sex and year, the Netherlands, 1976-2008 (source data: Osiris)[23]

Children of mothers who are HBsAg positive and who are born since 2003 onwards are invited for serological screening for HBV subsequent to completion of their infant vaccination series around 1 year of age. Of the 2007 birth cohort, 426 blood samples were received. Of these, 411 children (96.5%) had a sufficient anti-HBs titer, one (0.2%) had to be re-vaccinated and for 14 children (3.2%) the result is not available. One child in the 2007 birth cohort was screened in a peripheral laboratory and found to be HBsAg positive.

Adverse events

The number of reported AEFI with dTaP-HBV-IPV/Hib in 2008 was 100, which is higher compared to the number of reports in 2007 (n=73). However, in 2008 the hepatitis B vaccination for children with Down syndrome is included in the NIP, which may explain this increase.

Several clinical trials are performed to adverse events after HBV vaccination with or without other childhood vaccines.[25-27] No significant increase in any of several clinically important safety events was observed.

2.11 Pneumococcal disease

L.M. Schouls, S.C. de Greeff, J.M. Kemmeren

Pathogen

The current research in the CIb is focussed on possible changes in the pneumococcal population structure of the pneumococci and on changes occurring in the genomic region encoding the capsular polysaccharide. These analyses revealed a shift in the distribution of the genotypes of serotype 1 isolates during the period after the introduction of the vaccine. This is remarkable as serotype 1 is not included in the current conjugate vaccine and also because there has been a considerable increase in cases of invasive pneumococcal disease (IPD) caused by serotype 1 after the introduction of the vaccine. Further research will be needed to study the validity and consequences of this change. Apart from the reduction of the incidence of vaccine-type IPD no other significant changes in alterations in the pneumococcal population has been observed.

Disease

Epidemiology

Since 2009 IPD has become a notifiable disease for children up and until 5 years of age. For a description of epidemiological trends in the whole population we rely on laboratory surveillance data of the Netherlands Reference laboratory for Bacterial Meningitis (NRBM). This system covers about 80% of all cases of pneumococcal meningitis in the Netherlands. Data for other pneumococcal disease manifestations (pneumonia and sepsis) are only complete for 9 sentinel laboratories, covering about 25% of the total population in The Netherlands. Unless otherwise stated the numbers below reported by the 9 sentinel laboratories are extrapolated for the whole population (i.e. multiplied by 4).

Until June 2008 - i.e. two years after introduction of vaccination - we found a 67% reduction of the incidence of vaccine serotype IPD in children less than 2 years of age and a 44% increase of non-vaccine serotype IPD. Furthermore, we found no evidence of herd immunity in this period.[28]

These numbers are more pronounced if a longer post-vaccination period is analyzed. However, more recent data show a decrease in vaccine type IPD among unvaccinated cohorts born before 2006, suggesting there might be some herd-immunity effect going on. In the period June 2006 to September 2009 the incidence of IPD due to vaccine-types in children aged < 2 years decreased with 79% compared to the pre-vaccination period June 2004-June 2006, from 24.8 to 5.2 per 100,000, respectively ($p<0.0001$). Meanwhile the incidence of non-vaccine serotypes in this age-group increased by 14% from 11.7 to 13.3 per 100,000 ($p=0.3$) (see Figure 15).

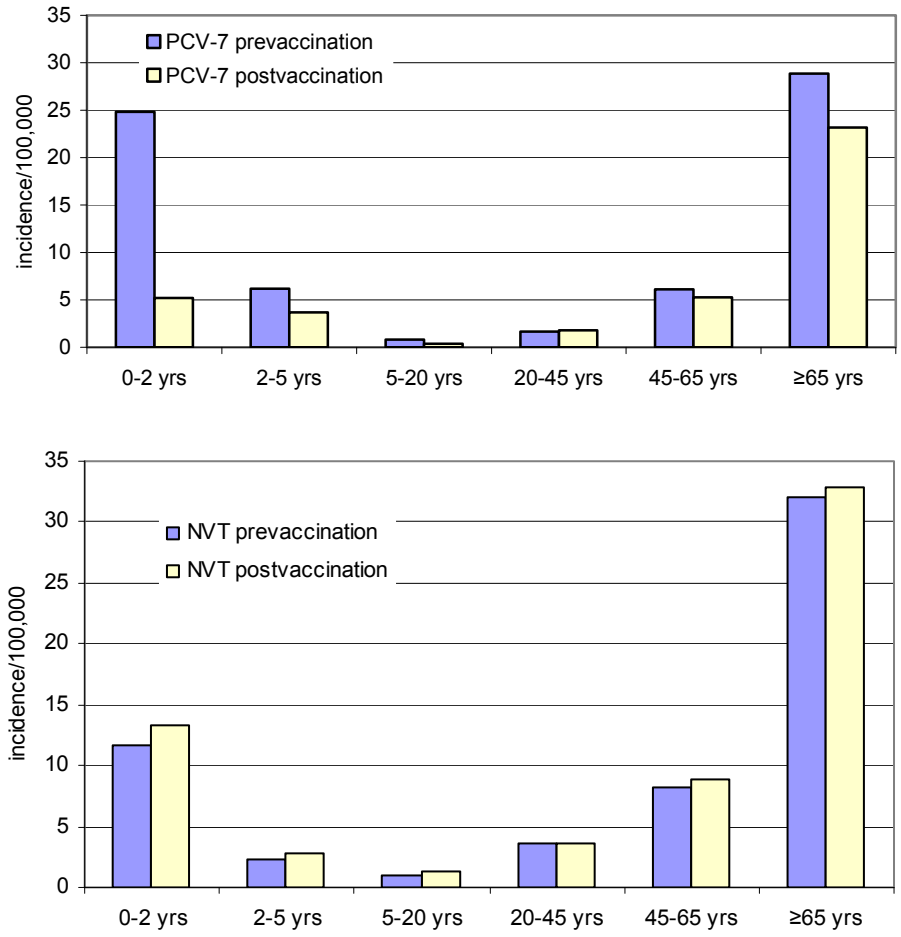

Figure 15 Age-specific incidence of vaccine type IPD (upper figure) and non-vaccine type IPD (lower figure), in blue before introduction of vaccination (June 2004-June 2006) and in yellow in the post-vaccination period (June 2006-Sept 2009). Incidences are calculated on cases reported by the 9 sentinel laboratories, but extrapolated for the whole population

A reduction of vaccine type IPD has also been observed in other age-groups, which was partly counterbalanced by an increase in non-vaccine type IPD (see Figure 15 and 16). Nevertheless, the overall incidence in IPD in the 0-2, 2-5, and ≥65 years age groups decreased with 50% ($p<0.0001$), 23% ($p=0.052$), 10% ($p=0.0005$), respectively. In the 5-20 yrs and 45-65 yrs age-group the incidence remained stable, while in the 20-45 years age group a 5% increase was observed ($p=0.34$).

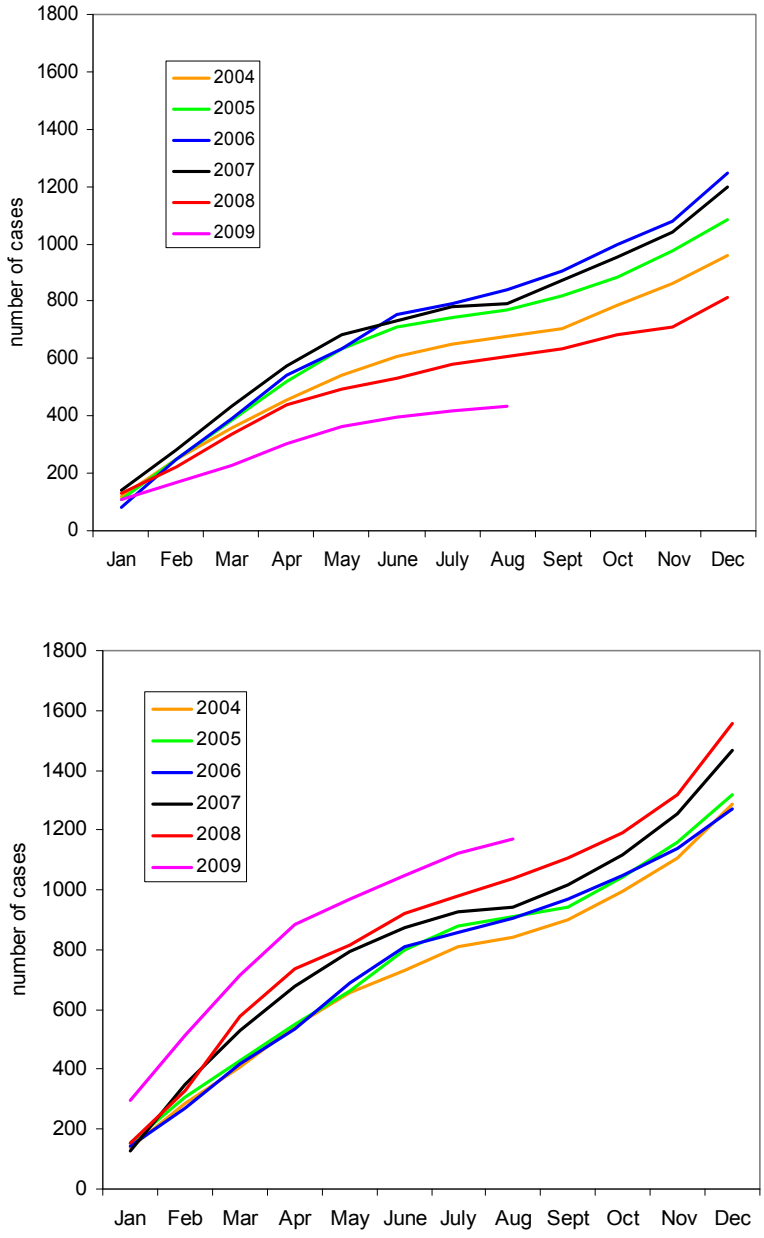

Figure 16 Cumulative number of vaccine-type IPD (upper) and non-vaccine type IPD (lower) per year in patients older than 2 years of age

To obtain more insight in clinical pictures and outcome of invasive pneumococcal disease, clinical characteristics of IPD patients reported by these 9 sentinel laboratories are extracted from hospital records in an enhanced surveillance.
Based on discharge diagnoses as registered in the National Medical Register the incidence of hospital admission because of meningitis, sepsis and pneumoniae caused by pneumocci – i.e. ICD9 codes 3201 (pneumococcal meningitis), 0382 (pneumococcal septicemiae), 481 (pneumococcal pneumoniae) and 4823 (pneumoniae by Streptococcus)- decreased in the age-groups targeted for vaccination since 2006 (children from aged 3 months-2 years; see Figure 17).

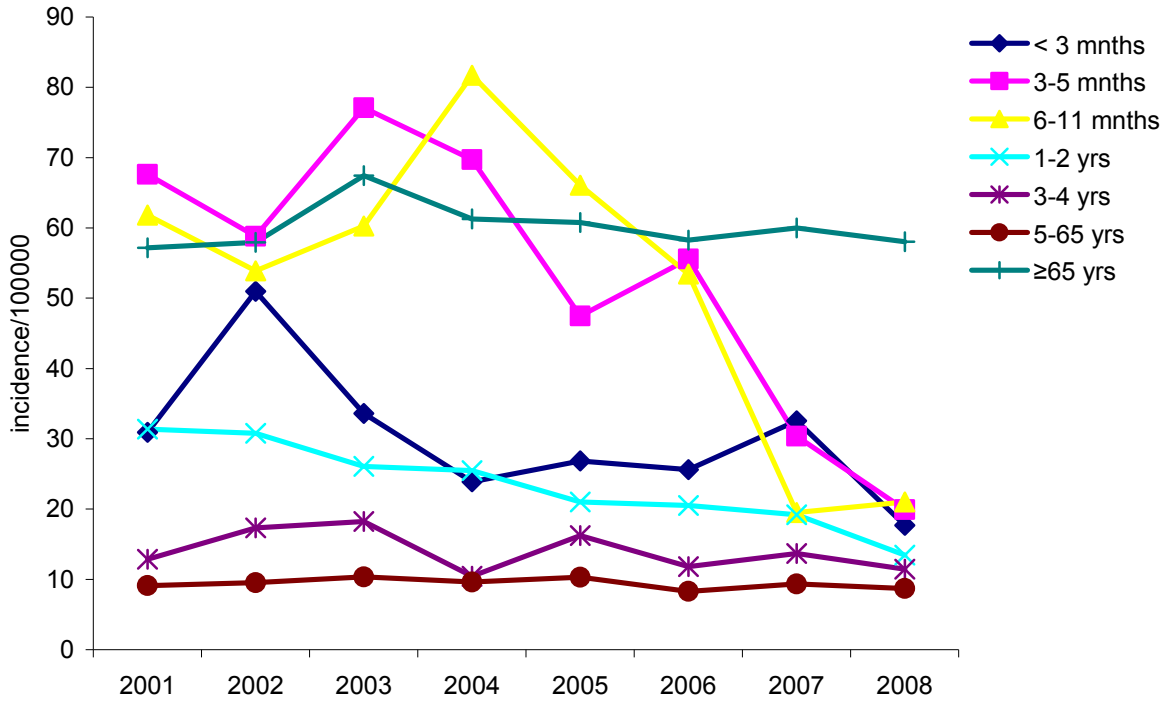

Figure 17 Age specific incidence of hospitalizations for pneumococcal related ICD-9 codes

Adverse events

Results from the passive safety surveillance for 2008 shows that, just like in 2006 and 2007, the addition of conjugate pneumococcal vaccine had little effect on the number of reported adverse events.[11, 12, Maas, 29]

A large-scale, postmarketing observational database safety study was conducted following 7-valent pneumococcal conjugate vaccine (PCV) licensure. It shows no association between Kawasaki disease and PCV.[30]

Five randomized, controlled studies showed that the safety and reactogenicity profiles of a novel 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D-conjugate vaccine and a licensed PCV were within the same range when administered for primary and booster vaccination in coadministration with other routinely used pediatric vaccines.[31] In a phase three randomized, double-blind, saline-placebo controlled study, the reactogenicity of an 11-valent PCV was assessed, given at 6, 10 and 14 weeks of age. It shows that the non-adjuvanted 11PCV was well tolerated by infants. Although the PCV group had a general pattern of having higher reaction rates compared to placebo, there were very few reactions among the 11PCV and placebo recipients that were of statistical significance.[32]

2.12 Human papillomavirus (HPV) infection

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Changes in the NIP

In March 2009, the catch-up HPV vaccination campaign for girls born between 1993 and 1996 was implemented.[33] National coverage after the first dose was 49.9%. Regional uptake ranged from 31-61%. For background characteristics, analyses showed that vaccine uptake was lower among those with at least one parent born abroad and among those who also had declined MMR vaccination. Areas with low social-economic status experienced lower vaccine uptake as did areas with a higher proportion of voters for the Christian Union or the Reformed Political Party. For implementation aspects, vaccine uptake was positively associated with smaller distance between home and vaccination centre, organization of information meetings and less use of local media.[34] In April 2010 HPV vaccination through the NIP will start targeting girls 12-years of age (i.e. birth cohort 1997), also using the bivalent HPV vaccine.

Pathogen

Now that HPV16 and HPV18 vaccination has been introduced in pre-adolescent girls, attention should be drawn to changes in HPV genotype distribution (HPV16/18 replacement for other (potentially) high risk-HPV types not included in the vaccine) and changes in L1 antigenicity of the circulating HPV16/18 genotypes. Beforehand the frequency of these events is considered (very) low, as HPV is a stable DNA virus and even when vaccination would cover all eligible girls, pressure will only be put on half of its potential hosts. Nevertheless, to detect these changes it is essential to obtain baseline HPV genotype diversity patterns prior to vaccination. In this context several studies were initiated and conducted in 2008 and 2009. Data on the occurrence of high risk-HPV-infections (HPV16/18/others) in in female and male STI clinic visitors are currently analyzed. In addition, baseline genital and blood samples from a cohort of 14-16 year-old (un)vaccinated girls will be analyzed for HPV (sero)prevalence. Taken together with two recently published cross-sectional studies describing the HPV prevalence in Dutch women,[35 36] a solid basis is formed to which HPV genotype occurrence can be compared post vaccination. In the unlikely case of reduced vaccine efficacy later on, the baseline samples can serve as a reference when it comes to the assessing the drift in the composition of the L1 capsid protein of circulating HPV16/18 variants.

Disease

Epidemiology

HPV infections

No new results became available on HPV (sero)prevalences in the Netherlands.

HPV-related cancers

Since the 1980s, cervical cancer screening with the Pap smear has been offered to women in the age-range 30-64 years in The Netherlands through an organized program. The coverage for the program smears (any smear that was primary and taken in the calendar year,or the first 3 months thereafter, in which the women was eligible for the program given her birth year) was 66.1% in 2008 (N. van der Veen, RIVM/V&Z, personal communication). In 2003, 2.5% of the women were recommended to have a follow-up smear and 0.7% of the women received an immediate referral.

Between 2000 and 2006, every year 600 to 700 women are diagnosed with cervical cancer (see Table 9).[37] Over the past nine years, on average 222 fatal cases are reported per year (see Table 10).[38] Cancers

related to HPV infections do not only include cervical cancer, but also cancer of the vagina, vulva, penis, anus, mouth and (oro)pharynx. HPVs are estimated to cause at least 80% of anal cancer and at least 40-60% of vulvar, vaginal and penile cancer.[39] Table 9 shows the number of men and women who were diagnosed with these types of cancer between 2000-2006. The number of men and women who died between 2000-2008 from these types of cancer are shown in Table 10.

Table 9 Number of new ano-genital, mouth, pharynx and cervical cancer cases in the Netherlands from 2000-2006, by cancer-type*

	2000	2001	2002	2003	2004	2005	2006
Men							
Ano-genital							
-penis (C60)	77	92	101	104	115	108	117
-anus (C21)	49	49	50	63	51	53	65
Mouth (C01-C06)	466	431	456	494	530	536	497
Pharynx (C09-C14)	377	356	368	379	404	391	401
Women							
Cervix (C53)	683	607	651	607	704	684	685
Ano-genital							
-vulva/vagina (C51-C52)	278	288	292	317	307	319	339
-anus (C21)	61	76	59	68	58	78	84
Mouth (C01-C06)	323	344	323	353	343	362	373
Pharynx (C09-C14)	127	154	155	140	156	137	159

* Number of new cancer cases are based on the Dutch cancer registry (NKR)[37]

Table 10 Number of deaths related to ano-genital, mouth, oropharynx and cervical cancer in the Netherlands from 2000-2008, by cancer type*

	2000	2001	2002	2003	2004	2005	2006	2007	2008
Men									
Ano-genital									
-penis (C60)	20	23	13	20	23	21	14	31	26
-anus (C21)	11	18	15	12	11	19	11	16	17
Mouth (C01-C06)	133	129	119	140	136	148	137	145	145
Oropharynx (C09-C10)	70	69	65	73	77	63	73	66	64
Women									
Cervix (C53)	258	243	187	214	203	235	214	204	244
Ano-genital									
-vulva/vagina (C51-C52)	108	101	111	118	98	106	114	101	118
-anus (C21)	15	16	17	10	13	19	15	10	16
Mouth (C01-C06)	90	87	89	114	102	86	94	94	90
Oropharynx (C09-C10)	19	26	37	37	34	24	24	28	30

* Number of deaths related to cancer are based on the Dutch cancer registry (NKR) and Statistics Netherlands (CBS)[37, 38]

Genital warts

Compared to 2007, the number of diagnoses of genital warts at the STI centers increased with 20% to a total of 2,465 diagnoses. At general practitioners, there was also an increase in the reporting rate for genital warts compared to preceding years for women to 120 episodes per 100,00 population. The reporting rate for men remained stable at 85 episodes per 100,000. At the STI centers, in line with

previous year most diagnoses were made in women aged 20-24 years (18%) followed by men heterosexual men in the same age group (12%). A co-infection with *Chlamydia* was found in 11% of the female cases with genital warts, 9.8% of the heterosexual male cases and 14.7% of the men who have sex with men.[40]

Adverse events

After the first dose of HPV vaccination in the Netherlands, 446 reports were received via the spontaneous reporting system (degree of reporting: 23.2:10,000).[41] 16% of reports were mainly local effects; 84% were systemic effects, including 8 severe effects. 157 girls consulted their general practitioner or went to a hospital (degree of reporting: 8:10,000). 59% of the reports were of a side effect; in 41% the event was coincidental. There were 638 reports during the vaccination sessions (degree of reporting 45:10,000). The largest numbers were vasovegetative effects, including fainting or near-fainting (n = 569; degree of reporting: 40:10,000). The degree of reporting of tightness of the chest or skin effects was 2:10,000. The assistance of a general practitioner or ambulance was summoned for 10 girls (degree of reporting: 0.7:10,000). The questionnaire study (response 68.7%; n = 3646) showed that 92.1% of the girls had local effects. In 1.6% these symptoms were severe. Systemic effects occurred in 91.7%, mostly concerning myalgia, fatigue and headache; 0.7% had fever (>or= 39.5 degrees C). 1.5% of girls called for medical assistance. No unexpected or serious side effects with a causal relationship with the vaccination occurred following administration of 192,119 doses. Correspondingly to other studies,[42-44] the incidence of adverse events after the first dose of HPV vaccination is high, but the symptoms are mostly mild and transient.

3 Future NIP candidates

3.1 Rotavirus infection

I.H.M. Friesema, J.M. Kemmeren

Pathogen

Strain variation

In 2008, the RIVM joined an European study of gathering information about circulating rotavirus types. A total of 168 rotavirus positive samples were typed at the RIVM during this year (A. Kroneman, RIVM/CIb, personal communication). The G-type could be detected in 164 samples with G1 the most common (62.8%), followed by G3 (12.2%) and G9 (10.4%). G2 and G4 were less common (6.7% each), and G6 and G12 were both detected once. P[8] was the most prevalent circulating P strain (149/163 = 91.4%). Three other P strains were also found: P[4] (7.4%), P[6] (0.6%) and P[14] (0.6%). Finally, 60.7% of the samples contained serotype G1P[8] and 10.7% G3[P8].

Disease

Epidemiology

The Working Group Clinical Virology reports weekly the number of rotavirus positive results.[45] In 2008, this number was comparable to 2006 and higher than the other years. The reported frequencies per week and the mean week frequency per year are shown in Figure 18. Exact data about hospitalization for rotavirus are not available. With the use of the ICD-codes 86-93, 5589 as reported in PRISMANT and the reports of the Working Group Clinical Virology an estimation of the hospital admissions can be made. Figure 18 shows the estimated percentage of hospitalizations caused by rotavirus compared to the total number of all gastro-enteritis hospitalizations. For children aged younger than 5 years, the mean percentage per year was 72% in 2008, and was between 47% and 57% in the years 2000-2007 (see Table 11). An estimated 14-19% of all gastro-enteritis hospitalizations (all ages) is caused by rotavirus infections in the age group 0-5 years. The estimated number of hospital admissions among children less than 5 years of age amounted to 5387 in 2008, the highest number since 2000 (see Table 11).

Noticeably, the fraction of rotavirus infection in the elderly (70+), based upon data from 8-12 Dutch laboratories (ISIS), appears to increase dramatically from 0.5% (2001-2003), to 3% in 2005 and 7.5% in 2007. Nevertheless, small children are most affected by rotavirus, as can be seen in Figure 19. More recent data are not available as ISIS does not record rotavirus diagnostics anymore.

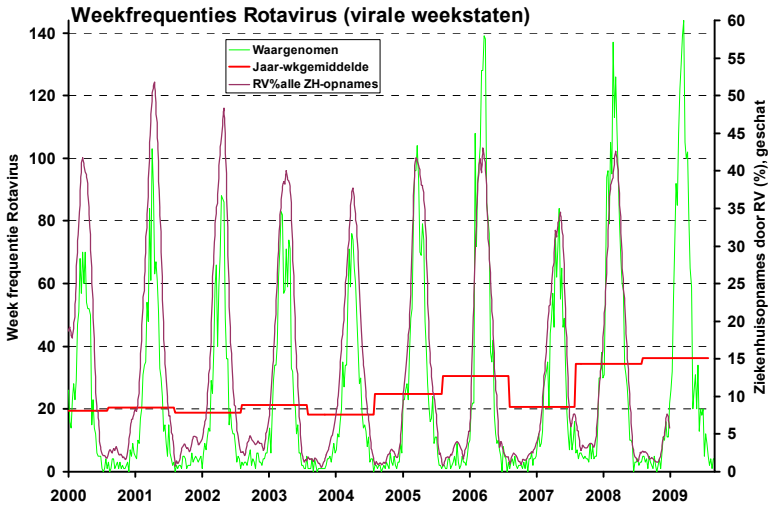


Figure 18 Weekly reports of rotavirus positive results (Working Group Clinical Virology) and the mean week frequency per year. The estimated percentage of hospitalizations caused by rotavirus compared to all gastro-enteritis hospitalizations

Table 11 PRISMANT-data about gastro-enteritis hospitalizations among children < 5 years of age and estimations of rotavirus hospitalizations[45]

Year	Number of gastroenteritis hospitalizations	Estimated % rotavirus	Estimated number of rotavirus hospitalizations
2000	6084	51.8	3152
2001	6159	56.7	3492
2002	6255	52.7	3296
2003	7276	48.5	3529
2004	6514	47.3	3081
2005	7761	55.5	4307
2006	9384	54.4	5105
2007	8051	50.1	4034
2008	7482	72.0	5387

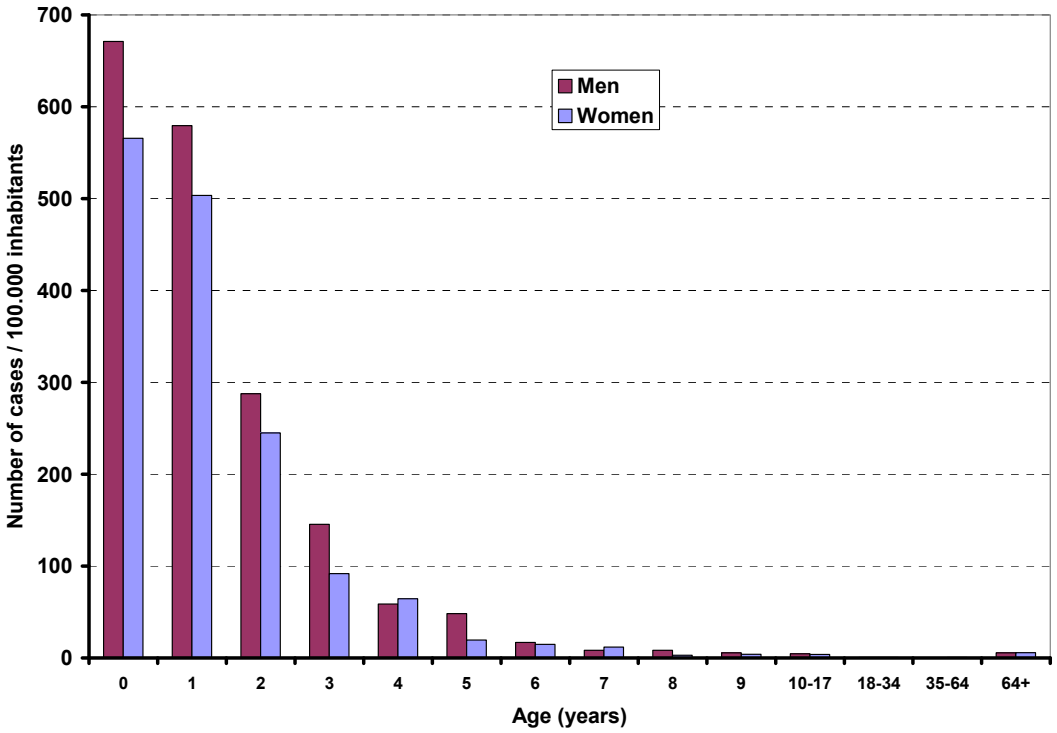


Figure 19 Age and sex distribution of rotavirus infections as reported by ISIS between 2001-2007, N=3757[45]

Adverse events
Postmarketing surveillance for adverse events after rotavirus vaccination is still ongoing. In a trial in which healthy Indian infants received two doses of Rotarix or placebo, no significant difference in the incidence of solicited symptoms were observed.[46] Another trial in which healthy infants received hexavalent vaccine concomitantly with either Rotateq or placebo, only rates for conjunctivitis and rash were significant higher in the Rotateq-group. However, the number of these reports was small. No deaths or cases of intussusception were reported during the course of this study.[47] A review of Hua et aldoes not suggest an elevated risk for Kawasaki disease after Rotateq vaccination.[48]

3.2 Varicella Zoster Virus (VZV) infection

E.A. van Lier, J.M. Kemmeren, H.J. Boot, H.E. de Melker

Pathogen
Strain variation
Herpes viruses have a very stable genome and a low mutation rate. No evidence for recombination among wild-type VZV-strains has yet been found.[49]

Disease

Epidemiology

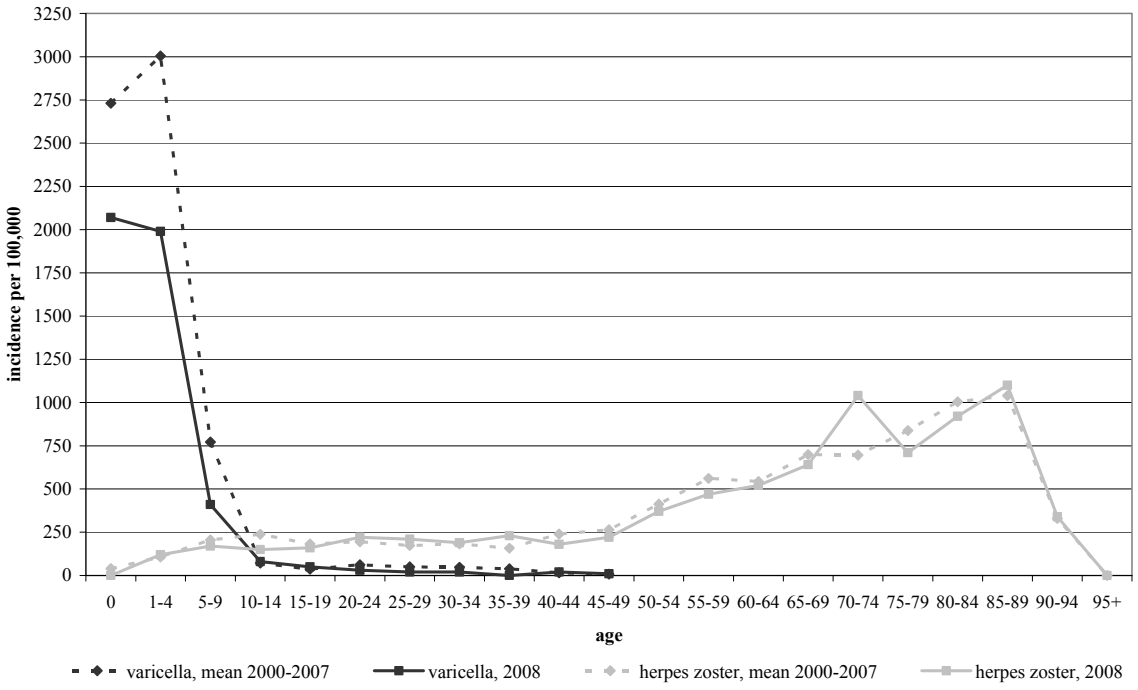
Incidence

From the sentinel surveillance network of the Netherlands Institute of Primary Health Care (NIVEL) the number of patients with varicella[50] or herpes zoster[51, 52] consulting a general practitioner (GP) was obtained (see Table 12). The incidence of varicella in 2008 was rather low. From the literature it is known that periodic larger outbreaks of varicella occur with an inter-epidemic cycle of 2 to 5 years.[53] In contrast the incidence of herpes zoster is stable over the years, which is consistent with literature.[54] The incidence of GP consultations (per 100,000 inhabitants) because of varicella is highest in the age groups below 5 year whereas the incidence of GP consultations because of herpes zoster is highest in the age groups above 50 year (see Figure 20).

Table 12 Incidence/100,000 of GP consultations due to varicella or herpes zoster, 2000-2008

	2000	2001	2002	2003	2004	2005	2006	2007	2008
Varicella*	200	240	320	270	250	190	300	210	160
Herpes zoster	330	320	320	330	310	350	370	310	340

* varicella cases in persons older than 49 are only sporadically reported by GP's and are therefore not included



(Note: varicella cases in persons older than 49 are only sporadically reported by GP's and are therefore not included)

Figure 20 Incidence of GP-consultations per 100,000 for varicella and herpes zoster, incidence 2008 versus mean incidence 2000-2007

Hospitalization

The number of hospitalizations with discharge code varicella (ICD-9 group 052) or herpes zoster (ICD-9 group 053) were obtained from the registry of Prismant (National Health Care Registry)[55] and the incidence is displayed in Table 13. Clinical admissions were included only (admissions for one day were excluded). In contrast to the GP consultations the incidence of hospital admissions due to varicella in 2008 was not lower in comparison to other years. The incidence of herpes zoster hospital admissions is – like the GP consultations – stable for the various years.

The incidence of hospital admissions due to main diagnosis varicella is highest among 0-year olds. The incidence of hospital admissions due to main diagnosis herpes zoster is highest among the oldest age groups (see Figure 21).

Table 13 Incidence/100,000 of hospitalizations due to main/side diagnosis varicella or herpes zoster, 2000-2008

	2000	2001	2002	2003	2004	2005	2006	2007	2008
Varicella									
- main	1.3	1.5	1.4	1.7	1.7	1.5	2.0	1.4	1.7
- main + side	2.0	2.3	2.2	2.5	2.6	2.2	2.9	2.2	2.4
Herpes zoster									
- main	2.3	2.5	2.7	2.2	2.5	2.2	2.0	2.0	2.1
- main + side	5.0	4.9	5.1	4.9	5.0	4.3	4.0	4.0	4.0

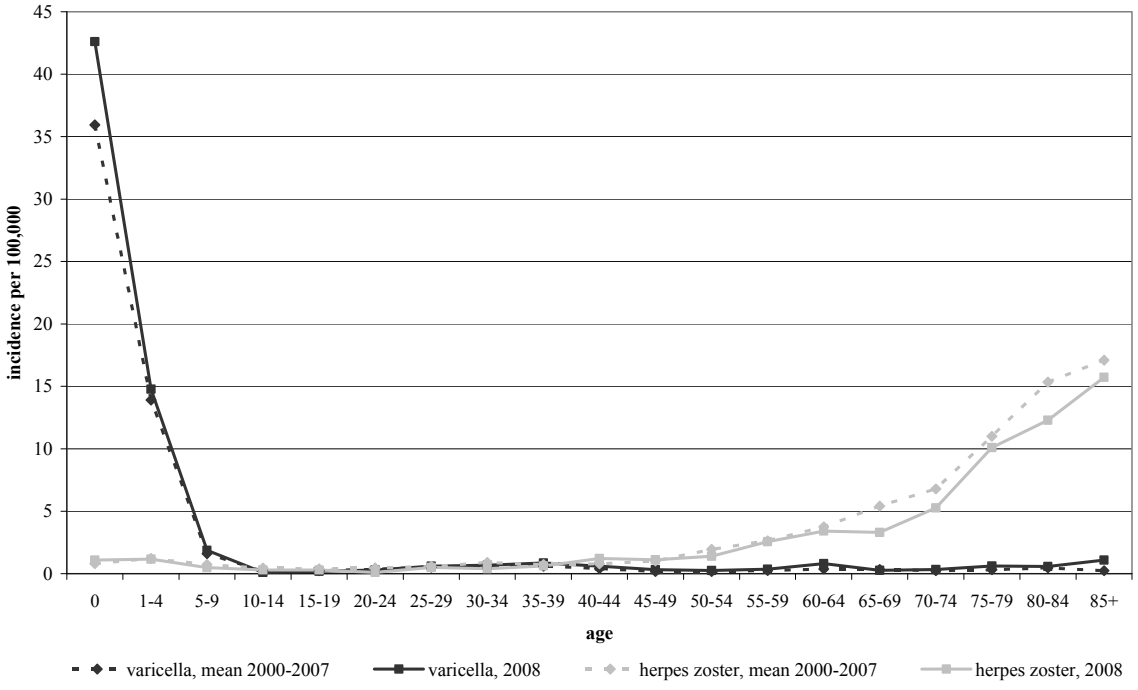


Figure 21 Incidence of hospitalizations per 100,000 for main diagnosis varicella and herpes zoster, incidence 2008 versus mean incidence 2000-2007

Death

The number of deaths due to main diagnosis varicella (ICD-10 code B01) or herpes zoster (ICD-10 code B02) were derived from Statistics Netherlands (see Table 14).[56] In 2008 there were no reported deaths due to main diagnosis varicella and 14 deaths due to main diagnosis herpes zoster.

Table 14 Number of deaths due to varicella or herpes zoster, 2000-2008[8]

	2000	2001	2002	2003	2004	2005	2006	2007	2008
Varicella	1	3	4	6	4	1	3	5	0
Herpes zoster	14	13	26	14	15	15	24	21	14

Cost-effectiveness

In 2009 the potential effects of programmatic herpes zoster vaccination of elderly was assessed by using an evaluation model for introducing a new vaccine in the Dutch National Immunisation Programme. Apart from protection against the occurrence of herpes zoster, the herpes zoster vaccine also reduces severity. However, the efficacy is suboptimal and the duration of protection is uncertain. The cost-effectiveness ratio for introduction of the vaccine in the Netherlands for 70-year olds, which was the most optimal age in terms of cost-effectiveness (€21,716 per QALY) was estimated to be just above the socially accepted threshold in the Netherlands of €20,000 per QALY (assuming simultaneous vaccination with influenza, 75% coverage, a vaccine price of €77, application costs of €6.45 per vaccination and a duration of protection of 7.5 years). The prevented disease burden is in particular related to a decrease in postherpetic neuralgia. Due to limited vaccine efficacy a considerable part of the disease burden caused by herpes zoster will remain, even with optimal acceptance of programmatic vaccination.

Adverse events

Chickenpox

In a study on the association of acute cerebellar ataxia (ACA) and vaccinations and varicella zoster infection, we found that, according to age-specific seroprevalence data the incidence rate of ACA was 5/100,000 VZV infections for children up to 5 years. According to the literature an ACA-rate of 0.15/100,000 doses VZV-vaccine is reported. Therefore, uptake op VZV vaccine in the immunisation programme is expected to diminish the incidence rate of ACA.[18]

Last year, the Advisory Committee on Immunisation Practices (ACIP) decided to remove the preference for MMRV above MMR+V administration from their recommendations because of a signal of increased risk for seizures detected among children aged 12-23 months after administration of MMRV vaccine.[57] These findings were confirmed by Jacobsen et al.[58] who found an increase in the risk of febrile convulsions in days 5-12 following vaccination with a first dose of MMRV (ProQuad/SP-MSD) as compared to MMR+V. To date, this result is not found for the MMRV vaccine Priorix-Tetra/GSK, although the database used in this trial is not large enough yet to allow any inferences to be made on actual incidences of febrile convulsion or differences in incidence between children receiving MMRV or separately administered MMR and varicella vaccines.[59] Furthermore, Priorix-Tetra/GSK led to a higher incidence of fever, albeit mainly of a lower grade, after the first dose, and more frequent mild local reactions after the second dose.[59, 60] These differences may arise from a local interaction between the MMR and varicella components that does not occur when the vaccines are administered separately.

Herpes zoster vaccination

The results of a combined analysis from two clinical trials shows that Zostavax is generally well tolerated in subjects 50-59 years of age and in subjects >= 60 years of age[61] consistent with data from

previously reported Zostavax clinical trials.[62-64] Although the proportions of subjects who reported nonserious clinical adverse events were generally higher in the group of subjects 50-59 years of age than in the group comprised of subjects >= 60 years of age, most were mild of moderate in intensity.

3.3 Meningococcal serogroup B disease

L.M. Schouls, S.C. de Greeff, J.M.Kemmeren

Pathogen
Analyses of the *porA* and *fetA* genes have not revealed any significant changes in 2008/2009 in the composition of the *Neisseria meningitidis* serogroup B strains causing invasive disease compared with the previous year. These analyses were performed by the Netherlands Reference Laboratory for Bacterial Meningitis (NRBM).

Disease
Epidemiology
Since 2000 the number of patients with meningococcal B disease has been decreasing, as can be seen in Figure 22 and Table 15. In 2008 the number of cases has decreased to 123, especially in young infants a decrease can be seen. The reason for this decreased incidence remains enigmatic. Possibly, natural fluctuation may explain this decreasing trend.

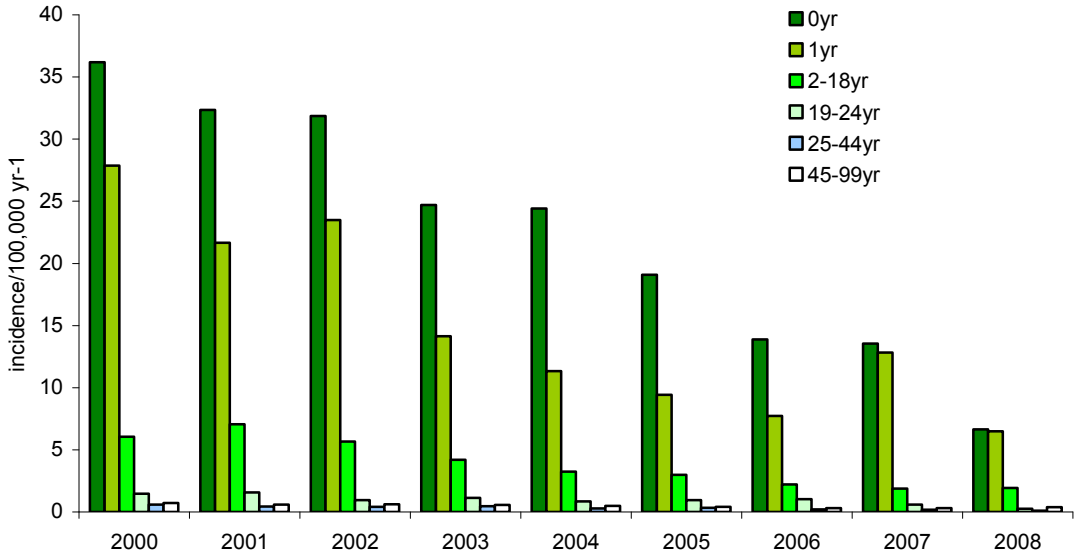


Figure 22 Age-specific incidence of meningococcal B disease by year, 2000-2008

Table 15 Absolute number of patients with meningococcal B disease per age-category from 2000-2008

	2000	2001	2002	2003	2004	2005	2006	2007	2008
0 yr	73	67	65	50	49	37	26	25	12
1 yr	56	44	49	29	23	19	15	24	12
2-18 yr	198	233	189	142	110	102	75	64	65
19-24 yr	17	18	11	13	10	11	12	7	3
25-44 yr	30	22	20	23	14	16	10	7	5
44-99 yr	43	36	39	36	32	27	20	21	26
total	**417**	**420**	**373**	**293**	**238**	**212**	**158**	**148**	**123**

Adverse events

One month after a New Zealand-wide vaccination campaign started, a child aged 4 years with Henoch-Schonlein purpura onset 3 days after vaccination was identified. The risk of Henoch-Scholein purpura following vaccination with a group B meningococcal vaccine was therefore assessed through active hospital safety monitoring. There was no increase in the relative incidence of Henoch-Scholein purpura cases who received one or more further vaccine doses (rechallenge).[65] A phase II trial to determine the safety, reactogenicity and immunogenicity in infants aged 6-8 months showed that the meningococcal B vaccine was well tolerated with no vaccine related serious adverse events. Local reactions occurred in 61%-66% of the vaccines following each dose, and systemic reactions occurred in 64%-72% of the vaccines.[66]

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References

1. Tacken M, Mulder J, van den Hoogen H et al. Monitoring Nationaal Programma Grieppreventie 2008. Nijmegen: LINH, IQ healthcare; 2009.
2. National Institute for Public Health and the Environment. www.rivm.nl/griepprik/voor_wie/.Nov 2009.
3. Commissie voor Praktische Tuberculosebestrijding. Handboek TBC-bestrijding Nederland. The Hague: KNCV Tuberculosefonds; 2008.
4. Health Council of the Netherlands. Vaccination against cervical cancer. The Hague: Health Council of the Netherlands; 2008.
5. Van Lier EA, Oomen PJ, Oostenbrug MWM et al. Immunization coverage National Immunization Programme in the Netherlands: year of report 2009. Bilthoven: National Institute for Public Health and the Environment; 2009. RIVM report 210021010.
6. Bijkerk P, van Lier EA, van Vliet JA, Kretzschmar MEE. Staat van Infeciteziekten in Nederland 2008. Bilthoven: National Institute for Public Health and the Environment; 2009. RIVM report 210211005.
7. Infectieziekten R. Meldingen Wet Publieke Gezondheid. Infectieziekten Bulletin 2009;20.
8. Mooi FR, van Loo IH, van Gent M et al. Bordetella pertussis strains with increased toxin production associated with pertussis resurgence. Emerg Infect Dis 2009;15:1206-13.
9. Mooi FR. Adaptation of Bordetella pertussis and vaccination: the small escape? Infect Genet Evol 2009;doi:10.1016/j.meegid.2009.10.007.
10. Willems RJ, Kamerbeek J, Geuijen CA et al. The efficacy of a whole cell pertussis vaccine and fimbriae against Bordetella pertussis and Bordetella parapertussis infections in a respiratory mouse model. Vaccine 1998;16:410-6.
11. Maas van der NAT, PHaff TAJ, Wesselo C, Vermeer-de Bondt PE. Adverse Events Following Immunisation under the National Vaccination Programme of the Netherlands. Number XIII - Reports in 2006. Bilthoven: National Institute for Public Health and Environment; 2007. RIVM report 240071004.
12. Maas van der NAT, Zonnenberg-Hoff IF, David S et al. Adverse Events Following Immunisation under the National Vaccination Programme of the Netherlands. Number XIV - Reports in 2007. Bilthoven: National Institute for Public Health and Environment; 2008. RIVM report 205021003.
13. David S, Vermeer-de Bondt P, van der Maas N. Lokale verschijnselen na revaccinatie met DKTP bij vierjarigen. NTvG; Accepted for publication.
14. de Melker HE, Kramer MA. The National Immunisation Programme in the Netherlands: Developments in 2008. Bilthoven: National Institute for Public Health and the Environment; 2009. RIVM report 210021009.
15. Miller E, Goldacre M, Pugh S et al. Risk of aseptic meningitis after measles, mumps, and rubella vaccine in UK children. Lancet 1993;341:979-82.
16. Miller E, Andrews N, Stowe J, Grant A, Waight P, Taylor B. Risks of convulsion and aseptic meningitis following measles-mumps-rubella vaccination in the United Kingdom. Am J Epidemiol 2007;165:704-9.
17. Lee CY, Tang RB, Huang FY, Tang H, Huang LM, Bock HL. A new measles mumps rubella (MMR) vaccine: a randomized comparative trial for assessing the reactogenicity and immunogenicity of three consecutive production lots and comparison with a widely used MMR vaccine in measles primed children. Int J Infect Dis 2002;6:202-9.
18. Maas van der NA, Bondt PE, Melker de H, Kemmeren JM. Acute cerebellar ataxia in the Netherlands: a study on the association with vaccinations and varicella zoster infection. Vaccine 2009;27:1970-3.
19. Hahné S, Mollema L, te Wierik M et al. Measles outbreak in the Netherlands, 2008. Emerging Infectious Diseases; Accepted for publication.

20. Jackson LA, Jacobson RM, Reisinger KS, Anemona A, Danzig LE, Dull PM. A randomized trial to determine the tolerability and immunogenicity of a quadrivalent meningococcal glycoconjugate vaccine in healthy adolescents. Pediatr Infect Dis J 2009;28:86-91.
21. Jackson LA, Baxter R, Reisinger K et al. Phase III comparison of an investigational quadrivalent meningococcal conjugate vaccine with the licensed meningococcal ACWY conjugate vaccine in adolescents. Clin Infect Dis 2009;49:e1-10.
22. Ostergaard L, Lebacq E, Poolman J, Maechler G, Boutriau D. Immunogenicity, reactogenicity and persistence of meningococcal A, C, W-135 and Y-tetanus toxoid candidate conjugate (MenACWY-TT) vaccine formulations in adolescents aged 15-25 years. Vaccine 2009;27:161-8.
23. Koedijk FDH, van Houdt R, Hahné SJM et al. Incidentie en moleculaire epidemiologie van acute hepatitis B in Nederland, 2004 – 2007. NTvG; Accepted for publication.
24. van Houdt R, Koedijk FD, Bruisten SM et al. Hepatitis B vaccination targeted at behavioural risk groups in the Netherlands: does it work? Vaccine 2009;27:3530-5.
25. Zangwill KM, Eriksen E, Lee M et al. A population-based, postlicensure evaluation of the safety of a combination diphtheria, tetanus, acellular pertussis, hepatitis B, and inactivated poliovirus vaccine in a large managed care organization. Pediatrics 2008;122:e1179-85.
26. Thisyakorn U, Pancharoen C, Chuenkitmongkol S, Ortiz E. Immunogenicity and safety of a DTaP-IPV//PRP-T vaccine (Pentaxim) booster during the second year of life in Thai children primed with an acellular pertussis combined vaccine. Southeast Asian J Trop Med Public Health 2009;40:282-94.
27. Marshall H, McIntyre P, Roberton D, Dinan L, Hardt K. Primary and booster immunization with a diphtheria, tetanus, acellular pertussis, hepatitis B (DTPa-HBV) and Haemophilus influenzae type b (Hib) vaccine administered separately or together is safe and immunogenic. Int J Infect Dis 2010;14:e41-9.
28. Rodenburg GD, de Greeff SC, Jansen AGCS et al. Impact of the pneumococcal conjugate vaccination two years after introduction in the National Immunization Program in the Netherlands. Submitted.
29. Maas van der NAT, Zonnenberg-Hoff IF, Moorer N et al. Adverse Events Following Immunisation under the National Vaccination Programme of the Netherlands. Number XIV - Reports in 2008. Bilthoven: National Institute for Public Health and Environment; 2009. RIVM report in preparation.
30. Center KJ, Hansen JR, Lewis E, Fireman BH, Hilton B. Lack of association of Kawasaki disease after immunization in a cohort of infants followed for multiple autoimmune diagnoses in a large, phase-4 observational database safety study of 7-valent pneumococcal conjugate vaccine: lack of association between Kawasaki disease and seven-valent pneumococcal conjugate vaccine. Pediatr Infect Dis J 2009;28:438-40.
31. Chevallier B, Vesikari T, Brzostek J et al. Safety and reactogenicity of the 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) when coadministered with routine childhood vaccines. Pediatr Infect Dis J 2009;28:S109-18.
32. Ugpo J, Lucero M, Williams G et al. Reactogenicity and tolerability of a non-adjuvanted 11-valent diphtheria-tetanus toxoid pneumococcal conjugate vaccine in Filipino children. Vaccine 2009;27:2723-9.
33. de Melker HE, Conyn-van Spaendonck MA, Boot HJ, Coutinho RA. [Introduction to vaccination against cervical cancer]. Ned Tijdschr Geneeskd 2009;153:658-61.
34. Rondy M, van Lier A, van de Kassteele J, Rust L, de Melker H. Determinants for HPV vaccine uptake in the Netherlands: a multilevel study. Vaccine; Accepted for publication.
35. Lenselink CH, Melchers WJ, Quint WG et al. Sexual behaviour and HPV infections in 18 to 29 year old women in the pre-vaccine era in the Netherlands. PLoS One 2008;3:e3743.
36. Coupe VM, Berkhof J, Bulkmans NW, Snijders PJ, Meijer CJ. Age-dependent prevalence of 14 high-risk HPV types in the Netherlands: implications for prophylactic vaccination and screening. Br J Cancer 2008;98:646-51.
37. Netherlands Cancer Registry. www.ikcnet.nl; Nov 2009.
38. Statistics Netherlands. www.cbs.nl; Nov 2009.
39. World Health Organization. WHO - position paper (meeting report): WHO.

40. Koedijk FDH, Vriend HJ, van Veen MG et al. Sexually transmitted infections, including HIV, in the Netherlands in 2008. Bilthoven: National Institute for Public Health and the Environment; 2009. RIVM report 210231005.
41. Maas van der NA, Kemmeren JM, Melker de HE. Safety of the bivalent human papillomavirus vaccine--results following administration of more than 192,000 doses. Ned Tijdschr Geneeskd 2009;153:A964.
42. Harper DM, Franco EL, Wheeler C et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. Lancet 2004;36*4*:1757-65.
43. Pedersen C, Petaja T, Strauss G et al. Immunization of early adolescent females with human papillomavirus type 16 and 18 L1 virus-like particle vaccine containing AS04 adjuvant. J Adolesc Health 2007;40:564-71.
44. Medicines and Healthcare products Regulatory Agency www.mhra.gov.nl; Nov 2009.
45. Van Pelt W, Friesema I, Doorduyn Y, de Jager C, van Duynhoven Y. Trends in Gastro-enteritis in Nederland. Notitie met betrekking tot 2007. Bitlhoven: National Institute for Public Health and the Environment; 2008. RIVM project V/210221.
46. Narang A, Bose A, Pandit AN et al. Immunogenicity, reactogenicity and safety of human rotavirus vaccine (RIX4414) in Indian infants. Hum Vaccin 2009;5:414-9.
47. Ciarlet M, He S, Lai S et al. Concomitant use of the 3-dose oral pentavalent rotavirus vaccine with a 3-dose primary vaccination course of a diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated polio-Haemophilus influenzae type b vaccine: immunogenicity and reactogenicity. Pediatr Infect Dis J 2009;28:177-81.
48. Hua W, Izurieta HS, Slade B et al. Kawasaki Disease After Vaccination: Reports to the Vaccine Adverse Event Reporting System 1990-2007. Pediatr Infect Dis J 2009;28:943-947.
49. Loparev VN, Rubtcova EN, Bostik V et al. Distribution of varicella-zoster virus (VZV) wild-type genotypes in northern and southern Europe: evidence for high conservation of circulating genotypes. Virology 2009;383:216-25.
50. Donker GA. Continuous Morbidity Registration Sentinel Stations the Netherlands 2008. Utrecht: Nivel; 2009.
51. Bartelds AIM. Continuous Morbidity Registration Sentinel Stations the Netherlands 2001. Utrecht: Nivel; 2002.
52. Verheij RA, Te Brake JHM, Abrahamse H, Van den Hoogen H, Braspenning J, Van Althuis T. Netherlands Information Network of General Practice (LINH): Facts and figures on GP care in the Netherlands. Utrecht/Nijmegen: NIVEL/WOK; 2008.
53. Plotkin SA, Orenstein WA, Offit PA. Vaccines. Philadelphia: Elsevier; 2008.
54. Deckers JGM, F.G. S. Health information from primary care: final report December 1, 2001 - March 31, 2004. Utrecht: Netherlands Institute for Health Services Research (NIVEL); 2004.
55. Prismant. National Medical Registration. Utrecht: Prismant; 2000-2008.
56. Statistics Netherlands. Deaths by main primary cause of death, sex and age. Voorburg: CBS; 2000-2008.
57. Update: recommendations from the Advisory Committee on Immunization Practices (ACIP) regarding administration of combination MMRV vaccine. MMWR Morb Mortal Wkly Rep 2008;57:258-60.
58. Jacobsen SJ, Ackerson BK, Sy LS et al. Observational safety study of febrile convulsion following first dose MMRV vaccination in a managed care setting. Vaccine 2009;27:4656-61.
59. Czajka H, Schuster V, Zepp F, Esposito S, Douha M, Willems P. A combined measles, mumps, rubella and varicella vaccine (Priorix-Tetra): immunogenicity and safety profile. Vaccine 2009;27:6504-11.
60. Gillet Y, Steri GC, Behre U et al. Immunogenicity and safety of measles-mumps-rubella-varicella (MMRV) vaccine followed by one dose of varicella vaccine in children aged 15 months-2 years or 2-6 years primed with measles-mumps-rubella (MMR) vaccine. Vaccine 2009;27:446-53.

61. Sutradhar SC, Wang WW, Schlienger K et al. Comparison of the levels of immunogenicity and safety of Zostavax in adults 50 to 59 years old and in adults 60 years old or older. Clin Vaccine Immunol 2009;16:646-52.
62. Macaladad N, Marcano T, Guzman M et al. Safety and immunogenicity of a zoster vaccine in varicella-zoster virus seronegative and low-seropositive healthy adults. Vaccine 2007;25:2139-44.
63. Oxman MN, Levin MJ, Johnson GR et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med 2005;352:2271-84.
64. Tyring SK, Diaz-Mitoma F, Padget LG et al. Safety and tolerability of a high-potency zoster vaccine in adults >/= 50 or years of age. Vaccine 2007;25:1877-83.
65. Sexton K, McNicholas A, Galloway Y et al. Henoch-Schonlein purpura and meningococcal B vaccination. Arch Dis Child 2009;94:224-6.
66. Jackson C, Lennon DR, Sotutu VT et al. Phase II meningococcal B vesicle vaccine trial in New Zealand infants. Arch Dis Child 2009;94:745-51.

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Appendix 1 Overview changes in the NIP since 2000

Table A1 NIP 1st July 2001 – 31st August 2002

(change: aP added at 4 years of age, for all children born on or after 1 January 1998)

Age	Injection 1	Vaccine 1	Injection 2	Vaccine 2
2 months	DTwP-IPV	DTPw-IPV vaccine/NVI	Hib	Hib vaccine/NVI
3 months	DTwP-IPV	DTPw-IPV vaccine/NVI	Hib	Hib vaccine/NVI
4 months	DTwP-IPV	DTPw-IPV vaccine/NVI	Hib	Hib vaccine/NVI
11 months	DTwP-IPV	DTPw-IPV vaccine/NVI	Hib	Hib vaccine/NVI
14 months	MMR	MMR vaccine/NVI		
4 years	DT-IPV	DT-IPV vaccine/NVI	**aP**	**Acellulair pertussis vaccine/GSK**
9 years	DT-IPV	DT-IPV vaccine/NVI	MMR	MMR vaccine/NVI

Table A2 NIP 1st September 2002 – 28th February 2003

(change: Men C added at 14 months of age, for all children born on or after 1 June 2001)*

Age	Injection 1	Vaccine 1	Injection 2	Vaccine 2
2 months	DTwP-IPV	DTwP-IPV vaccine/NVI	Hib	Hib vaccine/NVI
3 months	DTwP-IPV	DTwP-IPV vaccine/NVI	Hib	Hib vaccine/NVI
4 months	DTwP-IPV	DTwP-IPV vaccine/NVI	Hib	Hib vaccine/NVI
11 months	DTwP-IPV	DTwP-IPV vaccine/NVI	Hib	Hib vaccine/NVI
14 months	MMR	MMR vaccine/NVI	**Men C**	**NeisVac-C/Baxter**
4 years	DT-IPV	DT-IPV vaccine/NVI	aP	Acellulair pertussis vaccine/GSK
9 years	DT-IPV	DT-IPV vaccine/NVI	MMR	MMR vaccine/NVI

* birth cohorts 01/06/1983-31/05/2001 were vaccinated in a catch-up campaign that started in June 2002

Table A3 NIP 1st March 2003 – 31st December 2004

(change: Hib given combined with DTwP-IPV at 2, 3, 4 and 11 months of age, for all children born on or after 1st April 2002*; and HBV added for infants in specified risk groups at 2, 4 and 11 months of age, for all children born on or after 1 January 2003)

Age	Injection 1	Vaccine 1	Injection 2	Vaccine 2
2 months	**DTwP-IPV/Hib**	**DTwP-IPV/Hib vaccine/NVI**	**HBV****	**HBVAXPRO/SP MSD**
3 months	**DTwP-IPV/Hib**	**DTwP-IPV/Hib vaccine/NVI**		
4 months	**DTwP-IPV/Hib**	**DTwP-IPV/Hib vaccine/NVI**	**HBV****	**HBVAXPRO/SP MSD**
11 months	**DTwP-IPV/Hib**	**DTwP-IPV/Hib vaccine/NVI**	**HBV****	**HBVAXPRO/SP MSD**
14 months	MMR	MMR vaccine/NVI	Men C	NeisVac-C/Baxter
4 years	DT-IPV	DT-IPV vaccine/NVI	aP	Acellulair pertussis vaccine/GSK
9 years	DT-IPV	DT-IPV vaccine/NVI	MMR	MMR vaccine/NVI

* Indicated is the birth cohort from which children received at least one injection of the newly introduced vaccination.
** Only children of whom at least one parent was born in a country where hepatitis B is moderately or highly endemic and children of whom the mother tested positive for HBsAg.

Table A4 NIP 1st January 2005 – 31st December 2005

(change: wP replaced by aP at 2, 3, 4 and 11 months of age, for all children born on or after 1 February 2004)*

Age	Injection 1	Vaccine 1	Injection 2	Vaccine 2
2 months	**DTaP-IPV/Hib**	**Infanrix IPV+Hib/GSK**	HBV**	HBVAXPRO/SP MSD
3 months	**DTaP-IPV/Hib**	**Infanrix IPV+Hib/GSK**		
4 months	**DTaP-IPV/Hib**	**Infanrix IPV+Hib/GSK**	HBV**	HBVAXPRO/SP MSD
11 months	**DTaP-IPV/Hib**	**Infanrix IPV+Hib/GSK**	HBV**	HBVAXPRO/SP MSD
14 months	MMR	MMR vaccine/NVI	Men C	NeisVac-C/Baxter
4 years	DT-IPV	DT-IPV vaccine/NVI	aP	Acellulair pertussis vaccine/GSK
9 years	DT-IPV	DT-IPV vaccine/NVI	MMR	MMR vaccine/NVI

* Indicated is the birth cohort from which children received at least one injection of the newly introduced vaccination.
** Only children of whom at least one parent was born in a country where hepatitis B is moderately or highly endemic and children of whom the mother tested positive for HBsAg.

Table A5 NIP 1st January 2006 – 31st May 2006

(change: HBV added at birth for children of whom the mother tested positive for HBsAg; and Infanrix IPV+Hib/GSK replaced by Pediacel/SP MSD at 2, 3, 4 and 11 months, for all children born on or after 1 February 2005)*

Age	Injection 1	Vaccine 1	Injection 2	Vaccine 2
At birth	**HBV****	**HBVAXPRO/SP MSD**		
2 months	**DTaP-IPV-Hib**	**Pediacel/SP MSD**	HBV***	HBVAXPRO/SP MSD
3 months	**DTaP-IPV-Hib**	**Pediacel/SP MSD**		
4 months	**DTaP-IPV-Hib**	**Pediacel/SP MSD**	HBV***	HBVAXPRO/SP MSD
11 months	**DTaP-IPV-Hib**	**Pediacel/SP MSD**	HBV***	HBVAXPRO/SP MSD
14 months	MMR	MMR vaccine/NVI	Men C	NeisVac-C/Baxter
4 years	DT-IPV	DT-IPV vaccine/NVI	aP	Acellulair pertussis vaccine/GSK
9 years	DT-IPV	DT-IPV vaccine/NVI	MMR	MMR vaccine/NVI

* Indicated is the birth cohort from which children received at least one injection of the newly introduced vaccination.

** Only for children of whom the mother tested positive for HBsAg.

*** Only children of whom at least one parent was born in a country where hepatitis B is moderately or highly endemic and children of whom the mother tested positive for HBsAg.

Table A6 NIP from 1st June – July/August 2006

(change: pneumococcal vaccination added at 2, 3, 4 and 11 months of age, for all children born on or after 1st April 2006; and introduction of combined vaccine DTaP-HBV-IPV/Hib at 2, 3, 4 and 11 months of age for children in specified risk groups born on or after 1st April 2006 [as a consequence a HBV vaccination at 3 months of age is added])

In general

Age	Injection 1	Vaccine 1	Injection 2	Vaccine 2
2 months	DTaP-IPV/Hib	Pediacel/SP MSD	**Pneumo**	**Prevenar/Wyeth**
3 months	DTaP-IPV/Hib	Pediacel/SP MSD	**Pneumo**	**Prevenar/Wyeth**
4 months	DTaP-IPV/Hib	Pediacel/SP MSD	**Pneumo**	**Prevenar/Wyeth**
11 months	DTaP-IPV/Hib	Pediacel/SP MSD	**Pneumo**	**Prevenar/Wyeth**
14 months	MMR	MMR vaccine/NVI	Men C	NeisVac-C/Baxter
4 years	DT-IPV	DT-IPV vaccine/NVI	aP	Acellulair pertussis vaccine/GSK
9 years	DT-IPV	DT-IPV vaccine/NVI	MMR	MMR vaccine/NVI

Specified risk groups

Age	Injection 1	Vaccine 1	Injection 2	Vaccine 2
At birth	HBV*	HBVAXPRO/SP MSD		
2 months	**DTaP-HBV-IPV/Hib****	**Infanrix hexa/GSK**	**Pneumo**	**Prevenar/Wyeth**
3 months	**DTaP-HBV-IPV/Hib****	**Infanrix hexa/GSK**	**Pneumo**	**Prevenar/Wyeth**
4 months	**DTaP-HBV-IPV/Hib****	**Infanrix hexa/GSK**	**Pneumo**	**Prevenar/Wyeth**
11 months	**DTaP-HBV-IPV/Hib****	**Infanrix hexa/GSK**	**Pneumo**	**Prevenar/Wyeth**
14 months	MMR	MMR vaccine/NVI	Men C	NeisVac-C/Baxter
4 years	DT-IPV	DT-IPV vaccine/NVI	aP	Acellulair pertussis vaccine/GSK
9 years	DT-IPV	DT-IPV vaccine/NVI	MMR	MMR vaccine/NVI

* Only for children born to mothers tested positive for HBsAg

** Only children of whom at least one parent was born in a country where hepatitis B is moderately or highly endemic and children of whom the mother tested positive for HBsAg.

Table A7 NIP from July/August 2006 – 31st December 2007

(change: in July/August 2006 there was a transition from separate simultaneous DTP-IPV and aP vaccines to a combined formulation DTaP-IPV vaccine for children at 4 years of age born from July/August 2002 onwards. This DTaP-IPV vaccine replaces the DT-IPV given previously at 4 years of age; in September/October 2006 the MMR vaccine of NVI is replaced by MMR Vax of GSK and Priorix of SP MSD, for children born from July/August 2005 onwards)

In general

Age	Injection 1	Vaccine 1	Injection 2	Vaccine 2
2 months	DTaP-IPV/Hib	Pediacel/SP MSD	Pneumo	Prevenar/Wyeth
3 months	DTaP-IPV/Hib	Pediacel/SP MSD	Pneumo	Prevenar/Wyeth
4 months	DTaP-IPV/Hib	Pediacel/SP MSD	Pneumo	Prevenar/Wyeth
11 months	DTaP-IPV/Hib	Pediacel/SP MSD	Pneumo	Prevenar/Wyeth
14 months	MMR	**MMR vaccine/NVI, Priorix/GSK, M-M-R VaxPro/SP MSD**	Men C	NeisVac-C/Baxter
4 years	**DTaP -IPV**	**Triaxis Polio (SP MSD)**		
9 years	DT-IPV	DT-IPV vaccine/NVI	MMR	MMR vaccine/NVI

Specified risk groups

Age	Injection 1	Vaccine 1	Injection 2	Vaccine 2
At birth	HBV*	HBVAXPRO/SP MSD		
2 months	DTaP-HBV-IPV/Hib**	Infanrix hexa/GSK	Pneumo	Prevenar/Wyeth
3 months	DTaP-HBV-IPV/Hib**	Infanrix hexa/GSK	Pneumo	Prevenar/Wyeth
4 months	DTaP-HBV-IPV/Hib**	Infanrix hexa/GSK	Pneumo	Prevenar/Wyeth
11 months	DTaP-HBV-IPV/Hib**	Infanrix hexa/GSK	Pneumo	Prevenar/Wyeth
14 months	MMR	**MMR vaccine/NVI, Priorix/GSK, M-M-R VaxPro/SP MSD**	Men C	NeisVac-C/Baxter
4 years	**DTaP-IPV**	**Triaxis Polio (SP MSD)**		
9 years	DT-IPV	DT-IPV vaccine/NVI	MMR	MMR vaccine/NVI

* Only for children born to mothers tested positive for HBsAg

** Only children of whom at least one parent was born in a country where hepatitis B is moderately or highly endemic and children of whom the mother tested positive for HBsAg.

Table A8 NIP from 1st January 2008 onwards

(change: in 2008 the hepatitis B vaccination for children with Down syndrome born on or after 1 January 2008 is included in the NIP; and from July to mid-December 2008 Pediacel/SP MSD was replaced by Infanrix IPV+Hib/GSK at 2, 3, 4 and 11 months; and since February 2008 Infanrix IPV/GSK is also available for 4 year olds; and from September 2008 MMR vaccine/NVI is replaced by Priorix/GSK and from the end of October 2008 also by M-M-R VaxPro/SP MSD)

In general

Age	Injection 1	Vaccine 1	Injection 2	Vaccine 2
2 months	DTaP-IPV/Hib	**Pediacel/SP MSD, Infanrix IPV+Hib/GSK**	Pneumo	Prevenar/Wyeth
3 months	DTaP-IPV/Hib	**Pediacel/SP MSD, Infanrix IPV+Hib/GSK**	Pneumo	Prevenar/Wyeth
4 months	DTaP-IPV/Hib	**Pediacel/SP MSD, Infanrix IPV+Hib/GSK**	Pneumo	Prevenar/Wyeth
11 months	DTaP-IPV/Hib	**Pediacel/SP MSD, Infanrix IPV+Hib/GSK**	Pneumo	Prevenar/Wyeth
14 months	MMR	**MMR vaccine/NVI, Priorix/GSK, M-M-R VaxPro/SP MSD**	Men C	NeisVac-C/Baxter
4 years	DTaP -IPV	Triaxis Polio (SP MSD), **Infanrix IPV/GSK**		
9 years	DT-IPV	DT-IPV vaccine/NVI	MMR	**MMR vaccine/NVI, Priorix/GSK**

Specified risk groups

Age	Injection 1	Vaccine 1	Injection 2	Vaccine 2
At birth	HBV*	HBVAXPRO/SP MSD[1]		
2 months	DTaP-HBV-IPV/Hib**	Infanrix hexa/GSK	Pneumo	Prevenar/Wyeth
3 months	DTaP-HBV-IPV/Hib**	Infanrix hexa/GSK	Pneumo	Prevenar/Wyeth
4 months	DTaP-HBV-IPV/Hib**	Infanrix hexa/GSK	Pneumo	Prevenar/Wyeth
11 months	DTaP-HBV-IPV/Hib**	Infanrix hexa/GSK	Pneumo	Prevenar/Wyeth
14 months	MMR	**MMR vaccine/NVI, Priorix/GSK, M-M-R VaxPro/SP MSD**	Men C	NeisVac-C/Baxter
4 years	DTaP-IPV	Triaxis Polio (SP MSD), **Infanrix IPV/GSK**		
9 years	DT-IPV	DT-IPV vaccine/NVI	MMR	**MMR vaccine/NVI, Priorix/GSK**

* Only for children born to mothers tested positive for HBsAg

** Only children of whom at least one parent was born in a country where hepatitis B is moderately or highly endemic and children of whom the mother tested positive for HBsAg.

[1] HBVAXPRO/SP has been replaced temporarily by Engerix-B Junior due to delivery problems

Appendix 2 Composition of vaccines used in 2009

Vaccine	Composition
Pediacel/SP MSD RVG 32118 Diphtheria, tetanus, 5 component acellular pertussis vaccine, inactivated poliomyelitis vaccine and conjugated *Haemophilus influenzae* type b-vaccin (adsorbed) 0.5 ml	Purified diphtheria toxoid > 30 IU Purified tetanus toxoid > 40 IU Purified pertussis toxoid (PT) 20 µg Purified filamentous haemagglutinin (FHA) 20 µg Purified fimbrial agglutinogens 2 and 3 (FIM) 5 µg Purified pertactin (PRN) 3 µg Inactivated type 1 poliovirus (Mahoney) 40 DU Inactivated type 2 poliovirus (MEF-1) 8 DU Inactivated type 3 poliovirus (Saukett) 32 DU *Haemophilus influenzae* type b polysaccharide (polyribosylribitol phosphate) 10 µg conjugated to tetanus toxoid (PRP-T) 20 µg absorbed to aluminium phosphate 1.5 mg
MMR vaccine/NVI RVG 17654 Mumps, measles and rubella vaccine 0.5 ml	Mumps virus (Jeryl Lynn) > 5000 p.f.u. (plaque forming unit) Measles virus (Moraten) > 1000 p.f.u. Rubella virus (Wistar RA 27/3) > 1000 p.f.u.
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 Al3+
Prevenar/Wyeth EU/1/00/167 Pneumococcal saccharide conjugated vaccine (adsorbed) 0.5 ml	Pneumococcal polysaccharide serotype 4* 2 µg Pneumococcal polysaccharide serotype 6B* 4 µg Pneumococcal polysaccharide serotype 9V* 2 µg Pneumococcal polysaccharide serotype 14* 2 µg Pneumococcal oligosaccharide serotype 18C* 2 µg Pneumococcal polysaccharide serotype 19F* 2 µg Pneumococcal polysaccharide serotype 23F* 2 µg *Conjugated to the CRM197 carrier protein and adsorbed to aluminium phosphate 0.5 mg
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+}
HBVAXPRO/ SP MSD EU/1/01/183 Hepatitis B vaccine for children and adolescents 0.5 ml	Hepatitis B-virus surface antigen, recombinant* HBsAg) 5µg Adsorbed to amorphe aluminiumhydroxyphosphatesulphate 0.25 mg *yeast strain *Saccharomyces cerevisiae* (2150-2-3)

Infanrix Hexa/GSK EU/1/00/152 Diphtheria, tetanus, pertussis (acellular component), hepatitis B (rDNA), inactivated poliomyelitis vaccine and conjugated *Haemophilus influenzae* type b-vaccine (adsorbed) 0.5 ml	Adsorbed diphtheria toxoid > 30 IU Adsorbed tetanus toxoid > 40 IU Adsorbed pertussis toxoid (PT) 25 µg Adsorbed filamentous haemagglutinin (FHA) 25 µg Adsorbed pertactin (PRN) 8 µg Adsorbed recombinant HBsAg protein 10 µg Inactivated type 1 poliovirus (Mahoney) 40 DU Inactivated type 2 poliovirus (MEF-1) 8 DU Inactivated type 3 poliovirus (Saukett) 32 DU Adsorbed purified capsular polysaccharide of Hib (PRP) 10 µg covalently bound to tetanus toxoid (T) 20-40 µg
Triaxis Polio/SP MSD RVG 27569 Diphtheria, tetanus, pertussis (acellular component) and inactivated poliomyelitis vaccine (adsorbed) 0.5 ml	Purified diphtheria toxoid > 2 IU Purified tetanus toxoid > 20 IU Purified pertussis toxoid (PT) 2.5 µg Purified filamentous haemagglutinin (FHA) 5 µg Purified fimbrial agglutinogens 2 and 3 (FIM) 5 µg Purified pertactin (PRN) 3 µg Inactivated type 1 poliovirus (Mahoney) 40 DU Inactivated type 2 poliovirus (MEF-1) 8 DU Inactivated type 3 poliovirus (Saukett) 32 DU adsorbed at aluminium phosphate 0.33 mg
MMR Vax /SP MSD RVG 17672 Mumps, measles and rubella vaccine 0.5 ml	Mumps virus (Jeryl Lynn) > 5000 TCID50 (tissue culture infectious doses) Measles virus (Schwartz) > 1000 TCID50 Rubella virus (Wistar RA 27/3) > 1000 TCID50
Priorix/GSK RVG 22052 Mumps, measles and rubella vaccine 0.5 ml	Mumps virus (RIT 4385) > 103.7 CCID50 (cell culture infectious doses) Measles virus (Schwartz) > 103.0 CCID50 Rubella virus (Wistar RA 27/3) > 103.0 CCID50
Infanrix IPV + Hib / GSK RVG 22123 / RVG 34567 Diphteria, tetanus, pertussis (acellular component), inactivated poliomyelitis vaccine and conjugated *Haemophilus influenzae* type b-vaccine (adsorbed) 0.5 ml	Adsorbed diphtheria toxoid > 30 IU Adsorbed tetanus toxoid 20 - 40 IU Adsorbed pertussis toxoid (PT) 25 µg Adsorbed filamentous haemagglutinin (FHA) 25 µg Absorbed pertactin (PRN) 8 µg Inactivated type 1 poliovirus (Mahoney) 40 DU Inactivated type 2 poliovirus (MEF-1) 8 DU Inactivated type 3 poliovirus (Saukett) 32 DU *Haemophilus influenzae* type b polysaccharide 10 µg
Infanrix IPV / GSK RVG 34568 Diphtheria, tetanus, pertussis (acellular component), inactivated poliomyelitis vaccine 0.5 ml	Adsorbed diphtheria toxoid > 30 IU Adsorbed tetanus toxoid > 40 IU Adsorbed pertussis toxoid (PT) 25 µg Adsorbed filamentous haemagglutinin (FHA) 25 µg Absorbed pertactin (PRN) 8 µg Inactivated type 1 poliovirus (Mahoney) 40 DU Inactivated type 2 poliovirus (MEF-1) 8 DU Inactivated type 3 poliovirus (Saukett) 32 DU

M-M-R VaxPro / SP MSD EU/1/06/337/001 Mumps, measles and rubella vaccine 0.5 ml	Mumps virus (Jeryl Lynn) > 12,500 TCID50 (tissue culture infectious doses) Measles virus (Enders' Edmonston) > 1000 TCID50 Rubella virus (Wistar RA 27/3) > 1000 TCID50
Engerix-B Junior RVG 24290 Recombinant hepatitis-B-vaccin (adsorbed) 0.5 ml	Hepatitis B-virus surface antigen, recombinant 10 µg
Cervarix / GSK	

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

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