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The National Immunisation Programme in the Netherlands

Developments in 2007

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Abstract

The National Immunisation Programme in the Netherlands

Developments in 2007

The National Immunisation Programme (NIP) in the Netherlands is effective and safe. Surveillance and research are important to determine whether adjustments are necessary.

This report gives an overview of relevant developments in 2007 with regard to availability of vaccines, vaccine effectiveness, adverse events, disease burden, health economic aspects and international perspectives that are relevant for the NIP.

The programme remained unchanged in 2007 with exception of the DTaP-IPV (diphtheria, tetanus, acellular pertussis, inactivated polio vaccine) booster vaccination for four-year-olds for which two vaccines of different manufacturers were used. Most of the current target diseases of the NIP are under control because the vaccination coverage is higher than 95% in general. After introduction of pneumococcal vaccination in 2006, this disease was less often reported for children less than two years of age.

To further improve the NIP several recommendations were made. The most effective strategy for protecting young children who are not yet vaccinated against pertussis will be studied. In addition, a reduction of the target age of the second MMR vaccination (measles, mumps, rubella) is considered. Another study focuses on the frequency of pneumococci vaccination (two versus three vaccinations and a booster at the age of 11 months).

In 2008, the National Health Council is considering the desirability of universal hepatitis B vaccination, and the introduction of vaccination against human papillomavirus for girls, rotavirus, and varicella and herpes zoster. In this report recommendations for surveillance and research were made for these diseases.

In addition, recommendations for hepatitis A (cost-effectiveness analysis of routine vaccination), tuberculosis and influenza (maintaining vaccination of a selective group), meningococcal B disease (investigation of decreasing trend), and respiratory syncytial virus (vaccine development) are included in the report.

Key words:

National Immunisation Programme, MMR, DTaP-IPV, *Haemophilus influenzae* type b, hepatitis B, meningococcal C disease, pneumococcal disease

Rapport in het kort

Het Rijksvaccinatieprogramma in Nederland

Ontwikkelingen in 2007

Het Rijksvaccinatieprogramma (RVP) in Nederland is effectief en veilig. Surveillance en onderzoek zijn van belang om te beoordelen of aanpassing nodig is.

Dit rapport geeft een overzicht van alle relevante ontwikkelingen in 2007 van beschikbaarheid van vaccins, vaccineffectiviteit, bijwerkingen, ziektelest, gezondheidseconomische aspecten en internationale perspectieven die relevant zijn voor het RVP.

In 2007 bleef het RVP ongewijzigd, uitgezonderd de DKTP (difterie, kinkhoest, tetanus, polio) boostervaccinatie voor vierjarigen waarvoor twee vaccins van verschillende fabrikanten zijn gebruikt. De meeste van de huidige ziekten die met het RVP worden bestreden zijn onder controle door de nationale vaccinatiegraad die over het algemeen boven 95% ligt. Na de introductie van pneumokokkenvaccinatie in 2006 is deze ziekte bij kinderen onder de twee jaar al iets minder vaak gevonden.

Het rapport beschrijft diverse plannen om het RVP te verbeteren. Zo wordt onderzocht wat de effectiefste manier is om jonge kinderen te beschermen die nog niet zijn ingeënt tegen kinkhoest. Ook wordt overwogen om de leeftijd van de tweede BMR-prik (bof, mazelen, rubella) te verlagen. Een ander onderzoek kijkt naar de frequentie van de pneumokokkenvaccinatie (twee tegenover drie keer bij zuigelingen, gevolgd door een booster op de leeftijd van 11 maanden).

De Gezondheidsraad beraadt zich in 2008 over de wenselijkheid universeel tegen hepatitis B te vaccineren. Ook beraadt zij zich over de introductie in het RVP van vaccinatie tegen humaan papillomavirus (HPV) voor meisjes tegen baarmoederhalskanker, rotavirus en varicella (waterpokken) en herpes zoster (gordelroos). In dit rapport staan enkele aanbevelingen voor surveillance en onderzoek naar deze ziekten. Daarnaast geeft het aanbevelingen voor hepatitis A (kosten-effectiviteitanalyse voor routinevaccinatie), tuberculose en influenza (behoud van vaccinatie voor een selecte groep), meningokokken B (onderzoek naar dalende trend) en respiratoir syncytiaal virus (vaccinontwikkeling).

Trefwoorden:

Rijksvaccinatieprogramma, BMR, DKTP, *Haemophilus influenzae* type b, hepatitis B, meningokokken C, pneumokokken

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List of abbreviations

ABCs	Active Bacterial Core Surveillance system
ACIP	Advisory Committee on Immunization Practices
AEFI	Adverse Events Following Immunization
AIS	Adenocarcinoma In Situ
aP	acellular Pertussis
BCG	Bacil Calmette Guerin
CDC	Centre for Disease Control and Prevention
CEA	Cost-Effectiveness Analysis
CER	Cost-Effectiveness Ratio
CI	Confidence Interval
CIb	Centre for Infectious Disease Control
CMR	Continuous Morbidity Registration Centres
CSF	Cerebrospinal Fluid
cVDPV	circulating Vaccine-Derived Polio viruses
DALY	Disability Adjusted Life Years
DTP	Combination of Diphtheria, Tetanus, and Pertussis vaccines
EA	Regional Vaccination Administration Centre
ECDC	European Centre for Disease Control and Prevention
FHA	Filamentous Haemagglutinin
GBS	Guillain-Barré Syndrome
GGD	Municipal Health Service
GP	General Practitioner
GSK	Glaxo Smith Kline
HBIG	Hepatitis B Immunoglobulin
HBV	Hepatitis B Virus
Hib	<i>Haemophilus influenzae</i> type b
HLA	Human Leukocyte Antigen
HPV	Human Papillomavirus
hrHPV	high risk genotype HPV
ICD	International Classification of Diseases
ICER	Incremental Cost-Effectiveness Ratio
IgM	Immunoglobulin M
ILI	Influenza-Like Illness
IMTA	Institute for Medical Technology Assessment
IPD	Invasive Pneumococcal Disease
IPV	Inactivated Polio Vaccine
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 Programme Influenza Prevention
NRBM	Netherlands Reference laboratory for Bacterial Meningitis
NTR	Netherlands Tuberculosis Register
NVI	Netherlands Vaccine Institute
PCR	Polymerase Chain Reaction
PIENTER	Assessing Immunization Effect To Evaluate the NIP
Prn	Pertactin
PRV	Pentavalent Rotavirus Vaccine
Ptx	Pertussis toxoid
QALY	Quality Adjusted Life Years
RCC	Regional Certification Commission
RIVM	National Institute for Public Health and the Environment
RSV	Respiratory Syncytial Virus
SMEI	Severe Myoclonic epilepsy in infancy
SP MSD	Sanofi Pasteur MSD
TB	Tuberculosis
UK	United Kingdom
USA	United States of America
VDPV	Vaccine Derived-Polio Virus
VE	Vaccine Effectiveness
VLP	Virus Like Particles
VWS	Ministry of Health, Welfare and Sports
VZV	Varicella Zoster Virus
WHO	World Health Organisation
XDR	Extremely Drug Resistant
YLD	Years Lived With Disability
YLL	Years of Life Lost

Summary

This report gives an overview of the developments in 2007 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 future NIP vaccine candidates (hepatitis A, rotavirus, varicella zoster, meningococcal serogroup B disease, respiratory syncytial virus and human papillomavirus (HPV)).

In 2007, no changes in the vaccination schedule were made, with exception of the vaccine used for the DTaP-IPV booster vaccination of four-year-olds. Most of the target diseases of the current NIP are largely under control. The high incidence of reported and hospitalized pertussis cases since 1996 is sustained. Preliminary results of a pertussis transmission (BINKI) study show that cocooning strategy is likely to be effective in reducing morbidity and mortality in infants. A modest reduction of cases of pneumococcal meningitis in the age group 0-2 years was visible after the introduction of vaccination with seven-valent pneumococcal vaccine in 2006. The frequency of reported adverse events remained stable in 2007 compared to 2006.

Several recommendations regarding surveillance, research and control of vaccine preventable diseases in the Netherlands are given. For pneumococcal disease we recommended to study the effectiveness of 2+1 versus 3+1 dose schedule; for MMR to consider reducing the age of MMR-2 vaccination from nine to four years; For hepatitis B to consider universal vaccination since both universal infant vaccination as vaccination around 12-years of age was shown to be cost-effective; for tuberculosis to continue the selective BCG vaccination strategy; for influenza to monitor the vaccine uptake and effectiveness after lowering the age criterion to 60 years; for hepatitis A to explore the potential impact of universal vaccination on population level; for rotavirus to consider whether or not to include rotavirus vaccination in the NIP given the substantially disease burden but low probability of being cost-effective; for varicella zoster to obtain further insight into the disease burden in the Netherlands based on hospital admission data and to study the cost-effectiveness of zoster-vaccination in elderly; to follow the ongoing vaccine development of both meningococcal serogroup B and respiratory syncytial virus and the advice to include HPV-vaccination for girls into the NIP and prepare a plan to monitor the impact of HPV-vaccination.

In the report some issues of current interest in the field of routine vaccination into the NIP are discussed. They include the relevance of disclosure of surveillance data of the NIP via the internet, availability of vaccination outside routine vaccination programmes (NIP+), and the relevance of linkage of vaccination status to disease data.

We conclude that 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 as new vaccines become available.

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 Programme Influenza Prevention (NPG) currently to individuals aged 65 years and over, 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) ¹	Injection 2
At birth (<48 hours)		HBV ²	
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

¹ 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.

² 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 2007

In 2007, no major changes in the NIP were made with exception for the booster DTaP-IPV vaccinations of four-year-old children. Two vaccines, Triaxis and Infanrix, with a different content of pertussis, diphtheria and tetanus antigens were used. More extensive information is described in chapter 2. Overall changes in the NIP since 2000 are summarised in Annex 1. Information on the composition of the vaccines used in 2007 is given in Annex 2.

1.3 Role of 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 office for National Coordination of Infectious Disease Control joined CIb. Since then CIb became responsible for the direction of the NIP, but 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 vaccines¹; 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 will change. Regional vaccination administration centres will become part of the CIb by January 2008. Thus RIVM spans the whole chain from intervention, surveillance, research, and control.

1.4 Vaccination coverage in the NIP

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 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. In 2008, national coverage levels for all vaccines used in the Netherlands exceeded the 90% level and met the standards provided by the World Health Organisation (WHO). Vaccination coverage for sucklings 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 (Table 2).

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 is 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.²

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

Report-year	Cohort	Vaccination coverage (%)									
		Sucklings*				Toddlers*				School-children*	
		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

Report-year	Cohort	Vaccination coverage (%)		
		Sucklings*		
		HBV ¹	HBV ²	
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 (sucklings), five years (toddlers), and ten years (school-children)

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

¹ Only for children of whom at least one parent was born in a country where hepatitis B is moderately or highly endemic

² Only for children of whom the mother tested positive for HBsAg.

2 Current National Immunisation Programme

2.1 Diphtheria

F.R. Mooi, F. Reubsaet

For changes in combination vaccines including diphtheria see the paragraph on pertussis (paragraph 2.2). In 2007 three cases of cutaneous diphtheria were notified caused by *C. diphtheriae* and *C. ulcerans*. The two *C. diphtheriae* infections most likely originated from the Philippines and the strains were found to be toxin negative by polymerase chain reaction (PCR) and Elek-test. The *C. ulcerans* strain was found to produce toxin (Elek-test) and was PCR positive. The availability of diphtheriae antitoxin antibodies for human use in Europe is being investigated.

2.2 Pertussis

F.R. Mooi, S.C. de Greeff, T.W. de Graaf, N.A.T van der Maas

Vaccine

Recent changes in the NIP

The following changes that occurred in the vaccination programme in 2007 (see chapter 1) are relevant with regard to pertussis (component): In 2007, two vaccines were used for booster vaccinations of four-year-old children, Triaxis Polio (from Sanofi Pasteur MSD (SP MSD)) and Infanrix-IPV (from Glaxo Smith Kline (GSK)). These vaccines differ with respect to the content of pertussis, diphtheria and tetanus antigens (Table 3). The effect of the difference in pertussis antigen doses was assessed in children primed with the NVI whole cell vaccine and subsequently boosted with a high dose (similar to Infanrix, data from the Apeldoorn study^{1 3}) or a low dose vaccine (Triaxis Polio). It was observed that the latter vaccine induced significantly lower titers against pertussis toxoid (Ptx), pertactin (Prn) and filamentous haemagglutinin (FHA) (Table 4). Titers against fimbriae were not determined.

Serology plays an important role in the diagnosis of pertussis in the Netherlands. Several recent developments may affect the accuracy of pertussis serodiagnosis. First, most serology (~70%) is now performed outside the RIVM with commercial kits, the quality of which is subject to debate.⁴ Second, IgG titers against Ptx are used in some assays to diagnose pertussis. In contrast to the whole cell vaccine, the recently introduced acellular vaccines induce high titers against Ptx. Thus it is problematic to use high Ptx titers to distinguish between infection and vaccination.

This problem is aggravated by the introduction of a booster vaccination with an acellular vaccine. As yet it is not clear whether these factors result in under or over estimation of pertussis. We propose to survey the commercial kits used in the Netherlands and to evaluate these kits. In the long term the use of antigens not included in acellular vaccines may be required to improve the accuracy of pertussis serodiagnosis.

¹ In the Apeldoorn study an ACV containing only pertussis components was used, designated Acellulair Kinkhoestvaccin.

Table 3 DTaP-IPV vaccines used for booster immunizations of four-year-old children in 2007

Vaccine ^{1,2}	Producer	Ptx (ug)	FHA (ug)	Prn (ug)	Fim2,3 (ug)	D-toxoid	T-toxoid
Infanrix-IPV	GSK	25	25	8		25 Lf	10 Lf
Triaxis Polio	SPMSD	2.5	5	3	5	≥ 2 IE (2 Lf)	≥ 20 IE (5 Lf)

¹ Triaxis Polio was used by all vaccination agencies in the period Jan to Dec, except the agency in Zuid-Holland. The latter agency used Infanrix IPV in the period May to Dec.

² Both vaccines contain IPV type 1-40, type 2-8, and type 3-32 D-Ag/dose.

Table 4 Effect of boosters with acellular vaccines containing different amount of pertussis antigens on the immune response in four-year-old children primed with the NVI whole cell vaccine¹

Vaccine	Producer	N	Ptx	FHA	Prn
aK ^a	GSK	43	64.6 (54.0-77.2)	236.9 (199.7-281.0)	144.7 (127.9-163.9)
Triaxis Polio ^b	SPMSD	35	20.2 (15.7-32.0)	108.5 (93.6-125.7)	94.4 (82.9-107.4)

¹ GMT's are given in EU/ml based on the FDA standard. Values between brackets are 95% confidence intervals. aK: Acellular vaccines with pertussis components only. Per dose 25 ug Ptx, 25 ug FHA, and 8 ug Prn.

^a Reference (5)

^b Unpublished

Effectiveness

No evidence was found for waning immunity four years after the preschool booster with the GSK acellular pertussis vaccine (Acellulair Kinkhoestvaccin, same aP composition as Infanrix), as the estimated vaccine effectiveness (VE) remained relatively high, 74%-84%, in the vaccinated cohort.⁵ In 2007, most four-year-old children were boosted with a vaccine (Triaxis Polio) which contains lower doses of Ptx, FHA, Prn, tetanus toxoid and diphtheria toxoid. In contrast to the previous booster vaccine, Triaxis Polio contains fimbriae. It is not clear whether the changes in booster vaccination will affect (long-term) efficacy against pertussis.

Adverse events

The number of reported adverse events following immunization (AEFI) with DTaP-IPV/Hib in the first half year of 2006 was 736, compared to 593 in 2005. This increase is due to more complete reporting following the introduction of the acellular combination vaccine in January 2005. The addition of conjugate pneumococcal vaccine had little influence on the number of adverse events.⁶ No new categories of adverse events were revealed.

Recently a case-control study confirmed that there is no causal relation between whole-cell pertussis vaccine and encephalopathy or encephalitis.⁷ In fact, in Australia 11 of 14 children with alleged vaccine encephalopathy appeared to have a SCN1A mutation.⁸ This mutation is associated with Severe Myoclonic epilepsy in infancy (SMEI). Most mutations are 'de novo' and not inherited. To see if this mutation plays a role, together with the section for genetic counseling of the UMC Utrecht, RIVM-CIB will investigate all complex febrile convulsions or epilepsy reported to us in the years 1997-2006.

Pathogen

Strain variation

There were no major changes in the frequencies of pertussis toxin and pertactin types compared to previous years. In 2007, 100% (N=24) of the clinical isolates carried Prn2 and PtxA1, i.e. types not found in the vaccines used. The changes observed in the frequencies of *fim3* alleles were more dynamic (Figure 1). Strains with the non-vaccine type Fim3 subunit (Fim3-2) have decreased in frequency since 2002. The P3 strain, which contains a mutation in the pertussis toxin promotor, which confers increased virulence and pertussis toxin production⁹, was found in 96% of the isolates, which is comparable to previous years. It should be noted that the amino acid detected polymorphisms are relatively minor (comprising one to five amino acids per protein) and may be important primarily in individuals with waning immunity.

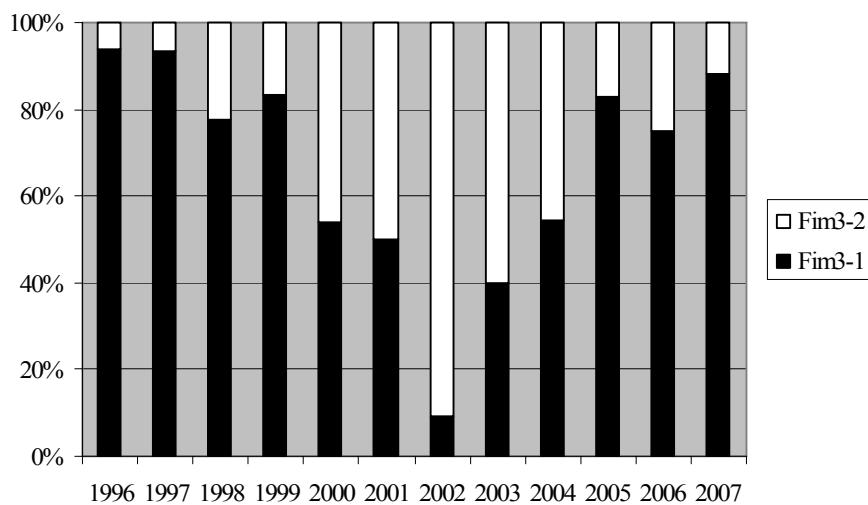


Figure 1 Temporal trend in frequencies of *fim3* alleles. The *fim3*-2 allele codes for a subunit that is distinct from the type used in the vaccine

Disease

Epidemiology

After the sudden upsurge in 1996-1997, the incidence of reported and hospitalised pertussis cases remained significantly higher compared to the period prior to 1996, with epidemic peaks occurring every two to three years (Figure 2) In agreement with this pattern, the number of reported cases showed an increase in the first half of 2007.¹⁰

Since 1996, ten children have died from pertussis: two in 1996, two in 1997, one in 1998, three in 1999, one in 2004 and one in 2006. All children were less than three months of age, except for a girl in 2006. This girl was 11 years old and was vaccinated conform the NIP. The girl was asthmatic and mentally and physically handicapped. These conditions may have contributed to the severity of pertussis and her death.

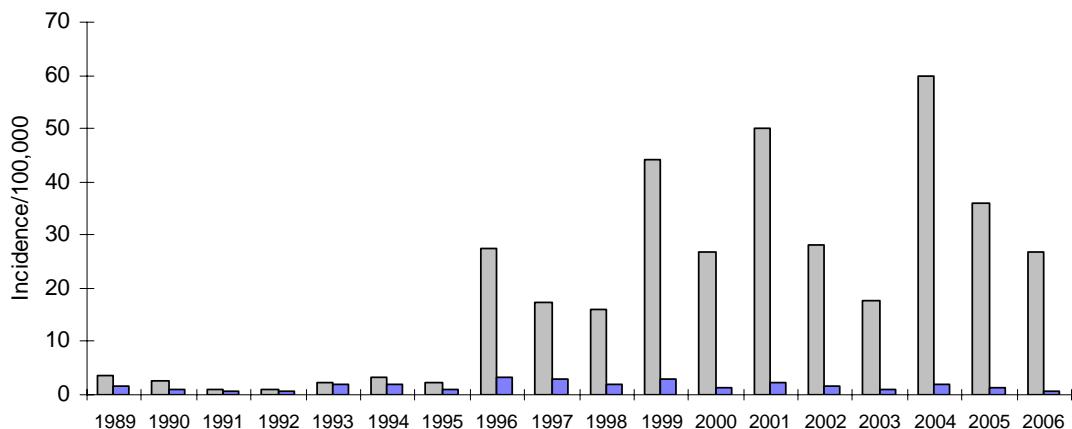


Figure 2 Incidence of notifications (grey bars) and hospitalisations (blue bars) due to pertussis by year in 1989-2006

The introduction of the preschool booster-vaccination for four-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 3).

Since the introduction of the preschool booster, the number of hospitalized infants with pertussis shows a decreasing trend. This suggests that transmission from siblings to susceptible infants may have been reduced as a result of the preschool booster. In contrast, since the end of the 90's the incidence of notified and hospitalized cases among adolescents and adults has remained constant or showed a slight increase (Figure 4). It should be noted that coverage of hospital data in 2006 was lower than in previous years (91.8% in 2006 versus 96.7% in 2005).

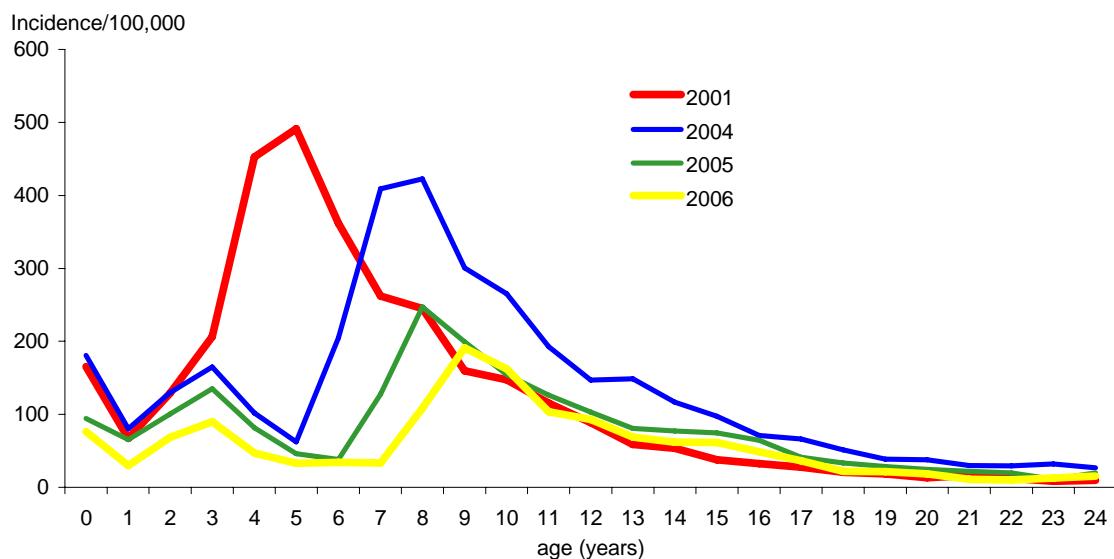


Figure 3 Age-specific incidence of notified cases in 2001 (before introduction of the preschool booster for four-year-olds) and in 2004 to 2006 (after introduction of the preschool booster for four-year-olds)

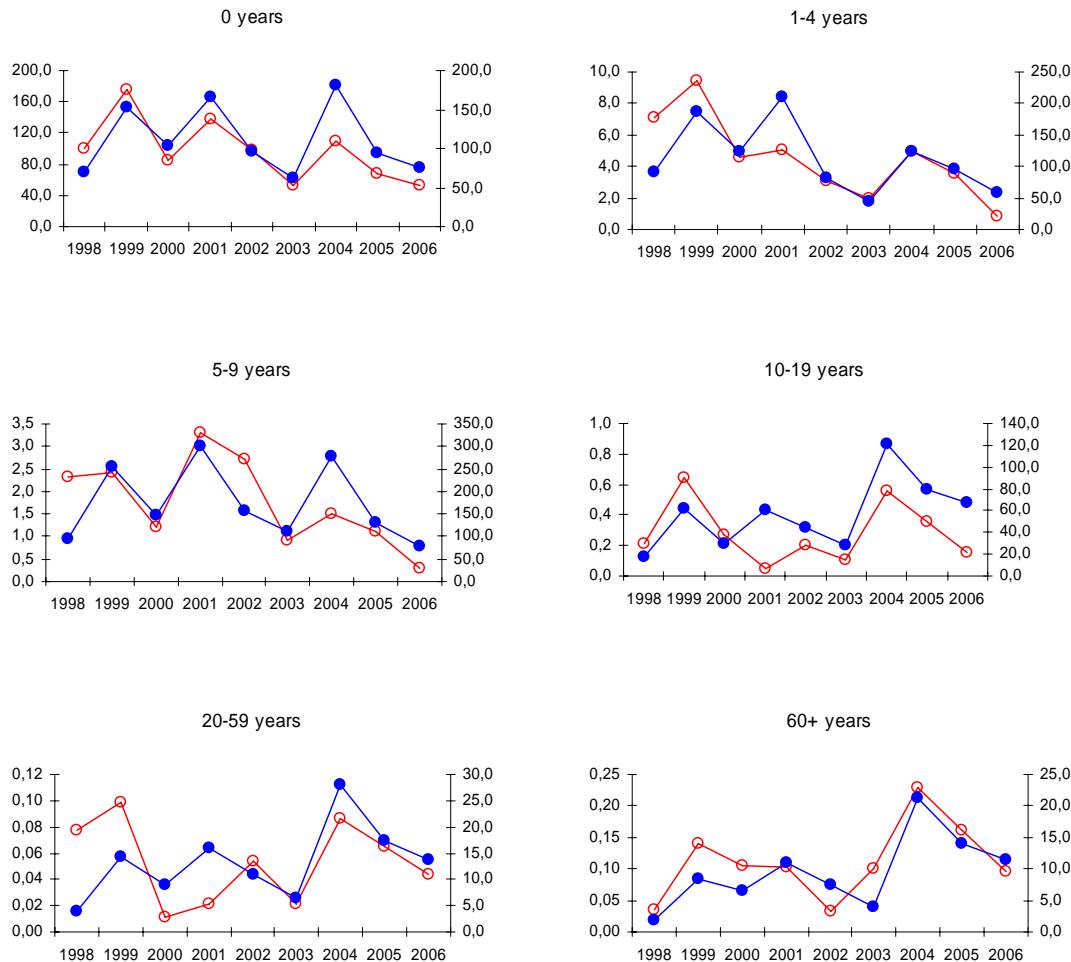


Figure 4 Annual incidence of hospitalizations on left axis (red line, open dots) and notified pertussis cases on right axis (blue line, closed dots) by age category in 1998-2005

From February 2006 until August 2007, 109 infants and their 411 family members have been included in the study on the transmission of pertussis to infants (BINKI-study). The study aims to assess the main sources of pertussis infection in infants too young to be directly protected by vaccination. With this knowledge the most effective vaccination strategy can be developed to prevent severe pertussis in young infants. Preliminary results indicate that 25% of the mothers, 10% of the fathers and 21% of the siblings in the study had introduced pertussis in the household and thus most likely transmitted the infection of the infant. Consequently, vaccination of approximately 4,000 mothers is expected to prevent the hospitalization of one infant.² Further studies are required to determine whether cocooning is a cost-effective way to protect the age category for which pertussis is most severe.

² With an annual birth cohort of $\pm 200,000$ infants and an average number of 200 infants hospitalized for pertussis each year, vaccination of $\pm 4,000$ mothers is expected to prevent the hospitalization of one infant.

Burden of disease

In the last five years, yearly around 200 patients have been admitted to hospitals because of pertussis; of these circa 75% are infants less than six months of age who are unvaccinated or incompletely vaccinated.

Preliminary results from the BINKI-study show that for all hospitalized infants included in the study (n=109) coughing symptoms were reported, for 97% whooping was reported. Median duration of hospital admission for all children, including those admitted to IC, was seven days. More severe symptoms were frequently reported, such as collapse (39%), cyanosis (77%), posttussive vomiting (79%) and apnea (64%). 55% of the hospitalized infants were administered extra oxygen. Sixteen children were admitted to the IC, seven received artificial respiration. Median duration of IC admission was eight days. For 64 infants (59%) severe complications were reported, being (% of total): conjunctivitis (21%), convulsion (9%), weight loss (47%), subconjunctival haemorrhages (7%), pneumonia (4%) and secondary otitis media (6%).

Besides severe morbidity in infants, an infant with pertussis in the household has substantial effect on the other family members. Most parents find caring for a child with pertussis very distressing. Many parents report sleep disturbances and this may also have consequences for work productivity.

Recommendations for vaccination, surveillance, and control

In addition to the peak age of hospital admissions among young infants, the observed increase in lethality in the Netherlands and the United Kingdom (UK)^{9, 11} in the last decade further underlines the importance of introducing vaccination strategies which, directly or indirectly, protect 0-6 month old infants who are too young to be (fully) immunized. Indirect protection of infants may be achieved by decreasing the circulation of *B. pertussis* by cocooning (vaccination of individuals around the newborn), or booster vaccinations of adolescents and adults. The transmission (BINKI) study has provided evidence that the cocooning strategy is likely to be effective in reducing morbidity and mortality in infants. Based on these results we propose to carry out a study on the cost-effectiveness of cocooning so that a recommendation can be made for the introduction of cocooning.

In the period 2001-2007 the largest increase in pertussis cases was seen in the age category 10-20 years. 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 set up a study to investigate the disease burden due to pertussis in adolescents and adults.

Further, we propose to carry out modelling and cost-effectiveness studies to determine the optimal age for a possible adolescent or adult booster. In 2008/2009, data on pertussis serology (pertussis toxin, pertactin and FHA) becomes 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.

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.

We recommend to further characterize the P3 strain, the emergence of which is associated with the resurgence of pertussis. Identification of genes which have contributed to the fitness of this strain may point to vaccination strategies which will decrease the burden of pertussis. Preliminary data suggest that increasing the level and persistence of pertussis toxin antibodies may be important.

The whole cell vaccine conferred some protection against the second causative agent of pertussis, *B. parapertussis*.¹² It is not clear whether the recently introduced aP vaccine also confers some protection against *B. parapertussis*. We therefore recommend monitoring of *B. parapertussis* infections in the Netherlands. Further, the efficacy of the acellular vaccine against *B. parapertussis* should be studied in a mouse model. Present pertussis vaccines do not induce sufficient long-term immunity and research aiming to improve pertussis vaccines should be stimulated.

Finally, we recommend to closely monitor the various changes in the vaccination programme which have been, or will be, implemented (see above). For this, data on side-effects, efficacy, immunogenicity and circulating strains need to be systematically collected. Specifically, the cohorts which have been boosted at the age of four with a low dose of pertussis antigens should be followed. Waning of immunity and pertussis incidence should be compared with a cohort receiving a high booster dose.

2.3 Tetanus

S.J.M. Hahné, P.E. Vermeer-de Bondt

Vaccine

Recent changes in the NIP

There have been no recent changes in the routine schedule of tetanus vaccination in the NIP, but the composition of the combination vaccines used in the NIP has changed (see Annex 1 and 2). Only limited data is available on the long-term effects of these changes on tetanus titers. Serological surveillance into tetanus immunity therefore remains a priority.

Adverse events

Based on reported adverse events coupled with titer studies and the experiences from others (i.e. Sanquin), it appears that late local reactions are not linked to high titres and not to the (life long) number of previous doses of tetanus vaccine. Therefore, there is no need for concern to give tetanus vaccination in case of wounds or administration of DTP in the case that diphtheria or polio vaccination is due.

Disease

Epidemiology

There is limited data available on the incidence of tetanus in The Netherlands. In hospital episode statistics, seven patients with tetanus were reported in 2006. However, this data source is prone to misclassification: patients with tetany can be reported as tetanus, and verification of the diagnoses (or e.g. age and vaccination status) is not possible. At RIVM, one case of tetanus was reported in 2006 (through request of immune globuline or advice). This case concerned a four-year-old child not vaccinated because of a religious exemption. Two other cases of possible tetanus, with unknown vaccination status for tetanus, have been non-conclusive, since tetanus could not be ruled out by high anti-tetanus titres and no other definite diagnosis could be made.

Tetanus will be mandatory notifiable again from 2009 onwards.

International perspectives

WHO published a position paper on tetanus vaccination in May 2006.¹³ This paper highlights that there is no generally accepted threshold of antibody level yet to indicate adequate protection.

Recommendations for vaccination, surveillance, and control

The main aim of the analyses of the PIENTER-2 data 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.

2.4 Poliomyelitis

H.G.A.M. van der Avoort, W.A.M. Bakker

Vaccine

Recent changes in the NIP

There are no changes in the vaccine policy regarding poliomyelitis. IPV remains 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, 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 will result in a new version of this plan in the beginning of 2008. The plan contains guidelines for the strategy to use the vaccine in outbreak situations, tailored to the Dutch situation, based on current 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 vaccinees, 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 Centre for Disease Control and Prevention (CDC) Atlanta, confirm these observations, but also document the genetic variability and evolution rates of OPV viruses from doses administered at birth and after challenge of these vaccines.

Developments on Sabin-IPV

In the light of the different post-eradication immunization and containment strategies considered, polio vaccine development remains actual today. The development of Sabin-IPV plays an important role in the WHO polio eradication strategy. Therefore, responding to WHO's call for new polio vaccines, the NVI initiated in 2007 the development of Sabin-IPV (injectable, formalin-inactivated vaccine, based on attenuated 'Sabin' poliovirus strains). For that NVI's current IPV production process, based on wild-type polio virus, was used as starting point. Further, monovalent Sabin type 1, 2 and 3 OPV from a

WHO pre-qualified Developing Country Vaccine Manufacturer (Bio Farma, Indonesia) was used as starting material for the down-stream processing and inactivation process development studies. This approach supports the following three potential advantages: 1) the use of Sabin-strains requires a less strict containment regime for production facilities in the post-eradication era; 2) production could be performed locally (after technology transfer) by current pre-qualified OPV manufacturers; 3) a fall-back scenario to the use of OPV (the so-called 'warm-base') remains open to fight unforeseen outbreaks after eradication.

Preliminary results showed that Sabin-IPV can be produced in this way at lab-scale. However, the monovalent Sabin OPV strains behaved somewhat different in the column purification steps when compared to the wild-type processing. Therefore, the procedure has to be adapted and optimized. The obtained trivalent product will be used for pre-clinical formulation studies, further characterization, and immunogenicity studies in rats.

Pathogen

Strain variation

Wild type 2 poliovirus has been eliminated globally: the last isolate dates from Egypt 1998. However, a large outbreak of type 2 circulating-VPV in Northern Nigeria warns against the use of mOPV 1 and 3 only. The Nigeria outbreak is the 10th outbreak for cVDPV detected in recent years.

The running definition of a VDPV is based on sequence divergence to the Sabin prototype stains in the OPV vaccine: Sabin-like isolates with more than 1% divergence are labelled VDPV. Suspected isolates also showed antigenic changes that usually could be detected by an ELISA test with cross-absorbed type specific antisera.

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 immunodeficiency related-VDPVs for more than three months. VDPVs detected from environmental samples or from stool surveys that cannot be linked to cases or immunocompromized persons are named ambigious-VDPV's. Almost all these viruses can in principle cause epidemics under not or incompletely vaccinated populations.

Recent experience (e.g. data from the Nigeria P2 VDPV outbreak) has shown that in practice also less divergent strains can have circulating and neurovirulent properties and can escape present WHO recommended methodology for screening of OPV isolates for VDPVs (PCR and ELISA). Specific mutations are determinants for development of Sabin-like isolates to cVDPV.

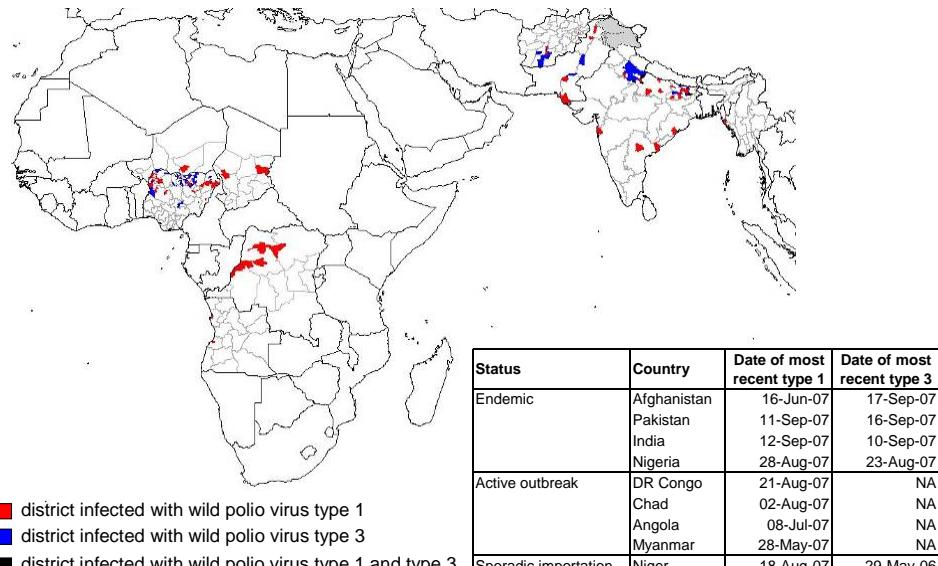
Genetic sequencing of all polioviruses isolated in the Netherlands guarantees detection of all wild polioviruses and VDPVs. Global application of this sequencing strategy for characterization of polio isolates is too costly. New screening policies are being developed and implemented for rapid detection of all pathogenic VDPVs.

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 four countries have never stopped endemic poliovirus circulation: India, Pakistan, Afghanistan and Nigeria. The extensive use of mOPV1 in India and Nigeria has almost eliminated this serotype in the two big reservoirs (Uttar Pradesh and Kano state). The number of P3 cases in these two regions 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. Almost all of the countries that experienced P1 circulation as result of import from the big epidemic that started in 2003/4 in Nigeria and reached via East Africa to the Arabic Peninsula and Indonesia, have stopped circulation successfully.

Wild Poliovirus infected districts*, 10 Apr 2007 - 09 Oct 2007



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

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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 2007 is again at least as big as in 1992. The number of polio cases worldwide has dropped however dramatically, and thus there is clearly also a lower chance for importation of wild poliovirus or 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

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, and recommended continuation of the present surveillance activities. 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 PIENTER-2 study, that measures sero-immunity against vaccine preventable diseases in a representative selection of the Dutch population, identify new risk groups for poliovirus infection and/or transmission, adequate measures will be taken to overcome these deficiencies.

2.5 Haemophilus influenzae serotype b (Hib) disease

L.M. Schouls, S.C de Greeff

Vaccine

Recent changes in the NIP

Until June 2006 children at risk for contracting hepatitis B received the DT5aP-IPV-Hib vaccine Pediacel and separately hepatitis B vaccine. From June 2006 onwards these vaccines were replaced by the combined DT3aP-IPV-Hib-HepB vaccine Infanrix hexa. These vaccines are quite similar in composition and only differ in the number of pertussis components. The amount of conjugated Hib polysaccharide and the amount of tetanus toxoid, which is used as carrier protein, are identical in both vaccines. Therefore, no effects on the efficacy of Hib vaccination are to be expected from this change.

Effectiveness

Evidence has been provided that in the UK the use of the combination vaccine DTaP-IPV-Hib resulted in reduced antibody titers against Hib.¹⁴ Recently, Denoël et al.¹⁵ showed that avidity maturation of anti-Hib antibodies was lower when primary vaccination was performed with DTaP mixed with Hib, compared to DTaP co-administered with Hib. However, both regimens elicited functional antibodies that conferred protection in an infant rat protection assay.¹⁵

Pathogen

Strain variation

A recent study by the RIVM showed that two types Hib strains exist.¹⁶ These types, designated type I and type II, differ considerably in the composition of a number of genes encoding the Hib polysaccharide capsule. Analysis of the two types of Hib strains revealed that, at least for the strains studied, type I strains contain twice as much surface bound polysaccharide as do type II strains. In the pre-vaccination era in the Netherlands, type II strains made up approximately 5% of all Hib strains isolated from patients with invasive Hib disease. Remarkably, all the type II strains were isolated from children younger than four years of age. Within two years after the introduction of the Hib vaccine in the NIP type II strains were no longer isolated from Dutch patients. Consequently, all vaccine failures are caused by type I Hib strains. This suggests that the higher amount of surface bound polysaccharide makes type I strains less sensitive for the bactericidal effect of anti-capsular antibodies compared to type II strains and that this makes type II strains less fit to survive in vaccinated individuals.

Disease

Epidemiology

Since the introduction of vaccination in 1993, the reported number of patients with *H. influenzae* type b (Hib) disease has decreased (Figures 5 and 6). Nevertheless, in 2002-2004 the number of patients with Hib disease increased, while in the last two years the number is decreasing again (Figure 5).

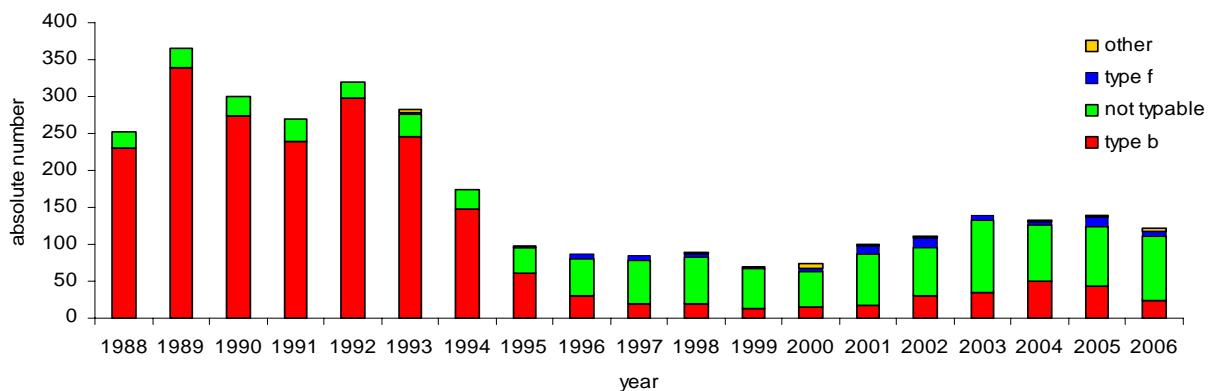


Figure 5 Absolute number of *H. influenzae* isolates by type, 1988-2006 (source: NRBM)

Figure 6 shows an unexplained increasing trend of the number of vaccine failures between 2000 and 2005. In 2006, 16 vaccine-failures have been reported which was slightly lower than in 2005 (19). Unexpectedly, the number of adult patients with Hib disease increased since 2001 as well, with nine cases in 2001 to 34 in 2004. However, in 2005 and 2006 the number of cases of invasive Hib disease in adults had decreased to 12 and ten cases, respectively. Until September 2007, nine children born after 1993 have been reported with Hib-disease of which five were vaccinated. In addition, there were seven cases of invasive Hib disease in patients born before 1993. Extrapolating these numbers for 2007, would result in similar numbers of Hib disease as in 2006. In the beginning of 2009, invasive Hi-infections will become notifiable like other diseases included in the NIP that are not yet notifiable (mumps, tetanus).

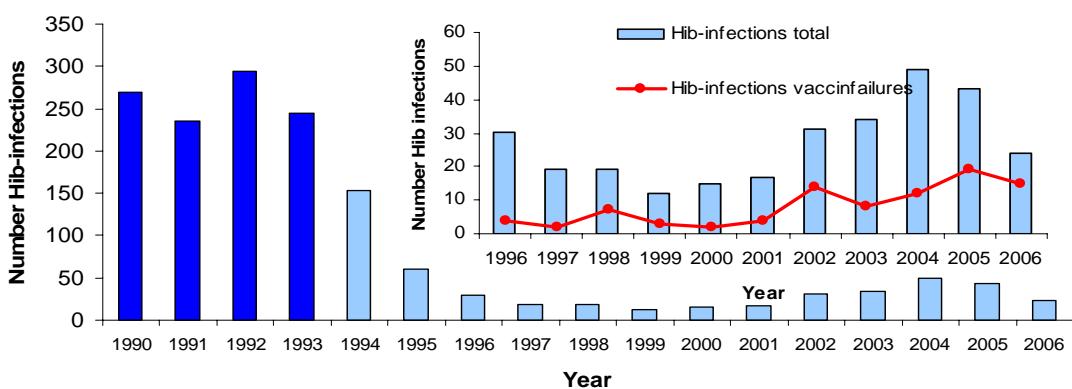


Figure 6 Reported number of invasive Hib infections and vaccine failures by year. Dark blue bars represent number of infections before introduction of vaccination. Inset: Hib infections in the last ten years and number of vaccine failures

International perspectives

The UK and Ireland have introduced a booster dose of Hib vaccine at twelve months into their NIP to overcome waning vaccine induced immunity and to extend protection against Hib disease. This strategy has led to a decrease in vaccine failures. In the Netherlands a booster dose has been part of the Hib vaccination schedule from the moment it was introduced in the NIP. From 10 September 2007 onwards, the UK has started a Hib vaccination catch-up program for children born between 13 March 2003 and 3 September 2005 (aged between two years and four years and five months). These children were either too young or too old to receive a booster during previous campaigns (<http://www.immunisation.org.uk/files/CMO230707.pdf>). Up till now the UK and the Netherlands were the only countries to report increased vaccine failures. Recently, Howie et al.¹⁷ reported the re-emergence of Hib disease in The Gambia following successful elimination after Hib vaccination in their NIP. The Gambia vaccination schedule does not include a booster vaccination and as a result The Gambia may now experience an increase in vaccine failures similar to that observed in the UK.

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 finding that one of the two circulating capsular genotypes of Hib was no longer isolated from cases with invasive disease within two years after introduction of Hib vaccination in the NIP introduction of Hib vaccination suggests a direct effect of the vaccination. The genotype that was no longer isolated seems to produce less surface bound capsular polysaccharide. To confirm this finding more Hib strains with the two capsular genotypes need to be investigated. Also archival collections of Hib strains in other countries need to be analyzed to investigate a similar shift in composition of the Hib population. The population-based serum collection (PIENTER-2) 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 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

Mid 2006, the NVI MMR vaccine could temporarily not be produced as a result of a GMP update of the production process. It was replaced by two other products: The vaccines used since October 2006 are MMR-II produced by Sanofi Pasteur MSD, and Priorix, produced by GSK. MMR-II is used in one province only ('Zuid Holland'). NVI's own MMR vaccine was available again by mid 2007; remaining stocks of MMR-II and Priorix were finished prior to restarting the NVI MMR vaccine.^{18, 19}

The NVI MMR vaccine is produced under license of SPMSD. Both the NVI-MMR and MMR-II are based on the mumps Jeryl Lynn strain, whilst Priorix is based on the mumps RIT 4385 strain.

An adaptation of the SPMSD MMR-II vaccine was registered recently, but is not on the market yet in the Netherlands. In the adapted vaccine, human albumine used in the production of MMR is replaced by recombinant albumine.

A recent review of mumps vaccines²⁰ concluded that Jeryl Lynn based vaccines had very good vaccine effectiveness (VE) in early trials (>95%) and have been used to eliminate mumps from Finland. However, more recent data suggest the VE may be lower than 70%.²¹ This is consistent with the

observation during the mumps outbreak at a Dutch hotel school in 2004, where a high proportion (85%, n=66) of cases was vaccinated at least once.²²

The RIT 4385 strain is derived from the Jeryl Lynn strain, but the review did not include information on the VE of this vaccine. Regarding the Rubini strain, the review concluded that it has an unacceptable low VE, consistent with WHO opinion on this vaccine. Alternative vaccine strains include the Urabe, Leningrad-3 and Leningrad-Zagreb, which have high VEs but are associated with a severe side-effect (aseptic meningitis). However, vaccine induced meningitis may for some of these strains be more benign than the complications among vaccine failures. This could be a reason to re-value the relative merits of strains other than Jeryl Lynn (but not Rubini).

Disease

Epidemiology

The epidemiology of mumps in the Netherlands is not well understood, since limited information is available on occurrence of disease; it is not a notifiable disease. From the beginning of 2009 onwards, mumps will be notifiable.

During 2006, specimens (filter paper blood, oral fluid, throat swab, urine) were obtained from 23 clinical (parotitis) and four non-clinical (contact) persons and tested for the presence of specific IgM antibodies using different mumps IgM EIA assays commercially available, and for the presence of viral RNA by newly developed mumps RT-PCR methods adopted from literature.²³ Four persons were serologically confirmed by one or more IgM tests, one of which was associated with recent MMR vaccination. Mumps virus RNA could not be detected in any of the specimens of these persons, partially related to non-optimal sampling (more than one week post onset of symptoms).

Through laboratory surveillance, nine cases were reported in 2006, similar to the 13 reported in 2005 (source: virological weekly reports).²⁴ There were nine hospital admissions recorded for mumps in 2006, a similar number compared to previous years (six in 2005).³⁴

Diagnosis

Recent comparative studies by RIVM suggested that the sensitivity of different serological assays for mumps IgM vary widely.²⁵ The lack of sensitivity is related to the type of EIA test used but probably mostly related to the lack of IgM antibody formation, particularly for mumps parotitis in persons who had received one or two doses of the MMR vaccine during childhood (Van Binnendijk et al. manuscript in preparation)^{25, 26} and this requires further study including an inventory of assays used by Dutch virological laboratories. Detection of mumps viral RNA by RT-PCR in e.g. urine and oropharyngeal specimens increases the overall sensitivity of the diagnosis in these patients.

Pathogen

No RT-PCR positive samples became available in 2006 for phylogenetic analysis of mumps virus.

International perspectives

Nationwide outbreaks of mumps have occurred since 2004 in the United Kingdom (UK), Canada, and the United States of America (USA). All of these were caused by genotype G. The outbreak in the UK declined during 2006, having peaked during the first quarter of 2005. The US outbreak peaked in April 2006.²⁷ During 2006, several mumps outbreaks occurred in Europe (Spain and Austria).^{28, 29} A high proportion of cases in all of these outbreaks were in vaccinated individuals.

³ Coverage of hospital data in 2006 was lower than in other years (8.7% missing records versus 3.3% in 2005).

⁴ Since August 2007 the number of requests for laboratory testing for mumps at RIVM-LIS increased, suggesting an increased circulation of mumps. Combined with anecdotal reports from municipal health authorities, it appears that there is an outbreak mainly among unvaccinated individuals in low vaccination coverage areas, with some cases amongst vaccinated individuals.

Recommendations for vaccination, surveillance, and research***Vaccination***

The relative merits of strains other than Jeryl Lynn (but not Rubini) should be evaluated.

Surveillance

There is to date no indication that the increased circulation of mumps as observed in other European countries and the US is also present in the Netherlands. Although the epidemiological information on mumps in the Netherlands is limited, it is unlikely that a large increase in incidence would have been missed. However, mumps parotitis is not a notifiable disease and laboratory investigation, if carried out, is restricted to specific IgM antibody detection in serum. This laboratory method lacks sensitivity particularly in persons who have received one or two doses of the mumps vaccine. Hence, many of the mumps parotitis cases may be missed. Given the increased circulation elsewhere and the doubts about the VE of the vaccines used here, it is important to enhance mumps surveillance in the Netherlands. The laboratory methods should be improved in this respect, by incorporating other suitable techniques in the surveillance such as RT-PCR, and by collecting samples suitable for this surveillance (e.g. oral fluid).

Furthermore, data from the population-based serum collection (PIENTER-2) could provide insight in the changes in seroprevalence of mumps since 1995-1996 in both vaccinated and unvaccinated cohorts. From these data an inference can be made on the circulation of mumps in the population.

Notification data available from 2009 onwards will contribute to the sensitivity of surveillance. We propose to add to this the surveillance of mumps through the existing sentinel physicians system (CMR, NIVEL) from 2009 onwards for three main reasons. Firstly, it would allow evaluation of the completeness of notification. Secondly, when oral fluid samples of all clinical cases of mumps would be tested (IgM and PCR), the specificity of the clinical diagnosis can be evaluated. Lastly, virological sampling would allow monitoring of circulating mumps genotypes.

2.7 Measles

S.J.M. Hahné, R.S. van Binnendijk

Vaccine***Recent changes in the NIP***

For an overview of changes in the MMR vaccine used during 2006 in the NIP see the paragraph on mumps.

Availability of new vaccines

See first section of mumps paragraph.

Disease***Epidemiology***

In 2006, only one case of measles was notified. This concerned a 32 year old male, vaccinated once (at age of four years), who probably acquired the infection in Hungary. The case was diagnosed based on a positive IgM, and PCR (urine and throat). Viral RNA could be recovered from the urine specimen; sequence analysis confirmed an imported wild type measles virus (genotype D5).³⁰

During 2006, three hospital admissions for measles were recorded (source: LMR data), none of whom were notified. It is unknown whether these cases were laboratory confirmed. Through laboratory surveillance (virological weekly reports), one case was reported during 2006.

During 2007 (up to end of October), seven cases of measles occurred, in two clusters.³¹ The index case in the first cluster was an unvaccinated air-hostess who acquired measles most likely during a flight to Brasil. In the hospital where she was admitted, three health care workers subsequently acquired measles. Of these, one was fully vaccinated (twice). Two were unvaccinated and received post-exposure MMR vaccine within three days after exposure. The virus was genotype D5.

The second cluster concerned two men who had been on the same flight to London, and came down with measles 12 days later. Both men were unvaccinated. One of the two men passed measles on to his unvaccinated son of two years of age. The viral genotype in this cluster was B3.1.

The pattern of having imported cases only, with only few secondary transmissions, suggests that sufficient herd-immunity is present in the Netherlands. However, this is most likely not the case for the low vaccination coverage areas, where the most recent measles outbreak occurred in 1999/2000. A new outbreak in these areas is to be expected.

Apart from the bible-belt, The Netherlands is close to elimination of measles. Certification of elimination demands more of the surveillance: merely an absence of notified cases may not be sufficient. Seroprevalence data from PIENTER-2 will be available in 2008, and will provide insight in the immunity against measles.

In addition, it may be possible to improve the sensitivity of surveillance by systematically offering laboratory diagnosis to clusters of cases of rash illness. A surveillance protocol for measles and rubella is being prepared, which will include recommendations for laboratory testing for clusters of rash illness. This will be based on the rash illness surveillance pilot carried out between 2003 and 2005.

Pathogen

The genotype of the single case in 2006 was D5.³⁰ The genotypes of the two clusters in 2007 were D5 and B3.1.

International perspectives

In 2005 and 2006, several large measles outbreaks have occurred in Europe.³² Outbreak investigations identified causes including: low vaccine coverage in sub-groups of the population^{33, 34}, low vaccine coverage in the routine programme³⁵, high susceptibility levels in older cohorts who are insufficiently vaccinated³⁶, and susceptibility in infants too young to have been vaccinated.³⁷

Recommendations for vaccination, surveillance, and research

Vaccination

It is under discussion whether the age of MMR-2 can be reduced from nine to four years, in order to reduce the susceptibility rate among school-aged children (see the research section). A potential disadvantage would be that this may lead to reduced rubella immunity among women of childbearing age. Particularly, PIENTER-2 data will be crucial to inform decisions on this.

The national plan for measles elimination in the Netherlands dates from 1999 (available from http://www.euvac.net/graphics/euvac/pdf/plan_netherland.pdf). It describes measures to improve control of measles. These should be updated to include specific interventions which respond to recent epidemiological observations: unvaccinated health care workers and travellers are the main risk groups for measles, particularly those born just prior to introduction of the measles vaccination programme in 1976. 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 2008, 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))

Preparedness for measles outbreaks

Considering that the most recent measles outbreak in the Netherlands occurred in 1999/2000, and low vaccination coverage areas continue to exist, a new measles outbreak in these areas is to be expected in the coming years.

A protocol for patient testing, notification, data collection and control of the outbreak is being prepared.

Research

The results of the PIENTER-2 study for measles will become available in 2008/2009. This will provide important information to decide on whether or not the first MMR vaccination should be given at an earlier age. Nowadays cohorts of pregnant women with vaccine-induced immunity may provide less maternal passive immunity to their newborns. Advancing MMR-1 may be necessary to close the window of susceptibility.

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). In this project, we plan to collect pre- and post exposure samples during the next measles outbreak in the low vaccination coverage areas. As the most recent outbreak in these areas was in 1999/2000, a measles outbreak is expected to occur imminently. By sampling in schools with low vaccination coverage, we hope to obtain information on correlates of protection in both vaccinated and unvaccinated individuals. In addition, a research project (SOR) is ongoing into correlates of protection and immunological memory in the context of measles vaccination.

2.8 Rubella

S.J.M. Hahné, R.S. van Binnendijk

Vaccine

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

Disease

Epidemiology

During the rubella outbreak in 2004/2005, 32 pregnant women were infected, resulting in 15 infants with congenital infection including 11 infants with congenital defects.³⁸

During 2006, six rubella cases were notified. One of these was a case of congenital infection resulting from the above mentioned outbreak. One case was a pregnant woman with alledged contact with rubella. Her infant tested negative by PCR. One case was considered as a false-positive IgM. The remaining three cases concerned three males none of whom were reported to have been vaccinated in the past. Unfortunately, all patients were diagnosed merely by serology, and samples for molecular typing were not obtained. For two of the cases, rubella was reported to have been acquired abroad (UK and Turkey). Through laboratory surveillance (virological weekly reports) 21 cases were reported in 2006. No additional information is available regarding these. Sensitivity of rubella surveillance will be improved by systematic laboratory testing of clusters of exanthema (see paragraph on measles).

Recommendations for vaccination, surveillance, and research

Vaccination

It needs consideration whether the measles elimination plan (see paragraph 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.³⁹

Surveillance

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

Research

The results of PIENTER-2 will be useful to study to what extend waning of the immune response is occurring in the Netherlands. In addition, the attack rate of the recent rubella outbreak can be estimated.

2.9 Meningococcal serogroup C disease

L.M. Schouls, S.C de Greeff

Vaccine

Availability of new vaccines

In January 2005, a quadrivalent meningococcal polysaccharide-protein conjugate vaccine, MCV4 (Menactra™) was licensed for use among persons aged 11-55 years in the USA. This vaccine contains capsular polysaccharides from serogroups C, A, Y, and W-135 conjugated to diphtheria toxoid. In May 2005, the Advisory Committee on Immunization Practices (ACIP) recommended routine vaccination with one dose of MCV4 for persons aged 11-12 years, persons entering high school. In June 2007, ACIP revised its recommendation to include routine vaccination of all persons aged 11-18 years with one dose of MCV4 at the earliest opportunity. ACIP continues to recommend routine vaccination for persons aged 19-55 years who are at increased risk for meningococcal disease.

Adverse events

Guillain-Barré syndrome (GBS) has been associated with receipt of MCV4.⁴⁰ Persons with a history of GBS might be at increased risk for post-vaccination GBS; therefore, a history of GBS is a relative contraindication to receiving MCV4. ACIP states that meningococcal polysaccharide vaccine (MPSV4) is an acceptable alternative for short-term protection against meningococcal disease (three to five years).

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 7). In 2006 only 4 cases of invasive meningococcal group C disease were reported. One was in an unvaccinated child aged 13 months and the other three were in adults (Table 5).

In 2007 from January until September, six patients with meningococcal C disease have been reported. Three were in unvaccinated children aged seven months, nine months and seven years. Since the introduction of Men C vaccination in the Dutch NIP no cases of meningococcal group C disease in previously vaccinated persons have been reported.

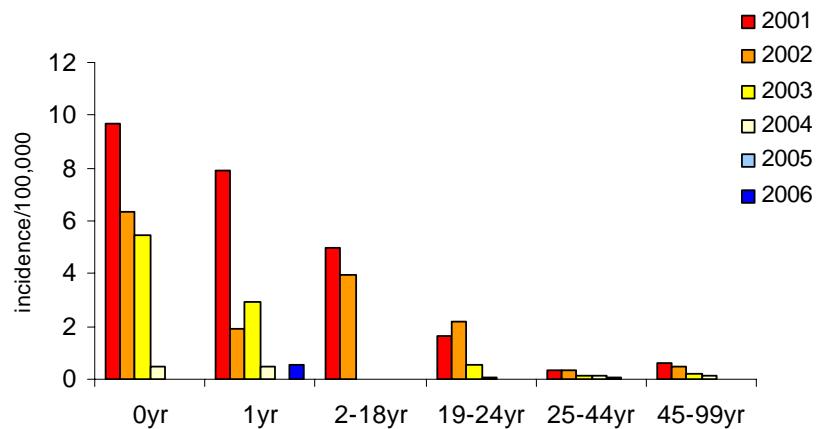


Figure 7 Age-specific incidence of meningococcal C disease by year, 2000-2006

Table 5 Absolute number of patients with meningococcal C disease

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

International perspectives

A recent paper by Spoulou et al.⁴¹ reported a vaccine failure in a four-year-old boy. The authors suggested that memory induced by the conjugate vaccine is not protective against acute meningococcal C infection. The patient described in their paper mounted an adequate antibody titer after revaccination on discharge of the patient, indicating there was no impairment of the patient's immune system. The authors argue that conjugate vaccine-induced memory may be too slow to protect against acute bacterial infections. Apparently, persistence of circulating bactericidal antibody over long periods may be crucial for the clinical protection of the vaccinee. In the UK there was evidence that protection offered by Men C vaccine given during infancy at two, three and four months of age, wanes after 12 months. Therefore, the vaccination schedule in the UK has been changed since September 2006. Currently, two doses of Men C vaccine are given during the primary immunizations at three and four months followed by a booster dose at 12 months. This booster is given as part of a combined Hib/Men C vaccine. In addition, as mentioned in the chapter on Hib, the UK has also started a Men C vaccination catch-up program for children born between 13 March 2003 and 3 September 2005 from 10 September 2007 onwards. Although the purpose is to offer a Hib booster, the vaccine used for this campaign is the Hib/Men C combination vaccine Monitorix™. The Men C component may offer some additional benefit to those children receiving it.

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, E.L.M. Op de Coul, F.D.H. Koedijk, J.M. Kemmeren, L. Isken, G.A. de Wit

Vaccine

Recent changes in the NIP

From January 2006 onwards, infants born to hepatitis B virus (HBV) carrier mothers are given a dose of HBV vaccine at birth, together with hepatitis B immunoglobulin (HBIG). Prior to this, only HBIG was given at birth and vaccination started at the age of two months. The main rationale for this change was that according to the Health Council, vaccination is more effective when started at birth rather than at the age of two months.⁴²

From June 2006 onwards (birth cohort from April 2006 onwards), infants with at least one parent born in a country of medium or high endemicity for HBV and children of HBV carrier mothers are given their HBV vaccination included in a combination vaccine (DTaP-HBV-IPV/Hib (Infanrix hexa)) instead of a separate injection. The rationale for this was to avoid giving three injections following introduction of universal infant pneumococcal vaccination. Infanrix hexa is given at two, three, four and 11 months, which means that one extra dose of HBV vaccine is introduced into the schedule. For infants born to carrier mothers this now adds up to five doses of HBV containing vaccine. The total amount of HBV-antigen in this new schedule is comparable to the previous vaccination schedule, since the HBV-antigen content in the combination vaccines is reduced.⁴³

Current target groups

Since 1st November 2002, a four year campaign to vaccinate high risk groups including outreach activities has been organised in the Netherlands. This campaign is coordinated by the Netherlands Association for Community Health Services (GGD Nederland). High risk groups targeted in this campaign are commercial sex workers, hard drug users, men having sex with men (MSM) and heterosexuals with multiple sex partners.

The campaign was evaluated in spring 2007 during an expert meeting⁴⁴, using information on notifications, molecular typing, pre-vaccination screening results, a case control study, research on risk behaviour, economic analyses and modelling. Consensus was reached that the campaign for MSM should be enhanced (whereby aiming to vaccinate 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. From 2009 onwards, the vaccination campaign will be coordinated by the RIVM-CIb.

Vaccine efficacy and effectiveness

Efficacy and immunogenicity

It is well known that a low percentage of vaccinated children do not respond (non-responders) or respond only marginally (low-responders) to HBV-vaccination.⁴⁵ According to the WHO, a HBV-vaccine schedule should induce a protective level of anti-HBs-antibodies (defined as ≥ 10 IU/l) in at least 95% of the vaccinated population.⁴⁶ The reasons for the occurrence of non- or low-response to HBV-vaccination are not fully understood, but the genetic make-up of the vaccinee (i.e. Human Leukocyte Antigen (HLA)-type) is one of them.⁴⁷ Concurrent vaccination (i.e. two vaccine injections or a combined vaccine) might reduce the serologic response to certain vaccine-antigens.⁴⁸ Vaccination with Prevenar and multicomponent childhood vaccines according to a four-dose schedule might have a negative influence of the HB immune response.⁴⁹⁻⁵¹ 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.

Effectiveness of vaccinating high risk populations

See section on modelling and economic evaluation.

Effectiveness of vaccination of children born to HBsAg positive mothers

Since September 2005, RIVM in collaboration with Regional Vaccination Administration Centres (EAs) 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 are now available. Of 1187 infants for whom a test result was available, 10 were found to be infected with HBV. Of those infants vaccinated according to the Dutch schedule (n=1105), 0.7% (eight children, 95% CI 0.3-1.4%) was infected; 10% (110 children, 95% CI 8.3-11.9%) was not infected, but had an insufficient titer (< 10 IU/l). Of those infants vaccinated according to the Dutch schedule and with a blood test taken within one year after the third vaccination, only 2% (95% CI 1.3-4.0%) was insufficiently protected. The proportion of infected children found is consistent with the published literature.

Vaccine coverage

In neonates born to HBsAg-positive mothers

Following the evaluation of the hepatitis B antenatal screening and neonatal immunization program in the Netherlands carried out by TNO⁵², no new information has become available of the vaccine coverage among infants born to HBsAg positive mothers. An evaluation of the entire programme to prevent perinatal transmission of HBV is recommended.⁴²

In children of parent(s) born in mid/high endemic countries

Data on vaccine coverage in this group is not yet available.

In behavioural high risk groups

Since the start of the campaign, November 2002, until 1st September 2007, a total of 78,263 persons were vaccinated.⁴⁴ Of these, 25% were MSM, 12% were prostitutes, 16% hard drug user, 46% heterosexuals with high rate partner change (for 1% sexual preference not recorded). Using assumptions on the population sizes, the proportion of individuals protected (by natural infection or immunisation) is 43% in prostitutes, 47% in drug users, and 51% in MSM.⁵³ In total, 79% of those receiving the first vaccine dose, received the second, and 60% received the third. Through the screening and vaccination campaign, information was obtained about the percentage of individuals that was infected in the past. Data regarding 1.11.2002 and 31.12.2006 showed that 9.6% of those targeted for vaccination had been infected with HBV in the past and that 0.7% was carrier (anti-HBc positive and HBsAg positive) and 9.6% was immune (anti-HBc positive and HBsAg negative). There were differences in prevalence among risk groups: of hard drug users, 14% were immune and 0.8% carrier, whilst of heterosexuals with high rate partner change 4.7% were immune and 0.6% were carrier (GGD Nederland, expert meeting 21 March 2007). In comparison, in the first national seroprevalence study in 1996 (PIENTER-1) 2.1% of the general population was anti-HBc positive and 0.2% was carrier.

Adverse events

As mentioned in the previous report of 2006 there is still debate on the possible association between multiple sclerosis (MS) and HBV vaccine. In 2008, we will explore the possibilities of several surveillance systems for their ability of determining accurate background incidence rates of MS.

Furthermore, we will start to design a monitoring system for detection of (auto)immunologic diseases that could possibly be brought into association with vaccinations.

Pathogen

Analysis of HBV mutants

Three different classes of mutant HBV strains can be recognized:

1: Antigenic mutants, which have isolated or multiple amino acid changes in the relevant antigenic region of the surface protein.

2: Antiviral resistance mutations, which have specific mutations in or near the active site of the polymerase gene resulting in a reduced susceptibility to antiviral medicines

3: Pre-core mutations, which results in a reduction or absence of HBeAg production, despite the presence of a high viral load.

Nation-wide molecular typing of the S-protein encoding gene of HBV isolates of acute HBV patients reported in OSIRIS is performed since 2004. Also children born to mothers chronically infected HBV are screened for a HBV infection (and response to vaccination). Currently, 10 children have been identified with a HBV infection and the S-region sequence of the HBV isolates of these children have been analysed for mutations. Furthermore, the C-region sequence of 132 acute HBV isolates from 2004-2005 has been determined in a pilot project (2004-2005), while in another pilot project (2006-2007) the S-region sequence of 138 chronically infected people has been determined.

Preliminary analyses for the presence of the three different classes of HBV-mutants have been performed on the sequence database of Dutch HBV isolates (Table 6).⁵

HBV immune-escape variants (such as G145R) have been suggested as reason for vaccine failure when first discovered.⁵⁴ Later on it turned out that these variants were mainly found in the context of passive immunity (HBIG) such as liver-transplant patients⁵⁵ and children born to HBV infected mothers.⁵⁶ Sporadically antigenic variants are also found in chronically infected people⁵⁷ or blood donors.^{57, 58} The two G145R mutants were in both cases originated from children born to HBV-infected mothers, and this mutant was not found among acute or chronically infected people.

Table 6 Presence of three classes HBV-mutants in sequence database of Dutch HBV isolates

	HBV infection		
	Acute	Chronic	Children ¹
Reported cases (2004-2007)	~1000	~6000	9
S-region sequence	449	138	9
Immune escape mutation (G145R)	0	0	2
Antiviral resistance ²	2	0	0
C-region sequence	132	0	9
Pre-core mutation ³	10	n.r.	1

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 (YMDD) has been given

³ Only the result of the most important pre-core mutation (G1896A) has been given; n.r.: not relevant

Lamivudine was the first antiviral approved for treatment of active chronic HBV infections. It is however known that long term monotherapy with Lamivudine favours the selection resistance mutations (YMDD to YIDD or YVDD), which are completely resistant to lamivudine.⁵⁹ Two HBV

⁵ The HBV-sequence database is a joined initiative of RIVM, the GGD Amsterdam, GGD Rotterdam and Erasmus MC.

isolates of acutely identified individuals (2/449) possessed these mutations. HBV strains with these mutations are apparently capable of transmission. It is important to monitor antiviral resistance among HBV strains, in order to inform strategies to prevent resistance and control its spread.

HBeAg-negative mutants are relatively common in the genotype D strains found in the Mediterranean region (~30%). The finding of the 10 HBeAg negative strains (G1896A) in the collection of 132 isolates indicates that these mutants are also present in the Netherlands. The HBeAg negative mutants were most prevalent among genotype D strains (8/26), and only sporadically found in genotype A (1/82) and E (1/7). If a pregnant woman has a high viral load it means that her child has a higher risk of becoming infected with HBV despite admission of immunoglobulines just after birth and active HB-vaccination. Pregnant women in the Netherlands are screened for the presence of HBsAg around the 12th week of pregnancy. HBsAg positive women (~700 yearly in the Netherlands) are subsequently screened for the presence of HBeAg. Women positive for both HBsAg and HBeAg are regarded as those with high viral load and might be eligible for antiviral treatment in the last trimester of their pregnancy. About one third of women originating from the Mediterranean are expected to have a moderate or high viral load despite the lack of HBeAg in their blood. One of the children, who were infected despite HBIg and HB-vaccination, was indeed infected with an HBeAg negative strain (see Table 6). Determining the actual viral load in the third trimester of pregnancy might be a more accurate way of selecting those pregnant women at increased risk of HBV transmission.

Disease

Epidemiology

In 2006, 240 cases of acute hepatitis B were reported in the Netherlands, a decrease of 20% compared to 2005 (2005: 299 cases, 2004: 293 cases). Of all cases, 182 were men (76%) and 58 in women (24%). The incidence rate for acute HBV in 2006 was 1.5 per 100000 and was higher in men (2.3) than in women (0.7) (Figure 8). Cases of HBV were fairly evenly distributed across the Netherlands (range of incidence by municipality: 0.2 – 5.1 per 100,000), with the highest rates in Rotterdam (5.1) and Amsterdam (4.4).

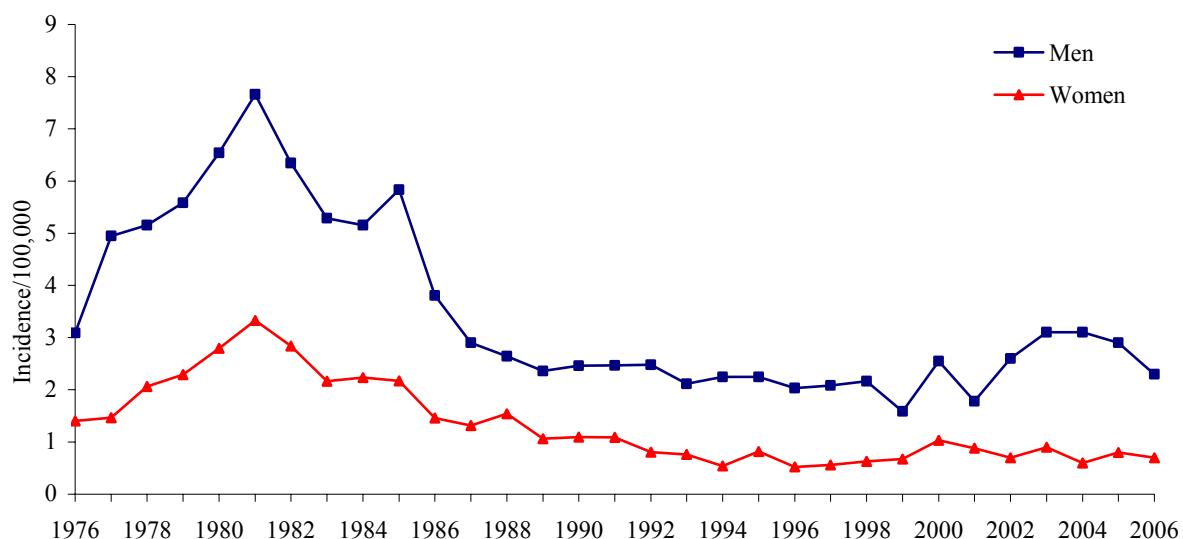


Figure 8 Incidence rate per 100,000 population of notified cases of acute HBV infection, the Netherlands, 1976-2006

Of the acute HBV cases, 79% (n=190) was born in the Netherlands, 18% (n=42) was born abroad and in 3% the country of birth was unknown. Of the cases born abroad, 12% came from HBV high endemic regions (HBsAg prevalence $\geq 8\%$), 67% from intermediate endemic regions (HBsAg 2-8%) and 21% from low endemic regions (HBsAg $\leq 2\%$).

Eighty-one percent of all acute HBV cases reported to be infected in the Netherlands, 13% reported an infection abroad and in 7% of the cases the country of infection was unknown. Heterosexual contact as well as MSM contact, were the most reported routes of transmission (both 32%).

Economic aspects

Currently, economic evaluation of universal immunisation is being investigated for the Netherlands. In this research, universal immunisation strategies (both for newborns and for adolescents) are compared to risk-based policies, as implemented in the Netherlands in recent years. The economic evaluation followed a stepwise approach, comparing different vaccination strategies in an incremental way, reflecting the actual Dutch situation as closely as possible:

- first, the cost-effectiveness of the selective immunisation of babies born to at least one parent originating from an endemic country was compared to screening pregnant women for hepatitis B carriership only (policy as implemented in 2003);
- next, the addition of a four-year risk-based policy to reach and vaccinate adult risk groups (MSM, hard-drug users, commercial sex workers and heterosexuals with high rates of partner change) in addition to the selective vaccination of newborns (as above) was added (policy as implemented in November 2002);
- an extension of the adult risk-based policy as described in the second step above for a period of 50 years;
- universal vaccination of all newborns, in addition to the continuation of risk-based vaccination of adults;
- universal vaccination of all twelve-year old adolescents, in addition to the continuation of both risk-based vaccination of newborns and adults.

Using the threshold of € 20,000 per Quality Adjusted Life Year, as often cited in the Netherlands, the risk based policies were found to be very cost-effective. This holds especially for the vaccination of newborns with parents born in endemic countries (cost per QALY below € 1,000). The adult risk-based strategy is also expected to be cost-effective, with ratios up to € 12,000 per QALY. A further extension of the current risk-based Dutch policy with universal vaccination of newborns is estimated to be also cost-effective, with ratios below € 5,000 per QALY in the least favourable estimate. The cost-effectiveness of a policy in which adolescents will be vaccinated depends heavily on the cost of developing a new infrastructure for vaccination at adolescent age. These costs are unknown at present. The cost-effectiveness of universal adolescent vaccination in comparison with universal newborn vaccination is relatively unfavourable the higher the annual costs for a vaccination infrastructure for adolescents are assumed to be.

In short, the current Dutch risk-based policy is expected to be very cost-effective. However, the extension of the risk-based policies with universal vaccination strategies, especially the universal vaccination of newborns, is also expected to be cost-effective. The Health Council will advise on possible changes in the NIP for HBV in 2008.⁶⁰

Modelling

The pilot campaign of vaccinating MSM in Amsterdam (initiated in 1998) was evaluated using a simple model⁶¹, adopted from the model for the whole Dutch population.⁶² The study shows that with the current vaccination coverage, the decline in incidence is small in the beginning. However, in time the effect of vaccination increases; with each year of the vaccination campaign, more additional infections are prevented by administering less additional vaccinations. In addition, large numbers of new infections will be prevented even with moderate increases in sexual risk behaviour. Our findings

also show that the effect of vaccination at the population level will be smaller than what expected if mainly low-risk men are vaccinated or if risk behaviour increases. Targeting vaccination and risk-prevention measures to the men displaying the most risky behaviour is the most effective policy to reduce the HBV epidemic.

Infection control

Commission iatrogenic HBV

Since January 2006 the Commission Prevention Iatrogenic Hepatitis B is coordinated by the CIB. The commission functions as an independent body advising individual clinically infected health care members and their employers on necessary work restrictions.⁶³

Guidelines and training

In October 2007 the Commission Prevention Iatrogenic Hepatitis B published a revised guideline for the advisement of individual clinical infected health care members and their employers on necessary work restrictions.

The guideline on HBV post exposure prophylaxis is implemented in 2007. This guideline is a multidisciplinary guideline for all professionals working in the field of infectious disease control. In 2008 a revised guideline for control of hepatitis B virus infection will be published, as part of the CIB infection control guidelines (http://www.rivm.nl/cib/infectieziekten/HepatitisB/Hepatitis_B_protocol.jsp).

Recommendations for vaccination, surveillance, and research

Vaccination

Within the programme to vaccinate high-risk groups against HBV, the focus should be on MSM, especially those displaying highest risk behaviour.

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.

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

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.

Vaccination with Prevenar and multicomponent childhood vaccines according to a four-dose schedule might have a negative influence of the HB 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.

2.11 Pneumococcal disease

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

Vaccine

Recent changes in the NIP

Vaccination with pneumococcal vaccine (Prevenar) has been introduced in the Dutch national vaccination program in April 2006. The vaccine is given to infants at two, three, four and 11 months of age at the same time as 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 five years of age in Europe. This seven-valent pneumococcal conjugate vaccine, also designated as PCV7, provides protection against invasive disease caused by the seven most prevalent serotypes in the USA.⁶⁴ In a 2001-2005 survey in the Netherlands around 68% of cases of pneumococcal meningitis among children younger than two years of age was caused by PCV7 serotypes (Figure 9). Ten-valent and 13-valent vaccines which have been developed are currently being tested in trials. These new vaccines should yield a higher coverage than the PCV7 and could in time replace the seven-valent vaccine.

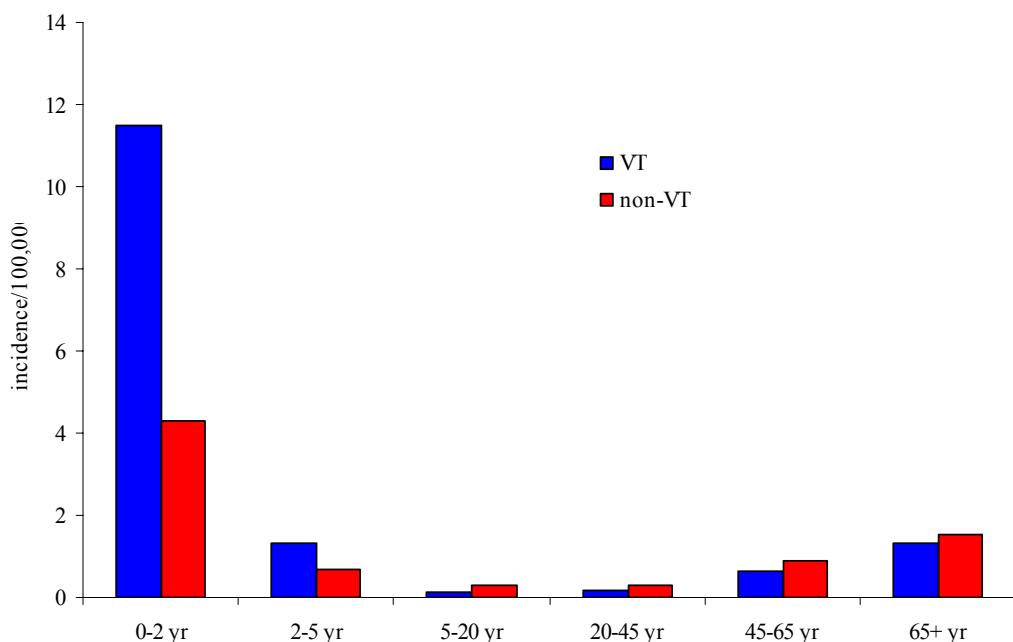


Figure 9 Age specific incidence of isolates from cerebrospinal fluid (CSF) or CSF and blood by serotype in the pre-vaccination period 2001-2005. Serotypes included in the PCV-7 vaccine are in blue (vaccine types, VT), the others in red (non-vaccine types, non-VT)

Adverse events

Comparing results of a questionnaire study on rare adverse events performed after introduction of DTaP-IPV/Hib with the results of a similar study performed after the introduction of Prevenar that is given simultaneously with DTaP-IPV/Hib since June 2006 showed that adding PCV7 had no

significant influence on the rate of reported adverse events. Other studies showed an increase of adverse events, especially fever when DTaP-IPV-HepB/Hib and 7PCV were administered simultaneously.^{50, 51, 65}

Disease

Epidemiology

In the Netherlands pneumococcal disease is not yet included in the mandatory notification system and there is no systematic collection of strains and clinical data. Monitoring of disease is based on a laboratory surveillance in which laboratories voluntary send their isolates from patients with invasive pneumococcal disease to the Netherlands Reference laboratory for Bacterial Meningitis (NRBM). Nevertheless, this system covers 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. The available data suggest that the incidence of pneumococcal disease has been more or less constant during recent years in the Netherlands. Before introduction of vaccination, between 200 and 250 cases of meningitis caused by pneumococci were recorded by the NRBM annually. Of these, approximately 80 were children aged ten years and younger. Without vaccination, children under the age of two years have the highest risk of developing meningitis caused by pneumococci (see Figure 10).

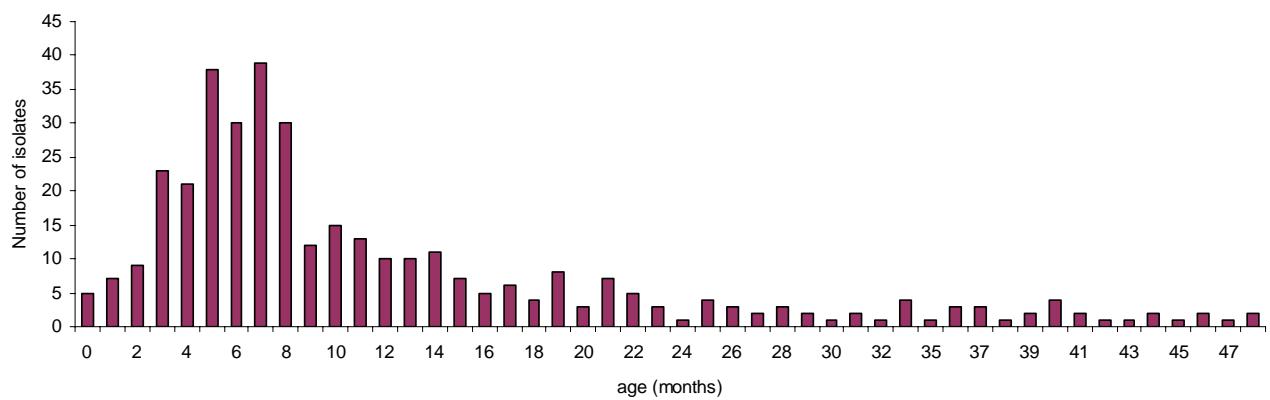


Figure 10 Age specific (age in months) annual number of isolates from cerebrospinal fluid (CSF) or CSF and blood (average from 2001-2005)

It is still too early to observe a major effect of the pneumococcal vaccination. However, comparison of the annual number of isolates collected from June 2006 to June 2007 shows a modest reduction in the youngest age groups in which children received pneumococcal vaccine, without signs of strain replacement so far (Figure 11).

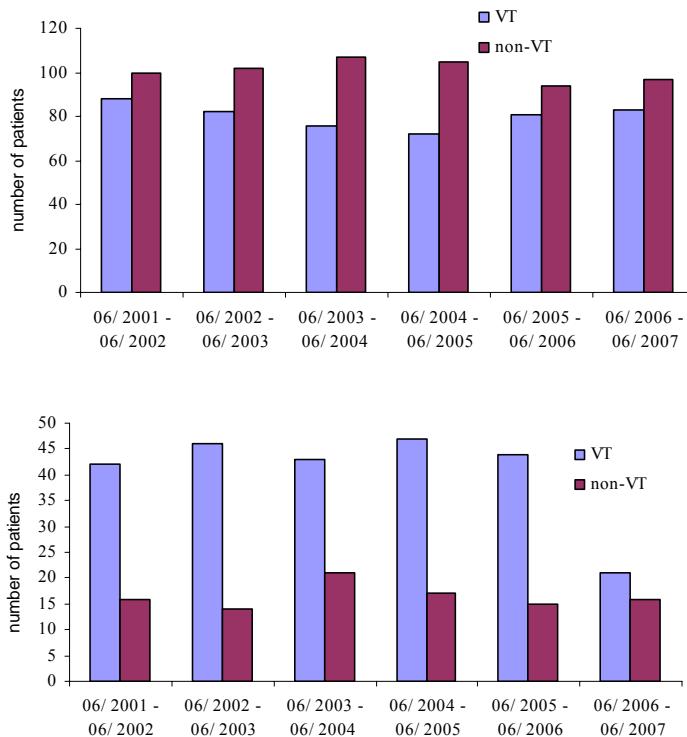


Figure 11 Number of cases of pneumococcal meningitis in the Netherlands. Upper panel, number of strains isolated from CSF or CSF and blood, patients aged 0-2 years; lower panel, number of strains isolated from CSF or CSF and blood, patients older than two years of age; vaccine types (VT) in blue; non-vaccine types (non-VT) in red. The displayed annual periods are from June to June the next year

International perspectives

The Netherlands has been among the first European countries to include PCV7 in their childhood immunization program. France, Germany, Norway and the UK have also included PCV7 in their national vaccination programs. Belgium, Greece and Switzerland recommend the use of PCV7 and Austria, Cyprus and Italy provide the vaccine in the private sector, while the vaccine is for free for high-risk groups. Remarkably, only Germany and the Netherlands use the same schedule for PCV7 vaccination. All other countries use slightly different time points for vaccination (Table 7).

Table 7 PCV7 vaccination schedules in various European countries

Country	PCV7 part of NIP						Recommended			Payment, free for high risk		
	FR	DE	LU	NL	N	UK	BE	EL	CH	AT	CY	IT
Age												
2 months	x	x	x	x		x	x	x	x			
3 months	x	x	x	x	x					x	x	
4 months	x	x	x	x		x	x	x	x	x	x	
5 months					x					x		
6 months								s			x	
11 months		x		x			x			x		
12 months	x				x			x	x			
13 months					x							
2 months-3 years										x		

Approximately half of the European countries use a four-dose regime, the other half use three-dose and Italy uses a single dose of PCV7. Most countries give a booster dose around the second year of life. However, in Luxembourg and Cyprus a booster dose is not given. The composition of the vaccination schedule may have impact on the effectiveness of the pneumococcal vaccination in the various countries.

In the USA the Active Bacterial Core Surveillance system (ABCs) of the CDC have compared invasive pneumococcal disease (IPD) rates in 2003 to those of 1998/1999. They found a 75% decline in IPD caused by all pneumococcal serotypes and a 94% decline in IPD caused by vaccine serotypes in children less than five years of age.⁶⁶ They also report declines in IPD in persons aged five years and older, demonstrating considerable herd effect. A recent study suggests that the herd effect has extended to infants younger than two months of age.⁶⁷ Following Prevenar introduction, the mean rates of IPD decreased significantly for all infants aged 0–90 days, from 11.8/100,000 live births to 7.2/100,000. The Canadian Calgary Area *S. pneumoniae* Epidemiology Research (CASPER) team conducted a prospective population-based surveillance for invasive pneumococcal disease. Comparison of a baseline average rate obtained between 1998 and 2001 with the rate in 2004 showed that IPD caused by vaccine serotypes decreased by 92.6% to 3.9 cases/100,000 population and by any serotype by 81.6% to 11.7 cases/100,000.⁶⁸ In contrast, the rate of IPD caused by non-vaccine serotypes remained unchanged. Among adults aged 65 years and older, the rate of IPD, caused by vaccine serotypes, decreased with 62.7% to 8.5 cases/100,000.

Recommendations for vaccination, surveillance, and control

Data on the number of cases of invasive pneumococcal disease in the Netherlands is obtained by the surveillance performed by the NRBm and the RIVM. The effects of introduction of PCV7 in the NIP will be monitored carefully by enhancement of the routine surveillance. 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 younger than five 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 nine 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 is being 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 will be in place from January 2008. The surveillance will become more complete and reliable if invasive pneumococcal disease would become a notifiable disease in the Netherlands. In the beginning of 2009 invasive pneumococcal disease for one- to five-year-olds will become a notifiable disease.

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 one and two years of age less well protected. The experience in the UK with the Hib and Men C conjugate vaccines lacking such booster suggest that this may lead to vaccine failures. Secondly, the use of three vaccination doses instead of the 4 doses that have been recommended by the manufacturer may provide less protective immunity. However, if a three doses regime would be as protective as a four doses regime the costs for vaccination against *S. pneumoniae* could be reduced by 25%. This merits investigations in which the effectiveness of a three and four 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 required vaccination strategy required to protect the elderly against pneumococcal infection.

3 Programmatic vaccination outside the NIP

3.1 Influenza

M.A.B. van der Sande, A. Meijer

Vaccine

Current target groups

In 2007, the Dutch Health Council issued a revised advice on medical indications for annual influenza vaccination. Most of the existing medical high risk groups (chronic pulmonary conditions, cardiac conditions, diabetes mellitus, kidney failure, and immunocompromised conditions) were maintained, with the exception of people suffering from furunculosis. The indication for vaccination based on increased risk due to advancing age was adjusted from an age criterion of 65 years and above, to 60 years and above.⁶⁹ The government, that provides free influenza vaccination to selected high-risk groups through the National Influenza Vaccination programme (NPG), followed this recommendation, although, influenza vaccination of 60-65 year-olds will not yet be included in NPG for the season 2007/2008 due to logistical reasons. Furthermore, the Health Council included a recommendation for annual vaccination of health care workers. As of yet, the government has not included this target group in the NPG either.

For the season 2006-2007, 82.1% of those aged 65 and above (with and without medical indication) accepted vaccination, and 74.5% of the total high-risk population (76.9% for the 2005-2006 season) for whom vaccination was recommended.⁷⁰

Availability and new developments

If an influenza pandemic would occur, the Netherlands plans to vaccinate the whole population once a pandemic vaccine has become available. The National Health Council has advised on the priority groups for vaccination with a pandemic vaccine, being health care professionals, followed by those at highest risk for morbidity and mortality. Currently, the Health Council is being asked for an advice on the potential merits and usage of a pre-pandemic avian influenza vaccine (see also international perspectives).

Effectiveness

Prior to the 2007 vaccination campaign, an international publication summarised available evidence of routine vaccination for elderly people, pointing the potential biases in study designs which hamper reliable estimates of effectiveness. Effectiveness estimates against virologically confirmed influenza are typically much higher than against more severe but less specific endpoints such as hospitalization and (specific) mortality. They conclude that proper randomised controlled trials are needed to provide better estimates of vaccine effectiveness in the elderly in spite of logistical and ethical hurdles.⁷¹ This paper echoed the concerns stated in a comparable publication the previous year prior to the start of routine vaccination campaigns.⁷² The European Centre for Disease Control and Prevention (ECDC) pointed out in a comment (26 October 2007) that it would be incorrect to conclude that vaccine effectiveness is close to zero in the elderly population, and while vaccine effectiveness estimates against complications are sometimes low, this could also be an underestimation due to the low specificity of such endpoints. In contrast, another recent publication concluded that during the period 1990-2000, influenza vaccination in the USA was associated with significantly reduced respiratory hospital admissions and all cause deaths.⁷³ In view of the limited opportunity for RCTs and the limitations of observational studies, it is likely that controversy on the estimated effectiveness of annual

influenza vaccines will persist. Nevertheless, all agree that annual vaccination should remain to be recommended for those at high-risk of complications.

Adverse events

During the 2006 vaccination campaign, four unexpected cardiac deaths in the Netherlands occurred on the day of vaccination during the 2006 vaccination campaign.⁷⁴ Following a rapid clinical and epidemiological analysis, no causal association was deemed likely.⁷⁵ However, this event revealed that no clear structure existed for notification and registration of potential adverse events following influenza vaccination. In 2007, awareness and procedures relating to the notification of potential side effects has been strengthened. As of now, all clinicians involved are being informed that all side effects should be reported to Lareb, the Netherlands Pharmacovigilance Centre, which together with the RIVM will analyse causality of associations.

Disease

Epidemiology

The incidence of influenza-like illness (ILI) among patients consulting general practitioners (GP) with respiratory complaints (sentinel surveillance) in the 2006-2007 season (week 40/2006 till week 20/2007) was 119 per 10,000 inhabitants. This incidence was lower than in 2005-2006 (165/10,000) and 2004-2005 (208/10,000), confirming previous observation on a declining ILI trend over time. The weekly incidence was above baseline (3/10,000) between week two and week 15 of 2007. The peak weekly incidence was reached in week nine with 6.7/10,000, which was also lower than in previous seasons (peak 2005-2006 14.5/10,000, peak 2004-2005 20.8/10,000). At the peak of the epidemic, 42.9% of ILI in the sentinel practices was associated with influenza virus infection compared to 23.0% of all tested ILI episodes.⁷⁶

During the year 2007, for 75 people, influenza was recorded as primary cause of death, and for 18 as secondary cause of death.

Pathogen

During the 2006-2007 season, the influenza epidemic in the Netherlands was dominated by influenza A(H3N2). During the season a new variant of A(H1N1) (A/Solomon Islands/3/06-like viruses) emerged worldwide alongside the already circulating variant (A/New Caledonia/20/99), with a poorer vaccine match. However, preliminary results indicated that up to February 2007, all Dutch A(H1) viruses were well matched to the vaccine strain.⁷⁷ Influenza A and B virus isolates from the sentinel surveillance for the 2005-2006 and the 2006-2007 seasons showed good sensitivity for the available neuraminidase inhibitors influenza antiviral oseltamivir and zanamivir. However, in 2005-2006 74% of the A(H3N2) viruses were resistant for the classical M2 proton channel inhibitors (amantadine and rimantadine) which are active against influenza A viruses only, and the preliminary results for 2006-2007 indicate that about 82% for the A(H3N2) viruses, but 0% of the A(H1N1) viruses were resistant against a M2 inhibitor. The international trend however, indicates a decrease in resistance for M2 inhibitors of A(H3N2) viruses.

International perspectives

For the coming 2007-2008 influenza season, WHO has updated her influenza vaccine recommendations for the Northern Hemisphere in February 2007. The influenza A(H1N1) strain A/Solomon Islands/3/2006 (H1N1)-like virus replaced the previous influenza A(H1N1) strain. The influenza A(H3N2) strain (A/Wisconsin/67/2005) and the influenza B (B/Malaysia/2506/2004-like virus) were maintained. In June, WHO reported that ongoing strain characterisation data showed that while most A(H3N2) strains were antigenically similar to the reference vaccine strain, an increasing proportion of A(H3N2) virus isolated later in the season showed antigenic differences to the selected vaccine strain. The absence of a sufficiently well characterised antigenically variant group including

the lack of corresponding egg isolates, precluded the selection of a new vaccine candidate for the 2007-2008 season. The first isolates of the 2007-2008 season gave no indication for a suboptimal vaccine match for the A(H3) strain.

Furthermore, WHO has identified several H5N1 virus isolates for the development of a pre-pandemic H5N1 vaccine. The haemagglutinin sequences of circulating H5N1 viruses separate into two distinct phylogenetic clades: clade 1 and clade 2. Since late 2005, clade 2 viruses have been primarily responsible for human infections, and multiple subclades within clade 2 have been distinguished. Trials are ongoing, and in the US the first pre-pandemic H5N1 vaccines have been licensed. ECDC recently issued a report in which they conclude that stockpiling of H5N1 vaccines might have a role in pandemic preparedness, but they do not recommend general vaccination prior to the start of a pandemic.

Recommendations for vaccination, surveillance, and research

Analysis of vaccine uptake and (clinical) effectiveness in particular among the newly indicated target groups needs to be further developed. Existing national GP research networks, with relevant long term data, could offer opportunities to explore these issues within their settings.

Strengthening and extending the sentinel surveillance network which combines clinical and virological data to enable daily notifications as requested by the ministry, would further also increase the power of the opportunistic VE calculations. This would also support the ongoing surveillance of antiviral resistance. Clinical and virological influenza surveillance in a nursing home network will be piloted, and could add further relevant data on vaccine uptake, antiviral resistance, burden of disease, and vaccine effectiveness in this vulnerable elderly population.

Insights into determinants of influenza transmission risks and routes in the population could be strengthened by the use of geographical information systems, combining virological and clinical data from a range of surveillance systems, and by utilising mathematical modelling. To what extent web-based surveillance can contribute to knowledge of influenza transmission and risk will be explored further. Current web-based systems are often based on a convenience sample, rather than a random sample with denominator details, and lack virological data, which introduces considerable bias and limits their potential contribution.

3.2 Tuberculosis

M.A.B. van der Sande, K. Kremer, M.R. Klein, H. Korthals Altes, C.G.M. Erkens (KNCV Tuberculosis Foundation), D. van Soolingen

Vaccine

Current target groups

In the Netherlands, the current target group for Bacille Calmette Guerin (BCG) vaccine consists of children of immigrants from high prevalence countries. In 2006 on request of the national Health Council, the RIVM/CIB in collaboration with the KNCV Tuberculosis Foundation developed a mathematical model to evaluate the cost-effectiveness of this selective vaccination approach. Based on the available Netherlands Tuberculosis Register (NTR) data, the model showed that 9270 (95% confidence interval (CI) 3719-∞) children need to be vaccinated to prevent one case of miliary tuberculosis (TB) or TB meningitis. The small number of serious TB cases occurring both in unvaccinated and vaccinated children (between 1996 and 2003, four cases were reported in the vaccinated children and six in the unvaccinated), yields a vaccine-efficacy of roughly 70%, with a lower 95%CI bound of zero. Therefore, the cost-effectiveness of this intervention extends into the non-

cost-effective range. Including data of another low-prevalence country with an identical BCG vaccination strategy in our study, would probably resolve the problem of these large confidence intervals. Overall, these data suggest that a selective vaccination policy targeting children from immigrants could on average be a cost-effective approach and should be continued.^{78, 79}

Availability of new vaccines and other new developments

According to the Global Plan to Stop TB, 2006-2015, the introduction of new, effective TB vaccines will be an essential component of any strategy to eliminate TB by 2050.⁸⁰

The current TB vaccine BCG protects against severe forms of TB in young children, but not against the most common and contagious form of TB in adults. Despite its widespread use in the last few decennia, BCG seems to have little impact on the global TB epidemic. It is generally assumed that about one third of the global population is infected with *Mycobacterium tuberculosis* and that about 10% will eventually develop TB disease.

In the past 5-10 years a number of significant initiatives have started with the aim to develop and test new TB vaccines. Industry, academia and private-public partnerships are leading the development and testing of novel TB vaccines. The largest support for TB vaccine development comes from the Bill & Melinda Gates Foundation through the Aeras Global TB Vaccine Foundation,⁶ and through the Grand Challenges in Global Health Initiative.⁷

There are different types of TB vaccines.^{81, 82} being developed, with respect to their ultimate aim and target population:

- 1) Pre-TB exposure vaccine – Aim: Priming; ultimately meant to replace BCG, main effect: protection to (severe) TB disease in young children (and latent infection) – may need boosting during adolescence.
- 2) Pre-TB exposure – Aim: Boosting of BCG-induced response⁸³; meant to supplement BCG, main effect: protection to TB disease.
- 3) Post-TB exposure – Aim: Prophylactic, to prevent TB disease in healthy people with latent TB infection, main effect: protection to TB disease (prevent reactivation - and perhaps shorten duration of prophylactic drug-treatment).
- 4) Post-TB exposure – Aim, Therapeutic, to reduce TB disease burden in patients, main effect: shorten duration of curative drug-treatment (reduce risk of relapse, and perhaps reduce transmission).

Most international efforts are directed towards the development of pre-TB exposure vaccines (that either work in conjunction with BCG or replace it). Very little effort exists for the development of a therapeutic TB vaccine.

The following types of TB vaccines are currently being developed and tested, with respect to their composition:

- 1) live attenuated vaccines
 - attenuated *Mycobacterium tuberculosis* strains
 - recombinant BCG⁸⁴
- 2) killed vaccines
 - killed BCG with adjuvants
 - inactivated *M. vaccae*⁸⁵
 - fragmented cell preparations of *M. tuberculosis*

⁶ <http://www.aeras.org>

⁷ <http://www.gch.org/Projects>

3) Subunit vaccines^{86, 87}

- recombinant proteins (incl. fusion proteins) with adjuvants
- recombinant plasmid DNA - in combination with protein, or (poly)peptide subunit
- recombinant viral vectored protein subunit⁸⁸
- recombinant viral capsid, virus-like-particles (non-replicating)
- synthetic compound antigens, polysaccharide-protein conjugate, lipid subunits

To date there are 20-30 TB vaccine initiatives in various stages of development and clinical testing.⁸ In 2007 there were nine phase-I clinical trials ongoing or completed; and one phase-IIa and one phase-III are currently ongoing. In the Netherlands, investigators from the Leiden University Medical Center, in collaboration with the Statens Serum Institute and Intercell AG, have successfully completed a phase-I clinical trial with very promising results on the so-called hybrid-1 (recombinant fusion protein of Ag85B and ESAT-6 in IC31 adjuvant). In the next three years there are at least another 18 phase-I clinical trials scheduled or anticipated.

The most advanced, albeit also rather controversial, is a heat-killed *M. vaccae* preparation that is currently tested in a phase-III efficacy trial in Tanzania. In the coming decade, a number of phase-III efficacy trials are expected to be completed, with hopefully one or more effective products for use in developing countries with high burdens of TB.

Disease

Epidemiology

In the Netherlands, the incidence of new *M. tuberculosis* infections decreased further in 2006 to 6.3/100,000 inhabitants. In total, 1021 TB patients were reported. Based on molecular typing, recent clustering of cases could be studied, and these data suggested that the percentage of patients recently infected declined from 35% in 2005 to 30% in 2006. One percent of isolates was multidrug resistant (MDR), none was extremely drug resistant (XDR). These results are comparable to those from previous years

International perspectives

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. 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 restrain the epidemic. 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 now in development, of which two are ready for clinical trials in humans. To this end clinical trial capacity in Africa, India, and East Asia is currently being build.

⁸ Presented by Retooling Task Force of the Stop TB Partnership, IUATLD meeting, November 2007, Cape Town, South Africa.

Recommendations for vaccination, surveillance, and research

As stated in the previous report, a selective BCG vaccination strategy, targeting children from high prevalence countries, should be continued. Also BCG vaccination for individuals travelling for longer than three months to high endemic countries should be continued. It remains important to further develop and implement advanced molecular typing techniques in order to create new insights in transmission patterns, which will assist a strategy aimed at elimination.⁸⁹ Finally, alertness towards the possible introduction of MDR or XDR *M. tuberculosis* remains vital.

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4 Future NIP candidate vaccines

4.1 Hepatitis A

A. Hofhuis, Y.T.H.P. van Duynhoven

Vaccine

Effectiveness

Through a randomized clinical trial, Bell et al. compared hepatitis A vaccine (HAVRIX) immunogenicity among infants born to immune and susceptible mothers, when administered in a two doses schedule. The results indicated that passively transferred maternal antibody persists in the majority of infants born to anti-hepatitis A-positive mothers for at least six months after birth and appears to interfere with the immune response to vaccination. However, compared with infants born to anti-hepatitis A-negative mothers and vaccinated on the same schedule, this interference manifested primarily by lower antibody concentrations rather than complete failure to respond to vaccination. Nevertheless, these findings support vaccination in the second year of life, rather than during the first year of life.⁹⁰

Van Damme et al. reviewed the long-term protection after hepatitis A vaccination. They concluded that immunocompetent persons, in particular travellers, can be reassured that they will have a long-term protection of at least 25 years, without requiring booster doses, after correct administration of a complete primary course of hepatitis A vaccines. Available data also showed that the immunogenicity of a combined hepatitis A and B vaccine (Twinrix) is comparable to that of the two monovalent vaccines.⁹¹

Pathogen

Strain variation

Travellers to high endemic countries, especially those whose relatives originate from Turkey and Morocco, and men who have sex with men constitute the two major risk groups for hepatitis A transmission in the Netherlands. However, the transmission within these two groups is very different. New hepatitis A virus strains are frequently imported by travellers, but they are limited in the extent and season of their spread. In contrast, hepatitis A is only occasionally imported into the male homosexual and bisexual population, but remains endemic and spreads to a large number of individuals without a seasonal pattern.^{92, 93}

The RIVM and the GGD Zuid-Holland West have designed a study to gain insight in the relative contribution of different pathways of hepatitis A transmission, including food. The relatedness of hepatitis A virus strains can be determined by means of sequence analysis of viral RNA, which could provide information on the spread and ways of contamination of food in the Netherlands.⁹⁴

Disease

Epidemiology

The number of notified cases of hepatitis A in the Netherlands increased from 212 cases in 2005 to 269 cases in 2006 (1.30 per 100,000 population and 1.65 per 100,000 population), although these numbers of cases are substantially lower than in 2004, with 447 cases. In 2006, 117 (43%) of the 269 cases were reported to be travel-related and only ten (4%) were related to contaminated food or water. Following the same trend as the total number of notified cases, the number of hepatitis A clusters also increased from 40 clusters in 2005 to 58 clusters in 2006, although again the total number of clusters was substantially higher in 2004 (78 clusters).⁹⁴

Following two related clusters of hepatitis A in Noord-Holland in January 2007 at a day-care centre (four cases) and in March 2007 at a primary school (six cases), respectively 300 and 150 persons were vaccinated by the public health service. The source of infection for the index patient remained unclear.⁹⁵

Burden of disease

Although rare, in some cases infection with hepatitis A virus may cause additional clinical manifestations, other than acute hepatitis A. A case report of Chitambar et al. described a 17-year old male with GBS in India, preceded by acute hepatitis A. Serum and CSF were positive for anti-hepatitis A virus IgM, IgG, and IgA. The onset of the syndrome was evident in week 3 of illness. The remarkably high titers of serum IgG appeared unique to a hepatitis A patient with the syndrome.⁹⁶ Although, this presentation of hepatitis A infection is unusual, a comparable case in Turkey was described by Kadanali et al. in 2006.

To evaluate the impact of acute hepatitis A on pregnancy outcome, Elinav et al. retrospectively reviewed consecutive hospital admissions of all (79,458) pregnant women who presented with hepatitis A during pregnancy from 1980 to 2005. Thirteen cases of second and third trimester hepatitis A infection were found and evaluated. All mothers recovered fully from the infection. Acute hepatitis A infection during pregnancy was associated with higher risk of maternal complications and preterm labour. However, this study is limited by the fact that only hospitalized pregnant women were included, and the diagnosis for admission might have influenced pregnancy outcome itself.⁹⁷

Economic aspects

In 2007, a study on cost-effectiveness of hepatitis A vaccination has been published. Rein et al. evaluated the economic impact of hepatitis A vaccination of all children aged 12 to 23 months in the United States, as compared with no vaccination and with the pre-existing regional policy of vaccinating high risk groups. Therefore a Markov model was developed which followed a single cohort from birth in 2005 through death or age 95 years. Compared with no vaccination, routine vaccination at age one year would prevent 172,000 infections, at a cost of \$ 28,000 per QALY saved. As an addition to the existing targeted high risk group vaccination policy, routine vaccination at age one year would prevent an additional 112,000 infections, at a cost of \$ 45,000 per QALY. The cost-effectiveness of nationwide hepatitis A vaccination in the USA compared with no vaccination or the pre-existing recommendations is similar to that of other accepted public health interventions such as pertussis vaccination of adolescents and adults and varicella vaccination in children.⁹⁸ The cost of € 23,000 (equals \$ 45,000) per QALY is slightly above the currently applied threshold of € 20,000 per QALY in preventive health care measures in the Netherlands.⁹⁹ However, although the incidence of hepatitis A of 1.5 per 100,000 per year in 2005 is comparable to the incidence in the Netherlands, the comparability of this cost-effectiveness ratio to the Dutch situation is questionable because of possible differences in epidemiology, health care system and discount rate.

International perspectives

October 2005, the Advisory Committee on Immunization Practices recommended extending hepatitis A immunization to all US children aged 12 to 23 months. They expected this nationwide routine immunization of infants to result in further reduction of the incidence in the country and possibly even lead to an environment for the eventual elimination of indigenous hepatitis A infection in the USA.^{98, 100} After the introduction of hepatitis A vaccination for children aged 12 to 23 months in the USA, reported overall hepatitis A incidence fell from 11.8 per 100,000 per year in 1995 to 1.5 per 100,000 per year in 2005.¹⁰⁰ It is difficult to determine to what extent this decline is due to vaccination and to what extent it represents a naturally recurrent decline in epidemic activity. However, the success of the hepatitis A immunization programme has resulted in the virtual elimination of age, racial, and regional differences in the past decade.^{100, 101}

Bauch et al. developed an age-structured compartmental model of hepatitis A transmission and vaccination in Canada to assess potential universal vaccination strategies. The national incidence of hepatitis A in Canada was 3.8 per 100,000 per year from 1995 to 2003, and even 1.4 per 100,000 per year from 2000 to 2003. The model predicts that universal vaccination at age one, with phasing out of targeted vaccination, would reduce reported incidence by 60% and mortality attributable to hepatitis A by 56%, relative to continued targeted vaccination, over 80 years. This study indicated that vaccinating at age one would be the best universal strategy from the health perspective of reduced morbidity and mortality. However, logistic and economic issues must also be weighed in considering alternative vaccination strategies. Targeted strategies tend to require fewer doses of vaccine on population level than universal policies. However, it usually is difficult to reach high coverage in at-risk groups, there is generally a greater cost per vaccine administered, and costly post-exposure interventions have to be available as long as only targeted vaccination is used. Additionally, targeted vaccination usually targets individuals that develop clinically apparent disease, rather than universal vaccination of children with sub-clinical infection. Nevertheless, these are responsible for significant, although under-reported, transmission.¹⁰¹

Recommendations for vaccination, surveillance, and research

The previous reports concluded that hepatitis A vaccination would probably not be cost-effective considering the already low incidence of hepatitis A in the Netherlands. However, some recent studies indicate that routine vaccination of young children between one and two years of age can result in substantial public health benefit as demonstrated by plummeting rates of acute hepatitis A, not only in the vaccinated cohorts but also in the whole population in areas where routine childhood vaccination has been implemented. Many authors state that this herd immunity should encourage other countries to start mass vaccination programmes against hepatitis A.^{90, 98, 100-103} In Canada vaccinating at age one would be the best strategy for reducing the burden of disease, from the health perspective of reduced morbidity and mortality. The national incidence of hepatitis A in Canada (1.4 per 100,000 per year from 2000 to 2003)¹⁰¹ is comparable to the current incidence in the Netherlands (1.65 per 100,000 per year).⁹⁴

Therefore it is advised to study the impact of universal vaccination of children between one and two years of age on morbidity and mortality in the Netherlands, using a dynamic model, taking the herd immunity effects into account, and to explore the cost-effectiveness. Also, the use of the combined hepatitis A and B vaccines, such as Ambix (GSK, for ages 1 to 15 year), could be studied as a scenario.

4.2 Rotavirus

A. Hofhuis, Y.T.H.P. van Duynhoven, M-J.J. Mangen

Vaccine

Effectiveness

In addition to the earlier performed large randomized placebo-controlled safety and efficacy trials, the dose response and efficacy of Rotarix was recently evaluated in a small study among Mexican children two to four months of age; 405 healthy infants were randomly assigned to one of three vaccine groups (virus concentrations $10^{4.7}$, $10^{5.2}$, and $10^{5.8}$ infectious units) and to a placebo group and were monitored to the age of two years. The vaccine/placebo was administered concurrently with DTP-HBV/Hib vaccine at two and four months of age. This study showed similar results as previous studies on Rotarix efficacy. The vaccine was well tolerated and efficacy was 100% against severe rotavirus gastroenteritis and 70% against severe (Ruuska and Vesikari's score of 11 and higher) gastroenteritis of any cause

with the vaccine at the highest virus concentration ($10^{5.8}$ infectious units). Pooling the three vaccine groups, efficacy after two oral doses was 80% against any gastroenteritis, and 95% (100% for the intermediate and higher dosages) against severe rotavirus gastroenteritis.¹⁰⁴

Vesikari et al. also assessed the efficacy of Rotarix in 2646 infants from six European countries during their first two years of life. Follow-up for gastroenteritis episodes was undertaken from two weeks post-dose two through the two consecutive rotavirus seasons (two efficacy follow-up periods) following vaccinations. During the first efficacy follow-up period (mean duration 5.7 months [standard deviation 1.2]), the vaccine efficacy was 87% for gastroenteritis of any severity, 96% for severe gastroenteritis, and 100% for admission owing to rotavirus gastroenteritis. During the second follow-up period vaccine efficacy for gastroenteritis episodes of any severity decreased to 72%, vaccine efficacy against severe rotavirus gastroenteritis decreased to 86%, and for admission owing to rotavirus gastroenteritis it decreased to 92%.¹⁰⁵

Rodriguez et al. evaluated the concomitant use of RotaTeq with licensed paediatric vaccines in the United States. In this study, antibody responses to the concomitantly administered vaccines were generally similar in RotaTeq and placebo recipients. RotaTeq was efficacious (efficacy of pentavalent rotavirus vaccine (PRV) against rotavirus gastroenteritis of any severity was 89.5%) and well tolerated when given concomitantly with paediatric vaccines licensed in the USA.¹⁰⁶ Block et al. evaluated RotaTeq at the end of shelf life. The vaccine was generally well tolerated, efficacious, and immunogenic at the end of shelf life.¹⁰⁷

Monitoring of rotavirus genotypes in a vaccinated population in Brazil (Rotarix vaccine coverage 54%), identified 21 viruses in 126 patients who came to two hospitals with gastroenteritis. All 21 rotavirus infections were with genotype P[4]G2, for which Rotarix appears to be less effective in preventing severe rotavirus gastroenteritis. Four children were infected despite their vaccination, and their infections were as severe as those in children who had not received the vaccine. This confirms that Rotarix does not provide complete protection against infection, and that post-licensure surveillance of a vaccinated population is necessary.¹⁰⁸

Adverse events

As mentioned in previous reports, there is no association between the two newly licensed rotavirus vaccines and intussusception. One year post-marketing surveillance of RotaTeq confirms this.¹⁰⁹ Although there is not a known association between receiving RotaTeq and Kawasaki disease, in a large pre-licensure trial there were five cases of Kawasaki disease among the 36,150 infants who received RotaTeq and one case among the 35,536 infants who received placebo. Furthermore, one year post-marketing adverse event surveillance of RotaTeq did report three cases of Kawasaki syndrome (also known as mucocutaneous lymph node syndrome).¹¹⁰

Pathogen

Strain variation

The current vaccines target the prevention of severe rotavirus illness caused by the 'common' rotavirus serotypes G1-G4. In Europe these strains have been found as causes of the majority of rotavirus episodes for which medical care was sought.¹¹¹ However, other rotavirus serotypes have emerged in the past decade, especially the G9 rotaviruses which are associated with more severe disease in Latin America.¹¹² G12 rotaviruses were first detected in 1987 in the Philippines, but no further cases were reported till 1998 in Thailand. Since then, G12 rotaviruses also have been detected in many parts of the world; the rotavirus strain G12P[8] was, identified in Bangladesh in 2002 and in Belgium in 2003¹¹³, in Hungary¹¹⁴ and Slovenia¹¹⁵ in 2005, and in the Netherlands in 2006.

The first season serotype-specific vaccine efficacy against severe rotavirus gastroenteritis, caused by G9 rotaviruses was estimated 100% (95%CI 67-100) for RotaTeq and 87% (95%CI 64-97) for Rotarix. The vaccine efficacy for G12 rotaviruses was not reported for Rotarix, but for RotaTeq it was estimated 100%, with very broad confidence intervals (95%CI <0-100).

The consequences of emerging antigenic or virulence rotavirus variants on the vaccine's effectiveness are unknown. Although a first natural rotavirus infection results in predominantly type-specific protection, subsequent infections result in broad protection, despite exposure to a restricted number of rotavirus types. Rotarix has shown to mimic this broad protection, because the vaccine is derived from the most common G1P[8] strain and replicates well in the gut. In contrast, RotaTeq is not expected to result in protection against other types than those included in the vaccine. RotaTeq is based on five human-bovine reassortant viruses which encode surface proteins corresponding to the most common human rotavirus antigens.

The following years a subset of rotavirus strains from several European countries, including the Netherlands, will be serotyped to obtain information on circulating strains (Rotavirus surveillance in Europe: determining the diversity of co-circulating rotavirus strains in consecutive rotavirus seasons, funded by SP MSD S.N.C and GSK Biologicals SA). However, we do not expect the strains circulating in the Netherlands to differ considerably from those reported in surrounding countries. As some of these countries will introduce rotavirus vaccination during the study period, the survey will also provide information on the effect of rotavirus vaccination on circulating strains.

Disease

Epidemiology

The number of positive tests for rotavirus and the estimated percentage of hospital admissions caused by rotavirus infection were relatively high in 2005 and 2006, compared to previous years. In 2006, 1585 diagnoses were registered by the virological weekly reports compared to 1304 in 2005, and 917–1079 in the previous years. In 2006, 47% of the hospital admissions for gastroenteritis of children aged younger than five was estimated to be caused by rotavirus, with an estimate of 4521 rotavirus admissions⁹ compared to 4494 admissions in 2005 and 3316 admissions in 2004.¹¹⁶ In the Netherlands, typing of rotavirus strains had been based on strains detected in outbreaks (mainly in elderly) and sporadic cases in epidemiological studies. From 2008 onwards a more systematic approach is aimed for.

Having performed a case-control study in US children (394 cases, 1242 controls), Dennehy et al. conclude that there are socioeconomic and environmental factors and aspects of a child's medical and dietary history that identify children at risk for hospitalization with rotavirus acute gastroenteritis. Breast feeding was protective against hospitalization for infants younger than six months of age (OR 5.1; 95%CI 1.2-13.2). Low-birth-weight (<2500 g) infants had increased risk for hospitalization (OR 2.8; 95%CI 1.6-5.0). Children in child care were more likely to be hospitalized, particularly for those of two years of age or older (OR 3.0; 95%CI 1.8-5.3).¹¹⁷

Burden of disease

The REVEAL study was conducted during 2004-2005 in selected areas of Belgium, France, Germany, Italy, Spain, Sweden, and the UK, as comprehensive data on the burden of rotavirus disease in Europe were lacking. Overall, rotavirus gastroenteritis was estimated to account for 27.8%-52.0% of acute gastroenteritis cases, and it was responsible for up to two-thirds of hospitalizations and emergency department consultations, as well as one-third of primary care consultations for acute gastroenteritis. The estimated annual incidence of rotavirus gastroenteritis was 2.07-4.97 cases/100 children less than five years of age, with the highest incidence among children 6-23 months of age (56.7%-74.2% of all rotavirus gastroenteritis cases).¹¹¹ Also, children with rotavirus gastroenteritis were more likely to have lethargy, fever, vomiting, and dehydration than were children with rotavirus-negative acute gastroenteritis. Dehydration was up to 5.5 times more likely in children with rotavirus gastroenteritis than in those with rotavirus-negative acute gastroenteritis.¹¹⁸

⁹ Coverage of hospital data in 2006 was lower than in other years (8.7% missing records versus 3.3% in 2005).

To evaluate the burden of rotavirus gastroenteritis in England and Wales, Harris et al. assessed the fraction of acute gastroenteritis in children younger than five years that may be attributable to rotavirus using multiple linear regression. Results suggest around 45% of hospitalizations, 25% of general practitioners consultations, 27% of National Health Service direct calls and 20% of accident and emergency consultations for acute gastroenteritis in this age group may be attributable to rotavirus. The annual incidence is estimated to be 4.5 hospitalizations, 9.3 accident and emergency consultations, and 28-44 general practitioners consultations per 1000 children younger than five years of age. The cost to the health service is estimated to be pound 14.2 million (€20.5 million) per year.¹¹⁹

New data suggest that rotavirus infection might also be systemic, with acute active viremia and extra-intestinal replication. In fact, most children infected with rotavirus are viremic, and clinical case reports of systemic sequelae to rotavirus infection in children continue to accumulate, suggesting involvement in systemic disease syndromes. However, the impact of systemic rotavirus on disease burden remains to be determined, as the associations between rotavirus viremia and clinical manifestations of infection are still unclear.¹²⁰⁻¹²⁴

Economic aspects

In 2006 a cost-effectiveness study for the introduction of rotavirus vaccine in the NIP was performed by the RIVM. From this study it was concluded that, although the introduction of the vaccine would be practically feasible and could probably reduce the burden of disease substantially, the introduction of rotavirus vaccine in the NIP would not be cost-effective, neither from the societal perspective nor from the third payer perspective. However, in contrast to the conclusion of the RIVM, another cost-effectiveness study in the Netherlands that was conducted by Goossens et al. on behalf of the Institute for Medical Technology Assessment (IMTA; funded by GSK), concluded that the introduction of rotavirus vaccine in the Dutch immunization program would be cost-effective.¹²⁵ The large differences seen in total cost-of-illness, in disability-adjusted life years (DALY's) and consequently in the cost-effectiveness ratio (CER), apart from the assumed vaccine costs, are mainly due to different assumptions on vaccine efficacy and assumed incidence numbers.

The RIVM assumptions on vaccine efficacy, based on published estimates of Ruiz-Palacios et al.¹²⁶ and Vesikari et al.¹²⁷, were considered to be a conservative scenario for vaccine efficacy. These were in the first season 75%, 75%, 85% and 90% for rotavirus cases requiring no medical help, rotavirus cases requiring only a GP visit, hospitalized rotavirus cases and fatal rotavirus cases, respectively. Whereas the used vaccine efficacy of Goossens et al. was higher: 87%, 96%, 100% and 100% respectively, based on the first season vaccine efficacy, observed in the latest clinical trials results conducted in European children.¹⁰⁵

However, Goossens et al.¹²⁵ made an underestimation when they assumed the waning of the vaccine effectiveness to be only 2%-point per year whereas the assumptions made for the RIVM study were more in line with the Vesikari publication (see Table 8).¹⁰⁵

From the data presented in the epidemiology paragraph it is clear that viral activity in the Netherlands can vary substantially from year to year, with the annual number of rotavirus hospitalizations varying from 2436 children to 4704 children in the past ten years.¹¹⁶ During the period 1996 to 2006, high numbers were observed in 1996, 2005, and 2006. Since the RIVM-study was based on the incidence in 1996-2004, it could not be ruled out that the RIVM assumption with regard to incidence is somewhat too conservative, while the estimate of IMTA is assumed to be appropriate for high-epidemic years/relatively high.¹²⁸

Table 8 Assumptions on waning of vaccine efficacy made by RIVM and IMTA, compared to the waning of vaccine efficacy between the first and second rotavirus season, observed in European children by Vesikari et al.¹⁰⁵

	Decrease of vaccine efficacy in European children according to Vesikari et al. 2007 ¹⁰⁵	Assumptions on waning vaccine effectiveness in cost-effectiveness studies	
		RIVM	IMTA ¹²⁵
Rotavirus cases requiring no medical help (any severity gastroenteritis)	15%	15%	2%-point per year
Rotavirus cases requiring only a GP visit (severe gastroenteritis)	10%	15%	2%-point per year
Hospitalized rotavirus cases	8%	5%	2%-point per year
Fatal rotavirus cases	8%	5%	2%-point per year

International perspectives

Kempe et al. assessed whether paediatricians in the USA would adopt the new rotavirus vaccine. The majority of paediatricians reported willingness to implement the new rotavirus vaccine, most within six months. Major barriers to optimal implementation included provider concerns about reimbursement issues and parental acceptance of the vaccine.¹²⁹

Several studies investigated the incidence and costs of rotavirus gastroenteritis or the impact and potential cost-effectiveness of rotavirus vaccination. However, the compatibility of these study outcomes to the Dutch situation is questionable because of possible differences in epidemiology, health care system and discount rate. Four recent studies are summarized below:

Jit et al. used a cohort model to investigate the potential cost-effectiveness of rotavirus vaccination in England and Wales. They concluded that rotavirus immunization could reduce the substantial short-term morbidity burden due to rotavirus, but is unlikely to be deemed cost-effective (RotaTeq pound 79,900 per QALY gained, RotaRix pound 61,000 per QALY gained) unless the vaccine is competitively priced.¹³⁰

Widdowson et al. assessed the health and economic impacts of a national rotavirus immunization program in the USA. A routine rotavirus immunization program would prevent 13 deaths, 44,000 hospitalizations, 137,000 emergency department visits, 256,000 office visits, and 1,100,000 episodes requiring only home care for children younger than five years of age in the USA. Routine rotavirus vaccination would unlikely be cost-saving in the USA at present.¹³¹

The REVEAL study evaluated the costs of community-acquired paediatric rotavirus gastroenteritis in seven European countries. The direct medical cost (from the societal perspective) per episode of rotavirus gastroenteritis ranged from € 27 to € 77 in the primary care setting, from € 135 to € 477 in the emergency department setting, and from € 1220 to € 1519 in the hospital setting. The majority of hospital-related costs were reimbursed by national health care payers, but the percentage of reimbursed costs declined progressively in the emergency department and primary care settings.¹³²

Fisher et al. used modelling of national hospital registry data to determine the incidence and direct medical costs of annual rotavirus-associated admissions over more than 11 years in Denmark. These admissions amount to associated direct medical costs of € 1.2-1.3 million per year.¹³³

Recommendations for vaccination, surveillance, and research

The introduction of the vaccine would be practically feasible and could probably reduce the burden of disease caused by rotavirus substantially. For a conscious decision whether or not to include universal rotavirus vaccination in the Dutch NIP, it is important to take the following into consideration:

As the consequences of emerging rotavirus variants, that differ antigenically or in virulence, on the vaccine's effectiveness are unknown, more research is necessary to determine circulating rotavirus serotypes among children younger than five years. The Netherlands participate in a European wide study to obtain information on circulating strains, and the effect of rotavirus vaccination on circulating strains, in several European countries. The current EU project involves only three pre-vaccination years. Depending on introduction of vaccination, a second phase of three post-vaccination years can be started. Which countries will be participating and how the follow up project will be financed is not yet clear.

Insight has to be obtained into vaccine acceptance among parents and health care workers.

When it is decided to introduce rotavirus vaccination in the Netherlands, post-marketing surveillance will be essential for further determination of VE, safety, and duration of protection, because of the decreased vaccine efficacy in the second season. Data on efficacy in third and fourth season are not yet available. Insight into changes in circulating strains is essential to study a possible shift.

4.3 Varicella Zoster Virus (VZV) infection

H.J. Boot, B.P. van der Zanden, A. van Lier, N.A.T. van der Maas, H.E. de Melker

Vaccine

Availability and new developments

Only one attenuated live vaccine strain against VZV is available (the OKA strain), which was developed in 1974 in Japan. The different VZV vaccines that are based on the OKA strain are licensed to prevent a primary VZV infection (chickenpox) and reactivation of VZV in latently infected nerve cells (herpes zoster, also referred to as shingles). Different formulations of monovalent VZV vaccines are available ($10^{3.3-4.3}$ plaque forming units (pfu) per dose), and different passage numbers (31 to 35 passages) of this vaccine strain are being used by different manufacturers.¹³⁴ VZV childhood vaccines are also available in combination with vaccines against measles, mumps, and rubella (MMRV, ie. ProQuad [SP-MSD, $10^{3.99}$ PFU OKA/Merck-strain] and Priorix-Tetra [GSK, $10^{3.3}$ PFU OKA/RIT-strain]).^{135, 136} For the prevention of herpes zoster only one vaccine is available: ZOSTAVAX (SP-MSD, $10^{4.3}$ pfu OKA/Merck-strain). In May 2006 this vaccine obtained European license to prevent herpes zoster in people above 60 years of age.¹³⁷ However, due to difficulties in varicella vaccine production ZOSTAVAX (SP-MSD) is not available on the European market. It is expected that this product will become available in 2008.

Effectiveness

Primary VZV infection (chickenpox)

Single vaccination with the monovalent VZV vaccine is highly effective in the prevention of severe clinical signs of a primary VZV infection (chickenpox). However, subclinical infections and infections with minor clinical signs are relatively frequently reported; up to 30% of the children experience a mild varicella infection between 2-8 years post vaccination.¹³⁸ To boost the initial immune response to the varicella component and to prevent (subclinical) breakthrough VZV-infection, it is advised by the EMEA to give a booster dose VZV (either single varicella, or MMRV combination vaccine), preferably within 3 months after initial vaccination.^{135, 136} In the USA, which introduced childhood varicella vaccination (at the age of 12-15 months) already in 1995, a second (booster) dose varicella vaccination has been added to the NIP in 2007. This booster dose should preferably be given in combination with the second MMR vaccination (i.e. as MMRV) at 4-6 years of age (at least three months after the first varicella vaccination).¹³⁹

The EMEA states that ProQuad should not be given concurrently with multicomponent childhood (DTaP and/or Hib-HBV) vaccines due to possible reduced immune responses against the pertussis, Hib and hepatitis B antigens.^{135, 140} However, in the USA concurrent vaccination is, on basis of the same study, allowed.^{139, 140} Priorix-Tetra can be given concurrently with several other childhood vaccines, including Infanrix-hexa.¹³⁶ No data is available of concurrent vaccination of Proquad or Priorix-Tetra with Men C.

VZV reactivation (herpes zoster)

The effectiveness of ZOSTAVAX is mainly based upon a large vaccine trial (n=38.546), conducted in the USA in elderly (≥ 60 years).¹⁴¹ This study showed that ZOSTAVAX is only partially effective, i.e. it reduces the incidence of herpes-zoster about half (51.3%), and post herpetic neuralgia by about two-thirds (66.5%) during a mean follow-up period of 3.13 years. Vaccine efficacy against herpes zoster is higher in people in the age group of 60-69 years (64%) than in people >70 year-of-age (38%). The prevented total burden of illness due to herpes zoster was also lower in the >70 year-of-age group (56.4%) in comparison to 60-69 year group (66.6%), but this difference was not significant.¹³⁷ It is currently unclear whether booster vaccination with a second dose of ZOSTAVAX will increase the overall vaccine efficacy. Furthermore, it is unknown how long protection will last. ZOSTAVAX can be given concurrently with influenza vaccination.¹³⁷

Adverse events

Chickenpox vaccination

The most common side effects found in clinical trials are: injection site reactions, fever and rash (including measles-like rash and varicella-like rash). The safety profile of MMRV is comparable to the safety profile of MMR and varicella given concurrently.^{135, 136} However, minor adverse reactions i.e. fever and measles-like rash were statistically significant increased in the ProQuad group in comparison to the group receiving concurrently MMR and varicella.¹³⁵

Herpes zoster vaccination

A statistically significant higher rate of injection site reactions was reported in the vaccine group in comparison to the non-vaccine placebo group (48.3% vs. 16.6%). Most ($\pm 85\%$) of these injection site reactions were, however, mild. Also the number of subjects which had one or more vaccine-related systematic adverse events was higher in the vaccine group in comparison to the placebo group (6.3% vs. 4.9%).^{137, 141} The frequency of VZV-like rashes within 42 days post vaccination was low (<1%) in both the vaccine and placebo group (vaccine group 0.1%; placebo groups 0.2%).¹⁴¹

Disease

Epidemiology

This paragraph gives an update on the epidemiology of varicella and herpes zoster in the Netherlands as published by de Melker et al. in 2006.¹⁴² 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, causing an underestimation of 8.7 % of all clinical admissions in that year. 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 side diagnosis from 2000 to 2006 is shown in the left panel of Figure 12. In 2006 the incidence of hospital admissions with main diagnosis varicella (ICD-9 group 052) was 1.95 per 100,000 and 2.88 for 100,000 for main and/or side diagnosis together.

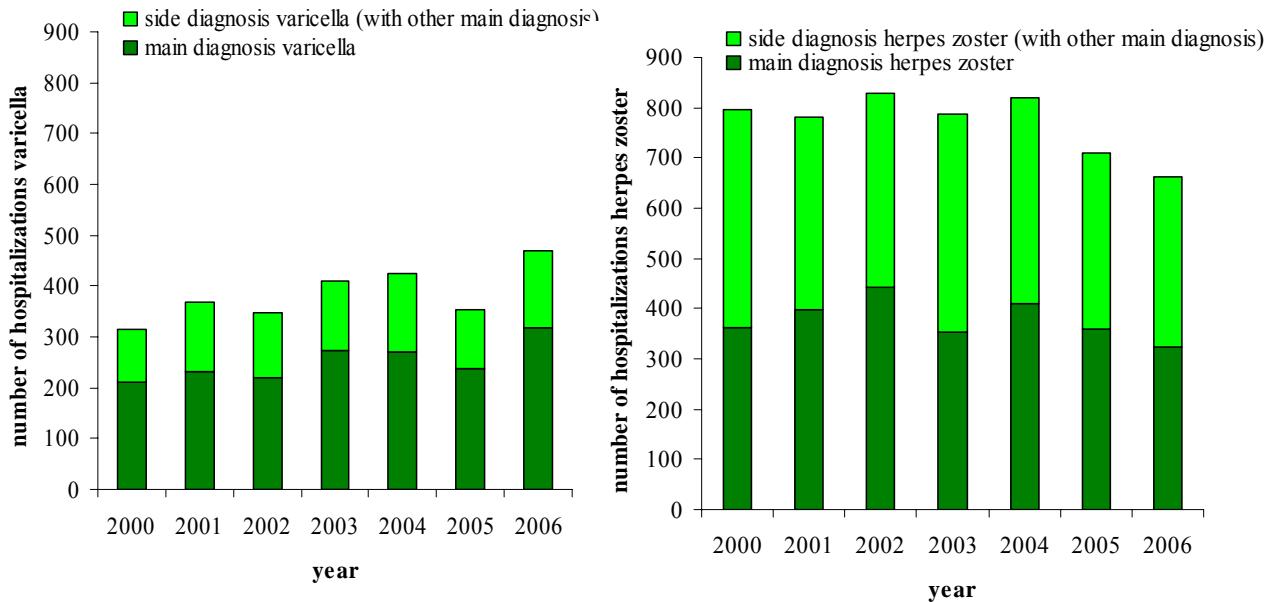


Figure 12 Number of hospitalizations with main or side diagnosis of varicella (left panel) and herpes zoster (right panel) from 2000-2006

Among 0-year-olds the incidence was highest with 58.2 and 79.1 per 100,000 for main and main/side diagnosis respectively. The incidence based on GP-consultations was 300 per 100,000 inhabitants and was highest for the 0- and one- to four-year-olds (respectively 3050 and 3310 per 100,000). For both sources this implies a higher incidence compared to the previous period, i.e. mean 1.5 hospitalizations with main diagnosis varicella per 100,000 (1.3 to 1.7) and 245 GP consultations per 100,000 inhabitants (190 to 320) in 2000-2005.

Herpes zoster

The number of hospitalizations with herpes zoster as main or side diagnosis from 2000 to 2006 is shown in the right panel of Figure 12. For herpes zoster, the incidence of hospital admissions with main diagnosis herpes zoster (ICD-9 group 053) in 2006 was 1.98 per 100,000 and 4.05 per 100,000 for main and/or side diagnosis together. The incidence of hospital admissions was highest among the oldest age groups (age 85+) with 18.57 and 39.90 per 100,000 for main and main/side diagnosis respectively. The incidence of hospitalizations with main diagnosis herpes zoster was slightly lower compared to the previous period, i.e. mean 2.4 hospitalizations per 100,000 (2.2 to 2.7). Data on GP consultations for herpes zoster was only available for the period 1997-2001. In 2001, the incidence based on GP-consultations was 320 per 100,000 inhabitants and was highest for 80- to 84-year-olds (830 per 100,000).

Intensified surveillance of varicella zoster virus associated hospital admission

To obtain more insight into the disease burden of varicella zoster virus in the Netherlands, we performed intensified surveillance of VZV associated hospital admission through the paediatric surveillance unit. However, in the period June 2006 till June 2007 only 37 patients were reported, a much lower number as expected based on hospital discharge data. For 6 of the 36 patients for which a questionnaire was returned, a severe underlying illness was reported (i.e. acute leukaemia). For 32 of the 36 patients one or more varicella complications were reported. The most often reported complications were bacterial or viral super infection (n=19), most frequently of the skin. Other

complications that were mentioned more than once were: stomatitis (n=7), pneumonia (n=6), fulminant/haemorrhagic varicella (n=4) and encephalitis / meningitis / cerebral vasculitis (n=3). For two of the 36 patients a herpes zoster complication was reported. One of the patients (without underlying disease) died due to varicella or complications. Of the 32 patients that were dismissed, 21 patients had residual symptoms like scars (n=9), residual ataxia (n=1) or other symptoms (n=11). The mean length of hospital stay of dismissed patients was 7.2 days (standard deviation 5.5 days; min 0 and max 22 days).

Burden of disease

Chickenpox

In a recent publication the seroprevalence of varicella zoster in various European countries is described showing that for all countries the incidence increases sharply in the first years of life. As described previously the seroprofile for the Netherlands shows a relatively low age of infection in comparison to others.¹⁴³ To rule out any test effects a subset of the sera has been retested, confirming the published results (Dr. Berbers RIVM, personal communication).

Economic aspects

In 2008 the results of a cost-effectiveness study including insight into disease burden due to herpes zoster in the Netherlands will become available. A model based economic evaluation of the herpes zoster vaccine for the USA by Pellissier et al. showed cost-effectiveness ratios from US\$ 16,229 (societal perspective, all herpes zoster data used) to 27,609 (payer perspective, immunocompetent data) per QALY gained.¹⁴⁴ Another study showed rather higher cost-effectiveness ratios and exceeded US\$ 100,000 per QALY gained for different combinations of age group and sex.¹⁴⁵ The parameters that changed the cost-effectiveness >20% were duration of immunity, cost, efficacy and side effects of the vaccine, the incidence and severity of post herpetic neuralgia (see also Brisson et al.¹⁴⁶), and the discount rate.

International perspectives

Chickenpox

Only two European countries have incorporated varicella vaccination currently into their recommendations for their national childhood immunization program (i.e. Germany and Greece). 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 program for adolescent with no history of chickenpox. Due to difficulties in varicella vaccine production, the MMRV combination vaccine of SP-MSD (ProQuad) is not available on the European market. It is expected that this product will become available in 2008. A dilemma for the implementation of varicella vaccination in our NIP is the recommendation to have two vaccinations in the second year of life.^{135, 136} At present, MMR is given at 14 months and nine years. Therefore replacement of MMR with MMRV will not comply with the recommendation for varicella vaccination. Introduction of varicella vaccination in our NIP will thus require adaptation of the current schedule.

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 life. Because universal childhood vaccination against chickenpox has been introduced in the USA from 1995 onwards the incidence of herpes zoster might start to increase.¹⁴⁷ No new USA-data on the incidence of herpes zoster has been published in 2007. Whether exogenous VZV-exposure indeed stimulates VZV-immunity is still a matter of debate. A recent report from the CDC found no protective effect of VZV-exposure on herpes zoster incidence in older adults (>65 years).¹⁴⁸

Recommendations for vaccination, surveillance, and research

Chickenpox vaccination

To assess the chickenpox associated burden of disease more accurately we plan to review patients' 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. 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 life due to herpes zoster infections in the Netherlands is performed. The results are expected in 2008. 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 will be subject of an assessment study using a structured approach.¹⁴⁹

4.4 Meningococcal serogroup B disease

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

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 Men B polysaccharide vaccine, which would have been a logical vaccine candidate. The Men B 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 in Western Europe. However, two candidate vaccines have recently been tested for safety and immunogenicity.¹⁵⁰ These outer membrane vesicle (OMV) vaccines, MenBvac and MeNZB, are prepared from a B:15:P1.7,16 and a B:4:P1.7-2,4 strain, respectively. The authors of the study suggest that the use of these monovalent vaccines separately or in combination would have considerable impact on serogroup B meningococcal disease in many countries. In the Netherlands porin type P1.7,16 was only found in 2% of the cases in 2005. However, P1.7-2.4 made up 27% of all cases of invasive Men B disease in 2005 and also 27% of the Men B cases in children younger than two years of age. Therefore, the use of the MeNZB, which has been used successfully in New Zealand, could theoretically cause a significant decrease in the number of cases in the Netherlands. Currently, several vaccine candidates are under investigation. The NVI has developed a multivalent OMV vaccine and is performing clinical trials to test the vaccine. The NVI vaccine contains a mix of nine different PorA types and can be adapted to fit other porine types if required. Current nonavalent NVI vaccine provides 66%-77% coverage in 0-1 year old children and similar coverage for individuals older than one year (Table 9).

Table 9 Vaccine coverage of the nonavalent NVI vaccine. (source NRBM)

	0-5 months	6-11 months	0-1 year	>1 year
Vaccine coverage	68%	66%	77%	71-76%

Many other components of the group B meningococcus are being tested for suitability by several vaccine developers. Examples are the less variable PorB and FetA outer membrane proteins, but also RmpM, Opa and OpcA, NspA, NadA, Omp85, TdfH and lipoprotein LP2086. Furthermore, all kinds of vaccine candidates are being found by so-called reverse vaccinology and some of these are under clinical evaluation as candidate vaccines.

Effectiveness

See section on international aspects.

Disease

Burden of disease

After 1980, there has been a remarkable 3-fold increase in Men B incidence. However, since 2000 the number of reported patients with meningococcal B disease has been decreasing, as can be seen in Figure 13 and Table 10. In 2006 the number of cases has decreased to 158, which was 2.7 times lower than the number of Men B cases seen in 2000. Until September 2007 only 100 cases of meningococcal B disease have been reported. This unexplained decrease in incidence is considerable and merits further investigation. Possibly, the current decrease reflects natural fluctuation. However, the steep Men B increase after 1980 coincided with a steep decrease in Men A incidence in the same time period, suggesting Men B occupied the niche previously taken in by Men A. In the current period no simultaneous increase of other meningococcal serogroups has been observed.

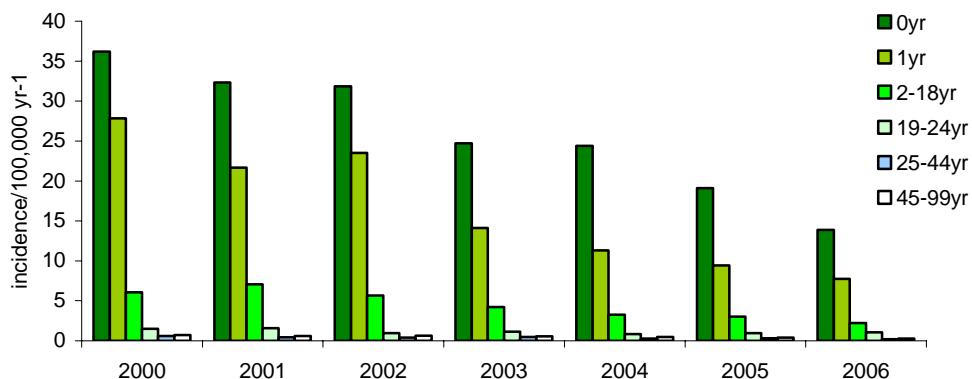


Figure 13 Age-specific incidence of meningococcal B disease by year, 2000-2006

Table 10 Absolute number of patients with meningococcal B disease per age-category from 2000-2006

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

International perspectives

The Netherlands is not the only country that experienced a declining number of reported cases of invasive Men B 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.¹⁵¹ In contrast, according to the EU-IBIS report, an increase in Men B has been observed in France and Portugal.

As described above there are two candidate vaccines, one of which is used in a nationwide vaccination program in New Zealand. This vaccine has been shown to be 73% effective in the first two years of the New Zealand immunization program. After introduction of the vaccine the number of cases of notified meningococcal disease dropped from 650 in 2001 to 160 in 2006.

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.

4.5 Respiratory Syncytial Virus (RSV) infection

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Vaccine

Availability and new developments

NVI is developing a recombinant live attenuated RSV vaccine based on a recent Dutch clinical RSV isolate (RSV-X), using reverse genetics. This technology allows attenuation of RSV by deletion of viral genes required for efficient infection of the host. The vaccine candidate, given intranasally, has been tested in an animal model, predictive of human disease. In the model, it does not cause pathology, does not detectably infect the lungs and protects against RSV-induced lung disease up to five months. As mentioned in the previous report the candidate vaccine is being developed further in cooperation with the Dutch company Nobilon and supported by funding from the Dutch 'Fonds Economische Structuurversterking'.

Pathogen

RSV strains A and B often co-circulate, with one or the other type dominant. There appears to be no clear correlation between dominant strain and disease severity. In the past season, RSV B was diagnosed more often than RSV among patients of GP's belonging to a sentinel surveillance network covering 1% of the Dutch population.

Disease*Burden of disease*

Epidemiological data on trends in RSV in the Netherlands are available through the virological weekly reports, in which laboratories report virological diagnosis. Based on these reports, the previous RSV season started in week 43 of 2006 and lasted till week 13 of 2007. Therefore, this year the RSV season was relatively long (23 weeks compared to an average of 18 week over 9 years). The peak of notifications occurred in week 51.⁷⁶

Data on the contribution of RSV to ILI/acute respiratory infections presentations to GPs are available via a NIVEL sentinel surveillance network covering 1% of the Dutch population. RSV was identified in 3.8% of patients presenting with an ILI, 4.9% of patients presenting with another upper respiratory tract infection and in 10.0% of the patients presenting with a pneumonia or bronchiolitis.⁷⁶

In the absence of an effective vaccine, palivizumab is still the mainstay for prevention among young children. Related next generation antibodies, such as MEDI-524, are still being tested for effectiveness.

Economic aspects

To expand on previous cost-effectiveness study showing that RSV vaccination is expected to be cost-effective with vaccine price below €80 per dose¹⁵², the NVI is planning to further cooperate with the RuG to establish the impact of RSV infection on the elderly and risk groups. A preliminary report indicated that the burden of disease in these groups may be considerably higher than in children. Data on such factors will become available after clinical trials have started, planned at the end of 2008/beginning of 2009.

Recommendations for vaccination, surveillance, and control

A new RSV vaccine will not be available in the near future. Ongoing long-term surveillance of epidemiological trends based on virological diagnosis and on burden of disease based on sentinel GP networks monitoring ILI will provide important baseline data once an effective vaccine is available and included in the Dutch NIP.

4.6 Human papillomavirus (HPV) infection

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Vaccine*Recent changes in the NIP*

The national Health Council is expected to advise the minister of health on the introduction of HPV vaccination in the Dutch NIP in the first half of 2008.¹⁰ A follow-up advice on the adjustment of the national screenings program for cervical cancer and the possible introduction of HPV screening is scheduled afterwards.

Availability and new developments

Two HPV-subunit vaccines are now available on the European market. The quadrivalent Gardasil® (SP-MSD, September 2006) contains Virus Like Particles (VLPs) of HPV-6, -11, -16, -18, and an aluminium adjuvant.¹⁵³ HPV-16 and -18 are the most prevalent genital carcinogenic genotypes, while HPV-6 and -11 are the causative agents of most (80-95%) genital warts. The bivalent Cervarix® (GSK,

¹⁰ On the 1st of April 2008, the Health Council advised on the minister of health to include HPV-vaccination for 12-year-old girls into NIP. This advice came along with an advice for a catch-up programme for girls in the age of 13-16 years.

September 2007) contains only the HPV-16/18 VLP's, but is adjuvanted with a new and more potent adjuvant (AS04) containing next to aluminium also monophosphoryl lipid A.¹⁵⁴

Effectiveness against high grade cervical lesions

Several reports have been published in 2007 concerning the effectiveness of HPV-vaccination on basis of randomized clinical trials (Gardasil¹⁵⁵⁻¹⁵⁸ and Cervarix¹⁵⁹ (for systematic review see Rambout et al.¹⁶⁰)).

The presented results are in line with earlier reports: i.e. a nearly 100% efficacy in preventing persistent (>1 year) HPV-16/18 infection of the cervix, and against HPV-16/18 induced pre-stages of cervical cancer (high grade cervical intraepithelial neoplasia (CIN2+) and adenocarcinoma in situ (AIS)). HPV-16/18 was found sporadically in high-grade lesions in the per-protocol vaccine group of both Gardasil¹⁵⁷ and Cervarix¹⁵⁹. This was, however, always in association with other high risk genotype HPVs (hrHPV). Additional analysis of these co-infection cases makes it conceivable that the high-grade lesions were not caused by HPV-16/18.^{154, 157, 159} The efficacy against transient (less than one year) genital HPV-16/18 infection is not complete (only 80-90%). Transient infection will most likely not induce cervical cancer, but will allow circulation and hampers the establishment of herd-immunity. The effectiveness of vaccination in the intention-to-treat population (women 16-26 years of age) of the vaccine trials is considerably lower.¹⁵⁵⁻¹⁵⁷ This is due to already existing HPV infections at the start of vaccination in a substantial part of the sexually active young women. Therefore, the efficacy of catch-up HPV-vaccination in sexually active adolescent girls and women will be reduced. No therapeutic effect of vaccination was found in women with an HPV16 or -18 infection (DNA positive) at the start of vaccination.¹⁶¹

Effectiveness against other anogenital disease

For Gardasil it was shown that this vaccine also protects against vulvar and vaginal intraepithelial neoplasia (100% efficacy (95% CI: 94-100%) in per-protocol analysis during an average of three year follow-up).¹⁶² Most of the genital warts are caused by an HPV-6 or -11 infection. Vaccination with Gardasil in the same pre-protocol population reported completely prevention of genital warts. No data is currently available on the efficacy of Cervarix against vulvar and vaginal intraepithelial neoplasia. Cervarix vaccination is not expected to protect against genital warts because HPV-6 and -11 VLPs are not part of this vaccine. No data on the effectiveness of HPV-vaccination on anogenital disease in men has been published yet.

Duration of protection

The duration of the induced protection is currently unclear. The presence of neutralising antibodies in the serum is seen as the key component for protection against persisting infections. Both for Gardasil^{163, 164} and Cervarix¹⁶⁵ it was shown that high antibody levels were present 4-5 years post-vaccination in 15-25-year-old women. For Gardasil it was shown that antibody levels for HPV16 remain clearly above those found for naturally infected women during five years follow up using a Luminex competition assay. Antibody levels against HPV-6, HPV-11, and HPV-18 are decreasing within 5 years to the same level as found in naturally infected women in Gardasil.¹⁶³ After Cervarix vaccination, antibody levels remain ten-fold higher than found in naturally infected women in HPV-16/18 specific ELISAs up to five years post vaccination.^{154, 165} Because the assays for evaluation of Gardasil and Cervarix antibody responses are based upon a different design a direct comparison is impossible. For Gardasil, strong anamnestic responses (n=87) were reported after a single Gardasil booster vaccination at five years after the primary series.¹⁵³ Bridging studies showed that higher antibody levels were induced in 10-15-year-old girls than in 16-23-year-old women for both vaccines.^{154, 166}

Partial cross protection against persistent infection with related high risk genotypes of HPV-16/18 (e.g. HPV-45, -33, and -52) has been reported for both Cervarix¹⁵⁹ and Gardasil.¹⁶⁷ Furthermore, for

Gardasil it has been reported that the incidence of disease (CIN2/3 and AIS) due to non-vaccine hrHPV genotypes is reduced.¹⁶⁷ Because the incidence of non-HPV16/18 hrHPV is relative low, long-term follow up periods are required to substantiate the claims of cross-protection.

Adverse Events

As described in the report of 2006 on the Dutch NIP, several clinical trials did not show any serious adverse event that was causally related to vaccination. A recent study among young women showed no differences in serious adverse events between the group vaccinated with Cervarix and the control group who was vaccinated with a control hepatitis A vaccine.¹⁵⁹ Although pregnant women were excluded from these trials as currently HPV vaccines are not licensed for these women, unintentional vaccinated pregnant women are reported sometimes. No differences in pregnancy (outcomes) were found between pregnant cases and controls. The occurrence of injection site symptoms and symptoms such as fatigue and headache were more often reported in the vaccine group than in the control group.¹⁵⁹ These results are in line with a placebo-controlled randomized trial of the FUTURE II Study Group (2007) among young women (ages of 15 to 26 years) and a case-control study of Reisinger et al. (2007) among males and females aged 9-15 years.¹⁶⁸ In both studies, significant differences between cases and controls were only reported for injection-site adverse events following vaccination with Gardasil. The finding of a (non significant) difference in incidence rates of arthritis between patients and controls during the four-years of follow-up in the clinical trials¹⁵³ stresses the need to monitor these and other possible autoimmune disorders more carefully.

After introduction of Gardasil vaccination in the USA, almost 4000 adverse events after vaccination with Gardasil were reported in the vaccine adverse events reporting system (VAERS) (based upon more than five million doses distributed). The majority of these adverse events were injection site reactions, but more serious adverse events, such as Guillan-Barre Syndrome (17 events) and deaths (nine events) were also reported.¹⁶⁹ These serious adverse events are being investigated by the CDC to establish whether these are related to Gardasil vaccination or not. Some of the events will occur coincidentally following vaccination, but are not due to vaccination.¹⁷⁰ In the Netherlands, six adverse events after vaccination with Gardasil have been reported by the Netherlands Pharmacovigilance Centre (Lareb) (based upon 7453 prescriptions according to the Foundation for Pharmaceutical Statistics reported in the period October 2006 to October 2007). None of these events was classified as serious adverse events.¹⁷¹

Pathogen

Strain variation

Extensive vaccination against HPV-16/18 might exert a higher evolutionary pressure in comparison to natural circulation. Vaccine-induced neutralizing antibody levels are much higher than those found after a natural infection,^{163, 165} probably resulting in a stronger selection pressure. The consequences of new antigenic or virulent variants are, however, expected to be small. Strains of one genotype but belonging to different lineages and with different pathogenic features are found to co-circulate.¹⁷² Furthermore, studies to determine cross-protection showed that both Cervarix¹⁵⁹ and Gardasil¹⁶⁷ are partly cross-protective against persistent infections with HPV-16/18 related genotypes.

Disease

Epidemiology

Persistent infections with hrHPV genotypes (notably HPV-16 and -18) are associated with the development of CIN and AIS, which may progress to cervical cancer. In industrialised countries cervical cancer screening programs are in place which reduces the burden of disease due to HPV-infection by timely detection of cervical lesions and pre-stage of cancer.

There are no data available on the incidence of HPV-16 and -18 in the general population in the Netherlands. Prevalence data are mainly available for women from the screening population.¹⁷³ In the Netherlands 84,5% of all cervical cancers are caused by HPV-16 (67,5%) and HPV-18 (17,0%), while also 70% of the high-grade lesions are caused by HPV-16 (55,8%) and HPV-18 (14,9%).¹⁷⁴ Recently, serum samples of a population-based study among persons aged 18 years and older (median age 49 years; interquartile range (IQR) 39-60 years), conducted in 2004 in Amsterdam, were tested on antibodies against 8 high-risk HPV types and 12 skin types. In this study, HPV-16 and -18 showed a seroprevalence of 24,0% and 24,1% respectively. Risk factors for HPV-16 and/or -18 seropositivity were female or homosexual male and increased risk of seropositivity when antibodies against one or more other hrHPV genotypes were present.¹⁷⁵

Burden of disease

Around 600 women per year are diagnosed with cervical cancer (www.ikcnet.nl). Of these cases, 211 fatal cases per year are reported on average based on the last five years (2002-2006, www.cbs.nl). The total disease burden expressed in DALYs comprises the years of life lost (YLL) and the years lived with disability (YLD) due to cervical cancer. Per fatal cervical cancer case the years of life lost amount to 20,5 years on average per case, resulting in 4,325 YLL per year for all fatal cases. A non-fatal case of cervical cancer is valued at 1,8 YLD and the assumption for a fatal case is 1,6 YLD on average. The total YLD for all cases amounts to 1,037 per year. The sum of YLL and YLD results in 5,363 DALYs per year for all reported cervical cancer cases. This burden of disease estimate does not comprise other HPV related diseases such as genital warts, vaginal or vulvar neoplasia or the pre-stages of cervical cancers (CIN grades), nor are the relatives of cervical cancer patients taking into account when measuring quality of life.

Genital warts were the most frequently diagnosed viral STI in the 2006 in the nationwide STI centers. In 2006, 1924 diagnoses of genital warts were recorded in 68977 new consultations (1149 in men and 775 in women), which was a decrease in the number of genital wart diagnoses by 10% compared to 2005. Most diagnoses were made among women and men aged 20-24 years (men 25%, women 42%). In the older age groups the number of infections is lower.¹⁷⁶

Economic aspects

The cost-effectiveness of a possible universal vaccination in combination with the existing screening program was examined using a Markov model developed by VUMC. This model simulates the natural history of cervical cancer for a cohort of women and uses multiple oncogenic HPV types, progression states of infection to CIN and cervical cancer, and the reduction of all states due to vaccination and screening.^{177, 178} The base analysis used the following assumptions: all 12-year-old girls are vaccinated with a compliance of 85%, VE is 95% with lifelong protection, vaccine price is set at 393 euros including administering costs and current screening is unaltered. Costs were discounted at 4% and effects at 1,5%. Simulating a cohort of 100.000 females (approximately one year cohort) resulted in a decline of cervical cancers from 600 (screening only) to 260 (vaccination and screening) and a reduction in fatal cases from 220 to 100 cases per year. The difference in health effects between the two scenarios amounted 5000 undiscounted QALYs and 2500 QALYs when discounting was performed. The incremental cost-effectiveness ratios (ICER, euros per QALY) estimations of all scenarios (e.g. vaccination plus screening compared to screening only) will be available at the beginning of 2008. The ICER is dependent on the assumptions made, e.g. a lower VE percentage, a higher vaccine price or waning immunity which would require a booster, which all would increase the ICER (higher costs per QALY). Uncertainties that were not modelled were a reduced transmission rate, reduction of anogenital cancers and possible cross-protection, all would favour the cost-effectiveness of vaccination.

Adjustment of the cervical cancer screenings program (e.g. introduction of HPV-screening) might

reduce the burden of disease due to hrHPV infections. This could translate into a higher ICER for HPV vaccination of preadolescent girls.

International perspectives

Many European countries are in the process of introducing HPV vaccination for pre-adolescent girls as part of their national immunisation programs (e.g. Italy, France, Germany, Belgium, Norway, UK).^{179, 180} Catch-up programs for older girls and women are often complementing the introduction of HPV vaccination. Different age-limits and different ways of organisation of these catch-up programs are used by these countries.

In the meantime many cost-effectiveness analyses (CEAs) are performed to aid decision making of a possible universal vaccination and several CEAs for different countries have been published already. Goldie et al. for instance explored the cost-effectiveness of a HPV-16/18 vaccination combined with existing screening modalities in the USA. Depending on, among other assumptions, vaccine efficacy (70-100%), start age and interval of screening, the cost-effectiveness ratios with a reduction in lifetime cancer risk >90% were between US\$ 20,000 and 60,000 (2002 US\$).¹⁸¹ Other studies for the USA comprised different comparisons of screening only and vaccination with screening, showing scenarios that would not be cost-effective to scenarios with US\$ 50,000 or less per QALY.^{182, 183} More recently, Brisson et al. estimated that vaccinating all 12 year old girls in Canada is likely to be cost-effective, as the costs per QALY gained are CAN\$ 20,500 and CAN\$ 31,000 for the quadrivalent and bivalent vaccine respectively, which are both below the Canadian threshold of CAN\$ 40,000 for cost-effectiveness.¹⁸⁴ ICERs between studies can vary greatly, e.g. for a discussion of the CEAs in the USA see Newall et al.¹⁸⁵ Unfortunately, for most European countries there are not CEAs published yet, while besides all model assumptions, different country specific data like screening modalities, HPV prevalence and treatments costs can influence cost-effectiveness considerably.

Finland has decided to not yet introduce HPV vaccination. Instead, Finland organises a large scale study with three arms which will compare different vaccination strategies in different regions, i.e. one region with vaccinations of both girls and boys, one with only girls and one without HPV-vaccination.^{179, 180} Results on effectiveness will be available in 2014. In the following years more information with regard to safety will become available from this large scale study.

Recommendations for vaccination, surveillance, and research

An advice of the Health Council on whether or not to implement HPV-vaccination for preadolescent girls into the NIP is expected in the first half of 2008. A positive advice on implementation of HPV-vaccination will most likely be accompanied on whether or not to recommend a catch-up for adolescent girls.¹¹

The age-specific incidence of hrHPV infections in girls and young women in the Netherlands is largely unknown. This data is especially relevant for determining the upper age-limit for cost-effective vaccination in a catch-up program for older girls and women. We have planned the analysis of a cross-sectional serum sample set of the Dutch population (PIENTER-1 and -2 cohorts) to assess the prevalence of serum antibodies against HPV-16 and -18. Women, who are not eligible for a catch-up vaccination due to their age, might profit from HPV-vaccination when they have not been infected before with relevant HPV-types. Whether it is possible to select and vaccinate those women in a cost-effective way, e.g. as part of a hrHPV screening program, remains to be determined.

To assess potential changes in the population of circulating HPV-16 and -18 strains -if vaccination will be introduced- we have planned to characterize a set HPV-16 and -18 isolates at a molecular level. The

¹¹ On the 1st of April 2008, the Health Council advised on the minister of health to include HPV-vaccination for 12-year-old girls into NIP. This advice came along with an advice for a catch-up programme for girls in the age of 13-16 years.

origins of these isolates are cervical samples of women (> 30 year). These women participated in HPV-screenings programs to evaluate the value of hrHPV testing in a cervical cancer screening program. We will also explore possible surveillance methods to assess background incidence of (autoimmune) diseases that occur frequently in the target group for vaccination ((pre-) adolescent girls). This will make it possible to anticipate on possible associations made between vaccination and these diseases. Furthermore, a surveillance plan to study the effectiveness of vaccination has to be developed using intermediate endpoints such as prevalence of (persistent) HPV infections and incidence of CIN lesions, but also cervical and anogenital cancer and genital warts.

HPV-vaccination is expected, in time, to have a profound effect on the cost-effectiveness of the current cervical cancer screening program, as the incidence of cervical lesions and cervical cancer will be reduced. Also, the potential change in the screening programme using HPV-detection methods needs to be assessed in relation to the cost-effectiveness of vaccination. To evaluate the direct and indirect effects of HPV vaccination programs, mathematical models that combine the effect of vaccination, reduced HPV transmission, and different cervical cancer and hrHPV screening programs to optimize the most (cost-) effective reduction of cervical cancer in the Netherlands need to be developed.

5 Issues of current interest for the NIP

In this chapter we discuss a few issues of current interest in the field of routine vaccination into a national immunisation programme. The topics discussed below are the relevance of disclosure of surveillance data of the NIP via the internet, availability of vaccination outside routine vaccination programmes (NIP+) and the relevance of linkage of vaccination status to disease data. Furthermore, in 2008 a strategic plan on research of the CIb/RIVM in the field of vaccine-preventable diseases will come available where other issues will be addressed. We further refer to the recent advice of the Health Council where the (future) NIP as a whole was reviewed.¹

Disclosure of NIP surveillance data via the internet

There is an increasing need to inform professionals on the status of the infectious diseases covered by the current or future NIP. By far the fastest and best accessible medium to perform such function is the internet. Many institutes and surveillance networks have such services in place such as the websites of the Health Protection Agency in the UK (<http://www.hpa.org.uk/>) and of the Centers of Disease Control in the USA (<http://www.cdc.gov/>). Surveillance also is a core activity of the European Centre for Disease Prevention and Control (ECDC). The ECDC is collecting data for various infectious diseases from dedicated surveillance networks such as EU-IBIS, EuroTB etc. and is storing the data in a central database named TESSy. It will communicate the results of the analysis of the aggregated data to the Community network using websites and the Eurosurveillance journal.

Although the reporting of the aggregated European data is important, there is a need for such a service at the national level as well. The main advantages are that such websites will display more detailed and timely data, which are particularly relevant for the Netherlands. Currently there are hardly any dedicated websites displaying relevant information on diseases covered by the Dutch NIP such as the incidence of disease, distribution of types, temporal changes and geographic distribution of cases. However, there is a website that displays such information for the agents causing bacterial meningitis (<https://isisportal.rivm.nl/>) in the Netherlands and the development of a similar website for pertussis is underway. The bacterial meningitis website may serve as an example for the disclosure of information on surveillance of other diseases covered by the NIP.

In last decade molecular typing methods have been increasingly contributing to epidemiological studies. This is also true for the study of the pathogens causing diseases that can be prevented by the NIP. Such studies may reveal changes in the pathogen population due to selective pressure in the immunized population. An example of such a change is the emergence of *Bordetella pertussis* vaccine escape variants. In order to be able to compare molecular typing data of Dutch isolates with those from isolates obtained in other parts of the world, disclosure of these data via internet accessible websites is highly desirable. Therefore, it is important to construct websites that display the molecular typing methods to be used, the international nomenclature for types and the currently known types. These web applications should facilitate queries to interrogate (inter)national surveillance databases for the occurrence, frequency of isolation, geographic distribution of isolates and of their associated clinical presentations. Currently no such web applications are available in the Netherlands for pathogens associated with the NIP. A project designed to construct web applications to interrogate molecular databases in the CIb will start in 2008.

Availability of vaccination outside routine vaccination programmes: NIP+

Aiming at optimising the potential health gains, it is desirable that effective and safe vaccines are available and can be used adequately. This could mean inclusion of a new vaccine in the NIP, but also the availability of vaccines for individuals outside the programme, having in mind specific risk groups,

financing from different sources, not AWBZ but through health insurance (basic package or additional package) or at own expense.¹⁸⁶

CIb takes the responsibility to inform the public on new vaccines, but also to advise the public whether it makes sense to be vaccinated at his/her own initiative. It will be studied how vaccines could be offered at the individual's own expense outside NIP; a pilot will be prepared for 2008.

Linkage of vaccination status to disease data

Insight into vaccination status is essential in monitoring the performance of the NIP both with respect to effectiveness and safety. Nowadays registration of vaccine coverage is one of the five surveillance methods used to monitor the programme together with disease surveillance, safety surveillance, immune surveillance and pathogen surveillance. As for many years the vaccination status is registered for all individuals who are eligible for vaccination in the Netherlands by the regional vaccination administrations. Internationally, reliable individual registration of vaccination and the high coverage in the Netherlands is well recognised. The new system PRÆVENTIS/Præmis which has been introduced recently offers further new opportunities to study for example timeliness and individual vaccination histories. Until now vaccination history has been used in some studies on the effectiveness of vaccination focusing on the time period rather close to vaccination. Furthermore, we did several studies for which we collected information on vaccination status after informed consent of parents. The disadvantage of this approach is that it is very laborious and that only for a part of the study subjects information can be collected. Also in the passive surveillance system of adverse events following vaccination, vaccination status is used to study the (causal) association of the event with (the time since) vaccination. Monitoring the programme can be further improved by linking vaccination status to disease surveillance. In particular, such datalinkage will have added value when studying the impact of vaccination on disease occurrence after vaccination against diseases for which prevention by vaccine is expected many years after vaccination (for example vaccination against human papillomavirus to prevent cervix cancer). It can also be used when studying possible adverse events occurring years after the vaccination course (for example MS after hepatitis B vaccination). The challenge will be to create linkage of vaccination status to disease surveillance to enable essential public health surveillance under the current juridical possibilities and respecting the privacy and integrity of the individual. We will explore the possibilities further in 2008.

6 Recommendations and plans for vaccination, surveillance, and research

In the disease-specific chapters recommendations and plans were made with regard to vaccination, surveillance and research. An overview of these specific recommendations is given below.

We divide the parts on surveillance and research into parts referring to those that already have been included in the CIb workplan for 2008, or are planned for 2008 otherwise (i.e. external finances) and those planned for the future.

Vaccination

- For pertussis the cost-effectiveness of cocooning strategy needs to be explored to reduce the disease burden among infants too young to be vaccinated who are infected within a family setting.
- 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.
- For mumps, the merits of vaccine strains other than currently used Jeryl Lynn strain should be evaluated.
- The results from the economical analyses of hepatitis B vaccination for universal infants or adolescent vaccination will be used in the advice of the Health Council that is being prepared and expected in 2008.
- For pneumococcal disease it is recommended to compare the effectiveness of a 2+1 versus 3+1 dose schedule internationally to assess whether a three dose regime would be as protective as a four dose schedule (see research).
- Selective BCG vaccination strategy, targeting children from high prevalence countries, should be continued as well as for those travelling for at least three months to high endemic countries.
- For influenza the revised advice by the Health Council on medical indications for annual vaccination including lowering the age criterion to 60 years and above should be implemented. Uptake of vaccine and effectiveness needs to be monitored.
- The potential impact of universal hepatitis A vaccination should be further explored on population level, i.e. including herd immunity effects
- 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, but is unlikely to be cost effective except for high endemic years.
- Further insight into the disease burden of varicella zoster will be useful in the forthcoming advice of the Health Council since through the paediatric surveillance unit as performed in 2006/2007 only a small part of the expected hospital admissions due to varicella were reported. Furthermore, the potential impact of routine varicella vaccination on herpes zoster is still a discussion point.
- Elderly could potentially benefit from herpes zoster vaccination. Insight into cost-effectiveness and disease burden according to age will become available in 2008.
- The ongoing vaccine development of both meningococcal serogroup B and RSV needs to be followed.
- In the beginning of 2008 the Health Council will advise on whether or not to include HPV-vaccination for girls into NIP. This advice will come along with that for a potential catch-up programme. A plan of implementation of vaccination, monitoring of safety and surveillance of

the impact on (persistent) HPV infection, precursor lesions and cancer needs to be prepared (see surveillance).

Surveillance (already planned activities in the CIB workplan for 2008 or otherwise)

- Notifications will be extended to all NIP-target diseases in 2008/2009 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.
- Finalizing and implementation of surveillance protocol for measles and rubella is planned for 2008.
- Surveillance to detect possible vaccine failures of meningococcal serogroup C disease will be continued.
- Monitoring the introduction of PCV7 in NIP by pneumococcal strains isolated for CSF or blood from children aged <5 years with invasive pneumococcal disease which are send to NRBm is maintained.
- Information on effects of PCV7 vaccination on morbidity and mortality will be collected from January 2008 prospectively.
- Strengthening and extending sentinel surveillance network for influenza is achieved, ongoing analysis based on daily notifications, linked to daily updates on crude mortality, will be possible.
- A pilot of clinical and virological influenza surveillance is set up to be integrated in the nursing home network.
- To study the use of web based surveillance on improvement of knowledge into influenza transmission risks and routes in the population.
- The possible introduction of MDR or XDR M. tuberculosis will be monitored.
- Circulating rotavirus serotypes in particular among children younger than five years will be determined.
- Any changes in incidence and disease expression of invasive disease caused by serogroup B meningococci will be monitored.
- To assess the potential changes in the population of circulating HPV-16 and HPV-18 if vaccination is introduced, we plan to characterize a set HPV-16 and -18 isolates.
- A surveillance plan to monitor both effectiveness and safety of potential HPV vaccination will be prepared.

Surveillance recommended (not yet planned in the workplan CIB for 2008)

- Set up a (sentinel) system for the systematic collection of *Bordetella* strains is recommended to study the changes in the pathogen population in relation to vaccination. This could also be useful for the collection of other pathogens relevant for the NIP.
- Set up a study to investigate the degree of severity of pertussis in adolescents and adults.
- Cohorts which have been boosted at the age of four with a low dose of pertussis antigens should be followed and compared with a cohort receiving a high booster dose for waning immunity and pertussis incidence.
- Mumps surveillance needs enhancement, i.e. add surveillance of mumps through the existing sentinel physicians system (CMR, NIVEL) from 2009 onwards to the notification data to evaluate specificity of clinical diagnosis and monitor circulating genotypes. Laboratory methods can be improved suitable for surveillance (e.g. RT-PCR, oral fluid)

Research (already planned activities in the CIB workplan for 2008 or otherwise)

- The availability of new national seroprevalence data following PIENTER-2 study will allow study of the seroprevalence of the (future) target disease of the NIP. Specific recommendations in this report were made with regard to pertussis (estimate frequency of infection), tetanus (evaluate Dutch guidelines for post-exposure prophylaxis), polio virus (identify new risk groups), Hib (reduced circulation of Hib), mumps, rubella, measles (circulation of MMR, antibody levels in vaccinated mothers, maternal immunity), hepatitis B (prevalence of chronic HBV infections in different ethnic groups) and HPV (prevalence type 16 and 18).
- For pertussis it is recommended to characterize the emerging P3 strain which is associated with the resurgence of pertussis, to identify genes which contribute to the fitness of this strain as well as to study efficacy of the acellular vaccine against *B. parapertussis* in a mouse model.
- Carry out modelling en cost-effectivity studies to determine the optimal age for an adolescent or adult booster of pertussis and to determine the cost-effectiveness of cocooning.
- Preparation of protocol for patient testing, notification, data collection and controlling during a measles outbreak.
- Research on correlates of protection and immunological memory in the context of measles vaccination and during a next measles outbreak.
- Development and implementation of advanced molecular typing techniques for new insights into transmission patterns of TB to assist elimination.
- Evaluate direct and indirect effects of HPV vaccination programs by mathematical models combining the effect of vaccination, reduced HPV transmission and screening programs.
- Explore possible surveillance methods on the feasibility of supplying accurate data on serious adverse events following HPV vaccination.
- Serologic evaluation of the HBV and Hib 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.

Research (not yet planned in the CIB workplan for 2008)

- Determine reasons for Hib-infection vaccine failures and functionality and avidity of the vaccine induced antibodies in children in which the vaccine failed. Furthermore it is recommended to assess the capsular genotype of Hib strains isolated in other countries to investigate shift in composition of Hib population after the introduction of vaccination.
- Include specific interventions in national plan for measles elimination in the Netherlands to be able to respond to imported cases and cases of unvaccinated health care workers. Consideration to adapt this plan to include rubella elimination.
- Estimate the burden of pneumococcal disease in inhabitants of nursing homes and the elderly in community.
- Investigate the effectiveness of a three (UK and Norway) or four doses regime (Netherlands) of Prevenar.
- Study impact of universal hepatitis A vaccination of children between one and two years of age on morbidity and mortality in the Netherlands by a dynamic model, taking the herd immunity effects into account and explore cost-effectiveness.
- Obtain more insight into vaccine acceptance of rotavirus vaccine among parents and health care workers.
- It is recommended to review of patients' records to obtain more insight into severity of varicella of hospitalized patients and to perform a capture-recapture analysis with data on hospital admissions for chickenpox to assess burden of disease.
- Investigate possible reasons for the decreasing trend in incidence of meningococcal serogroup B disease despite the lack of a vaccination programme.

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Appendix 1 Overview changes in the NIP since 2000

Table 11 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 12 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 13 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 14 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 15 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 16 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	Acellular 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	Acellular 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 17 NIP from July/August 2006 onwards

(change: in July/August 2006 a combined DTaP-IPV vaccine will be introduced at 4 years of age, for children born from July/August 2002 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	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	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.

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.

Appendix 2 Composition of vaccines used in 2007

Vaccine	Composition
Pediacel/SP MSD	
RVG 32118	Purified diphtheria toxoid > 30 IU
Diphtheria, tetanus, 5 component acellular pertussis vaccine, inactivated poliomyelitis vaccine and conjugated <i>Haemophilus influenzae</i> type b-vaccin (adsorbed)	Purified tetanus toxoid > 40 IU
0.5 ml	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
	<i>Haemophilus influenzae</i> type b polysaccharide (polyribosylribitol phosphate) 10 µg
	conjugated to tetanus toxoid (PRP-T) 20 µg
	absorbed to aluminium phosphate 1.5 mg
BMR vaccine/NVI	Mumps virus (Jeryl Lynn) > 5000 p.f.u. (plaque forming unit)
RVG 17654	Measles virus (Moraten) > 1000 p.f.u.
Mumps, measles and rubella vaccine	Rubella virus (Wistar RA 27/3) > 1000 p.f.u.
0.5 ml	Diphtheria-toxoid* > 5 IU
DT-IPV vaccine/NVI	Tetanus toxoid* > 20 IU
RVG 17641	Inactivated poliovirus type 1 > 40 DU
Diphtheria (adsorbed), tetanus (adsorbed) and inactivated poliomyelitis vaccine	Inactivated poliovirus type 2 > 4 DU
1 ml	Inactivated poliovirus type 3 > 7.5 DU
	*adsorbed to aluminium phosphate 1.5 mg Al3+
Prevenar/Wyeth	Pneumococcal polysaccharide serotype 4* 2 µg
EU/1/00/167	Pneumococcal polysaccharide serotype 6B* 4 µg
Pneumococcal saccharide conjugated vaccine (adsorbed)	Pneumococcal polysaccharide serotype 9V* 2 µg
0.5 ml	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	Neisseria meningitidis (C11-strain)
RVG 26343	Polysaccharide O-deacetylated 10µg
Conjugated meningococcal C saccharide vaccine (adsorbed)	Conjugated to tetanus toxoid 10-20 µg
0.5 ml	adsorbed to aluminium hydroxide 0.5 mg Al3+
HBVAXPRO/ SP MSD	Hepatitis B-virus surface antigen, recombinant* (HBsAg) 5µg
EU/1/01/183	Adsorbed to amorphe aluminiumhydroxyphosphatesulphate 0.25mg
Hepatitis B vaccine for children and adolescents	*yeast strain <i>Saccharomyces cerevisiae</i> (2150-2-3)
0.5 ml	

Infanrix Hexa/GSK	Adsorbed diphtheria toxoid > 30 IU
EU/1/00/152	Adsorbed tetanus toxoid > 40 IU
Difteria, tetanus, pertussis (acellular component), hepatitis B (rDNA), inactivated poliomyelitis vaccine and conjugated Haemophilus influenzae type b-vaccine (adsorbed)	Adsorbed pertussis toxoid (PT) 25 µg
0.5 ml	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	Purified diphtheria toxoid > 2 IU
RVG 27569	Purified tetanus toxoid > 20 IU
Difteria, tetanus, pertussis (acellular component) and inactivated poliomyelitis vaccine (adsorbed)	Purified pertussis toxoid (PT) 2.5 µg
0.5 ml	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	Mumps virus (Jeryl Lynn) > 5000 TCID50 (tissue culture infectious doses)
RVG 17672	Measles virus (Schwartz) > 1000 TCID50
Mumps, measles and rubella vaccine	Rubella virus (Wistar RA 27/3) > 1000 TCID50
0.5 ml	Mumps virus (RIT 4385) > 103.7 CCID50 (cell culture infectious doses)
Priorix/GSK	Measles virus (Schwartz) > 103.0 CCID50
RVG 22052	Rubella virus (Wistar RA 27/3) > 103.0 CCID50
Mumps, measles and rubella vaccine	
0.5 ml	

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

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