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H.E. de Melker | E.A. van Lier (eds)

The National Immunisation Programme in the Netherlands

Developments in 2008

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Abstract

The National Immunization Programme in the Netherlands
Developments in 2008

The National Immunization Programme (NIP) in the Netherlands is both effective and safe. Continuous surveillance and research are necessary in order to determine whether adjustment to the programme is needed. This report gives an overview of all developments in 2008 with regard to the availability of vaccines, vaccine effectiveness, adverse events, disease burden, health economic aspects and international perspectives that are relevant for the NIP.

In 2008 hepatitis B vaccination for children with Down's syndrome was added to the NIP – apart from that the programme remained unchanged. Because national vaccination coverage is high, most of the diseases currently covered by the NIP are under control. One exception is pertussis, of which the number of cases continues to be high and the peak for 2008 was earlier than expected. Furthermore, outbreaks of mumps and measles were observed, mainly among unvaccinated people.

The report gives recommendations for improving the NIP. In particular, research to enable optimizing vaccination schedules is necessary. This applies mainly to pertussis, pneumococcal disease and MMR (mumps, measles, rubella). In the short term, data from the so-called PIENTER-2 study on the reaction of the immune system to the vaccinations will become available. This information is important to see whether other vaccination schedules are necessary. Furthermore, the introduction of HPV-vaccination in 2009 will be monitored closely.

The National Health Council is considering vaccination against hepatitis B, rotavirus, varicella and herpes zoster. This report contains recommendations for future surveillance and research for these diseases and for hepatitis A (focusing on travel to countries where it occurs), tuberculosis and influenza (maintaining vaccination of selective groups and encouraging vaccination of health care workers), meningococcal B disease (further investigation of decreasing trend), and RSV (vaccine development).

Key words:
National Immunization Programme, MMR, DTaP-IPV, *Haemophilus influenzae* type b, meningococcal C disease

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Rapport in het kort

Het Rijksvaccinatieprogramma in Nederland
Ontwikkelingen in 2008

Het Rijksvaccinatieprogramma (RVP) in Nederland is effectief en veilig. Wel blijven constant toezicht en onderzoek van belang om te beoordelen of aanpassing nodig is. Dit rapport geeft een overzicht van alle ontwikkelingen in 2008 van beschikbaarheid van vaccins, vaccineffectiviteit, bijwerkingen, ziektelast, gezondheidseconomische aspecten en internationale perspectieven die relevant zijn voor het RVP.

In 2008 werd hepatitis B-vaccinatie voor kinderen met downsyndroom aan het RVP toegevoegd, verder bleef het RVP ongewijzigd. De meeste van de huidige RVP-ziekten zijn onder controle omdat de nationale vaccinatiegraad hoog is. Een uitzondering is kinkhoest, waarvan het hoge aantal gevallen aanhoudt en de piek in 2008 eerder viel dan verwacht. Tevens zijn uitbraken van bof en mazelen gesignaleerd, voornamelijk bij mensen die niet zijn gevaccineerd.

Het rapport doet aanbevelingen om het RVP te verbeteren. Vooral onderzoek naar optimale vaccinatieschema's is nodig, oftewel de leeftijd waarop kinderen worden ingeënt. Dat geldt vooral voor kinkhoest, pneumokokken en BMR (bof, mazelen, rodehond). Binnenkort zijn gegevens uit het zogeheten PIENTER-2 onderzoek beschikbaar over de reactie van het immuunsysteem op de vaccinaties. Dit is belangrijke informatie om te zien of andere vaccinatieschema's nodig zijn. Verder zal de invoering van HPV-vaccinatie in 2009 nauwgezet worden gevolgd.

De Gezondheidsraad beraadt zich over vaccinatie tegen hepatitis B, rotavirus, waterpokken en gordelroos. In dit rapport staan aanbevelingen voor toezicht en onderzoek naar deze ziekten en naar hepatitis A (aandacht voor reizen naar landen waar het voorkomt), tuberculose en griep (vaccinatie voor selecte groep behouden en voor personeel in de gezondheidszorg stimuleren), meningokokken B (verder onderzoek naar dalende trend) en RSV (vaccinontwikkeling).

Trefwoorden:
Rijksvaccinatieprogramma, BMR, DKTP, *Haemophilus influenzae* type b, meningokokken C

Preface

The National Institute for Public Health and the Environment (RIVM) informs the Ministry of Health, Welfare and Sports (VWS) on developments with respect to vaccine-preventable diseases that are relevant for the Netherlands.
This report gives an overview of the developments in 2008 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) and pneumococcal disease. Furthermore influenza and tuberculosis are discussed, as programmatic vaccination outside the NIP is in place. Finally, developments with regard to (potential) new target diseases are described: human papillomavirus (HPV) infection (included in the NIP starting in 2009), rotavirus infection, varicella zoster virus (VZV) infection, meningococcal serogroup B disease, respiratory syncytial virus (RSV) infection and hepatitis A. A similar report on the developments in 2007 was published earlier.[1]
The report is structured as follows. In chapter 1 a brief introduction is provided on the changes in the NIP during 2008, the changes in the organisational structure of the NIP, and vaccine coverage. Chapter 2 focuses on the diseases which are currently targeted in the NIP. The amount of new information that has become available in 2008 with respect to a certain disease, is reflected in the size of the section concerned. In chapter 3 programmatic vaccination outside the NIP is addressed. The NIP could be extended in the future with new target diseases, which are discussed in chapter 4. As a broader issue of current interest the necessity for research on alternative vaccination schedules is addressed in chapter 5. Finally, a summary of the recommendations on vaccination, surveillance and research provided in the separate sections is given in chapter 6.
The information provided in this report may contribute to the decision making process on the composition of the NIP.

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Contents

List of abbreviations

ACIP	Advisory Committee on Immunization Practices
AEFI	Adverse Events Following Immunization
aP	acellular Pertussis
BCG	Bacil Calmette Guerin
CDC	Centre for Disease Control and Prevention
CI	Confidence Interval
CIb	Centre for Infectious Disease Control, the Netherlands
CMR	Continuous Morbidity Registration Centres
CSF	Cerebrospinal Fluid
c-VDPV	circulating Vaccine-Derived Polio viruses
DTP	Combination of Diphtheria, Tetanus, and Pertussis vaccines
ECDC	European Centre for Disease Control and Prevention
ELISA	Enzyme-Linked ImmunoSorbent Assay
FHA	Filamentous Haemagglutinin
GBS	Guillain-Barré Syndrome
GGD	Public Health Service
GP	General Practitioner
GSK	Glaxo Smith Kline
HBIg	Hepatitis B Immunoglobulin
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
Hib	*Haemophilus influenzae* type b
HPV	Human Papillomavirus
hrHPV	high risk genotype HPV
ICD	International Classification of Diseases
IgM	Immunoglobulin M
ILI	Influenza-Like Illness
IPCI	Integrated Primary Care Information
IPD	Invasive Pneumococcal Disease
IPV	Inactivated Polio Vaccine
LCI	Preparedness and Response Unit of the CIb
MDR	Multidrug Resistant
Men B	Meningococcal B
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
NIH	National Institute of Health
NIP	National Immunisation Programme
NIVEL	Netherlands Institute for Health Services Research
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 Immunization Effect To Evaluate the NIP
Pneumo	Pneumococcal vaccination
Prn	Pertactin
Ptx	Pertussis toxoid
QALY	Quality Adjusted Life Years
RCC	Regional Certification Commission
RIVM	National Institute for Public Health and the Environment, the Netherlands
RSV	Respiratory Syncytial Virus
SNPG	Foundation National Influenza Prevention Programme
SP-MSD	Sanofi Pasteur MSD
TB	Tuberculosis
UK	United Kingdom
USA	United States of America
SOR	Strategic Research RIVM
VAERS	Vaccine Adverse Events Reporting System
VDPV	Vaccine Derived-Polio Virus
VE	Vaccine Effectiveness
VLP	Virus Like Particles
VWS	Ministry of Health, Welfare and Sports, the Netherlands
VZV	Varicella Zoster Virus
WHO	World Health Organisation
XDR	Extremely Drug Resistant
ZonMw	the Netherlands Organisation for Health Research and Development

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Summary

This report gives an overview of the developments in 2008 with regard to availability of vaccines, vaccine effectiveness, adverse events, epidemiology, disease burden, health economic aspects, and international perspectives that are relevant for the National Immunisation Programme (NIP) in the Netherlands. The report includes information with regard to the diseases included in the current NIP (diphtheria, tetanus, poliomyelitis, pertussis, *Haemophilus influenzae* type b, invasive pneumococcal disease, hepatitis B (risk groups), mumps, measles, rubella (MMR) and meningococcal serogroup C disease), programmatic vaccination outside the NIP (influenza and tuberculosis) and (potential) future NIP vaccine candidates (vaccines against human papillomavirus (HPV) infection, rotavirus infection, varicella zoster virus (VZV) infection, meningococcal serogroup B disease, respiratory syncytial virus infection and hepatitis A).

In 2008, no changes in the vaccination schedule were made, with exception of inclusion of the hepatitis B vaccination for children with Down syndrome (born on or after 1 January 2008) in the NIP. As from 2009 vaccination against human papillomavirus (HPV) will be included in the NIP as well.
Most of the target diseases of the current NIP are largely under control as a result of a generally high national vaccination coverage. However, the incidence of pertussis was not only still at a high level, but also showed an earlier epidemic peak than expected. Furthermore, a mumps outbreak occurred in 2007/2008, mainly in low vaccination coverage areas in the so-called Bible Belt. In 2008, a measles outbreak occurred, mainly among unvaccinated individuals because of anthroposophist beliefs.

Several recommendations regarding surveillance, research and control of vaccine preventable diseases in the Netherlands are given. Regarding pertussis modeling and cost-effectiveness studies to test and compare possible future pertussis vaccination strategies such as cocooning and adolescent or adult booster vaccinations are proposed. Furthermore, more research to identify the optimal schedule for pneumococcal and MMR vaccination is recommended.
In the short term, data on the prevalence of antibodies against different pathogens as measured in a population-based serum collection (PIENTER-2 study) will also become available. This will give information into the susceptibility gaps in the orthodox reformed that refuse vaccination on religious grounds. Furthermore, this will provide insight into the decrease of both vaccine induced and naturally induced antibodies in the general population. This is an important tool to study whether vaccination strategies need to be changed.
With regard to the uptake of HPV-vaccination of girls 12 years of age and the catch-up campaign (girls 13-16 years) it is essential to implement the monitoring plan including vaccine acceptance, safety, pathogen and disease surveillance.

An advice of the National Health Council regarding universal hepatitis B vaccination is expected in the beginning of 2009. Furthermore, the desirability of vaccination against rotavirus, varicella and herpes zoster is considered. In this report recommendations for surveillance and research are made for these diseases. In addition, recommendations for hepatitis A (attention for traveling to endemic countries), tuberculosis and influenza (maintaining vaccination of a selective group and encouraging vaccination against influenza for health care workers), meningococcal B disease (further investigation of decreasing trend), and respiratory syncytial virus (vaccine development) are included in the report.

In the report some issues of current interest in the field of routine vaccination into the NIP are discussed. Although it apparently is hard to change a vaccination schedule once it has been introduced, other vaccination schedules might be more attractive, for immunological, epidemiological and/or cost-effectiveness reasons. This accounts for pertussis, pneumococcal disease and measles and rubella in particular. More research is needed to study the effect of such potential schedule changes.

The NIP in the Netherlands is effective and safe. However, continued monitoring of the effectiveness and safety of the NIP is important, as well as regular review of epidemiological and vaccinological developments as new vaccines become available.

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1 Introduction

1.1 Background

In 2007, the 50-year anniversary of the Dutch National Immunisation Programme (NIP), a government-funded programme since 1957, was celebrated. Vaccination of a large part of the population in the Netherlands against diphtheria, tetanus and pertussis (DTP) was introduced in 1952. The 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.

Table 1 Vaccination schedule of the NIP from 2006 onwards

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

[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 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 2008

In 2008, no major changes in the NIP were made with exception of inclusion of the hepatitis B vaccination for children with Down syndrome (born on or after 1 January 2008) in the NIP. This vaccination was formerly administered by the physician. Overall changes in the NIP since 2000 are summarised in Appendix 1. Information on the composition of the vaccines used in 2008 is given in Appendix 2.

In 2008, the Health Council of the Netherlands has recommended the introduction of vaccination against human papillomavirus (HPV) for twelve-year-old girls through the NIP. Furthermore girls aged thirteen to sixteen at the time that HPV-vaccination is introduced are recommended to be vaccinated in the context of a catch-up programme.[2] In November 2008, the Minister of the Ministry of Health, Welfare and Sports (VWS) decided to introduce HPV-vaccination in the NIP in 2009.

1.3 Role of the Centre for Infectious Disease Control (CIb) in the NIP

In the Netherlands, the Ministry of Health, Welfare and Sports (VWS) decides on vaccination policy. The National Institute for Public Health and the Environment (RIVM) has a long-standing responsibility to inform the Ministry on relevant developments with regard to (future) components of the NIP based on surveillance and epidemiological and microbiological research.
Following the establishment of the CIb, in 2005 the CIb became responsible for the direction of the NIP and became also responsible for the coordination of the execution of the NIP. While the Dutch Health Council is the body to advise the ministry, based on new scientific data, on the future of the NIP and the desirability to change the programme by the inclusion of new vaccines[3], the CIb/RIVM supports this process by providing insight in the epidemiological situation in the Netherlands based on its surveillance and epidemiological analysis and delivers advice based on these analysis complemented by mathematical modelling, cost-effectiveness analysis and scenario analysis.
To fulfil this role, the organisational structure of the NIP on national level was changed. Regional vaccination administration centres have become part of the CIb by January 2008. Thus RIVM spans the whole chain from intervention, surveillance, research, and control.

1.4 Vaccination coverage

The national immunization coverage in the Netherlands has been excellent since the start of the NIP. A new management information system (PRÆVENTIS) has been brought into use in 2005 to register vaccination status. The introduction of this system offers new opportunities to analyse future vaccination coverage levels because vaccination coverage figures will be available at an individual level. New data on vaccination coverage are expected in June 2009, the data presented here are the same as in the former report on developments in 2007.[1] In 2008, national coverage levels for all vaccines used in the Netherlands exceeded the 90% level and met the standards set by the World Health Organisation (WHO). Vaccination coverage for newborns was reported to be higher for all vaccinations as compared to the previous year (Table 2). Among toddlers the vaccination coverage for DTaP-IPV has decreased with 0.6% as compared to the previous year. Table 2 shows a major increase in the vaccination coverage for HBV among 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.
Seven provinces reported over 90% vaccination coverage for all vaccines used. In the other five provinces Zeeland, Gelderland, Flevoland, Utrecht and Noord-Holland, the coverage for at least one vaccination among (pre)schoolchildren was slightly below 90%. Most municipalities with low vaccination coverage are situated in the so-called ‘Bible Belt’ where groups of orthodox reformed people live who refused vaccination for religious reasons.[4]

Table 2 Vaccination coverage per vaccine for age cohorts of newborns, toddlers, and school-children in 2006-2008

Vaccination coverage (%)											
		Newborns*					Toddlers*		School-children*		
Report-year	Cohort	DTaP-IPV	Hib	Men C	MMR	Cohort	DTaP-IPV	aP	Cohort	DT-IPV	MMR**
2006	2003	94,3	95,4	94,8	95,4	2000	92,5	89,3	1995	93,0	92,9
2007	2004	94,0	95,0	95,6	95,9	2001	92,1	90,8	1996	92,5	92,5
2008	2005	**94,5**	**95,1**	**95,9**	**96,0**	2002	**91,5**	**91,0**	1997	**92,6**	**92,5**

Vaccination coverage (%)			
		Newborns*	
Report-year	Cohort	HBV[a]	HBV[b]
2006	2003	86,7	90,3
2007	2004	88,7	92,3
2008	2005	**90,7**	**97,4**

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

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

[a] Only for children of whom at least one parent was born in a country where hepatitis B is moderately or highly endemic

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

2 Current National Immunization Programme

2.1 Diphtheria

F.R. Mooi, F. Reubsaet

Disease
Epidemiology
In the period 2000-2006, tox-plus strains *C. ulcerans* were isolated from the nasopharynx of a 59 year old not-vaccinated woman, not recently travelled abroad and from a 26 year old women with lymphangitis.; in 2007 three cases of cutaneous diphtheria were notified caused by *C. diphtheriae* (2 cases) and *C. ulcerans* (1 case). No diphtheria cases were reported in the first 28 weeks of 2008, and no diphtheria-related isolates were send for confirmation in the first 37 weeks of 2008 to the National Institute for Public Health and the Environment.

Recommendations for vaccination, surveillance and control
In 2009 data on the prevalence of diphtheria antibodies as measured in the so-called PIENTER-2 study, a population based serum collection, will become available. This will give information into the susceptibility gaps in the orthodox reformed that refuse vaccination on religious grounds. Furthermore, this will provide insight into the decrease of both vaccine induced and naturally induced antibodies in the general population (0-79 years).

2.2 Pertussis

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

Vaccine
Recent changes in the NIP
In 2008 two different pertussis vaccines were used for primo- and booster vaccinations. For primo-vaccination, initially, Pediacel was used and this vaccine was gradually replaced by Infanrix. For the preschool booster Triaxis-polio was first used and this vaccine was gradually replaced by Infanrix-IPV. The many changes of pertussis vaccines in the NIP during the last 10 years have made it difficult to study the protection of a particular vaccine, in particular on the long term. Table 3 gives the geometric mean titers as measured at about one year of age after vaccination with different pertussis vaccines used in the NIP in various years. The variation in geometric mean titers might have impact on the (long term) effectiveness of the different vaccines. Interpretation is hampered by the lack of level of antibody levels needed for protection against pertussis disease and or infection.[5]

Tabel 3 Postvaccination geometric mean titers (GMT's) after administration of the different whole cell vaccines (WCV) and acellular vaccines (ACV) in children in their first year of life

Administered vaccine	Age in months	N	Ptx	FHA	Prn	Fim2	Fim3
WCV* (1993)	12	92	6	11	36	**	318
WCV* (2001 and 2004)	12/14	86	7	15	40	**	337
ACV, Infanrix (2005)	12	92	134	422	410	6	2
ACV, Pediacel (2006/7)	12	98	119	177	180	38	156

* Samples taken before 1997 were separated from those taken after 1997 because of a production change of the WCV in 1997 (a raise in potency)

** Not determined for WCV

Effectiveness

In Table 4 the vaccine-effectiveness is shown for children aged 1 and 2 years. Vaccine-effectiveness was calculated with the screening method[6] using the number of notified patients per year and assuming annual vaccination coverage of 96%. Although the estimated percentages should not be interpreted as 'true' efficacies they give insight in trends in effectiveness of pertussis vaccination in the last decade. Because of small numbers of patients, for some years it was not possible to apply the screening method to estimate vaccine-effectiveness. The higher vaccine effectiveness in the 2006 and 2007 likely reflects better protection from the acellular vaccine which replaced the whole-cell vaccine in 2005.

Table 4 Estimated vaccine effectiveness 1997-2007 as measured by the screening method

	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
1 yr	29%	38%	63%	78%	73%	63%	29%	54%	72%	87%	92%
2 yr	-	32%	22%	52%	46%	41%	-	-	67%	58%	92%

Adverse events

The number of reported adverse events following immunization (AEFI) with DTaP-IPV/Hib in 2007 was 664, compared to 719 and 593 in 2006 and 2005 respectively. Since the introduction of the acellular combination vaccine in January 2005, numbers fluctuate, but are considerably lower, compared to the era of DTwcP-IPV-Hib vaccination. The number of reports following DTwcP-IPV-Hib ranged between 999 and 1082 for the years 2001 till 2003. In 2004 there was negative media attention on the effectiveness and safety of this whole cell vaccine, resulting in 1730 reports.[7]

The addition of conjugate pneumococcal vaccine for children born from April first 2006 onwards had little influence on the number of adverse events. No new categories of adverse events were revealed. Until October 2008, 51 children (6.4%; 95%CI 4.8-8.2) with more or less severe local reactions following the fifth DTaP-IPV booster dose at fours years of age were reported. More than 50% of these children had primary series with acellular DTP-IPV-Hib vaccine, introduced in 2005. In the same period of 2007 and 2006 we received 13 (1.6%; 95%CI 0.7-2.5) and 12 (1.4%; 95%CI 0.6-2.2) reports on local reactions respectively.

Other studies show that local reactions > 5 cm were reported in as many as 37% of children receiving their fifth dose of acellular pertussis combination vaccines, especially in aP primed infants.[8] A swelling of the entire upper arm is reported in 2% of the cases.[9] A small study (n=20) in children who experienced an extensive local reaction and received another dose of DtaP showed no consistent relationship between pre- and post-vaccination titers and the extensiveness of the local reaction.[10]

A trial in Canada showed that injection site reactions were less common in 4-6 year-old-children who received vaccine with lower content of pertussis and diphtheria toxoids, compared to a combination vaccine with higher content, without inferior immunogenicity.[11]

In 2008 we did a survey on adverse events following the fifth DTaP-IPV vaccination in children primed with whole cell pertussis. We will compare these results with a survey, starting in 2009, among children, who received acellular pertussis combination vaccine as an infant.

Pathogen

Strain variation

Two major changes were observed in the *Bordetella pertussis* population compared to previous years. First, strains expressing Fim2 increased in frequency from 7% in the period 2001-2007 to 48% in 2008. The Fim2 strains replaced Fim3 strains (frequencies in the two periods, respectively, 96% and 40%). Second, an increase in *ptxP1* strains from 7% in the period 2001-2007 to 27% in 2008 was observed. The *ptxP1* strains replaced the *ptxP3* strains (frequencies in the two periods, respectively, 93% and 65%). It is possible that these shifts in the *B. pertussis* population have been driven by the replacement of the whole cell pertussis vaccine by an acellular vaccine in 2005.

Disease

Epidemiology

Since the sudden upsurge in 1996-1997, the incidence of reported and hospitalised pertussis cases shows peaks every 2-3 years. Peaks were observed in 1999, 2001, 2004 and 2007 (Figure 1). The pertussis incidence was expected to decrease in 2008, as the previous year was an epidemic year. However, compared to 2007 an increase in incidence was observed in the first five months of 2008 (the incidence is extrapolated for the whole year).

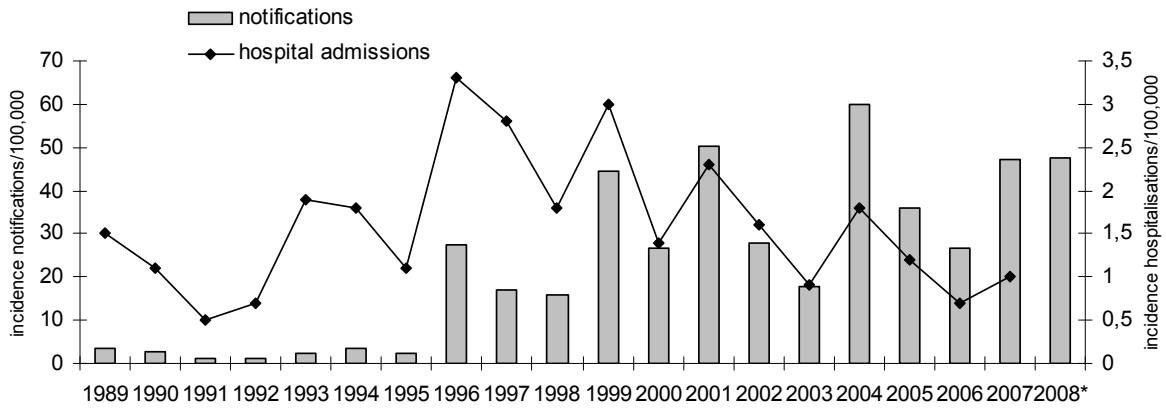


Figure 1 Incidence of notifications (grey bars) and hospitalisations (line) due to pertussis by year in 1989-June 2008. * Notifications in 2008 were extrapolated to a whole year. Data for hospitalisations are not yet available for 2008

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 (Figure 2).

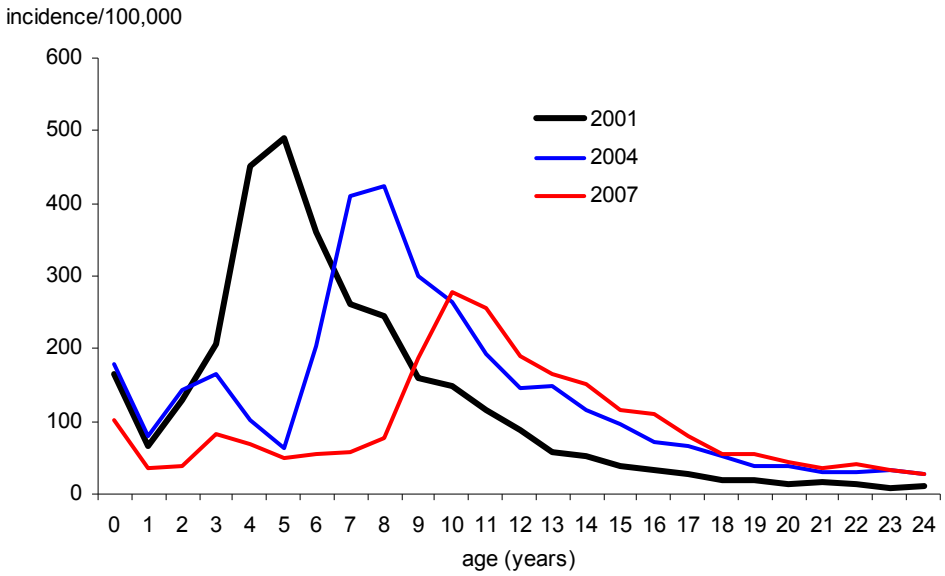


Figure 2 Age-specific incidence of notified cases in 2001 (before introduction of the preschool booster for four-year-olds) and in 2004 and 2007 (two epidemic years after introduction of the preschool booster for four-year-olds)

Since the replacement of the whole cell vaccine by an acellular vaccine in 2005, the incidence in children aged 2 years has decreased (Table 5), suggesting an increase in vaccine efficacy. Among adolescents and adults the incidence of notifications for pertussis shows an increasing trend.

Table 5 Age-specific incidence of notifications for pertussis in 2000-June 2008

	2000	2001	2002	2003	2004	2005	2006	2007	2008 until June
0 yr	104.6	165.6	97.0	62.3	179.3	94.4	75.3	102.5	122.1
1 yr	32.3	66.9	46.0	27.3	80.3	65.6	29.9	36.9	52.0
2 yr	77.6	128.8	72.6	44.5	142.9	100.6	68.7	39.8	43.6
3 yr	150.4	206.3	82.1	68.2	164.9	135.3	88.5	82.4	65.8
4 yr	243.1	452.7	130.7	41.5	101.6	81.7	46.1	69.0	57.6
5 yr	197.4	491.1	188.4	57.7	62.4	46.3	32.8	48.8	51.4
6 yr	173.2	361.8	195.2	143.1	204.8	38.2	34.1	53.8	64.0
7 yr	146.6	262.2	163.6	154.0	409.0	127.5	32.9	58.5	102.5
8 yr	123.0	244.8	131.5	120.0	422.9	247.2	109.9	75.9	95.3
9 yr	90.2	159.9	101.9	77.2	300.5	199.2	190.3	186.2	118.7
10-19 yr	29.9	61.2	44.2	28.4	120.6	78.8	68.0	145.2	213.4
20-59 yr	9.0	16.1	10.9	6.4	28.0	17.5	13.5	28.7	35.1
≥ 60 yr	6.6	10.9	7.4	4.0	21.2	14.1	11.4	23.3	28.8
total	26.6	50.0	27.9	17.6	59.8	36.0	26.6	47.4	60.4

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. No deaths were reported in 2007 and the first half of 2008. All 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 the introduction of the preschool booster, the number of hospitalized infants with pertussis shows a decreasing trend (Figure 3). This suggests that transmission from siblings to susceptible infants may have been reduced as a result of the preschool booster.

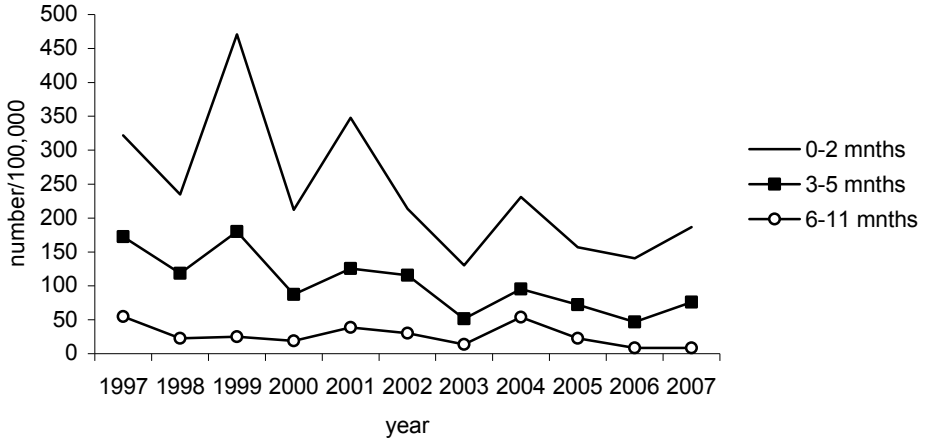


Figure 3 Number of hospitalized infants with pertussis per 100,000 and by age-group, 1997-2007

To identify which family members introduce pertussis in the household of an infant hospitalized for pertussis, we started a nationwide study (BINKI-study). From February 2006 until June 2008, 188 infants and their 693 family members have been included in the study. The enrolment of households ends in December 2008, but preliminary results indicate that in almost 70% of the infant cases the source can be found within the family, i.e. 23% of the mothers, 11% of the fathers and 23% of the siblings in the study had introduced pertussis in the household and thus most likely transmitted the infection of the infant. These results show that vaccinating family members, who are in close contact with newborns, is likely to reduce the disease burden due to pertussis among infants. Modeling- and intervention studies are needed to assess the most (cost) effective strategy to reduce the disease burden and to prevent pertussis in young infants.

Economic aspects
To reduce pertussis disease burden, universal vaccination of adolescents and adults is considered in many countries. Since not only health benefits, but also economical aspects should be considered when introducing new vaccinations, we estimated the medical costs associated with pertussis in the Netherlands (De Greeff et al., personal communication). The disease burden was estimated from the mandatory notification system, the National Medical Register (Prismant) and complemented with the number of clinically suspected cases by general practitioners. Estimates of disease burden in the period 1998-2005 were combined with data on health care consumption. The estimated yearly medical costs for pertussis were 1.76 million euro. Although infants represented 5% of cases, they accounted for nearly 50% of the total costs. The average cost per case was 1,490 euro in infants and approximately 75 euro at older ages.

Despite a high number of patients among both children and adults, the economic burden of pertussis is largely determined by costs for infant cases, making universal adolescent or adult booster strategies - to prevent pertussis in infants - at the moment economically less efficient.

Recommendations for vaccination, surveillance and control
The highest morbidity and mortality due to pertussis is found in 0-6 month old infants who are too young to be fully vaccinated. Protection of this age category is a primary aim of the vaccination programme. Direct protection may be achieved by neonatal vaccination. Indirect protection of infants may be realized by maternal vaccination or by decreasing the circulation of *B. pertussis* by cocooning (vaccination of individuals around the newborn), or booster vaccinations of adolescents and adults.
A study on the direct costs of pertussis carried out by the RIVM suggests that cocooning will be more attractive from an economical point of view than repetitive adolescent and adult vaccination. Therefore, we propose to carry out a study on the feasibility and effectiveness of maternal and neonatal vaccination and cocooning.

The current vaccination schedule is, in part, based on the immunogenicity of the NVI whole cell pertussis vaccine. This vaccine has been replaced by more immunogenic acellulair vaccines and it seems likely that the number, and spacing, of pertussis vaccinations can be changed, resulting in less doses and costs. Further, if cocooning, neonatal or maternal vaccination are introduced the first vaccination could be postponed by one month, possibly enhancing long term immunity. Therefore, we propose a study to compare the current schedule (2, 3, 4, 11 months and 3-4 yrs) with that of the schedule used in Scandinavia (3, 5, 12 months, 5-6 yrs).

The largest increase in pertussis cases in the last years, was seen in the age categories 10-20 years, 20-60 years and above. Although some studies indicate that morbidity and mortality of pertussis in adolescents and adults is significant, particularly in adults older than 60 years, reliable data are scarce. Yet these data are essential for cost-effectiveness studies. Therefore, we propose to investigate the disease burden due to pertussis in adolescents and adults. In line with this, we will participate in a study on the burden of several infectious diseases in elderly homes (SNIV study) in 2009, to estimate the incidence of pertussis among elderly.

To facilitate the decision making on future strategies, we propose to carry out modeling and cost-effectiveness studies to test and compare possible future vaccination strategies such as cocooning and adolescent or adult booster vaccinations. In 2008/2009, data on pertussis serology (pertussis toxin, pertactin, FHA and fimbriae) become available from the population-based serum collection in the general population (PIENTER-2); this offers the opportunity to update previous estimates on the frequency of infection for various age groups. In particular the high frequency of infection among adolescents and adults needs further confirmation.

With regard to the pathogen, it is highly recommended that a (sentinel) system is set up that allows the systematic collection of *Bordetella* strains to study the changes in the pathogen population in relation to vaccination. Such changes may reflect the emergence of strains which are less affected by vaccine-induced immunity. The sentinel system can also be used for the collection of other pathogens relevant for the NIP. The current system for the collection of strains has two important drawbacks. First, strains are not collected randomly and may not be representative for the whole population. Second, culture is being replaced by PCR in many medical laboratories, and this has resulted in a dramatic decrease in the number of strains sent to the RIVM.

2.3 Tetanus

S.J.M. Hahné, P.E. Vermeer-de Bondt

Vaccine

Recent changes in the NIP

In July/August 2006 a combined DTaP-IPV vaccine (Triaxis polio) replaced the DT-IPV vaccine (NVI) previously given at 4 years of age. This concerns children born from July/August 2002 onwards. The tetanus toxoid content of both vaccines is the same (> 20 IU).

Disease

Epidemiology

There is limited data available on the incidence of tetanus in The Netherlands. In hospital episode statistics, 6 patients with tetanus were reported in 2007 (compared to 7 in 2006). However, this data source is prone to misclassification: patients with tetany can be reported as tetanus, and verification of the diagnoses (and e.g. age and vaccination status) is not possible. In 2007, only one clinical case of suspected tetanus was reported on the RIVM laboratory forms. The very low anti-tetanus-toxine antibody titer did not rule out the clinical diagnosis. The patient was a 62 year old male with a history of a rusty nail wound 8 days prior to developing symptoms. He was treated with high doses human anti-tetanus immunoglobulins. The outcome is unknown. Tetanus is notifiable again since 1 December 2008.

International perspectives

A recent publication reported on the use of a Tetanus Quick Stick (TQS), a 'bed-side-test' to assess the immunity against tetanus in order to decide whether post-exposure prophylaxis is required in case of an injury. The TQS was demonstrated to be a valid instrument to measure the tetanus antibody concentration.[12, 13] A study by the same Belgian research group demonstrated that the TQS in patients below 61 years of age with a tetanus prone injury who anamnestically had an indication for tetanus vaccination (unknown or incomplete vaccination history, or last booster >10 years ago) led to a cost reduction of 2,27 euro per patient, compared to the situation when tetanus vaccination was given to all these patients.[14]

Recommendations for vaccination, surveillance and control

The main aim of the analyses of the population-based serum collection data (PIENTER 2-study) will be to study the level of protection in the Dutch population against tetanus. Results of this will be relevant e.g. to assess whether the current Dutch guidelines for post-exposure prophylaxis are adequate. PIENTER-2 tetanus results could also be analysed in combination with operational characteristics of the Tetanus Quick Stick (TQS), to assess its potential for use in Dutch clinical practice. By analysing tetanus IgG titers, it could be assessed in which proportion of individuals a TQS measurement could contribute to avoiding giving Tetanus Immune Globuline after a tetanus prone injury.

2.4 Poliomyelitis

H.G.A.M. van der Avoort

Vaccine

Recent changes in the NIP

There are no changes in the vaccine policy regarding poliomyelitis. IPV is and will be the vaccine of choice for protection against poliomyelitis within the NIP.

Availability and new developments

In line with a resolution accepted by the World Health Assembly in 2006 and reconfirmed in 2007, the WHO strongly advocates the extensive use of monovalent oral polio vaccine (mOPV) as best tool against circulation of a wild poliovirus or a Vaccine-Derived-PolioVirus (VDPV) after proven introduction of such viruses into populations with low or no vaccine coverage. Member countries are advised to prepare for the use of mOPV (P1 and P3) by making all necessary arrangements that permit use and guarantee the availability of these vaccines.

Discussions in the project team on updating the existing contingency plan for polio outbreak situations in the Netherlands have resulted in a new version of this plan in the beginning of 2008. The plan contains guidelines for the strategy to use polio vaccines in outbreak situations, tailored to the Dutch situation, based on recent knowledge and international expertise. Final decisions will be taken by the outbreak management team that will convene immediately after verification of the first signals that indicate import of wild poliovirus (or VDPV) in the Netherlands.

Effectiveness

The effectiveness of mOPV as best tool to fight/eliminate circulation of polioviruses (wild or VDPV) is well documented, especially for type 1. As a result of the lack of interference by P2 and P3 viruses in the vaccine, mOPV 1 induces three times more seroconversions in naïve vaccines compared to multivalent mOPV, provides higher and faster protecting antibody levels and provides better protection (lower levels of vaccine shedding) after challenge with a second dose of OPV. Results of a WHO-sponsored study on mOPV 1 in Egypt, performed at RIVM and CDC Atlanta, confirm these observations[15], but also document the genetic variability and evolution rates of OPV viruses from doses administered at birth and after challenge with these vaccines (van der Sanden et al., personal communication). The OPV paradox was again confirmed: the best way to generate and to fight VDPVs is use of OPV.

Pathogen

Strain variation

Wild type 2 poliovirus has been eliminated globally: the last isolate dates from Egypt 1998. However, the large outbreak of type 2 c-(irculating)VDPV in Northern Nigeria has caused already almost 200 cases. Vaccination efforts in Nigeria to stop this outbreak have been unsuccessful for several years. High population immunity against all three serotypes of polioviruses remains necessary. mOPV should only be used to fight circulating virus, in endemic countries and in outbreak situations.

The running definition of a VDPV is based on sequence divergence to the Sabin prototype strains in the OPV vaccine: Sabin-like isolates with more than 1% divergence are labelled VDPV.

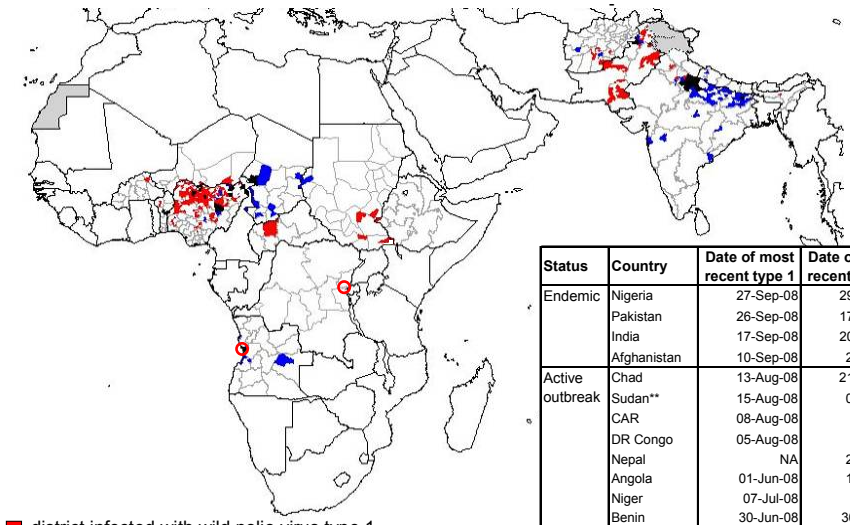
Global co-operation in the polio laboratory network has identified more than 40 immune-compromised persons (with or without symptoms for poliovirus infection) that have been shedding so called i-(mmunedeficiency- related)VDPVs for more than three months. Most of these patients have stopped

shedding spontaneously (although some after more than ten years) or have died. Only three patients are shedding virus at the moment (December 2008). Ambiguous or a-VDPVs have been detected from environmental samples or from stool surveys. The real source of these viruses cannot be established. Almost all these viruses can in principle cause epidemics under not or incompletely vaccinated populations.
Until recently all c-, i- and a-VDPV isolates also showed antigenic changes that readily could be detected by an ELISA test with cross-absorbed type specific antisera. This is not true anymore for all type 2 and type 3 VDPVs. Recent experience (e.g. data from the Nigeria P2 VDPV outbreak, and from a-VDPVs from Madagascar) has shown that in practice also less than 1% divergent strains can have circulating and neurovirulent properties and that VDPVs can escape present screening methods. Genetic sequencing of all polioviruses isolated in the Netherlands guarantees detection of all wild polioviruses and VDPVs. Global application of this sequencing strategy for characterization of polio isolates is too costly. This calls for a new definition of VDPVs and for new general diagnostic procedures for the detection of all VDPVs. CDC Atlanta has developed a new PCR based test that recognizes specific mutations known to be determinants for development of Sabin-like isolates to c-VDPV. Field testing of this new test in Specialized Reference Laboratories of the WHO Polio Laboratory Network (including RIVM) is presently ongoing. The proposed tests will be available for all laboratories of the Network after successful field testing, most likely by July 2009.

Disease

Epidemiology

The Global Polio Eradication Initiative has successfully reduced the annual number of poliomyelitis cases from about 350,000 at its start in 1988 to less than 1000 in 2007. Only 4 countries have never stopped endemic poliovirus circulation: India, Pakistan, Afghanistan and Nigeria. The extensive use of mOPV1 in India has almost eliminated this serotype in the big reservoirs Uttar Pradesh. However the number of P3 cases has grown, as could be expected. The choice to fight P1 first is driven by two findings: P1 outnumbered P3, but also was the virus type that spread much better, as all importations from endemic countries were P1.
The present situation in the other endemic counties in disappointing: Polio 1 circulation in Pakistan is demonstrated in districts that earlier were polio free for several years. The situation in Afghanistan remains stable: low but constant circulation levels have been see during the last years, due to the inability to reach all children because of dangerous and politically unstable situations. In Nigeria the main target to halve the number of infected districts in 2008 is not achieved, on the contrary more cases of polio have been diagnosed and again spread to surrounding countries is observed. A repetition of the events of 2003-5 when almost all African countries around the equator , as well as Jemen and Indonesia were hit by polio epidemics that all started from Northern Nigeria is feared again. Authorities in Saudi Arabia have made polio vaccination obligatory for all participants of the yearly hadj to Mekka hoping to prevent spread of poliovirus into the Asian continent.



Status	Country	Date of most recent type 1	Date of most recent type 3
Endemic	Nigeria	27-Sep-08	29-Aug-08
	Pakistan	26-Sep-08	17-Sep-08
	India	17-Sep-08	20-Sep-08
	Afghanistan	10-Sep-08	24-Jul-08
Active outbreak	Chad	13-Aug-08	21-Aug-08
	Sudan**	15-Aug-08	06-Jul-08
	CAR	08-Aug-08	NA
	DR Congo	05-Aug-08	NA
	Nepal	NA	27-Jul-08
	Angola	01-Jun-08	14-Jul-08
	Niger	07-Jul-08	NA
	Benin	30-Jun-08	30-Jun-08
	Burkina Faso	06-Jun-08	NA
	Ethiopia	27-Apr-08	NA

NA. Date of onset is prior to rolling 6-month period
**Final allocation of one case is under investigation

Figure 4 Wild poliovirus infected districts*, 15 April 2008 – 14 October 2008

Burden of disease

The last polio outbreak in the Netherlands occurred in 1992/3. Based on demographic figures one can expect that the number of unvaccinated persons in 2008 is again at least as big as in 1992. However, the number of polio cases worldwide has dropped dramatically, and thus there is clearly also a lower chance for importation of wild poliovirus of VDPV into the unvaccinated population in the Netherlands.

An increasing number of persons that have experienced poliomyelitis at young age is suffering from 'post-polio syndrome', often not recognized by general practitioners and medical specialists. In the Netherlands, it is estimated that there are about 20.000 post polio patients, with chronic fatigue and weakness in the same muscles that were affected during the period of illness 30-40 years ago.

International perspectives / economic aspects

Given the risks of generation of vaccine associated paralytic poliomyelitis (VAPP) and the occurrence of VDPVs with the potential to cause epidemics, more and more countries are switching to the use of IPV in their national vaccination programmes. The effectiveness of IPV in developing countries is however not very documented and the price of the vaccine and the invasive way of administration are clear drawbacks for developing countries to use IPV.

RIVM has participated in a WHO-sponsored study in Oman on the immune response of fractional doses of inactivated poliovirus vaccine (IPV) administered intradermally by a needle-free device. The study provides clear evidence that dose reduction (only 1/5 of the amount of antigen in regularly administered IPV is used) in combination with the child-friendly needle-free administration is an excellent and substantially more affordable alternative. Similar results have been obtained in a WHO-sponsored study in Cuba. These findings will drive global policy recommendations on IPV use in middle and low-income countries.

Global eradication of poliomyelitis is near: WHO strives to success before the new decennium. It is not realistic to keep donors interested in the programme for a longer period of time. Although the infrastructure set up for polio eradication in developing countries is more and more in use for other intervention programmes too, the actual impact of polio eradication efforts on other programmes is also enormous. Finishing the job in the four remaining endemic countries soon is a must as there are no real alternatives. In a recent meeting at National Institutes of Health (NIH) (Polio Immunization: Moving

Forward) international experts advised WHO to use IPV in combination with OPV in the end-game. Failure of the programme would lead within short time to many thousands of cases per year in countries where no system for routine vaccination is present. The Netherlands would without any doubt face new outbreaks of poliomyelitis under the risk population not vaccinated for religious reasons.

Recommendations for vaccination, surveillance and control
The European Regional Certification Commission (RCC) met in June 2007 in Copenhagen, on the occasion of the 5th anniversary of the Polio-free European Region. The RCC reviewed the data on poliovirus vaccination and surveillance and performed a risk assessment for transmission in the event of wild poliovirus importation for each of the 52 countries of the Region. The RCC considered that the Netherlands is at intermediate risk for such a transmission, as long as the surveillance activities, in place at the time will be continued at the present standards. Nationwide enterovirus surveillance and environmental surveillance in the risk area were considered as excellent and adequate tools for excluding poliovirus circulation in the Netherlands in the absence of surveillance of Acute Flaccid Paralysis, the WHO standard.
Should the outcome of the population-based serum collection (PIENTER-2 study), that measures the prevalence of antibodies against vaccine preventable diseases in a serum collection of the Dutch general population (0-79 years), identify new risk groups for poliovirus infection and/or transmission, adequate measures will be taken to overcome these deficiencies. An additional serum collection in this project/study offers insight into the immunity in socio-geographically clustered orthodox reformed individuals refusing vaccination on religious grounds.

2.5 *Haemophilus influenzae* serotype b (Hib) disease

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

Disease
Epidemiology
Since the introduction of vaccination in 1993, the number of patients with *H. influenzae* type b (Hib)-disease has decreased from 250 cases in 1993 to 12 cases in 1999 (Figures 5 and 6). However, in 2002-2005 the number of patients with Hib-disease increased significantly with a peak of 48 cases in 2004. After 2005 the annual number of cases decreased again to approximately 25 cases annually in the years 2006 and 2007 (Figure 5). The reason for the upsurge of cases of invasive Hib disease has remained enigmatic.

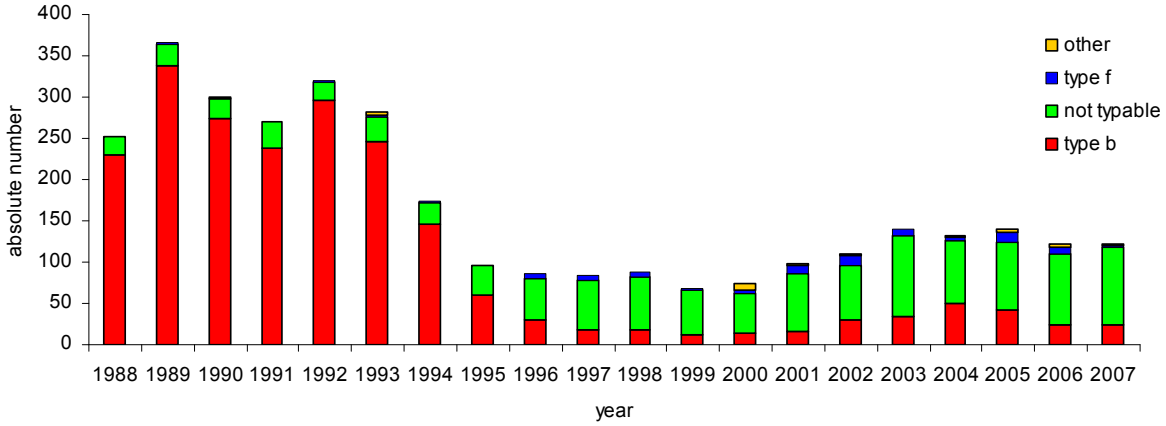


Figure 5 Absolute number of *H. influenzae* isolates by type, 1988-2007

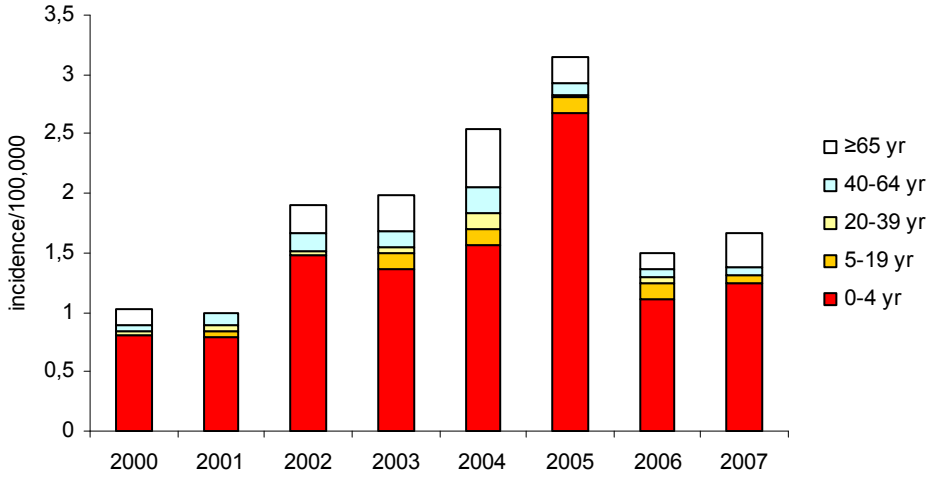


Figure 6 Age specific incidence of patients with invasive Hib disease by year

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 in 2006 and 2007 (Figure 7; the annual incidence per 100,000 is shown in Figure 8).

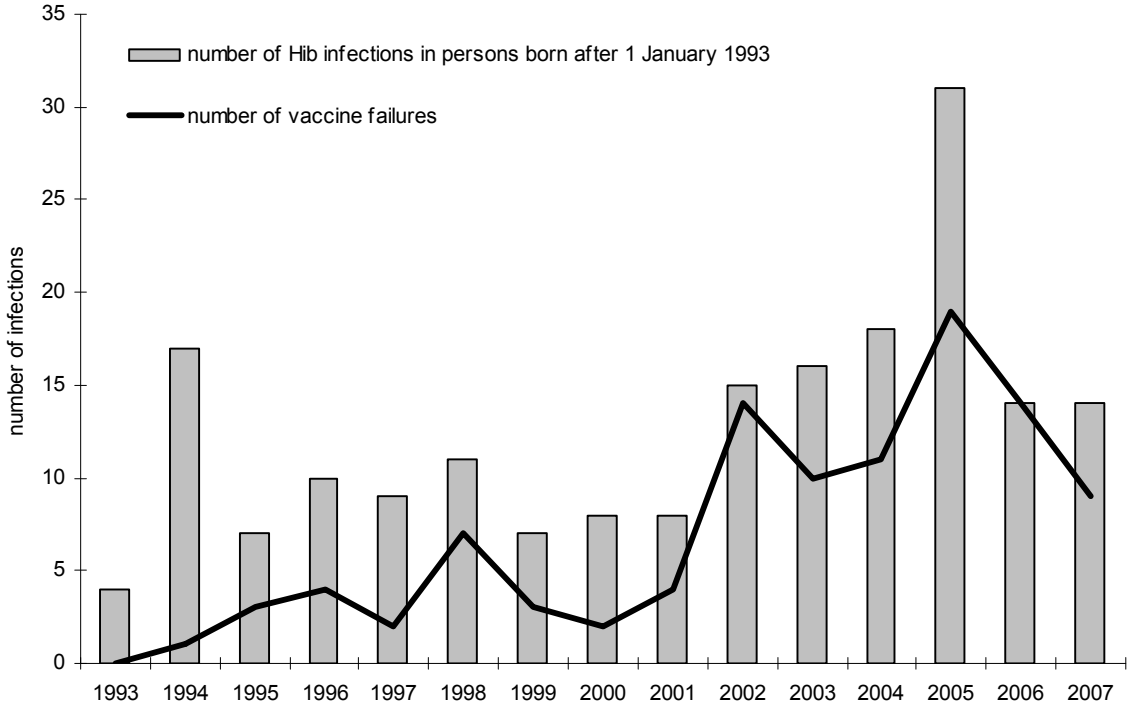


Figure 7 Annual number of Hib infections in persons targeted for vaccination (i.e. born after 1 January 1993) and number of vaccine failures

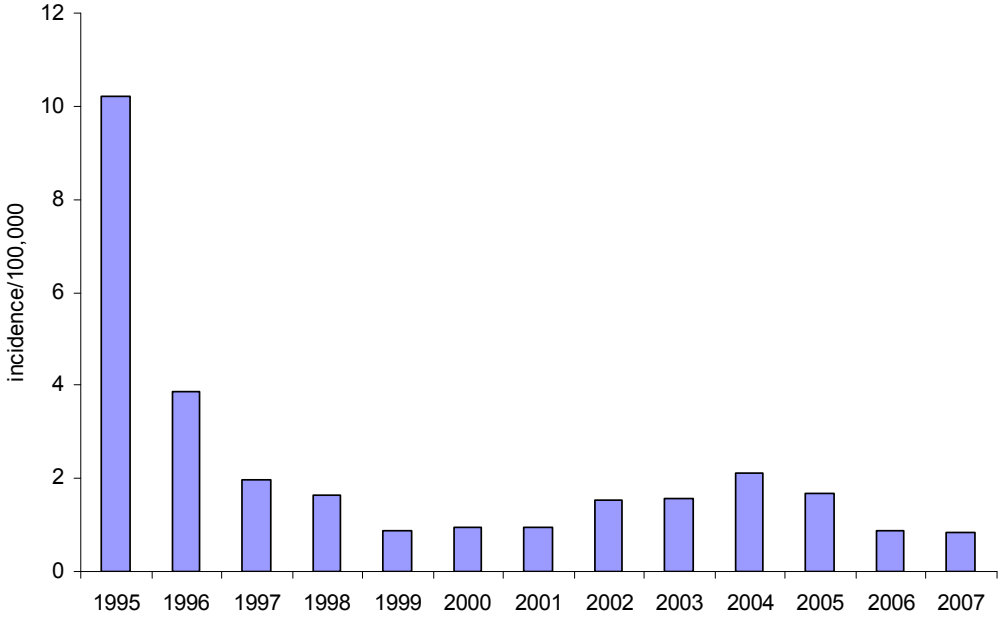


Figure 8 Incidence of invasive Hib infections in persons targeted for vaccination (i.e. born after 1 January 1993)

International perspectives

In countries where nationwide Hib vaccination is used the number of cases of Hib disease has dropped dramatically. However in the UK and in the Netherlands there was an upsurge of invasive Hib disease between 1999 and 2004. The majority of these cases were vaccine failures. In the UK, Oh et al. have studied the Hib carriage rate in individuals swabbed in 2005 and found a point prevalence of 4.2% in 6-16 year old children. No carriage could be detected in adults. This shows that Hib carriage was common during the sampling period in school-aged children suggesting they were a significant reservoir for ongoing transmission of Hib to susceptible individuals in the UK.[16]

However, it should be noticed that this cohort of children received the DT-whole cell pertussis-Hib combination vaccine as 3 doses in infancy without any subsequent booster. A booster has only been introduced since 2003 as a catch-up campaign for children under the age of four and since 2006 a booster dose at 12 months has been introduced in the routine schedule.

The reason for the vaccine failures in the UK and the Netherlands is still not completely clear. In the UK the increase rate of vaccine failures could in part be explained by the interaction of the Hib component of an acellular pertussis containing combination vaccine with the other components, resulting in a reduced primary immune response.[17] In the Netherlands the increase cannot be explained by interference of an acellular pertussis vaccine as this has only been used in infancy since 2005. Lee et al. showed that the avidity of the antibodies induced by the Hib conjugate vaccine in children experiencing vaccine failure was significantly lower than that of healthy controls. They conclude that children who experience Hib vaccine failure have a defect in immunological priming, leading to a qualitative difference in Hib-specific memory B cells. This leads to a decrease in functional activity of anti-Hib antibody and consequently to disease susceptibility.[18]

Low anti-PRP antibody avidity decreases the functional activity of anti-PRP antibody in the sera of these children experiencing vaccine failure, leading to disease susceptibility.

Recommendations for vaccination, surveillance and control

Further research is required to determine reasons for the occurrence of vaccine failures. This research should include study of the functionality and avidity of the vaccine induced antibodies in children in which the vaccine failed to protect against invasive Hib disease.

The population-based serum collection (PIENTER-2 study) established in 2006/2007 enables the study of vaccination on age-specific seroprevalence of Hib. In addition, comparison of serum samples collected in PIENTER-1 (1995/1996) and PIENTER-2 will enable the influence of natural boosting due to circulating Hib on the development of bactericidal activity of antibodies.

2.6 Mumps

S.J.M. Hahné, R.S. van Binnendijk

Vaccine

Recent changes in the NIP

Mid-2007, the NVI MMR vaccine was re-introduced in the Netherlands after it had been temporarily replaced by other MMR vaccines during part of 2006 and 2007.[1] Remaining stocks of M-M-RVAXPRO and Priorix were finished prior to restarting the NVI MMR vaccine.[19, 20] The NVI MMR vaccine, based on the mumps Jeryl Lynn strain, is produced in license of SP-MSD.

During a routine stability check in September 2008 of previously released batches of the MMR vaccines produced by the NVI, it appeared that some of the bottles in certain batches did no more meet the required concentration of mumps vaccine virus, although the concentration of virus was considered still to be above the level sufficient for immunogenicity. Subsequently, the Health Inspectorate decided that batches 133 and subsequent numbers should not be used, waiting for new test results. The measles and rubella vaccine virus content of the vaccines have been adequate throughout. To replace the NVI MMR vaccine, vaccines were purchased from GSK (Priorix) and SP-MSD (M-M-RVAXPRO). After a risk-assessment, the RIVM Centre for Infectious Disease Control did not see a reason to advise revaccination of children who may have received implicated MMR vaccine.[21]

Availability and new developments

An adaptation of the SP-MSD M-M-RVAXPRO vaccine was registered recently, and is now available in the Netherlands. In the adapted vaccine, human albumin used in the production of MMR is replaced by recombinant albumin.

Effectiveness

An overview of available mumps vaccines was recently published by the NVI. It concludes that the possibility of a genotype mismatch between the wild-type virus and the vaccine virus on the mumps vaccine effectiveness, as well as the possibility of waning vaccine-induced immunity should be further studied.[22]

Pathogen

Strain variation

Genotype D was the most frequently isolated genotype among the cases studied during the current outbreak.

Disease

Epidemiology

Limited information on the current epidemiology of mumps in the Netherlands is available as it is not a notifiable disease. When the new Public Health law will come into effect (December 1st, 2008) mumps will be notifiable.

In August 2007, a mumps outbreak was identified on basis of a genotype match of the mumps viruses isolated from several cases from different locations in The Netherlands, with subsequent spread to other regions.[23] Information on the outbreak was mainly derived from laboratory testing carried out by the RIVM-CIb. Based on these investigations and on the basis of unofficial reports, it is clear that only a minority of cases were offered laboratory testing, so the extent of the mumps outbreak is actually unknown. Therefore, a sentinel surveillance system was set-up which aimed to estimate the incidence

of mumps. For this, 15 GP practices in areas with low MMR coverage were invited to send information on characteristics of their practice population, the number of mumps cases seen, their vaccination status and the number of cases in their families. Data was collected retrospectively over three periods (1.9.2007 – 31.3.2008, 1.4.2008 – 30.6.2008 and 1.7.2008 – 31.12.2008). Information on complications of mumps infections is available from hospital episode statistics (data on 2008 will be available about mid 2009).
The laboratory testing of mumps disease included the testing of sera for the presence of mumps specific IgM antibodies and the testing of oropharyngeal specimens, urine and liquor for the presence of mumps virus (RNA) by realtime PCR. Most of these specimens were tested at RIVM, and obtained either through the network of the Public Health Services or through peripheral and hospital laboratories, and included patients who were hospitalized for meningitis or encephalitis. There were 10 hospital admissions recorded for mumps in 2007 (7 main diagnosis, 3 secondary diagnosis).
Between August 2007 and September 21, 2008, 235 cases with defined clinical symptoms were investigated, 127 of whom were confirmed by one or more laboratory tests. The median age of the laboratory confirmed patients was 13 years (range 0-56 years). Of these, 67% were males. The cases are mostly resident in low vaccination coverage areas in the so-called Bible Belt. Vaccination history was recovered from 212 of the 235 cases; 100 clinical cases had received one or two doses of the MMR vaccine and 42 of these were laboratory confirmed (20 cases with 1x MMR, 21 cases with 2x MMR).

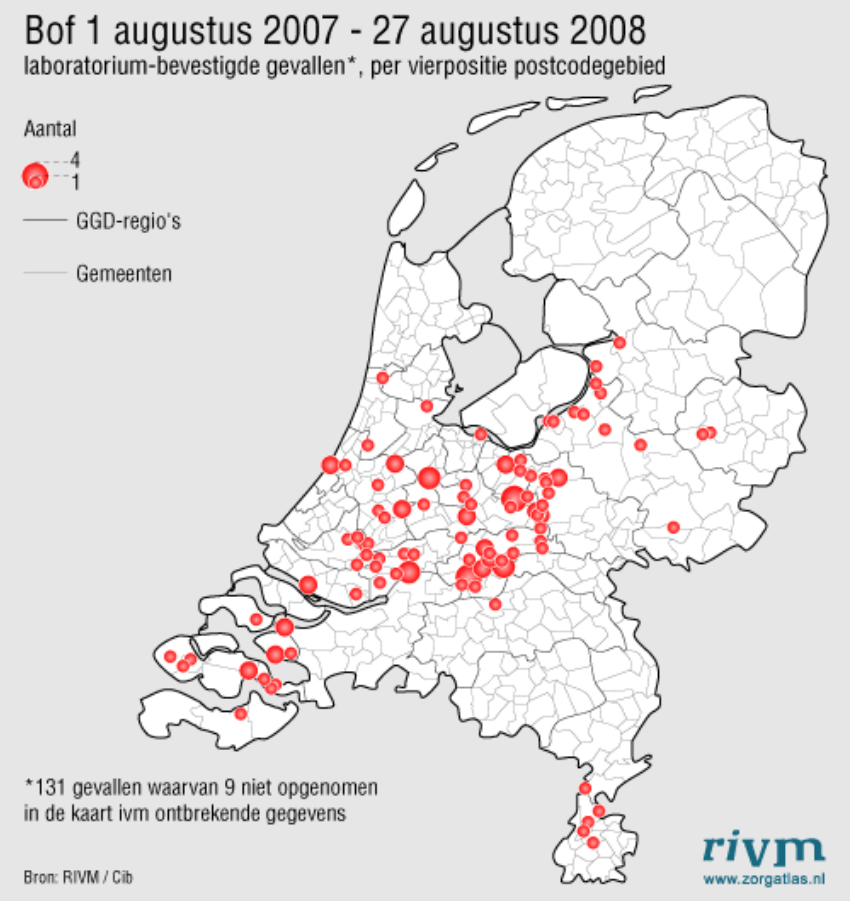


Figure 9 Geographic distribution of laboratory confirmed mumps cases, the Netherlands, 1.8.2007 – 27.8.2008

The here reported number of mumps cases is an underestimate of the true number of mumps infections that occurred, since laboratory testing was only carried out on a small proportion of cases. Furthermore, the estimate of the proportion of cases vaccinated is thought to be biased because vaccination was a recommended reason for laboratory testing. Hence, these observational data are not suitable for estimating vaccine effectiveness and a cohort study at primary schools was set up. Results of this will become available during 2009. To date, the ongoing mumps outbreak is mainly affecting the unvaccinated orthodox reformed community, with some spread to the vaccinated population. Among those eligible for one or two doses of mumps vaccine (79 persons), the reported reason for not being vaccinated was orthodox reformed religion for 47 persons (59%).

Diagnosis
The sensitivity of different serological assays for mumps IgM vary widely with the sensitivity affected by vaccination status of cases.[24] Vaccinated cases were predominantly confirmed by PCR, while unvaccinated cases were confirmed both by PCR and by mumps virus specific IgM testing. Research into this is proposed (see: recommendations).

International perspectives
Nationwide outbreaks of mumps have occurred since 2004 in many countries including the United Kingdom (UK), Canada, Bulgaria, Moldova and the United States of America (USA). In contrast to the ongoing Dutch outbreak, these were caused by genotype G.[25] A high proportion of cases in all of these outbreaks were in vaccinated individuals.
During 2008, Canadian Public Health authorities reported to have identified the Dutch mumps outbreak strains in the Netherlands Reformed community in Canada.

Recommendations for vaccination, surveillance and control
Vaccination
The relative merits of mumps vaccine strains should be evaluated. Information on this will become available from the ongoing vaccine effectiveness study, and from the proposed laboratory studies.

Surveillance
From 2009, mumps surveillance will be mainly based on notification data. In addition, a system for virological surveillance of circulating genotypes should be established. Oral fluid based surveillance may be a suitable method for this. One possibility is to include this surveillance within the existing sentinel physicians system (CMR, NIVEL). As the incidence of mumps is likely to be too low for this to provide useful data, alternatives need to be explored.

Research
During 2009, the ongoing vaccine effectiveness study (cohort study at primary schools) will be finalised.
In addition, proposed research aims are to:
- to assess the level of neutralisation provided by vaccine induced antibodies, against different wild-type mumps virus strains and to explore the association between phylogenetic characteristics and susceptibility to antibody neutralisation
- explore immunologic markers of individuals in whom mumps vaccine failure was observed
- explore the role of individuals with vaccine failure in transmission of wildtype mumps virus

During 2009, results of mumps virus specific antibody testing of the population-based serum collection (PIENTER-2 study) will become available and will be analysed.

2.7 Measles

S.J.M. Hahné, R.S. van Binnendijk

Vaccine

Recent changes in the NIP / availability and new developments

For recent changes in the NIP and availability of new vaccines and other new developments see the section on mumps (section 2.6).

Pathogen

Strain variation

During 2007, 10 cases of measles were reported in the Netherlands, of which nine occurred in clusters of four, three and two cases, respectively. The first two clusters were described in the previous NIP report.[1] The two genotypes involved were D5 and B3.1. The last cluster of two cases was confirmed as caused by a D4 strain, the index of which had most likely acquired the infection in the UK. The genotype associated with the outbreak starting in The Hague in 2008 is D8 (see next section).

Disease

Epidemiology

Of the 10 cases reported in 2007, five might have contracted measles infection abroad (Belgium, Brazil and UK). However, closer examination of the first two measles clusters (D5 and B3.1) revealed an association with travel by air of the index cases and subsequent nosocomial spread in the first cluster, rather than an association with molecularly identified cases in the countries visited.[26] Nine of 10 cases in 2007 were in adults (age range 25-42). The vaccination status was known for nine cases, of whom two were vaccinated. One of these was vaccinated as post-exposure prophylaxis. The other was a true vaccine failure in an adult who was vaccinated twice in childhood.[1, 26, 27]

The high proportion of importations among cases, coupled with the different genotypes and small cluster size, suggest that sufficient herd-immunity was present in the Netherlands during 2007.

During 2008, transmission of measles increased, mainly among unvaccinated individuals because of anthroposophist beliefs. This started with a cluster at two anthroposophist schools in The Hague.[28] Measles was subsequently spread at a anthroposophist youth camp in Drenthe, France and Switzerland to other regions, resulting in another cluster in a children's day care centre in Utrecht. Up to 27 November, 108 cases of measles were reported in 2008.

There was no spread to the non vaccinating communities in the Bible Belt. But a larger outbreak in the low vaccination coverage areas can still be expected. Therefore, during 2008, an outbreak response guideline was prepared (http://www.rivm.nl/cib/infectieziekten-A-Z/infectieziekten/morbilli/index.jsp#index_13).

International perspectives

In 2007, several large measles outbreaks have occurred in Europe. The largest outbreak occurred in Switzerland. The Swiss outbreak started in November 2006, with up to 13 February 2008, 1,405 measles cases reported. Of these, 85% was unvaccinated. The median age was 11 years.[29]

In 2008, UK public health authorities announced that endemic circulation of measles virus was re-established in the UK after a 14 year period of elimination.[30] The cause of this is reduced MMR coverage, mainly due to vaccine scares whereby MMR was falsely associated with autism. Given current levels of transmission, the 2010 goal of measles elimination from the European Region is unlikely to be achieved.

Recommendations for vaccination, surveillance and control

Vaccination

Further research to identify the optimal schedule for MMR vaccination is recommended (see below). To further measles elimination from the Netherlands, we recommend that the national plan for measles elimination in the Netherlands (1999) (available from http://www.euvac.net/graphics/euvac/pdf/plan_netherland.pdf) is updated (see report 2007). It needs consideration whether the plan can be adapted to include rubella elimination.

Surveillance

The surveillance protocol for measles and rubella surveillance needs to be finalised during 2009, with subsequent implementation. This protocol will include recommendations for enhanced surveillance, including reconciliation of cases reported through the three main surveillance systems (notifications, laboratory surveillance (virological weekly reports), hospital episode statistics (LMR data)).

Research

The results of the population-based serum collection (PIENTER-2 study) for measles will become available in 2009. This will provide insight into the immunity levels in specific age groups. Modelling will be used to assess the impact of a change in vaccination schedule, whereby lowering the age of the second MMR will be one of the scenarios studied.

The anticipated imminent measles outbreak in the Bible Belt provides an opportunity to study immunological correlates of protection against wild-type measles virus infection. This study proposal has been granted for funding by ZonMw (the Netherlands Organisation for Health Research and Development) (see report 2007). In addition, a research project (SOR) is ongoing into correlates of protection and immunological memory in the context of measles vaccination.

To inform the Dutch measles elimination plan, further research is needed in the main determinants of rejection of vaccination in the Netherlands (reformed religion, anthroposophical beliefs and critical attitudes towards vaccination). A study proposal has been submitted for funding at the ZonMW for this.

2.8 Rubella

S.J.M. Hahné, R.S. van Binnendijk

Vaccine

Recent changes in the NIP / availability and new developments

For recent changes in the NIP and availability of new vaccines and other new developments see the section on mumps (section 2.6).

Pathogen

Strain variation

During 2007 no rubella virus isolation or genotype was identified at the RIVM-CIb laboratory.

Disease

Epidemiology

During 2007, one rubella case was notified. Through laboratory surveillance (virological weekly reports) 14 cases were reported in 2007. No additional information is available regarding these.

International perspectives

The WHO European Region has a target to eliminate rubella by 2010.[31] Considering reported MMR coverage is very low in some countries in the region, this target is unlikely to be achieved.

Recommendations for vaccination, surveillance and control

Vaccination

It needs consideration whether the national Dutch measles elimination plan (see section on measles) can be adapted to include rubella elimination. During 2007, an economic analysis on antenatal screening for rubella immunity was carried out. It concluded that screening of unvaccinated pregnant women in low vaccination coverage areas may be cost-effective, but that varying assumptions regarding vaccine uptake changed this considerably. Recommendations, including continuing screening in unvaccinated women in low vaccination coverage areas, were made.[32]

Surveillance

See the section 'recommendations' of section 2.7 (measles). Particularly for rubella, obtaining samples for molecular analyses requires attention.

Research

Research regarding the optimal MMR schedule is mentioned in the measles research chapter.

2.9 Meningococcal serogroup C disease

L.M. Schouls, S.C. de Greeff, G.A.M. Berbers, J.M. Kemmeren, N.A.T. van der Maas

Vaccine

Effectiveness

Recently assessment of the antibody titres against the polysaccharides of MenC, A, Y and W135 in all sera (n= 7894) from the PIENTER-2 study, a population-based serum collection, using a multi immunoassay (MIA) with Luminex technology was completed.[33] Currently the analyses are ongoing, but preliminary results reveal that almost all children and adolescents vaccinated during the mass vaccination campaign in 2002 still possess antibody titres at the protective level against MenC and that these levels seem to increase with age. This is quite remarkable considering the fact that only a single vaccination was administered and that this vaccination already took place 5 years ago. In contrast, the antibody levels in the non-vaccinated cohorts were minimal, probably due to a decreased circulation of the bacterium.

Adverse events

Since 2005, reports to VAERS regarding postvaccination syncope in the US have increased from 0.30 reports per million doses distributed in 2002, to 0.54 per million doses distributed in 2006, primarily among females aged 11-18 years, and rarely, subsequent serious injuries have occurred.[34] To prevent syncope-related injuries, vaccine providers should follow the ACIP recommendation to strongly consider observing patients for 15 minutes after vaccination.[35] This advice can be regarded as a general precaution following all kind of injections. In the Netherlands Men C is scheduled at fourteen

months of age. The number of syncopes as an adverse event following immunization is very low at this age. During the catch-up campaign in 2002, the incidence of syncope was 2.12 per 10,000 among children of 1-5 years of age, compared to 20.9 and 18.9 per 10,000 among children of 6-14 and 15-18 years of age respectively.
A study to the reactogenicity of a MenC conjugate vaccine given concomitantly with DTaP-IPV-HBV/Hib to healthy infants in the first year of life showed that using a two-dose schedule is as safe and immunogenic as a three-dose regimen.[36] Furthermore, three phase III studies showed similar safety profiles for the heptavalent DTPw-HBV/Hib-MenAC and pentavalent DTPw-HBV/Hib vaccines. The difference observed in percentage of subjects with fever >39 ºC did not lead to differences in medically attended visits for fever.[37] In a randomized, double blind trial no significant differences were found in the incidence of adverse events between a meningococcal trivalent A/C/W135 polysaccharide vaccine and a tetravalent A/C/Y/W135 polysaccharide vaccine.[38]

Pathogen

Strain variation

See international perspectives.

Disease

Epidemiology

The incidence of meningococcal C disease has decreased sharply in all age-groups since the introduction of the conjugated meningococcal C vaccine (Figure 10). In 2007 only 9 cases of invasive meningococcal group C disease were reported. Two were unvaccinated children aged 7 and 9 months, respectively. One, was in an unvaccinated child aged 7 and all other cases were in unvaccinated adults (Table 6). Since the introduction of MenC vaccination in the Dutch NIP no cases of meningococcal group C disease in previously vaccinated persons have been reported.

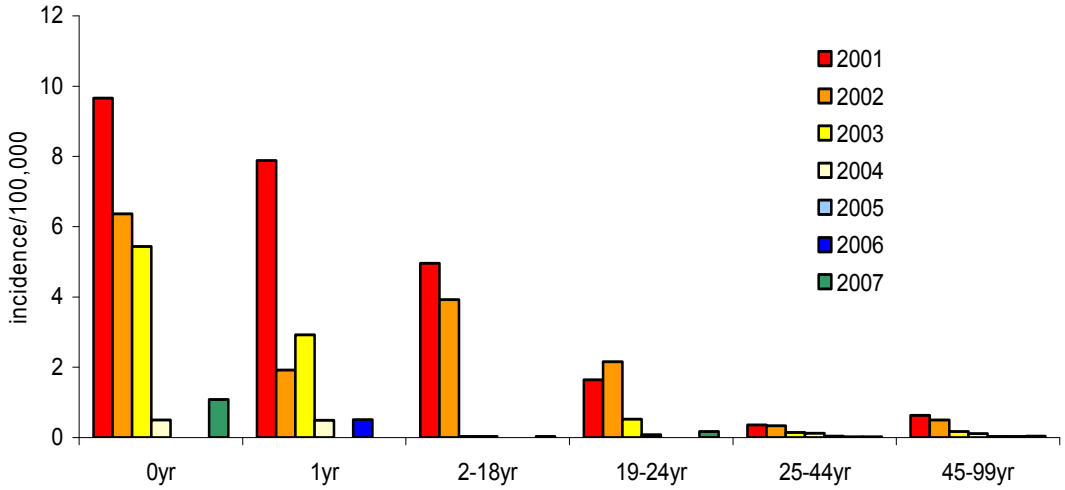


Figure 10 Age-specific incidence of meningococcal C disease by year, 2000-2007

Table 6 Absolute number of patients with meningococcal C disease

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

International perspectives
In countries that introduced MenC vaccination invasive group C meningococcal disease has dropped considerably. However, recently there were some reports that show that vaccination pressure may actually influence the composition of the circulating MenC strains. The first report came from Uria et al. They showed that 3 serogroup C N. meningitidis (MenC) isolates recovered from patients with invasive meningococcal disease resisted killing by bactericidal antibodies induced by the MenC conjugate vaccine. None of the patients had received the vaccine. The resistance of the isolates resulted from the presence of an insertion sequence, IS1301, in a region that is necessary for capsule biosynthesis and export. The altered sequence led to an increase in the amount of capsule expressed by the strains which in turn resulted in resistance to complement-mediated lysis in the presence of bactericidal antibodies.[39]
In Portugal Simoes et al. showed that capsular switch occurred during the 2002-2006 period. During their molecular surveillance they found 7 serogroup B strains that were genotypically identical to C strains, strongly suggesting that capsular switching occurred.[40]

Recommendations for vaccination, surveillance and control
Ongoing surveillance is required to be able to detect possible vaccine failures.

2.10 Hepatitis B

S.J.M. Hahné, H.J. Boot, F.D.H. Koedijk, M.E.E. Kretzschmar, J.M. Kemmeren, L.D. Isken, G.A. de Wit, M.A.B. van der Sande.

Vaccine
Recent changes in the NIP
No changes regarding the schedule or vaccine used for HBV vaccination within the NIP occurred during 2007.

Current target groups for HBV vaccination
In March 2007, it was recommended during an expert meeting that the vaccination of high risk groups should be enhanced for men who have sex with men (MSM), whereby aiming to vaccinate more MSM at a younger age, that it should be continued for prostitutes and hard drug users, and that it should be discontinued for heterosexuals with multiple partners. Following this recommendation, an information campaign was developed by Schorer aiming to improve coverage in young MSM. (http://www.b-a-man.nl/) From 2009 onwards, the vaccination campaign for behavioural high risk groups will be coordinated by the RIVM-CIb/LCI.

Vaccine efficacy and effectiveness

Efficacy and immunogenicity

Concurrent vaccination (i.e. administration of HBV vaccine with another vaccine either in the same syringe or with two concurrent injections) might reduce the serologic response to certain antigens in the vaccine.[41] Therefore, HBV vaccination with Prevenar or multicomponent childhood vaccines according to a four-dose schedule might lead to some decrease in the HBV and other immune responses.[42, 43, 44] Serologic evaluation of the vaccination response in a group of children at one year of age, who have been vaccinated simultaneous according to the current Dutch NIP schedule with Prevenar and Infanrix hexa, is expected to commence in January 2009.

Effectiveness of vaccinating high risk populations

See section on modelling and economic aspects.

Effectiveness of vaccination of children born to HBsAg positive mothers

Since September 2005, RIVM in collaboration with Regional Vaccination Administration Centres carries out serological evaluation of HBV vaccination in neonates of HbsAg-positive mothers. All neonates born to HBsAg-positive mothers from 2003 onwards who have completed a full series of vaccinations (HBIg at birth and hepatitis B vaccine) are eligible for the evaluation. Results of the evaluation of the vaccination of children born to HBsAg-positive mothers between 1.1.2003 and 31.12.2005 have been published in a RIVM report, and suggest that the proportion of children that got infected despite vaccination is not higher than what was expected based on the literature.[45] The serological evaluation will be continued at least until the end of 2009. A decision regarding subsequent implementation of the serologic screening of all infants born to HBsAg positive mothers in routine health care needs to be taken (see recommendations).

Vaccine coverage

Neonates born to HBsAg-positive mothers

The vaccine coverage among infants born to HBsAg positive mothers was 90.3%, 92.3% and 97.4% in birth cohort of 2003, 2004 and 2005, respectively.[4] An evaluation of the entire programme to prevent perinatal transmission of HBV, including uptake of antenatal screening, is recommended.[46]

Children of parent(s) born in countries where HBV is mid/high endemic

The vaccine coverage among infants born to (one or two) parents from endemic countries was 86.7%, 88.7% and 90.7% in birth cohort of 2003, 2004 and 2005, respectively. This is lower than the coverage for other vaccines in this group.[4] Since 1st June 2006 hepatitis B vaccine is delivered through a combination vaccine (Infanrix hexa). Uptake of hepatitis B different from the other antigens is therefore no more to be expected.

Behavioural high risk groups

The estimated vaccine coverage in MSM, drug users and commercial sex workers was 7%, 41% and 28% respectively between October 1998 - October 2007 (R. van Houdt, personal communication). However, a study by Schorer (Monitor) in 2008 estimated the hepatitis B vaccine coverage in MSM to be 48% (with an additional 10% who is incompletely vaccinated).[47]

Adverse events

Subsequent to publications linking HBV vaccination to MS, research was initiated at RIVM (see research). In 2008, a French research team reported the results of a study into the association between childhood MS and hepatitis B vaccination. They found no association between childhood MS and prior hepatitis B vaccination (OR 0.74; 95% CI 0.54-1.02). However, in a subgroup analyses of those compliant with the nationally recommended vaccinations, an increased risk for MS was found in

participants who had received Engerix-B (OR 1.74; 95% CI 1.03 – 2.95).[48] The interpretation of this finding in a subgroup analysis is hampered by the number of statistical tests (multiple testing).

Pathogen

Molecular epidemiology

Since January 2004, all Public Health Services in the Netherlands are requested to arrange sending of samples of all cases of acute HBV for genotyping to RIVM, the Amsterdam Public Health Laboratory, or the Rotterdam Virology Laboratory. The HBV-sequence database is a joined initiative of RIVM, the GGD Amsterdam, GGD Rotterdam and Erasmus MC. From January 2008 onwards all samples are requested to be sent to RIVM. In addition, samples from all infected children born to HBsAg positive mothers are subtyped.

Results of the molecular analyses of acute cases will be described in a RIVM report. The conclusions from the molecular epidemiological studies are that transmission of a specific genotype is ongoing among MSM in the Netherlands, whilst in heterosexuals there is more diversity in subtypes identified. Regarding mutant HBV strains, three groups can be distinguished (immune escape mutants, antiviral resistant mutants and pre-core mutants). Prevalence of these among acute and chronic HBV infections sequenced at RIVM were presented in the NIP report of 2007, and are updated below.

Table 7 HBV-mutants in sequence database of Dutch HBV isolates

	HBV infection			
	Acute	Chronic	Acute or chronic	Children[1]
Reported cases (Jan. 2004 - July 2008)	~1160	~6800		14
S-region sequence	583	312	51	13
Immune escape mutation (G145R)	0	0	0	2
Antiviral resistance[2]	2	2	0	0

[1] Children born to HBV-infected women and became infected despite HBIg and HB vaccination

[2] Only the result of the most important resistance mutation (M550V) has been given.

Disease

Epidemiology

In 2007, 1829 cases of HBV virus infection were reported in the Netherlands. Of these, 1563 (85%) were chronic and 226 (12%) were acute infections (for 40 notifications (2%) it was unknown whether it concerned an acute or chronic infection). The number of acute cases, 226, decreased with 6% compared to 2006, and shows a decreasing trend (2006: 240 cases, 2005: 299 cases, 2004: 293 cases). The incidence rate for notifications of acute HBV in 2007 was 1,4 per 100,000 and was higher in men than in women (2,1 and 0,7/100,000, respectively). The incidence in men is decreasing since 2003; in women it is stable (Figure 11).

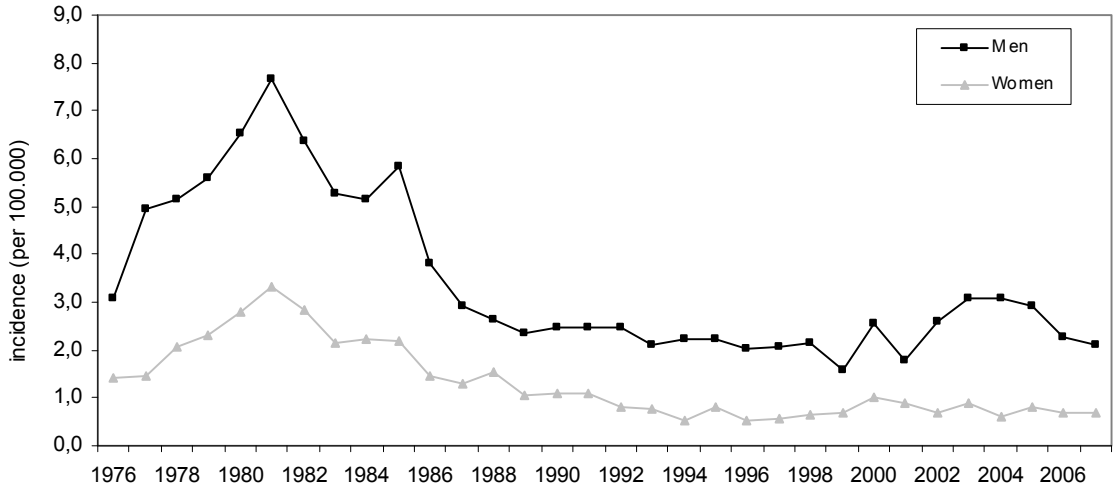


Figure 11 Incidence rate per 100,000 population of notified cases of acute HBV infection, the Netherlands, 1976-2007

For 77% of acute infections a most likely transmission route was reported. Of these, 44% reported male homosexual contact and 40% heterosexual contact as the most likely route. The number of cases reported to be due to male homosexual and due to heterosexual contact declined since 2003 with 27% and 18%, respectively.

Economic aspects

Previous economic analyses suggested that the current Dutch risk-based policy is highly cost-effective. The extension of the risk-based policies with universal vaccination strategies, especially the universal vaccination of newborns, was expected to have additional effect to reduce the incidence of HBV in the Netherlands.[49] The Health Council is expected to advise on possible changes in the NIP for HBV in 2008.[50]

Modelling

Modelling work previously reported in the NIP report has now been published.[51] It suggests that when targeting vaccination and risk-prevention measures to MSM, targeting specifically men displaying the most risky behaviour is the most effective policy to reduce the HBV epidemic.

Infection control

Guidelines and training

In May 2008 two revised guidelines as part of the CIb infection control guidelines were published. The first guideline is on the control of a hepatitis B virus infection. The revised version is more extended than the previous guideline (http://www.rivm.nl/cib/infectieziekten/HepatitisB/Hepatitis_B_protocol.jsp). The second guideline is on hepatitis B immunisation for the prevention of perinatal hepatitis B transmission (http://www.rivm.nl/cib/infectieziekten-A-Z/infectieziekten/HepatitisB/hepatitis_B_draaiboek.jsp).

Recommendations for vaccination, surveillance and control

Vaccination

- Within the programme to vaccinate high-risk groups against HBV, the focus should continue to be on MSM, especially those displaying highest risk behaviour and young MSM.
- Regarding the programme to prevent perinatal transmission of HBV, currently only the incidence of infection in vaccinated infants of carrier mothers is routinely assessed. A routine evaluation of the entire programme is recommended. In addition, a decision needs to be taken how the programme of testing of all infants of HBsAg positive mothers is to be continued.

Surveillance

- The assessment of existing data sources for their usefulness to study the incidence of rare events and their association with vaccination is recommended.
- It should be explored how surveillance of antiviral resistance can be carried out.

Research

- A pilot economic analysis of screening migrants for chronic HBV infection is ongoing. In addition, a ZonMW study proposal has been submitted to further explore costs and benefits of screening migrants. In contrast to the pilot, this proposal includes a cost-effectiveness analysis of screening for both HBV and HCV, and will also use dynamic modelling to assess effects of primary prevention (due to lowering viral load and vaccination of contacts).
- Vaccination with Prevenar and multicomponent childhood vaccines according to a four-dose schedule might have a negative influence of the HBV immune response. Serologic evaluation of the HBV vaccination response in a group of children at one year of age, who have been vaccinated simultaneous according to the current Dutch NIP schedule with Prevenar and Infanrix hexa is in preparation.
- The merits of screening for viral load and selective treatment with anti-virals during pregnancy in order to allow prevention of perinatal transmission should be assessed.
- In 2008 we will determine the background incidence of multiple sclerosis in a longitudinal observational database which contains data from computer-based patient records of general practitioners throughout the Netherlands (the IPCI database of the Erasmus University Rotterdam[52]). This incidence will be the baseline in monitoring the occurrence of multiple sclerosis when universal vaccination might be introduced. In the future, the database will be used for detection of other (auto)immunologic diseases with a suggested association with vaccinations.

2.11 Pneumococcal disease

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

Vaccine

Recent changes in the NIP

Vaccination with pneumococcal vaccine (Prevenar) has been introduced in the Dutch national vaccination programme in April 2006. The vaccine is given to infants at 2, 3, 4 and 11 months of age concomitantly with the DTaP-IPV/Hib combination vaccine albeit as a second injection in a different limb of the child.

Prevenar is the only licensed pneumococcal conjugate vaccine for protection of infants and children up to 5 years of age in Europe. This 7-valent pneumococcal conjugate vaccine, also designated as PCV7, provides protection against invasive disease caused by the 7 most prevalent serotypes in the USA.[53] Before introduction of the vaccine, around 68% of cases of pneumococcal meningitis among children younger than 2 years of age in the Netherlands were caused by PCV7 serotypes (Figure 12). Ten-valent and 13-valent vaccines have been developed and are currently being tested in trials. These new vaccines will yield a higher coverage than the PCV7 and will in time replace the 7-valent vaccine.

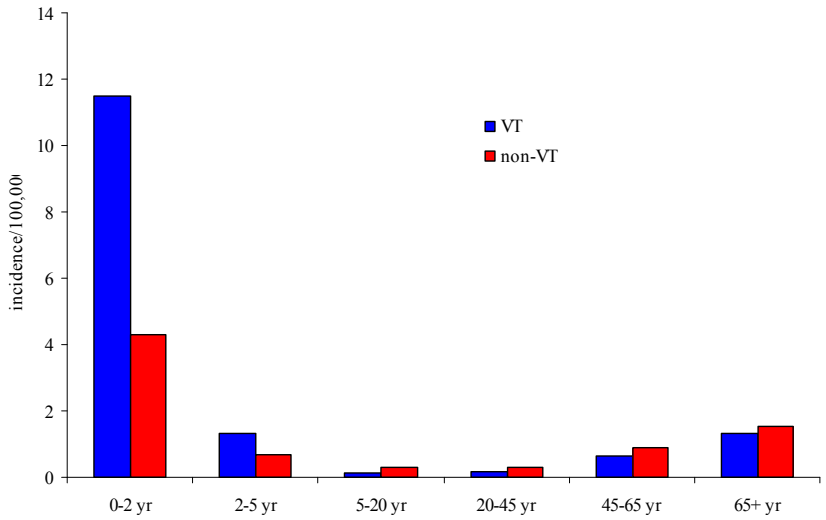


Figure 12 Age specific incidence of isolates from cerebrospinal fluid (CSF) or CSF and blood by serotype in the prevaccination period 2001-2005. Serotypes included in the PCV-7 vaccine are in blue (vaccine types, VT), the others in red (non-vaccine types, non-VT)

Effectiveness

Using samples obtained from an serological study where the effects of changes in pertussis vaccines in the NIP from 2004 till 2008 were studied[5], we also evaluated the immunogenicity of the pneumococcal vaccine. In one of the study arms, 96 children were included that were vaccinated with DTaP-IPV/Hib (Pediacel, Sanofi-Pasteur) and with PCV7. Blood samples were taken before and after booster vaccination at 11 and 12 months of age and this enabled us to monitor the serological responses induced by PCV7 after a 3+1 schedule according to the Dutch NIP. In Figure 13 the reverse cumulative distribution curves (RCDCs) of the 7 serotypes are depicted. After booster vaccination all subjects had antibody titres above the internationally accepted cut-off level of 0.35 µg/ml for 4 serotypes (4, 14, 19F, 23F). This correlate of protection was reached in 99% of the subjects for 2 of the remaining serotypes (9V and 18C) and in 95 % of the subjects for serotype 6B. For 2 serotypes (14 and 19F) more than 80% of the children were still protected at 11 months before the booster vaccination. For the other 5 serotypes the pre-booster vaccination geometric mean titres (GMT) were around or just below the cut-off level. We conclude that after booster vaccination the PCV7 offers good protection and the observed GMTs are comparable to those obtained in other vaccine studies.[54, 55, 56]

Comparison of the vaccine responses of this group of children with those born before April 2006 and thus receiving only Pediacel (n=98), revealed that PCV7 interferes with the response to Pediacel.[5] This observation emphasizes that combination of vaccines i.e. administered at the same time point may have its limitations and that every change in the NIP deserves a thorough (serological) evaluation.

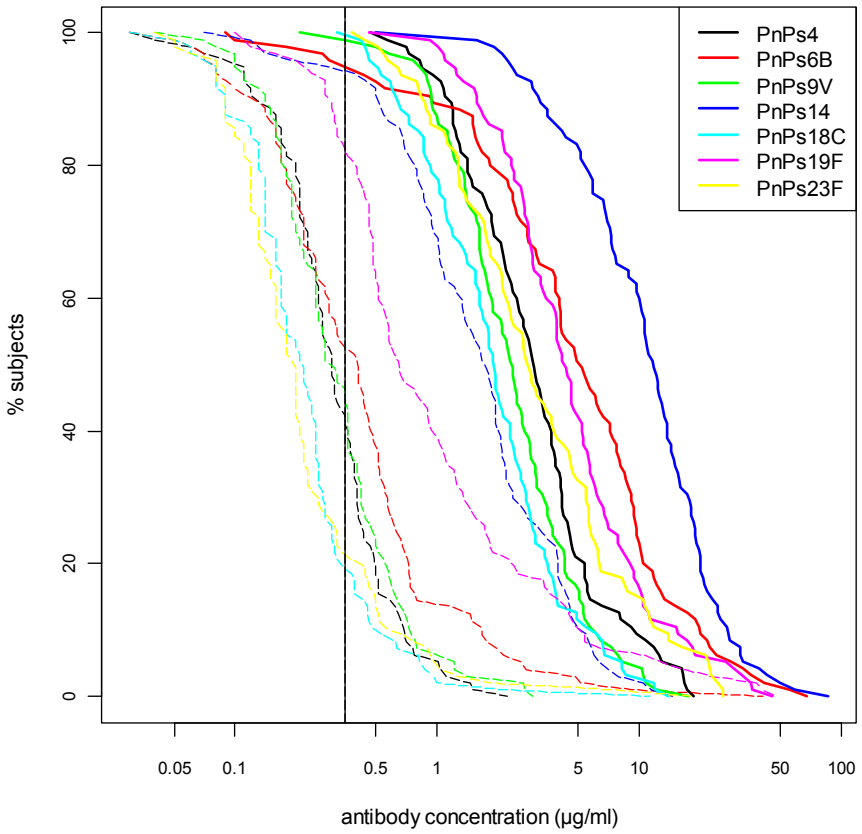


Figure 13 RCDCs for antibody titres against the 7 serotypes present in Prevenar. Each colour represents titres against a different serotype obtained in a group of 96 children. The dotted lines denote the pre-booster antibody levels at 11 months and the solid lines the post-booster antibody levels at 12 months. The vertical line indicates the cut-off of 0.35 µg/ml, which is considered as the protective antibody level

Adverse events

In 2007 the results of the passive safety surveillance contain a full year use of PCV7. Just like in 2006 the addition of conjugate pneumococcal vaccine had little effect on the number of reported adverse events. See for more information the section on pertussis.

A study on the reactogenicity of the 11-valent pneumococcal vaccine conjugated to non-typeable *Haemophilus influenzae*-derived protein D in the first two years of life showed a higher incidence of solicited adverse events compared to hepatitis A in the control group. Both vaccines were co-administered with combined DTPa-HBV-IPV/Hib vaccine. Of the children 40.1% had solicited local symptoms on the PCV11 injection site, compared to 26.3% on the HAV injection site. For the hexavalent vaccine this percentage varied between 37.9% and 43.4% in both groups. For solicited systemic symptoms it is not possible to determine which vaccine(component) is responsible, but fever > 38.0°C varies between 19.3% and 30.5% for consecutive dose. Overall the safety profile of PCV11, simultaneously administered with a hexavalent vaccine, was consistent with previous reports for both types of vaccines.[57]

In the Netherlands, a questionnaire on more rare, severe adverse events following infant combination vaccines, showed no significant change in frequencies of systemic adverse reactions of DTP-IPV-Hib and DTP-IPV-Hib + PCV7. In this study fever > 39.5°C was reported in 1.5% and 1.3% of the children receiving DTP-IPV-Hib and DTP-IPV-Hib + PCV7 respectively.[58]

Disease

Epidemiology

As off December 1st, 2008, when the new Public Health Act has been passed, pneumococcal disease will be a mandatory notifiable disease for children up and until 5 years of age. Until recently there has been no systematic collection of strains and clinical data and monitoring of disease was based on laboratory surveillance in which laboratories voluntary send their isolates from patients with invasive pneumococcal disease to the Netherlands Reference laboratory for Bacterial Meningitis (NRBM). This system covered about 80% of all cases of pneumococcal meningitis in the Netherlands. Data for other invasive and non-invasive pneumococcal disease (pneumonia, sepsis and otitis media) are incomplete due to the lack of a specific reporting system. However, in recent years a number of sentinel labs have reported all cases of invasive pneumococcal disease and sent the isolates to the NRBM. In addition, clinical data of the patients from whom these isolates originated have been collected by research groups of the CIb and the Wilhelmina Children's Hospital. These data are now being analyzed.

Comparison of the annual number of isolates collected during the pre- and post-vaccination era already shows a significant reduction in the number of vaccine type infections in children aged 0-4 years (Figure 14). This indicates that the vaccine is successfully reducing the number of cases of invasive pneumococcal disease. At the same time an increase of non-vaccine types is seen, although these are only small numbers. Until now there are no hints of a possible herd immunity effect. However, it may too early after introduction of nationwide vaccination to be able to observe such an effect.

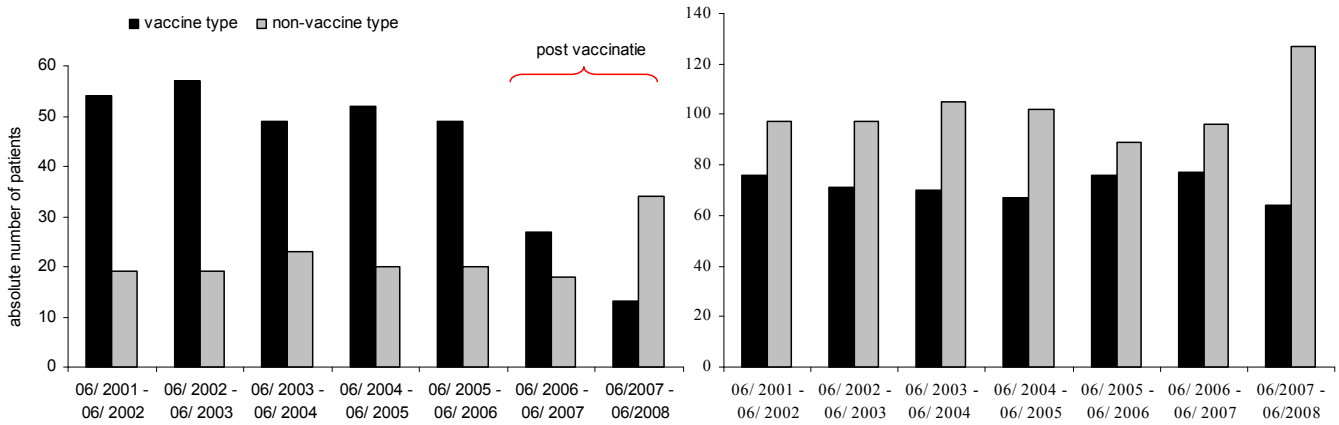


Figure 14 Number of cases of pneumococcal meningitis in the Netherlands. Left panel, number of strains isolated from CSF or CSF and blood, patients aged 0-4 years; right panel, number of strains isolated from CSF or CSF and blood, patients aged >4 years; vaccine types in black; non-vaccine types in grey. The displayed annual periods are from June to June the next year

Data on the number of cases of invasive pneumococcal disease in the Netherlands is obtained by the enhanced surveillance performed by the NRBM and the RIVM to monitor the effects of introduction of PCV7 in the NIP. Since introduction of vaccination in June 2006, all medical microbiological laboratories throughout the country are asked to send all their pneumococcal strains isolated from cerebrospinal fluid (CSF) or blood from children <5 years of age with invasive pneumococcal disease to the NRBM. In addition, the NRBM receives all pneumococcal isolates from all patients with invasive pneumococcal disease from 9 large laboratories (sentinels) that cover approximately 25% of the Dutch population. To assess the effects of vaccination on morbidity and mortality, information is gathered on the clinical manifestations and underlying disease of invasive pneumococcal disease. This

has been done retrospectively using questionnaires which are filled out by medical students checking patients' case histories. Furthermore, a prospective survey using an electronic system to collect these additional data has been started in January 2008. The surveillance will become even more complete and reliable when invasive pneumococcal disease will become a notifiable disease for 1-5-year-olds in the Netherlands by December 1st, 2008.

International perspectives

In the USA paediatric vaccination using Prevenar has been licensed and subsequently introduced in the vaccination schedule in 2000 for all children aged 2 to 23 months. As a result rates of IPD in young infants too young to receive the vaccine have decreased significantly. Mean rates of IPD for infants aged 0 to 90 days decreased 40% from 11.8 to 7.2 per 100 000 live births following PCV7 introduction. However, rates of non-vaccine serotypes remained stable providing evidence that vaccinating children has led to changes in pneumococcal carriage in infants too young to be vaccinated.[59]
More evidence for this serotype replacement came from another study. Hicks et al. found that in the USA the annual incidence of disease due to non-vaccine serotypes increased from an average of 16.3 cases/100,000 population during pre-vaccine years (1998-1999) to 19.9 cases/100,000 population in 2004 for children aged <5 years. A smaller but significant increase was also observed for 65+ adults amounting 27.0 during pre-vaccine years to 29.8 in 2004. Significant increases in the incidences of disease due to serotypes 3, 15, 19A, 22F, and 33F were observed among children during this period. Serotype 19A has now become the predominant cause of invasive disease in children in the USA. Remarkably, the incidence of disease due to these serotypes also increased among elderly persons.[60]

Recommendations for vaccination, surveillance and control

The pneumococcal vaccination schedules in the various European countries differ considerably. Two factors may lead to less effective protection. Firstly, the lack of a booster vaccination may lead to waning immunity, leaving children aged between 1 and 2 years of age less well protected. The experience in the UK with the Hib and MenC conjugate vaccines lacking such booster suggests that this may lead to vaccine failures. Secondly, the use of 3 doses instead of the 4 doses that have been recommended by the manufacturer may provide less protective immunity. However, if a 3 dose regime would be as protective as a 4 doses regime the costs for vaccination against *S. pneumoniae* could be reduced by 25%. This merits investigations in which the effectiveness of a 3 and 4 doses regime are compared.

Pneumococcal disease in the elderly is thought to be a considerable problem. However, no accurate figures on burden of pneumococcal disease in the elderly exist. To justify possible pneumococcal vaccination of this age group research to determine a more accurate estimation on the burden of disease is required. The CIb has developed diagnostic tools to determine whether a patient is infected with pneumococci and simultaneously determine the serotype of the infecting agent. The use of these tools to estimate the burden of pneumococcal disease in inhabitants of nursing homes and the elderly in community is recommended.

Pneumococcal vaccination of the elderly is under discussion. Many vaccination trials have been performed. However, these studies have yielded contradictory results. One of the problems associated with vaccination of the elderly is the impairment of the immune system in an aging individual. Therefore, research to determine effectiveness of the immune response after vaccination with pneumococcal conjugate vaccine at different ages is required. Such research may shed more light on the vaccination strategy required to protect the elderly against pneumococcal infection.

3 Programmatic vaccination outside the NIP

3.1 Influenza

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This section on influenza is to a large extent based on the 'Annual Report Respiratory Infections' by Dijkstra et al., 2008 [in Dutch].[61]

Vaccine
Recent changes in the NIP
The National Influenza Prevention Programme (NPG) is responsible for vaccine purchase and distribution, vaccination and organization and is funded by the Ministry of Health, Welfare and Sport. The Ministry decides which risk groups are offered free vaccination against influenza based on recommendations by the Health Council of The Netherlands. General practitioners (GP's) select their patients belonging to the risk groups, invite them for vaccination and vaccinate them. GP's are supported in this by the Foundation National Influenza Prevention Programme (SNPG), NVI and the RIVM through central vaccine purchase and distribution, information leaflets and a website for the risk groups, and a national publicity campaign. The RIVM monitors the efficiency, efficacy and quality of the NPG.

Based on recommendation of the Health Council of the Netherlands[62], the Ministry of Health, Welfare and Sport has decided to offer free vaccination to people from 60 years of age (instead of 65 years) starting October 2008. Repeating / chronic staphylococcal infections have been removed from the list of indications for free vaccination. Pulmonary and cardiovascular disorders as well as diabetes and chronic renal failure remain on the list as well as a number of specific target groups such as the immune compromised. The Health Council of The Netherlands has also recommended vaccination for health care personnel but this group has not been included in the NIP. Instead, vaccination is seen as the responsibility of the employer.

Availability and new developments
The Netherlands has the policy to obtain vaccines from two different producers to avoid short supply due to production failure in one company.

Effectiveness
During the 2007-2008 influenza season, using the sentinel surveillance system, swabs were taken from 377 influenza-like illness (ILI) patients with known influenza vaccination status. An influenza virus was found in 141 of these ILI patients, of whom 10 had received influenza vaccination. Of the 236 ILI patients that were found negative for influenza virus, 38 had received influenza vaccination. Based on these limited data, influenza vaccine effectiveness (VE), adjusted for age was 58.5% (95% CI: 9.5 – 80.9%). RIVM and NIVEL are participating in a European project to develop methods for measuring VE during the influenza season. This should provide a framework that makes it possible to measure real-time VE on a routine basis and to estimate VE in a pandemic situation, should such a situation occur.

Adverse events
Clinicians are stimulated to report adverse events to Lareb, the Netherlands Pharmacovigilance Centre. During the influenza campaign, starting in October 2007, Lareb received 27 reports on adverse events, 12 and 14 following Influvac® and Vaxigrip® respectively. In one report the manufacturer of the vaccine was unknown. Eight of the reports were Serious Adverse Events (SAE). The mean age of the patients was 55 years, with 10 male and 16 female patients. In one case the sex was unknown.

Pathogen
Strain variation
Influenza viruses constantly evolve and vaccines have to be reformulated every year. Influenza viruses were detected from week 1 to week 17 of 2008. The dominant virus strain early in the season was influenza A(H1N1) with influenza B predominating later in the season. A mismatch between the detected A(H1N1) and B viruses and the respective components in the 2007/2008 influenza vaccine was found during the 2007-2008 influenza season. Within the A(H1N1) viruses two variants were detected, one variant similar to the 2007/2008 vaccine reference strain A/Solomon Islands/3/06, and one variant similar to the vaccine strain recommended for the 2008/2009 season A/Brisbane/59/07. Influenza B-viruses belonged to the B/Yamagata/16/88-lineage whilst the vaccine strain for 2007/2008 belonged to the other, antigenically different, phylogenetic B/Victoria/2/87-lineage. Influenza A(H3N2) viruses were sporadically detected and were related to the 2007/2008 vaccine strain A/Wisconsin/67/05. The World Health Organization has recommended a different vaccine composition for the 2008-2009 influenza season with A/Brisbane/59/2007 (H1N1)-like virus, A/Brisbane/10/2007 (H3N2)-like virus, and B/Florida/4/2006-like virus (B/Yamagata/16/88-lineage).[63]
Worldwide and also in the Netherlands, there was a lot of attention in 2008 for the unexpected detection of influenza viruses A(H1N1) that were resistant against the antiviral drug oseltamivir. Although the influenza season in the Netherlands showed a mild course, over a quarter of influenza viruses A(H1N1) were found to be resistant.

Disease
Epidemiology
Routine surveillance of ILI and circulating influenza viruses takes place in a sentinel general practice network under the auspices of the Netherlands Institute for Health Services Research (NIVEL), and the National Influenza Centre (RIVM and the Erasmus University Medical Centre). In addition, swabs for virological examination are obtained from sentinel nursing homes and from non-sentinel (hospital) sources. The 2007-2008 season was a mild influenza season, consistent with previous years. Weekly consultation rates for ILI at sentinel GP's exceeded the baseline level of 5 per 10.000 people from week 2 to week 13 in 2008.

Burden of disease
The dominant influenza viruses during the 2007-2008 influenza season A (H1N1) and B are generally associated with mild epidemics. There have been no major changes in hospital admission rates for influenza and upper respiratory tract infections over the past 5 years. The number of deaths from influenza during the 2007-2008 influenza season was 79 (primary cause of death in 52 patients and secondary cause of death in 27 patients), the lowest number of the past 5 years. The focus of the influenza vaccination strategy remains on the elderly, the age group more likely to develop severe influenza-related outcomes. Although children are assumed to be important 'transmitters' of influenza, vaccination of otherwise healthy children is not considered. To generate evidence, in 2008-2009 RIVM, EMC and NIVEL will participate in an international study (EPIA) to quantify the burden of influenza in children in European countries, including The Netherlands. Some countries (USA, Canada, Finland, Austria) recommend vaccination of healthy children from six months old. Influenza vaccines are efficacious in children older than two but there can be a marked difference between vaccine

efficacy and effectiveness. Variability in study design and presentation of data has made a meta-analysis of safety outcome data not feasible.[64] For children under two years of age little data on efficacy, effectiveness and safety were available. Influenza vaccination trials among children are ongoing, for example the recent trial by Vesikari et al.[65]

Economic aspects
Cost-benefit analyses have been done for various potential target groups.[62] Episodes of influenza can lead to high costs from more GP visits, hospital admissions and higher mortality rates in people below 65 years of age who are otherwise healthy. This was the main reason to change the age criterion from >=65 to >=60.

International perspectives
The World Health Assembly has adopted in 2003 a Resolution urging Member States to increase vaccination coverage of all people at high risk, including the elderly and persons with underlying diseases, with the goal of attaining vaccination coverage of the elderly population of at least 50% by 2006 and 75% by 2010. These targets were endorsed by the European Parliament in 2005. The Netherlands is the only country in Europe that has already attained the WHO / EU targets for influenza vaccination coverage.[66, 67]

Recommendations for vaccination, surveillance and control
The National Influenza Prevention Programme was established in 1997. A few factors might explain the success of this programme relative to programmes in other countries:
- national public programme implemented through GP's;
- GP's organize the vaccination sessions, which include a personal invitation to each registered patient who belongs to the high risk group. Increasingly, GP's can invite patients in a fully automated way;
- payment of a standard amount (10.00 euro) to the GP for each vaccination;
- free vaccination for people in high risk group;
- central vaccine purchase system;
- nationwide publicity campaign.

These points pertain to the central role of the GP, financial support by the government and national coordination.

Nevertheless, there are a few reasons for concern:
- media attention with concerns of vaccine efficacy among the elderly might negatively affect vaccination acceptance;
- vaccination coverage among high risk young people remains relatively low;
- vaccination coverage among health care workers remains low.

There is a central role for continuing education and information of the public on possible consequences of influenza and the efficacy and side effects of vaccination. More research is needed on the burden of disease which could be used in cost-benefit analysis and on efficacy of vaccination of children (6 months - 2 years) and of older children with asthma.

3.2 Tuberculosis

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Data on tuberculosis are from the 'Annual Report Respiratory Infections' by Dijkstra et al., 2008 [in Dutch].[61] We acknowledge the input of S. Verver and J. Thole (Wageningen University).

Vaccine
Recent changes in the NIP
Vaccination against tuberculosis is currently not included in the NIP. In 2009, the Health Council of The Netherlands is expected to issue an advice about the future position of the bacille Calmette-Guérin (BCG) vaccine.

Availability and new developments
In the Netherlands, which is a low-incidence country, BCG vaccination is offered to travellers that are considered to be at risk because of a planned long-term (>3 months) visit to an endemic area (WHO-estimated incidence > 50 TB cases /100,000 population) or to children below 12 years of age with a parent from an endemic area.
New vaccines are being developed. An ideal vaccine would prevent TB infection as well as progression of latent infections to active disease in children and adults. However, it is unlikely that a single vaccine will meet all these needs. There are a variety of possible live and subunit vaccine types, each with their strengths and weaknesses. The European Commission supports an integrated project (TBVAC) for the development, preclinical and clinical evaluation of new TB vaccine candidates, The Leiden University Medical Center, BPRC Rijswijk, and ID-Lelystad (coordinator) are Dutch partners in TBVAC. The TuBerculosis Vaccine Initiative (TBVI) is a recently established foundation originating from TBVAC that is based in Lelystad and part of Wageningen University and Research Center. TBVI facilitates integrated, European efforts to develop safer and more effective vaccines against tuberculosis, that are globally accessible and affordable (www.tbvi.eu). KNCV Tuberculosis Foundation provides epidemiological support to develop vaccine field trial sites in various countries.

Effectiveness
BCG vaccine has a documented protective effect against meningitis and disseminated tuberculosis, particularly in children. It does not prevent primary infection and, more importantly, does not prevent reactivation of latent infection, the principal source of TB incidence in the community. The impact of BCG vaccination on transmission of tuberculosis is therefore limited.

Disease
Epidemiology
In 2007 there were 907 notifications of new tuberculosis patients and 53 notifications of patients who had experienced an earlier episode. The incidence of tuberculosis has declined from 8.8/100,000 people in 2002 to 5.9/100,000 in 2007.

International perspectives

The BCG vaccine has existed for 80 years and is one of the most widely used of all current vaccines, reaching >80% of neonates and infants in countries where it is part of the national childhood immunization programme. The Netherlands is one of the low-incidence countries where vaccination is limited to high risk groups. World wide TB is still one of the major causes of morbidity and mortality. Although WHO has reported estimated per capita TB incidence to be stable or falling in all six WHO regions in 2005, the increasing problem of multi-drug resistant TB and the emergence of extensively drug-resistant (XDR) TB, particularly in settings where many TB patients are also infected with HIV, poses a serious threat to TB control. Along with measures to strengthen basic TB control and programmatic management of drug-resistant TB, vaccination of those at risk for exposure to MDR TB with a more effective vaccine, is thought to be an important approach to curb the epidemic. The urgent need for a more effective TB vaccine and new vaccination strategies is expressed in the Stop TB Strategy, the Global Plan to Stop TB for 2006–2015 and the international targets for TB control. The Stop TB Partnership, an international network of more than 500 public and private organizations, has set the goal of having a new vaccine by 2015. Seven different types of vaccine are in development.

Recommendations for vaccination, surveillance and control

RIVM has published a study that concluded, based on data from children with severe TB between 1996 and 2003, that the strategy targeting immigrant children (1st and 2nd generation) from high-prevalence countries is on average cost-effective in the prevention of development of severe TB.[68] It should be stressed that the low prevalence of severe TB in the Netherlands leads to a very large confidence interval for vaccine efficacy. This in turn leads to an upper bound for cost-effectiveness extending in the non-cost-effective range. Selective BCG vaccination strategy, targeting children from high prevalence countries and individuals travelling for longer than 3 months to high endemic area's, should be continued until the final advice of the Health Council of the Netherlands becomes known. As this information has been lacking in the past, vaccine coverage should be carefully monitored to be able to evaluate future changes in the vaccination strategy in the Netherlands.

4 Future NIP candidate vaccines

4.1 Human papillomavirus (HPV) infection

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Vaccine

Recent changes in the NIP

On the 1st of April 2008, the Health Council advised the minister of Health to include HPV-vaccination for 12-year-old girls in the NIP and to conduct a catch-up programme for girls aged 13-16 years.[2] Various papers on prevention of cervical cancer both by secondary prevention (screening 30-60 year old women) and primary prevention (HPV-vaccination) were published in the 'Nederlands Tijdschrift voor Geneeskunde' after publication of the advice of the Health Council.[69, 70] A paper that argued that there are insufficient reasons yet to include HPV-vaccination in the NIP was published somewhat later.[71] In their response, the Health Council clarified that all such uncertainties with respect to disease burden, safety of the vaccine, effectiveness of HPV-vaccination against cervical cancer, duration of protection, type replacement and cost-effectiveness had been weighted.[72]

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 will start in March 2009. The first NIP cohort (i.e. those born between 1 January 1997 and 31 August 1997) will be offered vaccination after the summer holidays of 2009 (about September). Every year, 12-year old girls will be offered to start vaccination in September, which is for most girls the start of secondary school.

Availability and new developments

The quadrivalent vaccine Gardasil® including HPV-types 6, 11, 16 and 18 and the bivalent vaccine Cervarix® including only types 16 and 18, are the only available vaccines. These vaccines are registered on the European market. New vaccines including more L1 VLPs (Virus Like Particles) of more HPV genotypes and/or L2 are under development.[73]

Effectiveness

Recently, the US Food and Drug Administration approved expanded use of the vaccine Gardasil for prevention of certain vulvar and vaginal cancers caused by HPV-16 and -18 in girls and women aged 9 to 26 years. Over a 3-year study period, a large phase III trial showed an efficacy of Gardasil of 98% (95%CI 86-100%) in preventing high-grade vulvar and vaginal lesions associated with HPV-16 or -18 in women who were naïve to HPV-16 and -18 before vaccination. The effectiveness of vaccination in the intention-to-treat population (women 15-26 years of age) was considerably lower (44%; 95%CI 26-58%).[74] Through five years of study, Gardasil was effective for prevention of persistent infection (95.6%; 95%CI 83.3-99.5). There were no cases of HPV 6/11/16/18-related precancerous cervical dysplasia or genital warts in women (aged 16-23 years) who received the vaccine (n=235), and six cases in women who received a placebo (n=233) (efficacy 100%; 95% CI 12-100%).[75]
Cervarix provided 100% protection against HPV-16/18-related pre-cancerous lesions to HPV-naïve women aged 15-26 years for a follow-up period of so far 6.4 years.[76]

In a study among young women with pre-existing HPV infection, vaccination against HPV-16 and -18 did not increase the rate of viral clearance.[77] However, administration of the quadrivalent HPV vaccine to women positive for HPV-6,-11,-16, or -18 before vaccination, protected against infections and disease caused by HPV-types for which they were naïve at the start of vaccination.[78]
A study on the safety and immunogenicity of co-administered HPV-6, -11, -16, -18 vaccine with hepatitis B vaccine (RECOMBIVAX HB, Merck) showed that co-administration of both vaccines was generally well tolerated. No interference with immune response against the components of the HPV vaccine was found due to co-administration. Co-administration was also found to be non-inferior for the HB-vaccine response, in comparison to single HB-vaccination. However, the seroconversion rate for HB-vaccination was reduced with 1.0% (i.e. 96.5% vs. 97.5%; n= 466). Furthermore, the reported geometric mean titer of antibodies against HBV was considerably reduced (33%) when the vaccine was co-administrated with HPV-vaccine.[79] This could be relevant if co-administration of HPV- and HBV-vaccination within the NIP is considered.

Adverse events
School-based HPV-vaccination campaigns are being conducted in Canada, the United Kingdom and Australia. In advance of the implementation of a national HPV immunisation programme, a study of routine HPV-vaccination among adolescent schoolgirls in the UK achieved an uptake of 70% of two doses. Concerns about safety and efficacy were the main reasons that parents cited for refusing consent. No serious adverse events were recorded in this study.[80]
In the study on co-administered HPV and HBV vaccines mentioned earlier also no serious vaccine-related adverse events were reported.[79] The safety profiles of both vaccines were comparable to those previously reported for each of the individual vaccines.[75, 81]
A recent Australian study on the rate of anaphylaxis following school-based HPV-vaccination among women aged 15 to 25 years and older reported an incidence rate of 2.6 per 100 000 doses. The estimated rate was higher compared to other school-based delivery of vaccines, but overall rates were very low and women tend to have a higher rate of anaphylaxis than men.[82]
Brotherton et al. used the Brighton Collaboration case definition. This case definition uses only clinical signs and therefore a distinction between anaphylactic reactions and anaphylactoid reactions is impossible.[83] Since the FDA approved Gardasil in 2006, over 6000 adverse events were reported after vaccination with Gardasil in the vaccine adverse events reporting system (VAERS) in the USA. As described in the report of 2007 on the Dutch NIP, the majority of the reports were non-serious adverse events such as injection site reactions and headache. Serious adverse events reported to VAERS were Guillain-Barré Syndrome (GBS) (13 confirmed cases), of which two met the case definition of GBS and occurred in patients not receiving other vaccines. Five cases reports were vaccination with Menactra and Gardasil at the same time and will be further studied. The incidence of GBS in the vaccinated population is currently not higher than that of the general population.[84]
In the Netherlands, fourteen adverse events after vaccination with Gardasil (20782 prescriptions of Gardasil according to the Foundation for Pharmaceutical Statistics in the period November 2006 to June 2008) and four after vaccination with Cervarix (855 prescriptions of Cervarix over the period November 2007 to June 2008) have been reported by the Netherlands Pharmacovigilance Centre (Lareb). None of these events was classified as serious adverse events.

Pathogen

Persistence and clearance

Almost 2500 women attending a maternal and child health program in low-income neighbourhood in São Paulo (Brazil) enrolled between 1993-1997 in a cohort study. Among these women, the prevalence of infection with high risk HPV-types was 10.6% and the incidence rate was 6.1 per 1000 women months. For low risk HPV-types the prevalence and incidence amounted to 6.1% and 5.0 per 1000 women months respectively. Prevalent infections took longer to clear than incident infections. The mean duration of HPV-16 mono infection was shorter (11 months) compared to mean duration of HPV-16 co-infection (15.4 months).[85]

A study among 290 men (18-44 years) found that HPV infection in men was common (52.5%, 31.7% and 30.0% for any, oncogenic and non-oncogenic HPV infection). Within one year 29.2% acquired a new HPV infection (HPV-6, -11, -16 and -18: 2.8, 0.5, 4.8 and 0.8 per 1000 person months, respectively). The median time to clearance was similar for oncogenic and non-oncogenic infections (5.9 months).[86]

Koshiol et al.[87] conducted a systematic review and meta-analysis of the relation between HPV viral persistence and the risk of precancerous lesions. Their findings were that HPV persistence was more strongly linked with precancer and cancer than with equivocal or low-grade lesions. However, persistent infection was less strongly linked to precancer when women with transient infection were used as a referent group. Longer persistence, as detected by the absolute duration or time interval between measurements, was more strongly linked to precancer and cancer, but HPV genotype-specific persistence was no more related to risk of precancer than was repeatedly testing positive for HPV. The authors concluded that these findings validate HPV persistence as clinical marker and endpoint.

Acquisition

Data from a HPV prevalence study among Italian male sexual partners of women with cervical HPV infection, supported the hypothesis that HPV infection is more frequent in sexual partners of HPV positive women or women with cervical intraepithelial neoplasia indicating that men could represent an important source of HPV transmission between sexual partners.[88] Another study showed that the transmission from the penis to the cervix (4.9 per 100 person months) was substantially lower than that from the cervix to the penis (17.4 per 100 person months). Couples who transmitted HPV were more sexually active and used condoms less frequently.[89]

Goodman et al. reported the risk for acquisition of anal HPV infection examined in a longitudinal cohort study of 431 women from Hawaii. Seventy percent of women were positive for anal HPV infection at one or more clinic visits from baseline through a follow-up of average 1.3 years. The risk for incident high risk anal HPV infection was 19.5 per 1000 women months. Anal co-infection with multiple HPV-types was relatively common, i.e. 9.6 for any HPV and 9.5% for high risk HPV.[90]

Disease

Epidemiology of HPV-infection

Only limited data are available on the incidence of HPV-16 and -18 in the general population in the Netherlands. Recently, preliminary results on the seroprevalence of HPV-6, -11, -16, and -18 among girls aged 10-26 years of age in the general Dutch population was measured using the population-based serum collection of the PIENTER-2 study. The seroprevalence for HPV-6 and/or -11 was 4.2 % (95%CI 2.5-5.9%). The seroprevalence of HPV-16/18 in this age groups amounted to 4.4% (95%CI 2.6-6.2%). The overall seroprevalence increased with age to 16% at the age of 21 years and remained high among those in the age-group 22-26 years. A Dutch study among 18 to 29 year old women found a HPV point prevalence of 19%. HPV-16 en -18 prevalences in this study population were 2.8% and

1.4% respectively. There was an increase in HPV prevalence with age till 22 years, afterwards a plateau was reached.[91] In a randomized controlled population-based screening trial among women between 18 and 65 years of age, the prevalence of 14 types of hrHPV infections was determined. For all women, those in the age-category 18-24 years, the prevalence of HPV-16 and -18 was 7.5% and 2.3% respectively. The overall HPV-16 prevalence peaked at the age of 22 (prevalence 8%), while the overall HPV-18 prevalence peaked at the age of 24 (prevalence of 2.3%).[92]

Burden of disease
Still around 600 women per year are diagnosed with cervical cancer (www.ikcnet.nl). Over the last five years, on average 214 fatal cases are reported per year (2003-2007, www.cbs.nl). For 2003, the number of cancer cases due to HPV-infections have been estimated for both females and males.[93] The numbers are given in Table 8. It is clear that the disease burden is highest among females, but also among males cancer cases occur.

Table 8 Estimated number of cancer cases attributable to HPV-infection in the Netherlands in 2003, by cancer type[93]

Cancer type (ICD-10 code)	Incidence 2003[A] (n) men	Incidence 2003[A] (n) women	Incidence 2003[A] (n) total	Attributable Fraction (AF)[B]	Incidence attributable to HPV (n)
Cervix (C53)	-	584	584	100%	584
Ano-genital					
- penis (C60)	100	-	100	40%	40
- vulva/vagina (C51-C52)	-	303	303	40%	121
- anus (C21)	60	65	125	90%	113
Mouth (C01-C06)	478	342	820	3%	25
Oropharynx (C09-C10)	210	115	325	12%	39
Total	848	1409	2257		921

[A] Total number of new cancer cases in 2003 based on the Dutch cancer registry (NKR)[94]

[B] Attributable fraction (AF) based on assumptions of Parkin[95]

In line with 2006, genital warts were the most frequently diagnosed viral STI reported in all STI centers in the Netherlands in 2007. Compared to 2006, the number of diagnoses increased with 7% to 2061 (1,233 in men and 828 in women) (78,062 new consultations; 39,824 among men and 38,209 among women). Most diagnoses were made among men aged 20-29 years (46%) and among women aged 20-24 years (45%). A co-infection with Chlamydia was found in 10% of those being diagnosed with genital warts, while history of gonorrhoea, infectious syphilis or chlamydial infection was reported for 15% of the women and for 8% of the men diagnosed with genital warts.[96]
In a population-based study among women in various Scandinavian countries, 10.6% reported ever having had clinically diagnosed genital warts and 1.3% reported having experienced genital warts within the past 12 months. Rates of genital warts increased sharply with age and are highest in the youngest birth cohorts of women.[97]

Economic aspects
As reported in the previous report a cost-effectiveness analysis has been performed of HPV-16/18 vaccination of 12-year olds girls by a Markov model developed by VUMC. Furthermore, a cost-effectiveness analysis has been done by Erasmus University Rotterdam.
In both analyses life-long protection of the vaccine was assumed, 85% vaccination coverage, 90% vaccine efficacy, vaccine price of 125 euro per dose and discounting rates of 4% for costs and 1.5% for effects. The estimated cost-effectiveness ratios for universal vaccination of 12-year olds girls were 21.000 and 30.000 euro per QALY for VUMC and Erasmus, respectively. The number of cervical cancer cases prevented by vaccination amounted to 360 and 220 per 100.000 women, respectively. The models, differences and results are described and discussed in detail in the Health Council report and have been published.[98] The minister explicitly included cost-effectiveness as a demand in the tendering process of the two vaccines.

International perspectives
ECDC and WHO strategy papers have been published in 2008 to facilitate decision making process in various countries.[99, 100] They both address that secondary prevention by screening remains important. In those countries where screening programmes are not systematically organized, it remains first priority to set up or improve such programmes since the benefit of vaccination will be seen only decades from now. Furthermore, since HPV-types which are not included in the vaccine will continue to cause HPV-related cancer continuing screening programmes is essential.
In various European countries recommendations on the inclusion of HPV vaccines in the national immunization programmes have been made or are currently under review.[101, 102] Also for many countries cost-effectiveness analyses became available.[103, 104, 105, 106]
According to a study among 70,000 women from four Nordic countries (Denmark, Iceland, Norway and Sweden) only about one third of the women had ever heard about HPV. The most important correlates associated with ever having heard of HPV were a history of genital warts and educational level.[107]

Age-stratified world-wide data on HPV-DNA prevalences of types 16 and 18 in women show similar age-related trends across major regions, but prevalence differed by geographical areas.[108] HPV prevalence was highest among younger women for all major world regions with a peak in women aged <25 years of age, reflecting a higher probability of acquiring new infections at younger ages.[108] The shapes of the age curves for HPV infection declined in older ages or were characterized by a U shape, with a relatively higher HPV prevalence in younger and older ages. The higher prevalence in older age women could be a result of newly acquired HPV infections, reflecting differences in sexual behaviour across global regions, or reactivation of latent HPV infections.

For seroprevalence, in the German population (1-82 years; n=1797) the prevalence of antibodies against 34 HPV-types was measured using a Luminex/based multiplex serology. Overall 59.7% was seropositive for any HPV-type. The antibody prevalence for HPV-types 16 and 18 amounted to 7.1% and 3.8%, respectively. Antibody reactivity to more than one HPV-type was frequent: 24.5% were single positive, 11.5% reacted with two, 7.4% with three and 16.2% with more than three. The antibody prevalence to mucosal high risk types, most prominently HPV-16, was elevated after puberty in women but not in men and peaked between 25 and 34 years.[109] The population seroprevalence (0-69 years, n=2770) of HPV-types 6, 11, 16 and 18 were also measured in Australia using a competitive Luminex immunoassay (Merck). Among females and males 23.8% and 17.8% was positive for any of the HPV-types 6, 11, 16 or 18. The seroprevalence for HPV-6, -11, -16 and -18 amounted to 12.9%, 5.2%, 12.4% and 5.7% for women and 9.1%, 5.2%, 7.9% and 3.9% for males. Among females the peak occurred for HPV-6, -16 and -18 among 20-39 year-olds, while for HPV-11 was observed among 40-

49-year old women. Among males the peak for HPV-6 and -11 was seen for 40-49 year olds and for HPV-16 and -18 among 50-59 year olds.[110]

Recommendations for vaccination, surveillance and control
On request of the Ministry of Health in 2008 we set up a monitoring plan to prepare for possible inclusion of HPV-vaccination into the NIP. The need for monitoring and research alongside routine vaccination programme was stressed by the Health Council. We plan to study the acceptance of vaccination, the duration of protection offered by vaccination of 12-year olds in routine programme, the safety of the vaccine (i.e. reactogenicity, possible occurrence of rare severe side effects after wide spread vaccination, baseline incidence of immunological disorders), the effectiveness of vaccination in reducing (persistent) HPV-infections and on the longer run HPV-related precancer lesions and cancer. As mentioned in the previous annual report on the developments of the NIP, the possibility to link vaccination registration with disease registers is essential. The determination of the circulating HPV-types both in (persistent) HPV-infection and HPV-related disease is necessary to obtain insight into possible cross protection of the HPV-16/18 vaccine against other types and into the possible shift in types occurring after vaccination.

4.2 Rotavirus infection

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Vaccine
Availability and new developments
At present, two live rotavirus vaccines are available, both administered orally: Rotarix is administered in two doses, and Rotateq requires three doses.

Effectiveness
In 2006 the results of a phase III study in Latin America to the efficacy of Rotarix were presented over the first-year period.[111] A part of these infants, n=15,183, have now been followed until 2 years of age.[112] Vaccine efficacy against severe rotavirus gastroenteritis in the second year was 79% (95%CI 66-87) compared to 83% (95%CI 67-92) in the first year. Efficacy for the total period of follow-up was 81% (95%CI 71-87). The efficacy was serotype specific, with 82% (95%CI 65-92) for G1P[8], 81% (95%CI 68-89) for pooled P[8] G3, G4 and G9, and 39% (95%CI <0-84) for G2P[4]. Finally, the efficacy appeared to rise with an increase of the Vesikari scale, with a 82% (95%CI 73-89) efficacy for rotavirus gastroenteritis with a Vesikari's score of 11 or higher, and 97% (95%CI 84-99.9) with a Vesikari's score of 19 or higher.
In a small randomized placebo-controlled clinical trial with 178 infants in South Korea the seroresponse rate for serum anti-rotavirus IgA after vaccination with RotaTeq was tested to evaluate the immunogenicity and safety of the vaccine.[113] A seroresponse, defined as an increase of antibody titer by a factor three or more between baseline and approximately two weeks after the third dose, was found in almost all of the vaccine recipients (95% (95%CI 88-98)) compared to 14% (95%CI 6-26) of the placebo recipients.
Rotavirus vaccination using RotaTeq has been implemented in the routine vaccination of US infants in 2006. A preliminary comparison of the rotavirus season 2007/2008 with the pre-vaccine years 1991-2006 showed a delayed onset of the rotavirus season by 2-4 months.[114] Also, rotavirus activity appeared to have diminished in magnitude by >50% based upon the percentages of feceal samples testing positive for rotavirus. However, the rotavirus season of 2007/2008 was still ongoing and mean

coverage of rotavirus vaccine with one dose among infants aged 3 months and three doses among children aged 13 months was estimated to be 49% and 34% in March 2008, respectively.

Adverse events
Since the introduction of both RotaTeq and Rotarix, adverse effects of inoculation of the vaccines have been followed, with special focus on intussusception. The Rotavirus Efficacy and Safety Trial (REST)-study, involving approximately 70,000 children, demonstrated that the risk of intussusception was similar in vaccine and placebo recipients.[115] Between February 2006 and July 2007, a total of 165 cases of intussusception were registered in VAERS, the Vaccine Adverse Event Reporting System of the US, with RotaTeq administered or co-administered with other vaccines in 160 of these cases (97%). Haber et al. compared these data with results from the Vaccine Safety Datalink project and conclude that an intussusception risk similar in magnitude to that of Rotashield can be excluded, but continued monitoring in necessary.[116]
However, critical groups focus on the increase of VAERS-reports on intussusception and Kawasaki disease, following the uptake of Rotateq in the NIP of the USA.[117]

Pathogen
Strain variation
In Recife, Brazil, an ecological study was performed after introduction serotype G1P[8] vaccine (Rotarix).[118] The first three months of vaccination were compared to the same three months one year later. Group A rotavirus detection declined from 27% to 5%, and G2 serotype increased from 47% to 100%. However, a year before vaccination started, G2 strains were only detected in 7% of the cases. Therefore, the increase of the circulation of G2 strains could be the result of a natural shift.[119]
Of 558 rotavirus positive samples collected in southern Ireland between 2003 and 2006, 249 samples were G- and P-typed.[120] Single rotavirus infection was found in 86% (214/249) of these samples, consisting of G1 (65.1%), G2 (1.2%), G3 (16.1%), and G9 (3.6%). In most mixed infections G1 was involved (34/35). P[8] was the most prevalent circulating P strain, although also some P[6] and P[9] were detected.

Disease
Epidemiology / Burden of disease
The number of positive tests for rotavirus was 1,251 in 2007, which is lower compared to 2005 (1,324) and 2006 (1,583), but was still higher than in the previous years (2000-2004: 946-1,079).[121] Similar results were seen for the estimated percentage of hospital admissions caused by rotavirus infection: in 2007, an estimated 50.8% of the hospital admissions of children aged younger than five years was caused by rotavirus with an estimate of 4,039 admissions compared to 4,307 admissions in 2005 and 5,107 admissions in 2006.

International perspectives
In Germany, 32% of the children (< 24 months) who visited their general practitioner because of acute gastroenteritis had a rotavirus infection.[122] Furthermore, the symptoms of gastroenteritis were more pronounced and more persistent in children with a rotavirus infection.
A study to hospitalizations of children for enteritis in Italy showed highest incidence of rotavirus was seen in children younger than 5 years, and more specific in children aged between 1 and 2 years.[123]
Huppertz et al.[124] performed a systematic literature search to examine risk factors for severe rotavirus gastroenteritis. Infants born prematurely, infants with a low birth weight, and neonates admitted to neonatal intensive care facilities appear to have a higher risk of a more severe course when infected with rotavirus. Malnutrition and immunodeficiency can also contribute to the severity of rotavirus disease. Finally, rotavirus infection could be a contributing factor in the exacerbation of conditions,

such as celiac disease, acquired immunodeficiency, or renal complications. The results to the protective effect of breast feeding are variable, but exclusive breast feeding may offer some degree of protective against rotavirus disease as long as it is fed.[124, 125]
Gray et al.[126] made an overview about rotavirus. Day care centre attendees have a higher risk of developing rotavirus (median incidence 440 per 1000 children younger than 4 years per year) than was calculated for the general population of children under 5 years in the EU (median incidence 155 per 1000 children per year) and placebo recipients younger than 2 years in rotavirus vaccine trials (median incidence 134 per 1000 children per year).
Besides national vaccination in the United States of America, rotavirus vaccines are available in the National Immunisation Programme in Australia commencing July 2007 for babies born from 1 May 2007.

Recommendations for vaccination, surveillance and control
Introduction of the rotavirus vaccine could probably reduce the burden of disease substantially. However, as we previously reported it is unlikely to be cost-effective except for high endemic years. Both vaccines (RotaTeq and Rotarix) are practically feasible and appear to be safe. However, circulation of rotavirus types can change over time both naturally and as consequence of vaccination through elimination of illness by variants for which the vaccine protects. Surveillance of circulating strains can provide timely information when a drift occurs. Furthermore, little is known about long term efficacy and duration of protection of the vaccines. Nevertheless, main object of vaccination would be the protection of young children for developing severe rotavirus gastroenteritis.

4.3 Varicella Zoster Virus (VZV) infection

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

Vaccine
Availability and new developments
All vaccines are based on the same attenuated live vaccine strain against VZV (the Oka strain). Different monovalent vaccines against varicella are available (Provarivax/SP-MSD, Varilrix/GSK and Varivax/Merck); so far, only Provarivax has been registered and is available in the Netherlands.
There are also two vaccines against varicella available in combination with vaccines against measles, mumps, and rubella: ProQuad/SP-MSD[127] (not yet available in the Netherlands) and Priorix-Tetra/GSK.[128] For the prevention of herpes zoster only ZOSTAVAX (SP-MSD) has been registered.[129] However, this vaccine is not yet available in the Netherlands.

Adverse events
A signal of increased risk for seizures of any etiology is detected among children aged 12-23 months after administration of MMRV vaccine compared with administration of MMR vaccine. Therefore, the Advisory Committee on Immunization Practices in the USA no longer expresses a preference for the use of the combination measles-mumps-rubella-varicella vaccine over separate measles-mumps-rubella and varicella administration.[130]

Pathogen

Strain variation

The VZV genome is extremely stable, and all isolates belong to a single serotype. So far, three main genotypes of wild-type VZV have been distinguished.[131, 132, 133] In VZV strains that were isolated from the community, recombination events have been documented. Future recombination events could possibly alter the virulence of circulating VZV strains.[134]

Disease

Epidemiology

This section gives an update on the epidemiology of varicella and herpes zoster in the Netherlands as published by de Melker et al. in 2006.[135] Two databases were used for the estimation of incidence of varicella and herpes zoster. First, the registry of Prismant (National Health Care Registry) for the number of hospitalizations with discharge code either varicella or herpes zoster. It must be noted that a number of hospitals stopped their registration in 2006/2007, causing an underestimation of admissions in those years. Secondly, the sentinel surveillance network of the NIVEL was used to estimate the incidence of patients with varicella or herpes zoster consulting a GP.

Chickenpox

The number of hospitalizations with varicella as main or secondary diagnosis from 2000-2007 is shown in the left panel of Figure 15. In 2007 the incidence of hospital admissions with main diagnosis varicella (ICD-9 group 052) was 1.45 per 100,000 and 2.16 per 100,000 for main and/or secondary diagnosis together. Among 0-years old, the incidence was highest with 38.5 hospitalizations due to main diagnosis varicella per 100,000. The incidence based on GP consultations in 2007 was 210 per 100,000 inhabitants and was highest for the 0 and 1-4 year olds (respectively 2,350 and 2,840 per 100,000).[136] For both sources this implies a lower incidence compared to the previous period, i.e. mean 1.6 hospitalizations with main diagnosis varicella per 100,000 (range 1.3 to 1.7) and 253 GP consultations per 100,000 inhabitants (range 190 to 320) in 2000-2006.

Herpes zoster

The number of hospitalizations with herpes zoster as main or secondary diagnosis from 2000 to 2007 is shown in the right panel of Figure 15. For herpes zoster, the incidence of hospital admissions with main diagnosis herpes zoster (ICD-9 group 053) in 2007 was 2.05 per 100,000 and 4.05 per 100,000 for main and/or secondary diagnosis together. The incidence of hospital admissions was highest among the oldest age groups (age 85+) with 21.02 hospitalizations due to main diagnosis herpes zoster per 100,000. The incidence of hospitalizations with main diagnosis herpes zoster was slightly lower compared to the previous period 2000-2006, i.e. mean 2.3 hospitalizations per 100,000 (2.2 to 2.7).
It must be noted that the incidence of admissions for one day (not included in the figure above) decreased from 7.5 per 100.000 in 2002 to 4.0 per 100,000 in 2007. This decrease might be a result of the PINE study, which showed that a single epidural injection with steroids and local anaesthetics in the acute phase of herpes zoster is not effective for the prevention of long-term post herpetic neuralgia.[137]
The average annual incidence of herpes zoster based on general practitioner consultations was 332 (range 310-370) per 100,000 in the period 2002-2007 and is in the same range as in previous years. The incidence increased with age.[138]

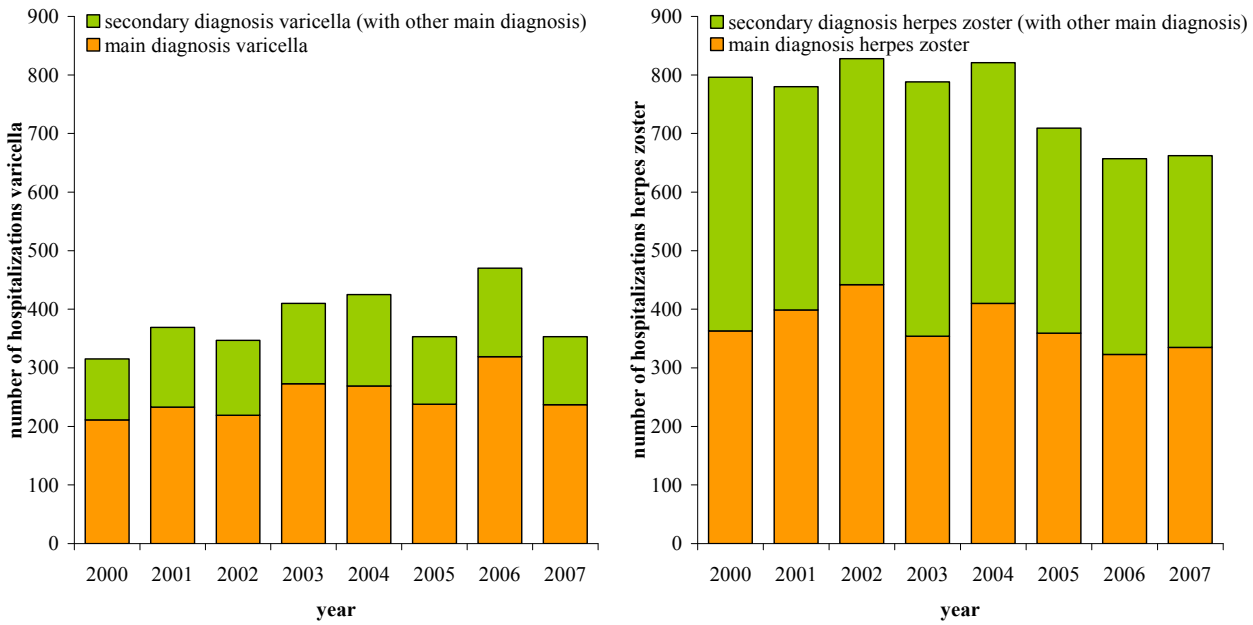

Figure 15 Number of hospitalizations with main or secondary diagnosis of varicella (left panel) and herpes zoster (right panel) from 2000-2007

Burden of disease

Chickenpox

As described previously the seroprofile for the Netherlands shows a relatively low age of infection in comparison to others.[139] An explanation for this might be a difference in social contacts and mixing patterns.[140]

Economic aspects

Chickenpox

Rozenbaum et al. provided an update of the literature on cost-effectiveness of varicella vaccination programmes (2003 up to December 2007). From a societal perspective, almost all studies showed that routine childhood vaccination is cost effective or even cost saving (benefit-to-cost ratios ranged from 1.45 to 19.33). Two studies, including the negative effect of varicella vaccination on the incidence of herpes zoster, showed positive net costs. From the health care perspective, five studies still showed a positive benefit-to-cost ratio. However, in four studies this was due to country specific setting regarding sick leave compensation.[141] Most studies in this review were based on a single dose of the varicella vaccine, while nowadays a second dose is recommended. A study in the US showed that from a societal perspective both a programme with one dose (benefit-to-cost ratio 4.37) and a programme with two doses (benefit-to-cost ratio 2.73) is estimated to be cost saving compared with no vaccination. However, the incremental dose was not cost saving (benefit-to-cost ratio 0.56) compared with a programme with one dose.[142]

Herpes zoster

For Canada it is estimated that vaccinating people of 65 years and older will cost $33,000 per QALY-gained (90% CI 19,000-63,000). This estimation was based on the following assumptions: efficacy against herpes zoster of 63%, efficacy against post herpetic neuralgia of 67%, no waning and a cost/course of $150.[143]

International perspectives

Chickenpox

Only three European countries have incorporated varicella vaccination currently into their recommendations for their national childhood immunization programme (i.e. Germany, Greece and Latvia). In some other countries (i.e. Spain and Italy) particular districts are applying childhood vaccination. Some other countries (i.e. Austria and Switzerland and districts in Spain and Italy) have a vaccination programme for adolescent with no history of chickenpox.[144]

In the United States, where varicella vaccination was introduced in the NIP in 1995, national vaccination coverage among children 19-35 months increased from 25.8% to 87.9% between 1997 and 2005.[145] Varicella incidence has declined by 90% in 2005 (compared tot 1995) in the varicella active surveillance sites of Antelope Valley (California) and West Philadelphia (Pennsylvania).[146] In this period, (complications) during varicella related hospitalizations also decreased.[147] However, the epidemiology is changing: the peak age of infection is now occurring among older children.[146, 148]

Herpes zoster

Exposure to VZV during adulthood might stimulate the cell-mediated immunity against reactivation of VZV, resulting in reduced chance of herpes zoster later in live. Because universal childhood vaccination against chickenpox has been introduced in the USA from 1995 onwards the incidence of herpes zoster might start to increase.[149] Studies monitoring the incidence of herpes zoster have shown inconsistent findings. Two studies showed no increase[150, 151], whereas three studies showed an increase in herpes zoster incidence.[152, 153, 154]

Recommendations for vaccination, surveillance and control

Chickenpox vaccination

To assess the chickenpox associated burden of disease more accurately we are reviewing patients' medical records to obtain more insight into the severity of disease of hospitalized patients in particular for those coded as varicella without specific complications. Furthermore, we consider performing a capture-recapture analysis with the data on hospital admissions for chickenpox and data collected through the paediatric surveillance unit, although reported numbers are low.

Introduction of universal varicella vaccination in the NIP as a combination vaccine (MMRV) will require an adaptation of the current immunization schedule (at present, MMR is given at 14 months and nine years; replacement of MMR with MMRV will not comply with the recommendation for varicella vaccination). What the different options are, and what the potential effects, if any, will be on immunity and protection against measles, mumps, and rubella has to be assessed.

Herpes Zoster

Information on hospital admissions and GP visits show that the disease burden is considerable. At the moment a study on reduction in quality of live due to herpes zoster infections in the Netherlands is performed. This data will be used to estimate the cost-effectiveness of herpes zoster vaccination in different scenarios. The feasibility of introduction of programmatic herpes zoster vaccination with ZOSTAVAX in older people in the Netherlands is subject of an assessment study using a structured approach.[155]

4.4 Meningococcal serogroup B disease

L.M. Schouls, S.C. de Greeff, G.A.M. Berbers

Vaccine

Availability and new developments

Group B *N. meningitidis* remains the predominant meningococcal serogroup causing about 50% of meningococcal disease worldwide. In many countries, like the Netherlands, it is the cause of more than 80% of all meningococcal disease. The disease can not be prevented by a MenB polysaccharide vaccine, which would have been a logical vaccine candidate. The MenB polysaccharide closely resembles a human neural cellular adhesion molecule making it an unsuitable vaccine component. Currently there are no licensed vaccines available to prevent meningococcal serogroup B disease. However, several vaccine candidates are under investigation. Examples are PorA, PorB and FetA outer membrane proteins, but also RmpM, Opa and OpcA, NspA, NadA, Omp85, TdfH and lipoprotein LP2086. One of the major problems encountered in the analysis of these candidate vaccines is variability. Virtually all immunogenic components tested so far appear to be variable in composition. This hampers the development of a vaccine that will protect against all MenB types.

At the 16th International Pathogenic Neisseria Congres in Rotterdam it became clear that two vaccine developments are very promising at the moment. The phase 2 trials with these newly developed vaccines are almost completed. The first candidate vaccine is developed by Novartis based on a novel approach called reverse vaccinology. Their investigational MenB vaccine contains 3 main protein antigens (NadA, fHBP and GNA 2132) which have been combined with the OMV PorA (P1.7-2,4) vaccine, that has been used for the New Zealand epidemic, to increase the potency and to create a broad coverage. The second candidate is developed by Wyeth and based on two subtypes of LP2086, which turns out to be the factor H binding protein (fHBP) also used by Novartis. It is striking that both vaccines contain the same factor H binding protein. Both vaccines are believed to provide a broad protection against infection of the many different Men B strain variants (>80%). All other vaccine candidates are still in the experimental stage or are being tested in phase 1 trials.

Disease

Burden of disease

Since 2000 the number of patients with meningococcal B disease has been decreasing, as can be seen in Figure 16 and Table 9. In 2007 the number of cases has decreased to 148. The reason for this decreased incidence remains enigmatic. Possibly, natural fluctuation may explain this decreasing trend.

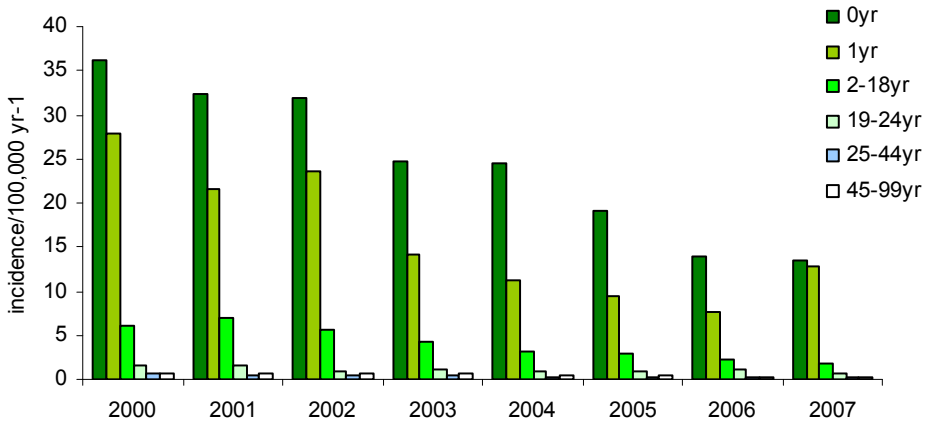

Figure 16 Age-specific incidence of meningococcal B disease by year, 2000-2007

Table 9 Absolute number of patients with meningococcal B disease per age-category from 2000-2006

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

International perspectives

The Netherlands is not the only country that experienced a declining number of cases of invasive MenB disease. A similar decline in the number of serogroup B cases is also seen in other countries, e.g. Belgium, Denmark, Ireland, Norway and the UK. In Denmark the incidence decreased from 4.4 in 1994 to 1.9/100 000 population in 2002.[156]

To control the MenB epidemic, New Zealand has administered from July 2004 a monovalent OMV PorA (P1.7-2,4) vaccine in the population under 20 years of age in a 3-dose schedule. Infants were given a fourth dose. With over 3.1 million doses of the so-called MeNZB vaccine delivered and a calculated vaccine effectiveness of 73% the incidence rate dropped from 17.4 in 2001 to 2.6 in 2007 per 100,000 inhabitants. Although this rate is still 1.7 times higher than the pre-epidemic rate, the Ministry of Health in New Zealand has decided quite controversially to cease the Men B vaccination programme from July 2008. In Cuba the MenB epidemic was also controlled with a strain specific OMV PorA (P1.7,16) vaccine but in contrast with New Zealand this vaccine is still included in the Cuban national infant schedule.

Recommendations for vaccination, surveillance and control

Ongoing surveillance is required to monitor any changes in the incidence and disease expression of invasive disease caused by serogroup B meningococci. The decreasing incidence of group B disease in the absence of vaccination is remarkable and needs to be investigated to determine its characteristics and to find possible causes. Preliminary results suggest that the decrease in meningococcal B disease in the cohorts eligible for meningococcal C vaccination is bigger than in the adult population not targeted for meningococcal C vaccination. However, further analyses will be performed to study these changes.

4.5 Respiratory Syncytial Virus (RSV) infection

W. van der Hoek, M.A.B. van der Sande

Vaccine

Availability and new developments

Despite many decades of research and different vaccine approaches, there is still no RSV vaccine available for routine use. Several groups, including the Netherlands Vaccine Institute, are developing vaccines against RSV. Even when a RSV vaccine would be available, some critical issues will have to be addressed before RSV vaccination can be introduced. This includes the possible differential effectiveness in elderly people and infants.

Disease

Epidemiology

In the context of influenza surveillance, sentinel GP's take swabs from patients with influenza-like illness (ILI) and acute respiratory infections. The samples are also tested for RSV. During the 2007-2008 season, RSV was found in samples taken by sentinel GP's from week 47 in 2007 to week 4 in 2008. Additional samples, without clinical information from virology laboratories show that the RSV-season started in week 43 of 2007, which is comparable to previous years. The RSV-season lasted 17 weeks (until week 8 in 2008) and was relatively short. Based on the numbers reported in the virology laboratories, levels remain similar compared to previous years; i.e. 2158 in 2007/2008 versus 1596-2399 in 1998/1999-2006/2007. However, only positive results are reported.

Burden of disease

RSV is a common cause of hospitalization due to lower respiratory tract infection in infants. There are no reliable estimates of disease burden but there are indications that clinical burden of disease associated with RSV is as great if not greater than influenza in patients of all ages.

Recommendations for vaccination, surveillance and control

There is long history of vaccine development for RSV which has seen major setbacks because of indications of more severe disease among vaccinated infants. Because of the high disease burden, especially among infants, development of an effective and safe RSV vaccine remains a priority.

4.6 Hepatitis A

I.H.M. Friesema

Vaccine

Effectiveness

Victor et al. have compared the effectiveness of hepatitis A vaccine (VAQTA) and immunoglobulin after exposure to the hepatitis A virus in a randomized trial in Kazakhstan.[157] A total of 1,090 contacts of index cases of hepatitis A, who were susceptible to the virus, were randomly assigned one dose of either the vaccine or the immunoglobulin. Rates of symptomatic infection with hepatitis A were low in both groups, although slightly higher in the vaccine group (4.4% compared to 3.3%). They concluded that hepatitis A vaccine may be a reasonable alternative to immunoglobulin for post-exposure prophylaxis.

Introduction of hepatitis A vaccination in preadolescents in Catalonia (Spain) reduced the incidence rates in the whole population from 5.51 per 100,000 person-years (1992-1998, pre-vaccination) to 2.98 per 100,000 person-years (1999-2005, post-vaccination).[158] The rate reduction was with 72% highest in the 10-19 years age group. The calculated prevented fraction in the 12-19 years age group was 90% (95% CI: 84.5-90.9). Finally, the vaccination effectiveness was calculated to be 99% (95% CI: 93.1-99.9).
In 1999, Israel was the first country to introduce a hepatitis A vaccine into its national childhood vaccination programme.[159] In the year before implementation, the incidence rate was 142.4 per 100,000, which declined to 45.2 per 100,000 in 2001 and 7.6 per 100,000 in 2007. Most effect was seen in children younger than 5 years (239.4 in 1998 to 2.2 in 2007) and aged 5-14 (310.3 in 1998 to 3.0 in 2007). The vaccination coverage of at least one dose increased in this period from 9% (< 5 years) and 15% (5-14 years) in 1998 to 89% and 68% in 2007, respectively.
In Argentina, the mean incidence of hepatitis A was 85.5 per 100,000 (95% CI: 66.7-104.3) in the period 1998-2002.[160] In 2003-2004, a large outbreak of hepatitis A occurred after which in 2005 vaccination for hepatitis A was included in the childhood immunization programme. In 2006, the vaccination coverage of the aimed group of children aged 12 months was 95%. In 2007, the overall incidence has declined to 10.2 per 100,000.
In Minsk, vaccination of 6-years old started in 2003, with between 2003 and 2006 a vaccination coverage of 98.6% in the age group 6-9 years.[161] Between 2003 and 2006, two cases of hepatitis A were reported among vaccinated children between 1-17 years (3.1 per 100,000) and 131 among unvaccinated children of the same age (62.1 per 100.000). The corresponding calculated OR was 0.05 (95% CI: 0.01-0.20). Thus estimating vaccine effectiveness at 95% (CI 80-99%)

Disease

Epidemiology

The number of notified cases of hepatitis A in the Netherlands decreased from 269 cases in 2006 to 156 cases in 2007 (1.65 per 100,000 population to 0.96 per 100,000 population).[162] This corresponds with the long-term decreasing trend since the early nineties. About half of the cases (79 cases, 51%) were reported to be travel-related, mostly after a visit to Morocco (35 cases, 22%). Only six cases (4%) appeared to be related to food or water. The source of infection was unknown for the remaining cases, also due to the long incubation period. Following the same trend as the total number of notified cases, the number of hepatitis A clusters also decreased. In 2007, 26 clusters were reported compared to 58 clusters in 2006.

International perspectives

In 2007, the CDC in the USA updated their recommendations concerning prevention of hepatitis A after exposure and in international travellers.[163] In the new recommendations, it is advised to administer one dose of single-antigen hepatitis A vaccine or immunoglobulin as soon as possible after exposure. Furthermore, all travellers to countries with high or intermediate endemicity of hepatitis A should be vaccinated or receive immunoglobulin before departure.

Recommendations for vaccination, surveillance and control

The incidence of hepatitis A is low in the Netherlands and remains decreasing. Previous reports already concluded that mass vaccination programmes would probably not be cost-effective. Nevertheless, as about half of the cases is travel-related (51% in 2007, 44% in 2006, 54% in 2005 and 39% in 2004) this could be a lead for further reduction of incidence by more education and/or specific vaccination programmes.

5 Issues of current interest for the NIP

Like the previous annual reports we will discuss in this chapter some highlights of current interests in the field of the Dutch National Immunisation programme. In the present report we will address the need for further research on evidenced based vaccination schedules.
At present children in the Netherlands are vaccinated at 2, 3, 4 and 11 months with DTaP-IPV-Hib 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 MMR-vaccine. Furthermore, at 4 and 9 years vaccination is offered against DTaP-IPV and DT-IPV and MMR, respectively. Importantly, based on the advice of the Health Council, no more than two shots are given at any moment.
Partly this schedule is based on scientific insights/opinions at the time of introduction of the vaccines. However, also practical issues were involved. Furthermore, once a specific schedule has been introduced, it apparently is hard to change given the potential influence of a change on the schedule as a whole and the use of combination vaccines. From 1962 until now the schedule of diphtheria, tetanus, pertussis, poliomyelitis vaccination did only change once, i.e. in 1999 the schedule was advanced with one month from 3, 4, 5 and 11 months to 2, 3, 4 and 11 months. The main reason for accelerating the schedule was to induce earlier protection against pertussis and invasive *Haemophilus influenzae* type b infection. In contrast, the composition of the vaccines used in the NIP has been subject to frequent changes.
Importantly, the accelerated vaccination schedule has been successful in reducing the target diseases. However, some issues remain or may have become suboptimal as a result of changes in epidemiology after universal vaccination. Furthermore, new scientific insights are arising such as age-specific factors related to the maturity of the immune system and the specific kind of vaccine, e.g. conjugated vaccines. These factors may indicate other schedules might be more attractive, for immunological, epidemiological and/or cost-effectiveness reasons.
Important issues that need reconsiderations of the current schedule in the Netherlands are:

1. Hospitalization of pertussis is highest among infants too young to be completely vaccinated. Therefore, the use of new vaccination strategies such as cocooning, neonatal vaccination or maternal vaccination needs to be explored.
2. For measles and rubella most women who recently became mothers have been offered vaccination prior to pregnancy. However, vaccine induced antibodies are lower in comparison to naturally induced antibodies. Therefore, maternal antibody persistence in children from vaccinated mothers might be shorter compared to those with naturally induced immunity. With the current schedule this may lead to a longer period of susceptibility and thus increased risk of infection when circulation of the virus occurs.
3. A third issue regards the schedule for conjugate pneumococcal vaccination. The most recent change to the vaccination schedule has been the inclusion of pneumococcal conjugate vaccine in 2006. The Health Council advised to vaccinate with conjugated pneumococcal vaccine with a 3+1 schedule i.e. 3 primary vaccinations at 2, 3 and 4 months of age and a booster vaccination at 11 months of age. Data on clinical efficacy of a 2+1 schedule was considered to be insufficient / too scarce. Therefore, to be certain sufficient clinical efficacy was obtained a 3+1 doses schedule was introduced. However, if a 2+1 schedule turns out to be as effective as a 3+1 schedule, a quarter of the resources needed for pneumococcal vaccination could be saved.

As a starting point we would like to address the three issues mentioned above, but we do realize that complexity might increase as a result of possible vaccination against new target diseases (HPV, rotavirus, varicella zoster).
In 2009 the CIb will start a study on the new generation conjugated 13-valent pneumococcal vaccines comparing the immunogenicity of the current 3+1 schedule with two different 2+1 schedules, i.e. at 2, 4 and 11 months and 3, 5 and 11 months. If the latter schedule would turn out to be the better one, studying a different timing for the remaining NIP components will become a new focus of attention. In earlier years it has been important to protect children as early as possible in life against diphtheria and poliomyelitis. However, as a result of mass vaccination the circulation of these pathogens has decreased enormously. Therefore, starting vaccination somewhat later in life, would not directly lead to high risk for the individual or the population as a whole for diphtheria or poliomyelitis reoccurrence. However, for pertussis delaying the start of vaccination will almost certainly lead to a significant increase in the number of infected young children. Therefore, we plan to include a trial arm with neonatal pertussis vaccination in the above mentioned pneumococcal study. Furthermore, in a separate study, we would like to address the feasibility of the cocooning strategy to protect against pertussis. This research line fits well within the aim of the ECDC to address evidence-based vaccination schedules.

6 Recommendations and plans for vaccination, surveillance, and research

In this chapter we give an overview of specific recommendations with regard to vaccination, surveillance and research. While some recommendations have been updated since the previous report, other recommendations are still applicable e.g. work is still in progress. We divide the parts on surveillance and research into parts referring to those that already have been included in the CIb work programme for 2009, those that are planned for 2009 through other means (i.e. external finances) and those planned for the future.

Vaccination

- For pertussis the feasibility of vaccination strategies aiming at the prevention of severe infection in infants too young to be vaccinated needs to be explored. We propose to carry out a study on the feasibility and effectiveness of maternal and neonatal vaccination and cocooning. Potential future changes in vaccination strategy for these young age groups might have impact on the pertussis vaccination schedule as a whole.
- The desirability to reduce the age of MMR-2 from nine to four years in order to reduce the susceptibility rate among school-aged children needs further discussion. A change of timing of MMR is also relevant if inclusion of V (MMR-V) would be foreseen.
- The relative merits of different mumps vaccine strains for inclusion into the NIP should be evaluated. Factors to consider include effectiveness and reactogenicity.
- The national Dutch measles elimination plan, covering surveillance and control of measles through vaccination, dates from 1999 and needs to be updated, taking into account the recent epidemiology of measles and opportunities to include rubella elimination.
- Recommendations on the issue of universal hepatitis B vaccination from the Health Council are expected early 2009.
- For pneumococcal disease it is recommended to compare the (cost-)effectiveness both in 3+1 and 2+1 schedule of the currently used 7-valent conjugated pneumococcal vaccine and the forthcoming more valent conjugated pneumococcal vaccine.
- Influenza vaccination coverage is high among the elderly and other high risk groups that are covered under the National Influenza Prevention Programme. Vaccination of health care workers is highly recommended and is offered by most employers but compliance remains very low.
- Selective BCG vaccination strategy, targeting children from high prevalence countries and individuals travelling longer than three months to high endemic areas should be continued until the results of the advice of the Health Council becomes available.
- HPV-vaccination will be included in the NIP in September 2009 with a catch-up programme for those born in 1993 to 1996 that will start in March 2009. On request of the Ministry of Health a plan of monitoring safety and surveillance has been prepared (see surveillance).
- In the consideration whether or not to implement rotavirus vaccination into the NIP it has to be taken into account that introduction of the vaccine would be practically feasible, could probably reduce the burden of disease caused by rotavirus substantially, especially in the young children, but is unlikely to be cost-effective except for high endemic years.
- The forthcoming data on disease burden based on discharge data of hospitalized patients with chickenpox should be used in the advice of the Health Council on whether or not to introduce universal chickenpox vaccination into the NIP. Furthermore, the potential impact of routine varicella vaccination on herpes zoster incidence is still unclear.

- The forthcoming results of the cost-effectiveness analysis of herpes zoster vaccination for elderly should be used in the future advice of the Health Council on potential programmatic use of this vaccine.
- The ongoing vaccine development regarding RSV and meningococcal serogroup B and the decreasing trend of meningococcal serogroup B disease has to be followed.
- Given the low and decreasing incidence of hepatitis A, universal vaccination is not (yet) recommended. As about half the cases acquire hepatitis A abroad, this could be a lead for further reduction of incidence by more education and/or specific vaccination programmes.

Surveillance (already planned activities in the CIb work programme for 2009 or otherwise)
- Notifications will be extended to all NIP-target diseases from December 1st, 2008 onwards by adding tetanus, mumps, *Haemophilus influenzae* type b disease and invasive pneumococcal disease for one- to five-year-olds to the list of notifiable diseases.
- Continuation of surveillance activities for poliomyelitis such as nationwide enterovirus surveillance and environmental surveillance in the risk area are considered as excellent tools for excluding poliovirus circulation.
- We will participate in a study on the burden of several infectious diseases in elderly homes (SNIV study) in 2009, to estimate the incidence of pertussis among elderly.
- The disappointing progress in the global polio eradication initiative does call for continuation of the surveillance activities in the Netherlands at the present level also in 2009.
- Genotyping of all Hib strains isolated from patients with invasive Hib disease will be performed.
- Laboratory surveillance of measles, mumps and rubella ('virologische weekstaten') should be integrated with the notification data. In addition, a surveillance protocol including the responsibilities of the different CIb departments as well as external stakeholders should be developed.
- Molecular surveillance for rubella infections should be enhanced so that progress towards elimination can be assessed.
- Molecular typing of all acute HBV strains is recommended so that the transmission in high-risk groups and others can be monitored more closely. In addition, surveillance of antiviral resistance should be explored.
- The introduction of HPV-vaccination into the NIP for 12-year-olds and the catch-up campaign of 13-16 year olds will be monitored with respect to acceptance of vaccination, possible shifts in the circulating HPV-types, safety, duration of vaccine protection, effectiveness of vaccination in reducing (persistent) HPV infections and on the longer run HPV-related precancer lesions and cancer.
- Surveillance of rotavirus serotypes could be a good tool for monitoring circulating serotypes and detect possible changes over time to estimate the potential future impact of vaccination.

Surveillance recommended (not included in the work programme CIb for 2009)
- To set up a (sentinel) system that allows systematic collection of *Bordetella* strains to study changes in the pathogen population in relation to pertussis vaccination.
- Possibilities to monitor HBV antiviral resistance need to be explored.
- The use of new diagnostic tools to estimate the burden of pneumococcal disease in inhabitants of nursing homes and the elderly in the community is recommended.
- Coverage of the tuberculosis vaccination policy within the Netherlands should be carefully monitored to be able to evaluate future changes in vaccination strategy.

Research (already planned activities in the CIb work programme for 2009 or otherwise)

- Assessment of antibody titres within the PIENTER-2 study (a population-based serum collection) against the different pathogens included in the NIP, to study potential immunity gaps in specific age groups. This is an important tool to study if the current vaccination policy is satisfactory or needs adjustment. Some disease specific items that will be addressed are: the high frequency of pertussis among adolescents and adults needs further confirmation, changes in Hib-circulation will be studied, the MMR schedule needs reconsideration, the HBsAg prevalence in ethnic minorities will be assessed, the impact of HBV vaccination of children of first generation migrants from endemic countries will be evaluated and antibody titres against 13 different pneumococcal serotypes will be determined.
- To facilitate the decision making on future pertussis vaccination strategies, we propose to carry out modeling and cost-effectiveness studies to test and compare possible future vaccination strategies such as cocooning and adolescent or adult booster vaccinations.
- Further research is required to determine reasons for the occurrence of Hib vaccine failures. This research should include study of the functionality and avidity of the vaccine induced antibodies in children in which the vaccine failed to protect against invasive Hib disease.
- Serologic evaluation of the HBV and Hib vaccination response in a group of children at one year of age, who have been vaccinated simultaneously according to the current Dutch NIP schedule with Prevenar and Infanrix hexa to study possible interference.
- The anticipated imminent measles outbreak in the Bible Belt provides an opportunity to study immunological correlates of protection against wild-type measles virus infection. In addition, a research project is ongoing into the correlates of protection and immunological memory in the context of measles vaccination.
- In 2009, the effectiveness of the current hepatitis B vaccination schedule for infants born to HBsAg positive mothers (0, 2, 3, 4, 11 months) will be compared with the previous schedule (2, 4, 11 months).
- A study to determine the background prevalence of MS will be carried out to provide a baseline which may be relevant when universal hepatitis B vaccination may be introduced.
- Assessment of changes in the composition of the pneumococcal population causing invasive pneumococcal disease in the Netherlands during the post-vaccination era.
- Immunogenicity study to compare the antibody response against 13 pneumococcal serotypes in a 2+1 and a 3+1 vaccination schedule using 13-valent pneumococcal conjugate vaccine.
- Estimates on the burden of disease from influenza in children will become available trough the ‘European Paediatric Influenza Analysis (EPIA) Group’, which started its research in 2008. These estimates are needed for realistic cost benefit analysis of influenza vaccination of children.
- RIVM is participating in a European project to develop methods for measuring vaccine effectiveness (VE) during the influenza season. This should provide a framework that makes it possible to measure real-time VE on a routine basis and to estimate VE in a pandemic situation, should such a situation occur.
- We will start to evaluate direct and indirect effects of HPV-vaccination programmes by mathematical models combining the effect of vaccination, screening programmes and co-infection non-vaccine HPV-types or other STIs.
- Insight into the severity of hospitalisations due to varicella is lacking. Therefore, medical records are reviewed to obtain more insight into the severity of chickenpox. A capture-recapture analysis with hospital data for chickenpox and data collected through the paediatric surveillance unit will be performed as well.
- Since herpes zoster vaccination is available, we will perform an assessment study on the feasibility of introduction of programmatic herpes zoster vaccination in older people in the Netherlands including cost-effectiveness.

Additional research needs (not included in the work programme CIb for 2009)

- We propose a study to compare the current pertussis schedule (2, 3, 4, 11 months and 3-4 yrs) with that of the schedule used in Scandinavia (3, 5, 12 months, 5-6 yrs).
- PIENTER-2 tetanus results could also be analysed in combination with operational characteristics of the Tetanus Quick Stick (TQS), to assess its potential for use in Dutch clinical practice. By analysing tetanus IgG titers, it could be assessed in which proportion of individuals a TQS measurement could contribute to avoiding giving Tetanus Immune Globuline after a tetanus prone injury.
- Assessment of anti-bactericidal activity in vaccine induced antibodies against Hib during the pre- and post-vaccination era to study the influence of natural boosting due to circulating Hib.
- In view of the national and international mumps outbreaks mumps vaccine failure, particularly the causes and the implications, should be studied.
- An economic evaluation of screening of migrants for HBV and HCV, to allow early treatment, should be carried out.
- The merits of screening for viral load and selective treatment with anti-virals during pregnancy in order to allow prevention of perinatal transmission of hepatitis B should be assessed.
- More research is needed on efficacy of influenza vaccination of children (6 months – 2 years) and of older children with asthma.

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Appendix 1 Overview changes in the NIP since 2000

Table 10 NIP 1st July 2001 – 31st August 2002

(change: aP added at 4 years of age, for all children born on or after 1st 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 11 NIP 1st September 2002 – 28th February 2003

(change: Men C added at 14 months of age, for all children born on or after 1st 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 12 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 1st 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 13 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 1st 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 14 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 1st 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 15 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 16 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 17 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 2008

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 10µg Conjugated to tetanus toxoid 10-20 µg adsorbed to aluminium hydroxide 0.5 mg Al3+
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 0.25mg *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

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

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