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The National Immunisation Programme in the Netherlands

Developments in 2006

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Rapport in het kort

Het Rijksvaccinatieprogramma in Nederland

Ontwikkelingen in 2006

In 2006 traden verschillende veranderingen op in het Rijksvaccinatieprogramma (RVP) in Nederland: kinderen die geboren worden uit moeders die chronisch geïnfecteerd zijn met hepatitis B krijgen vlak na de geboorte een hepatitis B vaccinatie; er is een ander vaccin geïntroduceerd voor difterie, kinkhoest (a-cellulair), tetanus, poliomyelitis en *Haemophilus influenzae* (DaKTP/Hib); vaccinatie tegen pneumokokken is toegevoegd op de leeftijd van 2, drie, vier en elf maanden; risicogroepen voor hepatitis B krijgen op diezelfde leeftijden een combinatievaccin voor DaKTP/Hib en hepatitis B; DTP en aK zijn gecombineerd in één vaccin op vierjarige leeftijd; en er zijn nieuwe BMR vaccins geïntroduceerd.

Op basis van informatie die in 2006 beschikbaar is gekomen wordt geadviseerd de introductie van vaccinaties voor de volgende ziekten te overwegen: hepatitis B (universele vaccinatie), rotavirus, waterpokken en humaan papillomavirus. Voor respiratoir syncytieel virus en meningokokken B zijn nog geen kandidaatvaccins beschikbaar en uitbreiding van het RVP met beschikbare vaccins voor hepatitis A, influenza en tuberculose wordt nog niet aanbevolen.

Het RVP is effectief en veilig, maar voortdurende bewaking hiervan is groot belang, omdat er regelmatig veranderingen optreden. Handhaven van de hoge vaccinatiegraad is essentieel om terugkeer van ziekten te voorkomen. Verder moet regelmatig bekeken worden of het RVP aangepast moet worden aangezien er steeds nieuwe vaccins beschikbaar komen.

Trefwoorden: Rijksvaccinatieprogramma, BMR, DKTP/Hib, hepatitis B, meningokokken C.

Abstract

The National Immunisation Programme in the Netherlands

Developments in 2006

In 2006 several changes were made in the Dutch National Immunisation Programme (NIP): Hepatitis B vaccination at birth was added for children born to mothers positive for hepatitis B surface antigen; a new vaccine for diphtheria, tetanus, pertussis (a-cellular), poliomyelitis and *Haemophilus influenzae* (DTaP-IPV/Hib) was introduced; vaccination against pneumococcal disease was added at two, three, four and eleven months; risk groups for hepatitis B receive a combined vaccine for DTaP-IPV/Hib and HBV at the same ages; DT-IPV and aP at the age of four years were combined in one vaccine; and new MMR vaccines were introduced.

As new information became available in 2006, the desirability to introduce vaccinations in the NIP for the following diseases could be (re)considered: hepatitis B (universal vaccination), rotavirus, varicella and human papillomavirus. For respiratory syncytial virus and meningococcal serogroup B disease no candidate vaccines are available yet. Extension of the programme with available vaccines for hepatitis A, influenza and tuberculosis is not (yet) recommended.

The NIP in the Netherlands is effective and safe. However, continued monitoring of the effectiveness and safety of the NIP is important as changes are made regularly. Maintaining high vaccine uptake is vital to prevent (re)emergence of diseases. Furthermore, the programme should be regularly reviewed as new vaccines become available.

Key words: National Immunisation Programme, MMR, DTP/IPV/Hib, hepatitis B, meningococcal serogroup C disease

Preface

The National Institute for Public Health and the Environment (RIVM) regularly informs the Ministry of Health, Welfare and Sports (VWS) on developments with respect to vaccine-preventable diseases that are relevant for the Netherlands.
In this report, we give an overview of the developments in 2006 for the diseases included in the current National Immunisation Programme (NIP): diphtheria, pertussis, tetanus, poliomyelitis, *Haemophilus influenzae* serotype b disease, hepatitis B (risk groups only), pneumococcal disease, mumps, measles, rubella, meningococcal serogroup C disease. Furthermore influenza and tuberculosis are discussed, as programmatic vaccination outside the NIP is in place. Finally, developments with regard to potential new target diseases are described: hepatitis A, rotavirus, varicella zoster virus infection, meningococcal serogroup B disease, respiratory syncytial virus (RSV) infection and human papillomavirus infection. A similar report on the developments in 2005 was recently published (in Dutch).[1] Also a more comprehensive report, covering developments until 2004, was published earlier.[2] In the latter report diseases were included for which at least phase III trials were running or for which it was expected that a vaccine would be available within ten years (RSV). The present report covers the same diseases with the exception of herpes simplex virus-2 since no relevant information has become available in 2005-2006.

The report is structured as follows. In chapter 1 a brief introduction is provided on the changes in the NIP during 2006, the changes in the organisational structure of the NIP, and vaccine coverage. Chapter 2 focuses on the diseases which are currently targeted in the NIP. The amount of new information that has become available in 2006 with respect to a certain disease, is reflected in the size of the section concerned. In chapter 3 programmatic vaccination is addressed. The NIP could be extended with new target diseases, which are discussed in chapter 4. Several broader issues of current interest in the field of routine vaccination in a NIP are addressed in chapter 5: considering effectiveness with any change in the NIP, vaccination of other age groups, acceptance of vaccination, discounting in economic evaluation studies and the role of notification in surveillance of vaccine preventable diseases. Finally, a summary of the recommendations on vaccination, surveillance and research provided in the separate sections is given in chapter 6.

We hope that this report will contribute to the decision making process on the composition of the NIP.

We acknowledge the Netherlands Vaccine Institute (NVI) and Helma Ruijs (RIVM) for their comments on previous versions of the report.

Contents

Abbreviations

ACIP	Advisory Committee on Immunisation Practices
AEFI	Adverse Events Following Immunization
BCG	Bacil Calmette Guerin
CDC	Centre for Disease Control and prevention
CER	Cost-Effectiveness Ratio
CI	Confidence Interval
CIb	Centrum voor Infectieziektenbestrijding (Centre for Infectious Disease Control)
CSF	Cerebrospinal Fluid
cVDPV	circulating Vaccine-Derived Polio Viruses
DALY	Disability-Adjusted Life Years
DNA	Desoxyribo Nucleic Acid
DT-IPV	Combination of Diphtheria, Tetanus and Inactivated Polio Vaccines
DTP	Combination of Diphtheria, Tetanus and Pertussis vaccines
DTP-IPV	Combination of Diphtheria, Tetanus, Pertussis and Inactivated Polio Vaccines
EU	European Union
FHA	Filamentous Haemagglutinin
GP	General Practitioner
GSK	Glaxo Smith Kline
HAV	Hepatitis A Virus
HBIg	Hepatitis B Immunoglobulin
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
Hib	*Haemophilus Influenzae* type b
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
IDU	Injecting Drug User
ICD	International Classification of Diseases
IgM	Immunoglobulin M
ILI	Influenza-Like Illness
IPV	Inactivated Polio Vaccine
IS	Intussusception
IQR	Interquartile Range
IU	International Units
LYG	Life Years Gained
MDR	Multidrug Resistant
Men B	Meningococci B
Men C	Meningococci C
ml	millilitre

MMR	Combination of Measles, Mumps and Rubella vaccines
MMRV	Combination of Measles, Mumps, Rubella en Varicella vaccines
MPL	Monophosphoryl Lipid
MS	Multiple Sclerosis
MSM	Men having Sex with Men
NIP	National Immunisation Programme
NIVEL	Netherlands Institute for Health Services Research
NRBM	Netherlands Reference laboratory for Bacterial Meningitis
NTR	National Tuberculosis Registry
NVI	Netherlands Vaccine Institute
OPV	Oral Polio Vaccine
aP	acellular Pertussis vaccine
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccine
PIENTER	Peiling Immunisatie Effect Nederland Ter Evaluatie van het Rijksvaccinatieprogramma (Assessing the immunisation effect of the Netherlands to evaluate the NIP)
wP	whole cell Pertussis vaccine
QALY	Quality Adjusted Life Years
RIVM	Rijksinstituut voor Volksgezondheid en Milieu (National Institute for Public Health and the Environment)
RSV	Respiratory Syncytial Virus
SP MSD	Sanofi Pasteur MSD
TB	Tuberculosis
TIG	Tetanus Immunoglobulin
UK	United Kingdom
USA	United States of America
VAERS	Vaccine Adverse Events Reporting System
VE	Vaccine Effectiveness
VLP	Virus Like Particle
VWS	Ministry of Health, Welfare and Sports
VZV	Varicella Zoster Virus
WHO	World Health Organisation
XDR	Extensively Drug Resistant
YLD	Years Lived with Disability
YLL	Years of Life Lost

Summary

This report aims to give an overview of the developments in 2006, regarding vaccines, epidemiology, pathogens, economic aspects, and international perspectives, that are relevant for the (future) Dutch National Immunisation Programme (NIP).

Several changes in the vaccination schedule were made in 2006: hepatitis B vaccination at birth was added for children born to mothers positive for hepatitis B surface antigen (January); Infanrix-IPV/Hib (GSK) was replaced by Pediacel (SP MSD) (January); vaccination against pneumococcal disease was added at ages two, three, four and eleven months (June); risk groups for hepatitis B receive a combined vaccine for DTaP-HBV-IPV/Hib at two, three, four and eleven months (June); DT-IPV and aP at the age of four years were combined in one vaccine (July/August); and the MMR vaccine of NVI was replaced by MMR vaccines of GSK and SP MSD (September/October). These changes highlight the importance of continued monitoring.

The frequency of reported adverse events remained stable in 2006 compared to 2005. The target diseases of the current NIP are largely under control, although the high incidence of pertussis since 1996 is sustained.

The desirability to introduce vaccinations in the NIP for the following diseases must be (re)considered: hepatitis B (universal vaccination); rotavirus (in case a significant decrease in vaccine-related costs can be expected); varicella (as soon as information on the burden of severe varicella-related disease becomes available); human papillomavirus (HPV) (considering the recent marketing licence for the first HPV-vaccine).
For respiratory syncytial virus and meningococcal serogroup B disease no candidate vaccines are available yet. Extension of the programme with available vaccines for hepatitis A, influenza and tuberculosis is not (yet) recommended.
It is recommended to investigate the possibility to extend the NIP in the future to older age groups, i.e. (pre-)adolescents and adults for pertussis, hepatitis B virus , HPV and zoster virus.

Several recommendations regarding surveillance, research and control of vaccine preventable diseases in the Netherlands are made. In general, maintaining high vaccine uptake is vital to prevent (re)emergence of diseases. Specific studies on vaccine acceptance are important to gain insight into reasons for (non)compliance with the current NIP, to predict the success of introduction of new vaccines, and for communication purposes.

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 the Netherlands, the National Immunisation Programme (NIP) has been a government-funded programme since 1957. The Ministry of Health, Welfare and Sports (VWS) decides on vaccination policy in the Netherlands. The Netherlands Vaccine Institute (NVI) is responsible for delivering all vaccines used within the NIP. The National Institute for Public Health and the Environment (RIVM), has an advisory role towards VWS.
Vaccination of a large part of the population in the Netherlands against diphtheria, tetanus and pertussis (DTP) was introduced in 1952. The NIP was implemented in 1957 offering DTP and poliomyelitis vaccination (IPV) to all children born from 1945 onwards. Nowadays also vaccination against measles, mumps, rubella, *Haemophilus influenzae* type b (Hib), meningococcal C disease (Men C), pneumococcal disease and hepatitis B (for risk groups only) are 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 to individuals aged 65 years and over, and individuals 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 July/August 2006 onwards

Age	Injection 1	Injection 1 (risk groups only)[1]	Injection 2
At birth		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 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 during 2006

Changes in the NIP since 2000 are summarised in Table 2. More extensive information regarding these changes can be found in Annex 1 and information on the composition of the vaccines used in 2006 is given in Annex 2.
In January 2006, the DTaP-IPV/Hib (Infanrix-IPV+Hib, Glaxo Smith Kline (GSK)) vaccine was replaced by a similar vaccine but containing additional *B. pertussis* proteins (Pediacel, Sanofi Pasteur MSD (SP MSD)). The exact date of implementation depended on the amount of Infanrix-IPV+Hib that was still in stock at the different child health clinics. Furthermore, since January 2006 hepatitis B vaccination at birth was added to the NIP for children born to mothers tested positive for hepatitis B surface antigen (HBsAg). In June 2006 (birth cohort from April 2006 onwards) vaccination against pneumococcal disease was added at ages two, three, four and eleven months. From that moment on, risk groups for hepatitis B received a combined vaccine for DTaP-IPV/Hib and hepatitis B to limit the number of injections to two. As a consequence one extra hepatitis B vaccination is received at three months of age. From July/August 2006 onwards DT-IPV and aP at the age of four years are combined in one vaccine. Furthermore the MMR (mumps, measles, rubella) vaccine of NVI was, due to shortages, in September/October 2006 replaced by other MMR vaccines of two different providers (GSK and SP MSD).

Table 2. Overview of changes in the NIP since 2000

Date of implementation	Change in NIP	Age (birth cohorts)
01/07/2001	Introduction of booster vaccination aP	four years (birth cohorts from 01/01/1998 onwards)
01/09/2002	Introduction of meningococcal C disease vaccination	fourteen months (birth cohorts from 01/06/2001 onwards)*
01/03/2003	Introduction of hepatitis B virus (HBV) vaccination for high risk groups only[1]	two, four and eleven months (birth cohorts from 01/01/2003 onwards)
01/03/2003	Introduction of combined vaccine DTwP-IPV/Hib	two, three, four and eleven months (birth cohorts from 01/04/2002 onwards)**
01/01/2005	Replacement of DTwP-IPV/Hib (NVI) with DTaP-IPV-Hib (Infanrix IPV+Hib (GSK))	two, three, four and eleven months (birth cohorts from 01/02/2004 onwards)**
~01/01/2006	Replacement of Infanrix IPV+Hib (GSK) by Pediacel (SP MSD)	two, three, four and eleven months (birth cohorts from ~01/02/2005 onwards)**
01/01/2006	Introduction of HBV vaccination at birth for risk groups only[2]	At birth (birth cohorts from 01/01/2006 onwards)
01/06/2006	Introduction pneumococcal disease vaccination	two, three, four and eleven months (birth cohorts from 01/04/2006 onwards)
01/06/2006	Introduction of combined vaccine DTaP-HBV-IPV/Hib (and introduction of HBV vaccination at three months) for risk groups only[1]	two, three, four and eleven months (birth cohorts from 01/04/2006 onwards)
July/August 2006	Introduction of combined DTaP -IPV vaccine	four years (birth cohorts from July/August 2002 onwards)
September/ October 2006	Replacement of MMR vaccine (NVI) by MMRvax (GSK) and Priorix (SP MSD)	fourteen months (birth cohorts July/August 2005 onwards)

1 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.

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

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

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

1.3 Changes in the organisational structure of the NIP

In July 2005 the units of the RIVM on infectious diseases (Centre for Infectious Disease Epidemiology, Diagnostic Laboratory for Infectious Diseases and Perinatal Screening, Laboratory for Vaccine Preventable Diseases, Microbiological Laboratory for Health Projection) and the National Coordination Centre for Outbreak Management (formerly based at GGD Nederland) were combined in the Centre for Infectious Disease Control (CIb) of the RIVM. The RIVM was already responsible for advising VWS about the NIP (on the basis of surveillance and research), but now VWS has also delegated the coordination of the execution of the NIP to the CIb. To fulfil this role, the CIb will change the organisational structure of the NIP on the national level.

1.4 Vaccination coverage

The national immunization coverage in the Netherlands has proven, over the years, to be excellent. In 2005 national coverage levels for all vaccines used in the Netherlands showed a further increase as compared to 2004. Immunization coverage figures exceed the 95% level and meet the standards provided by the World Health Organisation (WHO). Immunization coverage figures as at 1 January 2005 refer to age cohorts born in 1994 (nine-year-olds), 1999 (four-year-olds) and 2002 (infants). Vaccination coverage for the most vulnerable group (infants < six months of age) showed an increase of 0.2 % as compared to the previous year (97.8% and 97.4% for DTP-IPV3 and Hib3). Vaccination coverage levels for infants were reported to be higher than ever before (95.8% for DTP-IPV4 and 96% for Hib4). The same result was seen in MMR vaccination coverage levels for both infants (96.3%) and nine-year-olds (97.7%), and in DTP vaccination coverage levels for four-year-olds (95.2%). The vaccination coverage level for Men C (95.5%) can not yet be compared to previous years but exceeds the 95% level. Vaccination coverage for aP (93%) increased with 1%.

High national immunization coverage may mask variations within the country, however, regional and municipal immunization coverage figures also improved again. Almost all provinces reported over 90% immunization coverage for all vaccines used. Exceptions were Zeeland and Flevoland. Areas with low immunization coverage are – as known - concentrated in the so-called ‘Bible Belt’ where groups of orthodox reformed people live who refuse vaccination for religious reasons.

In 2005 a new management information system (PRAEVENTIS) 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 instead of cross-sectional figures.

Monitoring of vaccine coverage at national, regional and municipal level is carried out on a yearly basis. Vaccination coverage figures are published in yearly reports by the RIVM.[3,4]

2. Current National Immunisation Programme

2.1 Diphtheria

F.R. Mooi

For changes in combination vaccines including diphtheria see the section on pertussis (2.2). In 2005 no cases of cutaneous diphtheria were notified. One patient was admitted to hospital with diphtheria as the main diagnosis (international classification of diseases (ICD)-9 0328). No laboratory diagnosis for this case was available.

2.2 Pertussis

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Vaccine

Recent changes in the NIP

The following changes that occurred in the vaccination program in 2006 (see chapter 1) are relevant with regard to pertussis (component):

- In January 2006, the DTaP-IPV/Hib (Infanrix-IPV+Hib, GSK) vaccine was replaced by a similar vaccine but containing additional *B. pertussis* proteins (Pediacel, SP MSD) (Table 3). The change results in a (slightly) lower dose of filamentous hemagglutinin, pertactin and pertussis toxoid. Further, in contrast to the GSK vaccine, Pediacel contains serotype 2 and 3 fimbriae. Both vaccines have been shown to be efficacious in field trials.[5,6,7,8]
- The booster vaccination for four-year-olds consisted of two injections with, respectively, DT-IPV (NVI) and aP (acellulair pertussis vaccine, GSK). In the third trimester the two components were combined in a single injection (containing DTaP-IPV). Initially, the Triaxis Polio vaccine from SP MSD is used. This change will result in a significant lower dose of pertussis toxoid, filamentous hemagglutinin and diphtheria toxoid (Table 3). Triaxis Polio will be replaced by a vaccine with similar components produced under licence by the NVI in 2007/2008. The latter vaccine will result in an increased dose of pertussis toxoid, filamentous hemagglutinin and diphtheria toxoid compared to Triaxis Polio.
- Starting in June 2006, children belonging to the hepatitis B risk group (see hepatitis B vaccination) will be vaccinated four times with the DTaP-HBV-IPV/Hib vaccine (Infanrix hexa, GSK). The acellular pertussis component in this vaccine is comprised of filamentous hemagglutinin, pertactin and pertussis toxoid. This vaccine was chosen to limit the number of vaccinations per consult to two. It is currently the only available vaccine in Europe in which DTaP-IPV, HBV and Hib can be given in a single injection.

Consequently, these children will be vaccinated four times with HBV instead of three as was the case before.

The effect of the changes in vaccination against pertussis on antibody responses to components of DTaP-IPV-Hib vaccines are being monitored and evaluated.

Table 3. DTaP-Hib containing vaccines used in the past and current Dutch NIP

Vaccine	Producer	Vol (ml)	Ptx (ug)	FHA (ug)	Prn (ug)	Fim2, Fim3 (ug)	D-toxoid	T-toxoid	polio (D-antigen units)			Hib	Hib-tet	HBV (ug)
									type 1	type 2	type 3			
Acellulair pertussis vaccine (aP)	GSK	0.5	25	25	8	-	-	-	-	-	-	-	-	-
Infanrix-IPV+Hib	GSK	0.5	25	25	8	-	≥ 30 IU	≥ 40 IU	40	8	32	-	20-40	20-40
Pediacel	SP MSD	0.5	20	20	3	5	≥ 30 IU (15 Lf)	≥ 40 IU (5 Lf)	40	8	32	-	20	20
Infanrix hexa	GSK	0.5	25	25	8	-	≥ 30 IU	≥ 40 IU	40	8	32	10	20-40	20-40
Triaxis Polio	SP MSD	0.5	2.5	5	3	5	≥ 2 IU (2 Lf)	≥ 20 IU (5 Lf)	40	8	32	-	-	-
DT-IPV	NVI	1	-	-	-	-	≥ 5 IU	≥ 20 IU	40	4	7.5	-	-	-

Vaccine effectiveness

For a period of at least six months, four-year-olds will be boosted with a vaccine (Triaxis Polio) containing substantial lower doses of pertussis toxoid, filamentous hemagglutinin and diphtheria toxoid, compared to the previous booster vaccination. It is not clear whether this will result in a lower (long-term) efficacy.

Adverse events

The number of reported adverse events following immunization (AEFI) with DTaP-IPV/Hib in the first five months of 2006 (259) was stable, compared to 2005 (264). In 2005 the enhanced passive surveillance system received significantly less AEFI, mainly due to a decrease in DTaP-IPV/Hib reports. In 2005, we received 1036 reports of AEFI, of which 593 concerned DTaP-IPV/Hib, compared with 1730 in 2004 and 1019 in 2003.[9] No new categories of adverse events were revealed. The number of reported local reactions at four years of age increased after the introduction of aP in 2001, most prominently in 2003 and 2005.

In 2006 we conducted a questionnaire study on adverse events after booster vaccinations at four years of age. In total 1179 questionnaires were distributed to parents whose children were vaccinated and 812 (68.9%) were returned. After the booster dose 407 children (50.1%) were free from AEFI. Local reactions (particularly pain, reduced use of arm, redness and swelling) were mentioned in 281 (34.6%) of the children. It was remarkable that pain, reduced use of arm, redness or swelling was considerably more frequently mentioned for the left (DT-IPV) than the right (aP) arm. Mild local reactions were most common. Severe swelling and redness (>5 cm)

were mentioned in only 3 (1.1%) of the children. None of the children experienced extensive limb swelling (ELS).

Epidemiology of infection and disease

Based on various surveillance sources epidemic peaks occurred every two to three years (in 1996, 1999, 2001 and 2004). In Figure 1 notifications and hospitalizations for pertussis are displayed. The incidence in 1996-2005 was higher than in 1989-1995.

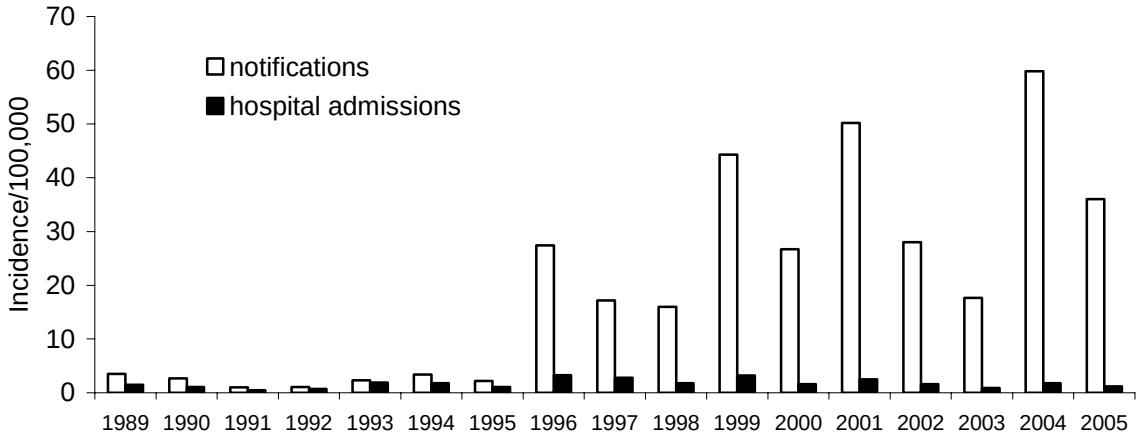

Figure 1. Incidence per 100,000 of notifications and hospitalizations for pertussis by year, 1989-2005

The number of deaths in the two periods also increased from 2 to 9, respectively. All deaths, except one in the five-nine year age group in 1993, were in infants less than three months of age. As in previous years, the yearly peak incidence for hospitalisations due to pertussis was observed among infants < three months of age.

The increase in pertussis notifications in recent years was predominantly caused by an increase in the number of cases among adolescents and adults.

Before 2001, the age-specific incidence according to notifications was highest for the five-nine year olds. Due to the introduction of the acellular booster vaccination (autumn 2001) the incidence in the targeted age-groups has strongly decreased (Figure 2).

There is evidence that the introduction of a booster vaccination for four-year-olds has also reduced the number of notified cases and hospitalizations among infants less than four months of age.

In April 2006 a study on the transmission of pertussis to infants (BINKI-study) was started. The study aims to assess the main sources of infection for pertussis in infants < six months of age. As secondary aims, cellular immunity and genetic predisposition for pertussis will be investigated. Final goal of the study is to come to the best vaccination strategy to prevent severe pertussis in infants that are too young to be protected directly by the current vaccination schedule. Until mid-October 49 infants and their household members were included in the study. Preliminary interim results show that for about half of the infants the most probable source of infection can be found, based on clinical symptoms and laboratory confirmation. Both mothers and siblings appear

frequently the primary case within the household. A small percentage of family members have laboratory confirmed pertussis, but do not report symptoms. Remarkably, in almost half of the families one or both parents are immigrants.

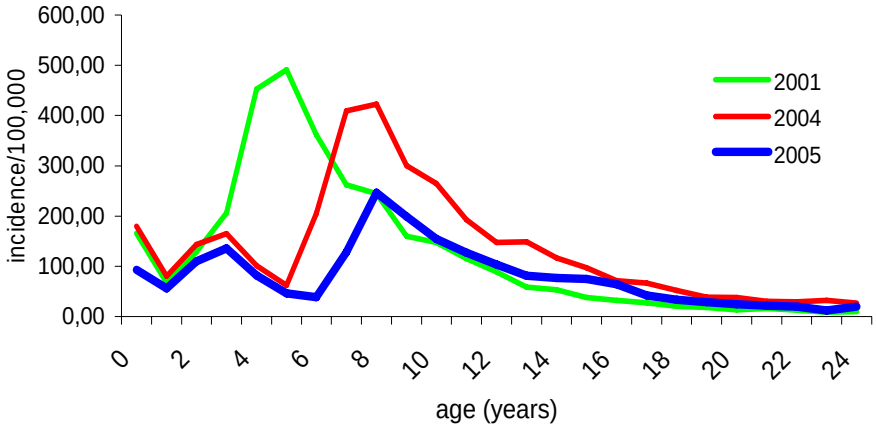

Figure 2. Age-specific incidence per 100,000 of notified cases in 2001 (before introduction of booster for four-year-olds) and 2004, 2005 (after introduction of booster vaccination)

Pathogen

Data from the Netherlands and the United Kingdom (UK) suggest that the pertussis case-fatality rate is increasing. In the Netherlands this increase is associated with the emergence of strains characterized by a mutation in the pertussis toxin promoter (P3 strains). Experiments in mice have shown that the P3 mutation increases virulence. However, in both countries the number of hospitalisations is decreasing (source: Hospital Episode Statistics UK and Prismant Netherlands). In the Netherlands this may be due to the introduction of the pre-school booster.

Recommendations for vaccination, surveillance and research

In addition to the peak of hospital admissions among young infants, the increase in mortality further underlines the importance of introducing vaccination strategies which, directly or indirectly, protect 0-6 month old infants which 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. In a report on the economic evaluation of prevention, based on international literature, more information with regard to cost-effectiveness of adolescents pertussis vaccination is given.[10] The most (cost-)effective strategy depends on the aim of vaccination; i.e. reducing morbidity in young infants or also targeting older age groups.

Direct protection of this age category may be achieved by maternal immunization. To obtain insight in the most effective vaccination strategies further development of dynamic pertussis models, based on the results obtained in the transmission study is desirable. Further, acceptance and ethical aspects of the various vaccination strategies should be investigated in particular with respect to maternal immunization.

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 of the whole population. Second, culture is being replaced by polymerase chain reaction (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*.[11] It is not clear if the recently introduced acellular pertussis vaccine (aP) also confers some protection against *B. parapertussis.* We therefore recommend that the efficacy of the acellular vaccine against *B. parapertussis* be studied in a mouse model.

Finally we recommend to closely monitor the many 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.

2.3 Tetanus

P.E. Vermeer-de Bondt, S.J.M. Hahné

Vaccine

Recent changes in the NIP

There have been no recent changes in the routine schedule of tetanus vaccination in the NIP. The vaccines used in the NIP have changed however (see Table 2). Only limited data are available on the long-term effects of these changes on tetanus titres. Since in tetanus the protection is solely dependent on (the persistence of) antibody levels this may be a concern.

For post-exposure treatment this information/reassurance is important as the decision whether a tetanus booster is necessary in tetanus prone wounds relies on the duration of persistence of adequate antibody titres.

Adverse events

No new studies/publications have added information that changed the safety profile of tetanus containing vaccines. One study looked into the risk of MS following tetanus vaccination.[12] This study showed a decreased risk, but it should be noted that several confounders could have played a role.

Epidemiology of infection and disease

Ever since tetanus was removed from the list of notifiable diseases (in 1999) keeping track of its incidence has been difficult. Tetanus is a diagnosis by exclusion, making monitoring even more complex. Serological data should be used cautiously in dismissing the diagnosis since the precise cut off level of protection is unknown. Coding of admission and death diagnosis in Prismant has been known to contain misclassification, e.g. tetany in stead of tetanus. These reports can not be subjected to the necessary verification. The data lack also information on age and vaccination status. Monitoring tetanus cases therefore relies solely on requests for antibody titres and requests for consultation and advice at the RIVM. In 2005 no cases were known to the RIVM and in Prismant there was a total of 7 cases. This is in line with the 0-7 cases in former years.

International perspectives

The UK guidelines (http://www.dh.gov.uk/assetRoot/04/13/79/30/04137930.pdf) are more restrictive in the use of tetanus boosters for post-exposure prophylaxis than the current Dutch guidelines.[13] In the UK, for persons who have had five previous tetanus vaccinations, boosters are no longer recommended for post-exposure prophylaxis. In tetanus prone wounds only TIG is given. The rationale behind this is that the booster response may be too late to prevent tetanus.

Recommendations for vaccination, surveillance and research

We recommend to evaluate the Dutch guideline for tetanus prophylaxis using national seroprevalence data ('PIENTER 2'), and incidence data on tetanus. To increase the reliability of the latter, we recommend making tetanus notifiable. We also recommend to evaluate the effectiveness of the current Dutch post-exposure policy. Making tetanus notifiable would allow this evaluation to be performed, provided information on vaccination status and time between injury and post-exposure prophylaxis is recorded.

2.4 Poliomyelitis

T.G. Kimman, H.G.A.M. van de Avoort

Vaccine

There are no new developments regarding the inactivated polio vaccine (IPV) currently used in the Dutch NIP. Internationally two developments are relevant, that is, first, an initiative, led by the WHO, to develop an IPV based on avirulent Sabin strains. If such a vaccine proves to be effective, its production would require less safety precautions. It could thus be produced cheaper

and be interesting for developing countries to produce in the end stages of the eradication campaign. Second, monovalent live oral polio vaccines (OPV) serotypes 1 and 3 have been officially registered for use. These vaccines give a quicker induction of protective immunity than classical trivalent OPV, and these vaccines would thus lead to quicker interruption of wild-type poliovirus transmission.
The major concern both with classical trivalent and with the new monovalent OPVs remains the emergence of virulent circulating Vaccine-Derived Polioviruses (cVPDVs).[14] Worldwide the number of cVDPVs isolates increases. It is currently investigated whether the use of monovalent OPV would even pose a greater risk in this respect than classical trivalent OPV.
Initiatives have been taken to renew the Dutch contingency plan in case of a polio outbreak. Developments that urge for a new plan are the availability and choice of OPV during an outbreak, and the concerns on the level of immunity in the elderly.[15]

Epidemiology of infection and disease
Internationally the polio situation remains a point of concern. In 2005 a large epidemic spread from Nigeria over Africa to Yemen, Saudi-Arabia and Indonesia. An important cause of this epidemic is the low routine vaccination coverage in many countries.[14]
According to the Global Polio Eradication Initiative, four countries (Nigeria, India, Pakistan and Afghanistan) are still polio-endemic. Egypt, which had been considered polio-endemic, has remained free of poliovirus transmission for over 22 months.
The following countries, however, have recently reported importations of polio in 2006, after previously being polio-free:

- Kenya (polio-free for over six years)
- Bangladesh (polio-free for over five years)
- The Democratic Republic of the Congo (polio-free for almost six years)
- Namibia (polio-free for almost ten years)

Other countries that have reported imported polio cases or cases related to an importation in 2006 are Angola, Ethiopia, Indonesia, Nepal, Niger, Somalia, and Yemen. Cameroon, Eritrea, Mali, and Sudan reported imported polio cases in 2005 but have not reported additional cases for over twelve months.
Outbreaks of poliovirus continue to be a risk until poliovirus is eliminated worldwide, and the risk for infection is still present for susceptible people. Therefore, the Netherlands with its relatively large cohort of non-vaccinated susceptible individuals remain at risk.

Recommendations for vaccination, surveillance and research
It is of importance to increase vaccination coverage not only in the Netherlands, but also in developing countries. As experiences with measles (1999-2000) and rubella (2004-2005) have shown, the non-vaccinating community in our country remains at risk for importation and further spread of viruses for which vaccination coverage in their community is low. Worldwide, most outbreaks of polio (posing a risk for importation of poliovirus into the Netherlands) are related to low routine vaccination coverage.

In case of a future outbreak in the Netherlands both non-vaccinated individuals and the elderly from the birth cohort of 1925-1945 are at risk. This birth cohort may suffer from waning immunity as demonstrated during a previous seroprevalence study in the general population and among orthodox reformed (PIENTER-project 1995-1996). Poliovirus-specific immunity in elderly should be studied in the second PIENTER-project (2006-2007) to examine whether the trend of waning immunity has continued or not. Furthermore, we recommend to update the national contingency plan in case of a polio outbreak. To examine the risk on the emergence of cVDPVs we recommend to analyse whether enteroviruses circulating in the Netherlands can recombine with polioviruses and give rise to virulent strains.

2.5 Haemophilus influenzae serotype b (Hib) disease

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

Epidemiology of infection and disease

Since the introduction of vaccination in 1993, the number of patients with *H. influenzae* type b (Hib)-disease has decreased. Nevertheless, since 2002 there has been a slight increase in the total incidence. Although most of this increase occurred among adults, also the number of vaccine failures increased since 2002. Figure 3 shows the annual number of patients with an infection due to *H. influenzae* according to type. In 2005 30 children born after 1993 have been reported with Hib-disease. Nineteen had been vaccinated, 10 had not been vaccinated and one child had been vaccinated only once. Consequently, the number of vaccine-failures in 2005 (19) is higher than in 2004, 2003 en 2002 (12, 10 and 15, respectively). However, in 2006 the number has decreased again, until December 2006 13 children born after 1993 have been reported with Hib-disease, of whom 8 were vaccinated.

In 2001-2004 the number of adult patients with Hib disease increased from 9 in 2001 to 32 in 2004. However, in 2005 only 12 patients born before 1993 were reported with Hib-disease. In 2006 the number of patients born before 1993 (12 until October) is expected to remain at a similar level as in 2005.

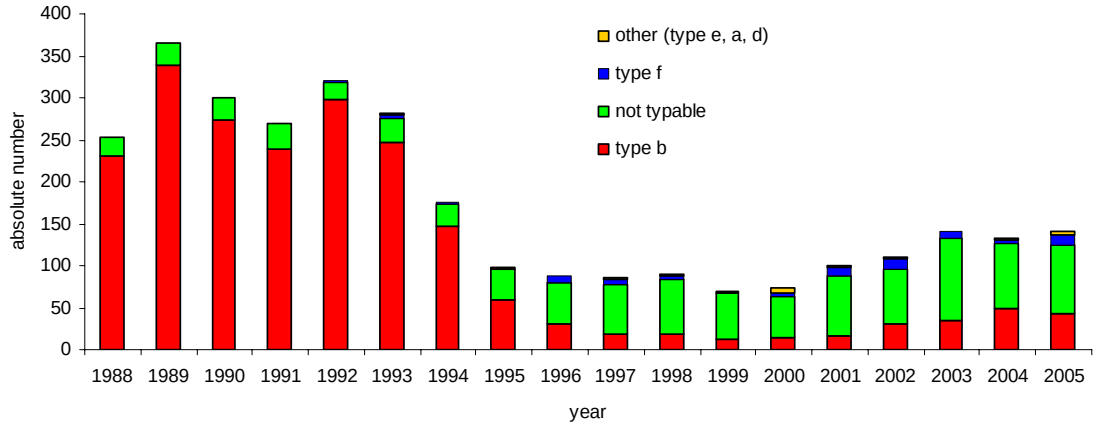

Figure 3. Absolute number of H. influenzae isolates by type, 1988-2005

Pathogen

Preliminary data of the RIVM show that two types of gene clusters encoding the polysaccharide capsule exist. The Hib vaccine that is used in the Netherlands is produced using a strain with the capsular genotype designated as cap-II. In the Netherlands, strains with cap-II made up approximately 5% of all Hib strains isolated from patients with invasive Hib disease. After the introduction of the Hib vaccine in the national vaccination programme this cap-II type was not isolated anymore. This may suggest a more effective protective immunity against cap-II strains.

International perspectives

Starting this year, both the UK[16] and Ireland[17] will introduce a booster dose of Hib vaccine at twelve months into their NIP. In the UK Hib vaccine was introduced in 1992 and is currently given to children at two, three and four months of age. Since 1999, there has been a relatively small but gradual increase in the number of cases in older children being reported. In 2003, a Hib booster campaign was carried out in which a single dose of Hib vaccine was given to all children aged six months to four years to boost their immunity. This reversed the increase in infections that had started to occur. Similar to the strategy used in the Netherlands, a booster dose of Hib vaccine is introduced to overcome waning vaccine induced immunity and to extend protection against Hib disease.

Recommendations for vaccination, surveillance and research

Further research is required to determine the role of the differences in the capsular gene cluster on vaccine effectiveness (VE). This year the possibility of including Hi(b) from 2007 onwards as a mandatory notifiable disease will be discussed.

2.6 Mumps

S.J.M. Hahné, R.S. van Binnendijk

Vaccine

The MMR vaccine in the NIP traditionally is a vaccine produced by the NVI. However, in July 2006, due to manufacturing problems, the NVI decided to purchase MMR vaccine from other companies for use in the NIP. NVI expects that its own MMR vaccine will be available again at the end of 2007.

The vaccines purchased are MMR Vax (registered in the Netherlands as MMR-II) produced by SP MSD, and Priorix, produced by GSK. MMR Vax will be used in one province only (‘South Holland’); in the rest of the country Priorix will be used.[18] There are differences in virus strains between the NVI, GSK and SP MSD vaccines. In Priorix, a different mumps strain (RIT 4385 strain) from the one in the NVI-MMR vaccine is used (Jeryl Lynn), whilst in both Priorix and MMR-II the measles strain (Schwarz) is different from the one used by NVI (Moraten). Moreover, the dosage of the respective vaccines are expressed in different units (p.f.u., TCID

and CCID). The differences in strains and dosages used are not expected to result in variation of effectiveness.
Regarding the VE of the mumps component of the MMR vaccine, new information has become available from the mumps outbreak in the UK in 1998-1999. The adjusted VE of having had any MMR vaccination was estimated to be 69% (95% CI 41-84%). Two doses of vaccine were more effective (88% (95% CI 62–96%)) than a single dose (64% (95% CI 40–78%)).[19] Although during outbreaks VE is usually underestimated this low estimate is a concern. Further field studies of the VE of mumps vaccination are recommended.

Epidemiology of infection and disease

Incidence

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. At the RIVM, 9 cases of mumps in vaccinated adolescents were diagnosed in 2005 and 2 cases in 2006 (up to October). However these latter cases were children one year of age who had shortly before received MMR vaccine, and were therefore discarded.
Two of the 9 cases of mumps, were in adolescents with partotitis and orchitis, and were described by Brummelen et al.[20] Both of these had been incompletely vaccinated in the past (one dose at age fourteen months). From both cases, mumps virus was detected by PCR, and proved to be genotype G (see below).
Through laboratory surveillance, 13 cases were reported in 2005 (Source: virological week data). There were 6 hospital admissions recorded for mumps in 2005, a similar number compared to previous years.

Diagnosis

Recent comparative studies by the RIVM suggested that the sensitivity of different serological assays for mumps IgM vary widely. This has recently also been reported in the literature, [21,22] and requires further study including an inventory of assays used by Dutch virological laboratories.

Pathogen

Five out of 8 cases of whom samples were investigated at the RIVM in 2005 revealed that these individuals had been infected with a mumps virus of the same genotype (G) as the one which had been responsible for the mumps outbreak in The Hague in 2004. It is unclear whether this reflected endemic transmission of this particular genotype in the Netherlands.

International perspectives

Nationwide outbreaks of mumps have occurred since 2004 in the United States of America (USA) and the UK, also caused by the G-genotype. The UK mumps outbreak started in 2004. Those most affected were young adults, who did not receive mumps as part of their childhood vaccinations as they were born before it was introduced.[23]

The USA outbreak started in December 2005. Although the age group most affected had been young adults aged 18-24 years, many of whom were college students, the outbreak had spread to all age groups.[24] Multiple factors might have contributed to the US outbreak of mumps. A review by the weekly early warning meeting organised at the RIVM ('Signaleringsoverleg') concluded that none of these factors were sufficiently present in the Netherlands to allow a similar large outbreak to occur. A feature documented during the US outbreak, is the delayed immunoglobulin M (IgM) response in vaccinated persons with mumps. It was recently highlighted that absence of IgM in persons with clinical illness compatible with mumps, should not be used to rule out the possibility of mumps.[25] In response to the mumps outbreak in the US, recommendations of the Advisory Committee on Immunization Practices (ACIP) were updated.

Recommendations for vaccination, surveillance and research

We recommend to make mumps a notifiable disease, since this would help to obtain more insight in the epidemiology of mumps in the Netherlands. The review of the list of notifiable diseases for the Netherlands is ongoing. In general, notification of NIP diseases can contribute to data needed to assess the effectiveness of the NIP.

Field studies to assess the effectiveness of the mumps component of the MMR vaccine are recommended. Particularly the relevance to vaccine effectiveness of the large sequence difference between the live vaccine strain used in the Netherlands (Jeryl Lynn, genotype A) and the wild-type strains currently circulating (genotype G) needs exploration. Enhanced surveillance of mumps, including appropriate laboratory confirmation is recommended. To be able to advise on this, further study of the sensitivity of different serological assays is recommended.

2.7 Measles

S.J.M. Hahné, R.S. van Binnendijk

Vaccine

Recent changes in the NIP

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

Availability of new vaccines and other developments

Measles vaccination via the aerosol route has been proven to be effective under field conditions.[26] In addition, dry powder measles vaccines are also being studied.[27] For the NIP, aerosolised single measles vaccines are not a priority. Aerosolised MMR vaccines, however, may have advantages for use in the NIP compared to the currently used product. At least one study into an aerosol MMR vaccine has been carried out.[28] So far, however, an aerosolised MMR vaccine has not been licensed in Europe.

Epidemiology of infection and disease

Notifications of measles

In 2005, three cases of measles in Dutch residents were notified. Two of these were siblings who most likely acquired the infection in France (see previous NIP report)[1]. The third case probably acquired the infection at an airport in New York.[29]

In 2006 (up to October), one case of measles has been reported, in a man who probably acquired the infection in Hungary.

The pattern of having imported cases only, without secondary transmission, suggests 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 expected, and an action plan for outbreak investigation and control is required.

Rash illness surveillance

In October 2006, the evaluation of the rash illness surveillance pilot, carried out by the RIVM, municipal health authorities and the University Medical Centre Utrecht between 2003 en 2005, was completed. Participants were recruited by municipal health authorities and included those presenting in a cluster (≥ 2) of patients with a rash illness or individual patients when there was a suspicion of measles or rubella. A total of 351 patients with a rash were included, of whom dried blood spots, saliva, urine and throat swabs were microbiologically tested. Due to the rubella outbreak during the study, many cases of rubella were identified. The positive predictive value of a clinical diagnosis of measles or rubella was very low. For rubella, the combination of an IgM test on dried blood and a PCR on oral fluid, had an optimal sensitivity. These samples are also adequate for sensitive measles surveillance and B19 virus diagnosis. During outbreaks, systematic laboratory testing of cases of rash illness is an important tool for outbreak investigation. In inter-epidemic periods, rash illness surveillance may contribute to certification of elimination and early warning. The sensitivity required for each of these aims, as well as the optimal organisation of this surveillance remain to be determined for the Netherlands.

Pathogen

In 2005, the two siblings were infected with a measles strain belonging to genotype D5, whilst the third case had a measles infection with one of the B3-cluster.[24] The genotype of the single case in 2006 (so far) could not be determined, as appropriate specimens were not available.

International perspectives

In 2005 and 2006, several large measles outbreaks have occurred in Europe.[30] Outbreak investigations identified causes including low vaccine coverage in sub-groups of the population,[31,32] low vaccine coverage in the routine programme,[33] high susceptibility levels in older cohorts who are insufficiently vaccinated,[34] and susceptibility in infants too young to have been vaccinated.[35]

Recommendations for vaccination, surveillance and research

Surveillance

It needs to be explored which sensitivity is needed in rash-illness surveillance in the Netherlands, and how this is organised the best way, by using results from the rash-illness surveillance pilot.

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 expected in the coming years.

Control during such an outbreak should focus on protecting the vaccinated population as well as trying to increase vaccine uptake in those having refused vaccination in the past. The former includes advancing the age of the second MMR vaccination[36] and vaccination of health care workers. The latter requires further research into knowledge, attitudes and practice of the different groups opposing vaccination.

A next measles outbreak would offer opportunities to evaluate vaccine effectiveness in the field, risk factors for vaccine failure, risk factors for non-vaccination, effects of waning immunity and correlates of protection. A study into the latter, by the RIVM and the Erasmus MC is ongoing. Especially the impact of waning immunity on susceptibility is an important question. Studies in mixed populations (vaccinated/non-vaccinated, particularly including older, vaccinated individuals) during an outbreak may lead to important observations.

Research

The availability of new national seroprevalence data following the current PIENTER 2 study will allow study of seroprevalence among infants. This may inform a change of first MMR vaccination to an earlier age.

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 section on mumps (2.6).

Epidemiology of infection and disease

During the rubella outbreak in the Netherlands in 2004-2005, 33 pregnant women were known to be infected, leading to 15 confirmed congenital rubella infections (CRI). Of these, 10 are known to have congenital malformations.[37] Further follow-up of the infants of mothers with rubella in pregnancy is ongoing. Of infected mothers, 32 belonged to the orthodox reformed community, whilst one was a Moroccan woman.

For information on the rash illness surveillance see the section on measles (2.7).

Pathogen

During the outbreak in 2004-2005, the strain responsible for the outbreak was a genotype 1g.

Recommendations for vaccination, surveillance and research

Surveillance

See the section 'recommendations' of section 2.7 (measles).

Antenatal screening

Policies and implementation for antenatal screening differ across the Netherlands, and opinions vary regarding its usefulness.[38,39] A study aiming to lead to evidence-based advice on antenatal screening for rubella is currently ongoing at the RIVM.[40]

2.9 Meningococcal serogroup C disease

L.M. Schouls, S.C de Greeff

Epidemiology of infection and disease

The incidence of meningococcal C disease has decreased sharply in all age-groups since the introduction of the conjugated meningococcal C vaccine. The most pronounced decrease was observed in the vaccinated age-groups (Figure 4 and Table 4). Probably due to the loss of this main reservoir of meningococcal disease the incidence also decreased in other age-groups (herd immunity). Until October only three patients with meningococcal C disease have been reported in 2006 (one in the group 25-44 years, and two in the group 45-99 years). Until now no cases in previously vaccinated persons have been reported.

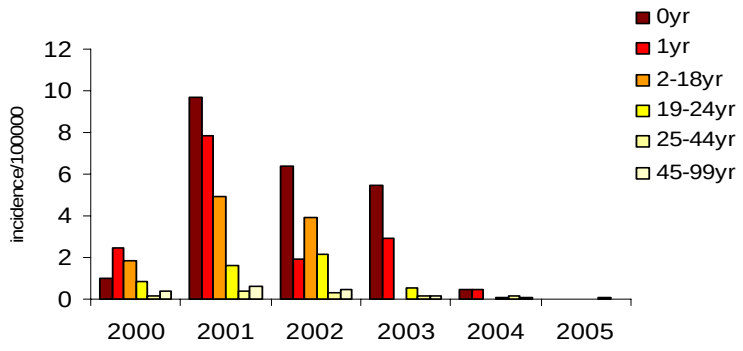

Figure 4. Age-specific incidence of meningococcal C disease by year, 2000-2005

Table 4. Absolute number of patients with meningococcal C disease

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

International perspectives

Also in the UK and Ireland – the first countries that introduced mass vaccination with the conjugate meningococcal C vaccine – the incidence of serogroup C disease strongly decreased after vaccination. The UK reports a decline of 93% [41] and Ireland of 96%. [42]

Since the end of November 1999, Men C vaccine has been included in the routine UK primary schedule for all infants at two, three and four months of age. Since there is evidence that protection offered by Men C vaccine when given in infancy wanes after twelve months,[43] the vaccination schedule in the UK will be changed this year. Under the new schedule two doses of Men C vaccine will be given with primary immunizations in the first year of life at three and four months followed with a booster dose at twelve months. This booster will be given as part of a combined Hib/Men C vaccine.

In July 2006, vaccination against meningococcal C and pneumococcal disease is also added to the routine childhood immunisation programme in Germany. To protect against meningococcal disease a single dose of the meningococcal C vaccine as early as possible in the second year of life. Because meningococcal disease morbidity in Germany is lower than that in many other European countries and because access to young people through the German medical care system is inconsistent, there will be no public health driven ‘catch-up’ campaign for older children. [44]

Recommendations for vaccination, surveillance and research

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, F. Abbink, J.M. Kemmeren, M.J.J. Mangen, J.E. van Steenbergen, J.L.E. Geraedts en G.A. de Wit

Vaccine

Recent changes in the NIP

From January 2006 onwards, infants born to HBsAg-positive mothers are given a dose of hepatitis B virus (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 is summarised in the recommendation from the Health Council.[45]

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 HBsAg-positive 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 eleven months, which means that one extra dose of HBV vaccine is introduced into the schedule. For infants born to HBsAg-positive mothers this now adds up to 5 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.[46]

Vaccination programme for high risk groups

The Netherlands is a low endemic country for HBV. Over the past decade, the mean incidence of notifications of acute HBV infection was between 1.4 and 2.0 per 100,000 inhabitants.[47] This low incidence is the main reason that the Netherlands, as the UK, Ireland and the Scandinavian countries, adopted a policy of vaccination targeted towards high-risk groups, rather than a policy of universal vaccination.[48] Since 1 November 2002, a four year campaign to vaccinate high risk groups including outreach activities has been organised in the Netherlands. This campaign was 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. In 2007 and 2008, the campaign will be continued. After this, high-risk group vaccination will be coordinated by RIVM-CIb.

In addition to this specific campaign, individuals working in medical professions, infants with at least one immigrant parent (HBV medium and highly endemic regions), children of HBsAg-positive mothers, and children with Down syndrome are also targeted to receive HBV vaccination.

Vaccine efficacy and effectiveness

Efficacy and immunogenicity

It is well known that a low percentage of vaccinated children does not respond (non-responders) or respond only marginally (low-responders) to HBV-vaccination. By definition of the WHO it is required that a HBV-vaccine induces a protective level of anti-HBs-antibodies (≥ 10 IU/l) in at least 95% of the vaccinated population.[49] The reasons for the relative high frequency 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.

The serologic response to the HBsAg in a multi-component combination vaccine might be reduced in comparison to a mono-valent HBV vaccine. A lower HBV-seroconversion rate was the reason for retraction of the Hexavax® (a HBV-containing hexa-valent vaccine of SP MSD) from the European market in 2005. Also concurrent vaccination (i.e two vaccine injections at different places during the same visit) might reduce the serologic response to certain vaccine-antigens. The results of two small-scale clinical trials that are highly comparable with our current HBV NIP-vaccination schedule - a 4-dosis schedule of Infanrix hexa concurrently given with Prevenar - have been reported.[50,51]. Concurrent Infanrix-hexa/Prevenar vaccination resulted in both cases in reduced HBV-antibody titers and seroconversion in comparison with Infanrix hexa only vaccination. The reported HBV-seroconversion rates after concurrent vaccination are, however, clearly above the WHO-limit of 95% responders (i.e. 97%,[50] and 99%[51]) at 1-3 month after the booster vaccination. However, in one study the 95% CI of the seroconversion rate was below the WHO-limit.[50] The reported 95% CI in the other study was above the WHO-limit, but due to aberrant statistical analysis this should be interpreted with caution.[51] Serologic evaluation of the HBV-vaccination response in a group of children at one year of age, who have been vaccinated according to the concurrent schedule with Infanrix hexa/Prevenar vaccination, is recommended.

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 the study 'Serological evaluation of hepatitis B vaccination in neonates of HbsAg-positive mothers' is carried out by RIVM and the Regional Vaccination Administration Centres. 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 at two, four and eleven months of age) are included in the evaluation. Preliminary results show that in the first year of this study 62% of eligible children has been reached. The small number of parents refusing participation in the study (< 3%) shows that the response will certainly increase. Not all children have been reached because older children do not visit the Child Health Clinic very frequently. Until September 2006 a total of 1011 children participated in the study. Over 90% of the children are fully protected (titer >= 10 IU/l) against hepatitis B. The percentage of children not fully protected (titer < 10 IU/l) and in need of an extra series of vaccinations is 8.7%. Although this percentage is higher than expected based on previous studies it can be explained by the

prolonged time-interval between the last vaccination and serological evaluation in older children. Eight children (1%) were found HBsAg-positive. Final results concerning the two, four, eleven vaccination schedule of hepatitis B will be available in 2007.

Vaccine coverage

In neonates born to HBsAg-positive mothers

In 2006 an evaluation of the hepatitis B antenatal screening and neonatal immunization program in the Netherlands was carried out by TNO.[52] Aim of the study was to find out how many neonates of HBsAg-positive mothers were immunized against hepatitis B and whether the vaccinations were given at the proper ages. All neonates born to HBsAg-positive mothers in 2003 were included in the evaluation. Information on immunizations - concerning both HBIg and HBV vaccine – were provided by the Regional Vaccination Administration Centres (EAs). Main results of the evaluation concerning the extent of the program were that only 87% of the expected number of children born to HBsAg-positive mothers were known at the administration centres. The expected number of children is based on the screening of all pregnant women in the Netherlands in week 14 of gestation. Of these 624 neonates known at the administration centres, 96% received both HBIg and a series of three HBV vaccinations. Although only 4% of these children was not fully immunized, a major part of these children (29%) did not receive one or more vaccinations at the proper age (HBIg at birth and HBV vaccine at ages two, four and eleven months). Unfortunately 33-39% of all known children born to HBsAg-positive mothers in 2003 was (temporarily) at risk for hepatitis B infection due to incomplete or untimely vaccinations.

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

Definitive data on vaccine coverage in this group are not yet available.

In behavioural high risk groups

In the period November 2002 till the end of 2005, 45,715 first vaccinations were registered, and 81% and 62% of these received a second and third vaccination, respectively. Eleven percent of the participants had serologic evidence of a past HBV infection and 0.8% was infected chronically. At the end of 2005, 52%-55% of the people eligible for the HBV vaccination under the behavioural risk programme was estimated to be still susceptible for HBV (Source: GGD Nederland).

Adverse events

The possibility that HBV vaccine may cause or exacerbate multiple sclerosis (MS) is under debate. Overall it seems that there is not enough evidence to establish or refute the existence of an increased risk of MS associated with HBV vaccine. Currently a systematic review on this topic is ongoing.

Epidemiology of infection and disease

Incidence of acute HBV infection

In 2005, 299 cases of acute hepatitis B were notified in the Netherlands (2004: 293 cases, 2002: 219 cases), of which 231 in men and 68 in women. The incidence rate for acute HBV in 2005 was 1.8/100,000. It was higher in men (2.9/100,000) than in women (0.8/100,000). Cases of HBV are 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). In 2005, the mean age at diagnosis for men was 38 (range: 9-67) and for women it was 31 years (range: 12- 60).

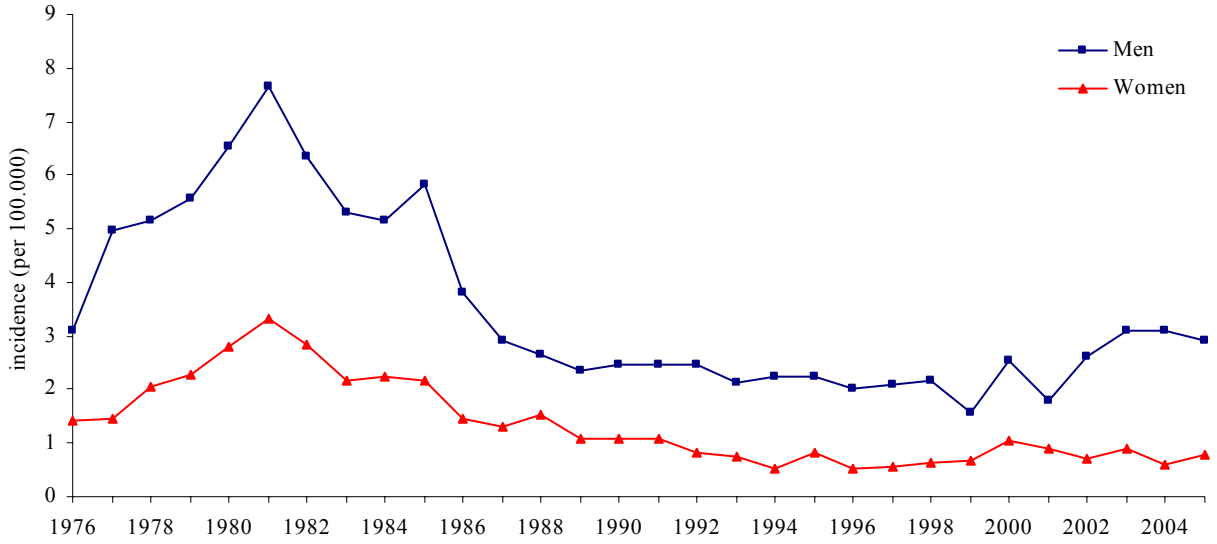

Figure 5. Incidence rate per 100,000 population of notified cases of acute HBV infection, the Netherlands, 1976-2005

Of the acute HBV cases 75% (n=225) was born in the Netherlands, 22% (n=67) was born abroad and in 2% the country of birth was unknown. Of the cases born abroad, 24% originated from HBV high endemic regions (HBsAg prevalence ≥ 8%), 67% from intermediate endemic regions (HBsAg 2-7%) and 9% from low endemic regions (HBsAg ≤ 1%). The incidence among persons born abroad was 3.9/100,000 (born in low endemicity country: 1.6/100.000; medium endemicity country: 4.3/100,000 and high endemicity country: 4.2/100,000)

Seventy-nine percent of all acute HBV cases reported to be infected in the Netherlands, 15% reported to have been infected abroad and in 6% of the cases the country of infection was unknown. Sexual contact is the most important transmission route (64%) of HBV in the Netherlands. In 2005, 53% of these cases was in MSM (2004: 57%) and 45% of the infections was heterosexually acquired (2004: 38%).

In 2005, 1,443 cases diagnosed with chronic hepatitis B were notified. The proportion of men increased from 46% in 2002 to 56% in 2005. The rate of chronic infections per 100,000 population was 8.8 in 2005 and has decreased slightly since 2002. In men, there was an increase, from 8.5 in 2002 to 10.1 in 2005. In women, the rates decreased from 9.7 in 2002 to 7.6 in 2005.

In 2005, the mean age at diagnosis for men was 38 (range: 1-86) and for women it was 34 years (range: 2-80).
In 2005, 76% of chronic HBV carriers was born abroad. Ninety-nine percent of these patients was born in a HBV high or intermediate endemic region. Import of HBV infections therefore continues to play an important role in the epidemiology of HBV in the Netherlands.

Pathogen

Molecular epidemiology

In 2004, a study was initiated to evaluate the effect of HBV vaccination among high-risk groups, in collaboration with the Municipal Health Services of Amsterdam and Rotterdam and the Erasmus MC.[53] Trends in HBV infections are studied and additionally blood samples are collected from all newly diagnosed acute HBV patients for genotypic analysis. The study is expected to provide additional insight in transmission networks within and between HBV risk groups in the Netherlands.
In 2004, 158 blood samples of acute HBV cases were genotyped (Table 5). The majority of the acute HBV cases was infected with genotype A (n=101, 64%). Of those, 49% was infected through MSM and 14% through heterosexual contact. Of the 35 cases with genotype D (22%), 54% was infected through sexual contact. Other genotypes are less common in the Netherlands: E (5%), F (4%), B (3%) and C (3%). Results of 2005 and 2006 are not yet available. Genotyping of all cases of acute HBV infection will continue until June 2007.

Table 5. Genotype distribution of acute case of HBV infection, 2004

Genotype	Route of transmission			Total
	MSM	Heterosexual	Else/unknown	
A	53	16	32	101 (64%)
B	-	1	3	4 (3%)
C	2	1	2	5 (3%)
D	5	14	14	33 (21%)
E	-	4	4	8 (5%)
F	1	3	3	7 (4%)

Modelling and economic evaluation

Using a mathematical model that included perinatal, horizontal childhood and sexual transmission, the transmission of HBV infection and the effect of different selective vaccination scenarios was investigated for the Netherlands. The vaccination scenarios analysed were: 1) the introduction of vaccination of children born to immigrants into the Dutch NIP in 2001, and 2) the vaccination program targeted to highly sexually active persons, which started in 2002.[54]
Modelling predicts show that the vaccination of children of immigrants can reduce the incidence of HBV infection by almost 30% over a time period of 50 years. This vaccination programme is

thus expected to be an effective alternative to universal infant vaccination. Vaccinating highly sexually active groups in a four-year catch-up campaign is expected to have only a short term additional effect. If continued over a long term period a targeted vaccination programme for highly sexually active risk groups is expected to have only a moderate additional effect.
The four-year vaccination program targeted to highly sexually active persons and starting in 2002 was evaluated by De Wit et al. (2006). They used a dynamic model that estimates future incidence of HBV in the population,[55] an age-specific economic model to estimate direct health care costs, life years lost from HBV infection and quality of life consequences of HBV infection, actual vaccination campaign data on the number of persons reached, the level of immunity from previous HBV infection, compliance with the three vaccinations scheme and programme costs. It was estimated that this four-year vaccination campaign would reach about 55,000 persons and would result in 1,400-5,300 infections prevented, depending on assumptions on the level of sexual activity of vaccinees. Costs per quality adjusted life years (QALY) gained are € 3,600 - € 19,000, the lower numbers reflecting vaccination targeted at the core risk-groups, the higher numbers reflecting a broader definition of risk-groups. Therefore, this four-year catch-up campaign was relatively cost-effective at a national level. However, the cost-effectiveness of the continuation of the program heavily depends on the amount and cost of (more expensive) outreach activities.
Currently, economic evaluation of universal immunisation is being investigated for the Netherlands. In a report on the economic evaluation of prevention, detailed information with regard to international studies on cost-effectiveness of universal hepatitis B vaccination is given.[10]

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.[56]

Guidelines and training

In 2006 integration was established of public health and intramural guidelines on HBV post exposure prophylaxis. The new guidelines will be implemented in all sectors in 2007.

Recommendations for vaccination, surveillance and research

- It is recommended to investigate opportunities to study the association between HBV vaccine and MS by performing an epidemiological study in the Netherlands.
- It is recommended to study the desirability and immunogenicity of the HBV (and Hib) component in the combination vaccine given to children of born to at least one parent from a HBV endemic country.
- Depending on the results of economic evaluation, universal immunization against hepatitis B needs to be reconsidered. Results of molecular surveillance need to be taken into account.

2.11 Pneumococcal disease

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

Vaccine

Recent changes in the NIP

Prevenar is the only licensed pneumococcal conjugate vaccine (PCV) for protection of infants and children up to five years of age in Europe. This 7-valent PCV, also designated as PCV7, provides protection against invasive disease caused by the 7 most prevalent serotypes in the USA.[57] In the Netherlands around 68% of cases of pneumococcal meningitis among children less than two years of age is caused by PCV7 serotypes (see Figure 6). Vaccination with Prevenar has been introduced in the Dutch NIP in April 2006. PCV7 is given to infants at two, three, four and eleven 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.

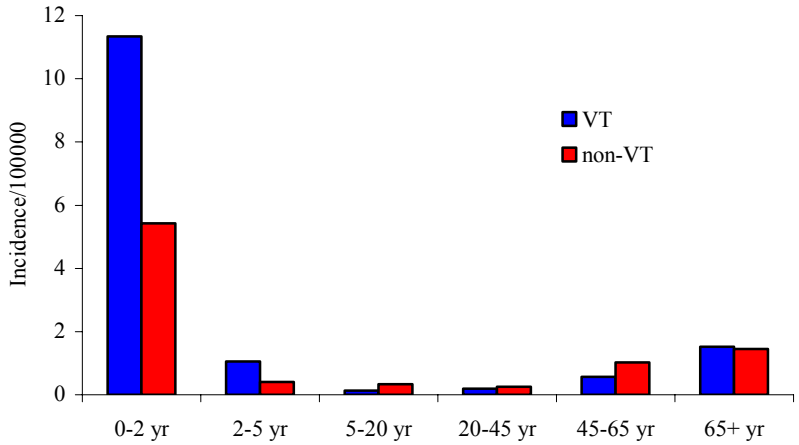

Figure 6. Age specific incidence of isolates from cerebrospinal fluid (CSF) or CSF and blood by serotype. Serotypes included in the PCV-7 vaccine are in blue, the others in red.

To assess possible interference of the Prevenar with other components of vaccination program the CIb is currently evaluating such effects. For this purpose serum samples are collected from children vaccinated with the Pediacel vaccine with or without the Prevenar vaccine.

Epidemiology of infection and disease

In the Netherlands pneumococcal disease is not notifiable and there is no systematic collection of strains and clinical data. The laboratories send their isolates from patients with invasive pneumococcal disease to the Netherlands Reference laboratory for Bacterial Meningitis (NRBM) on a voluntary basis. 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. Between 200 and 250 cases of meningitis

caused by pneumococci are recorded by the NRBM annually. Of these approximately 80 are children aged 10 and younger. Children under the age of 2 have the highest risk of developing meningitis caused by pneumococci (see Figure 7).

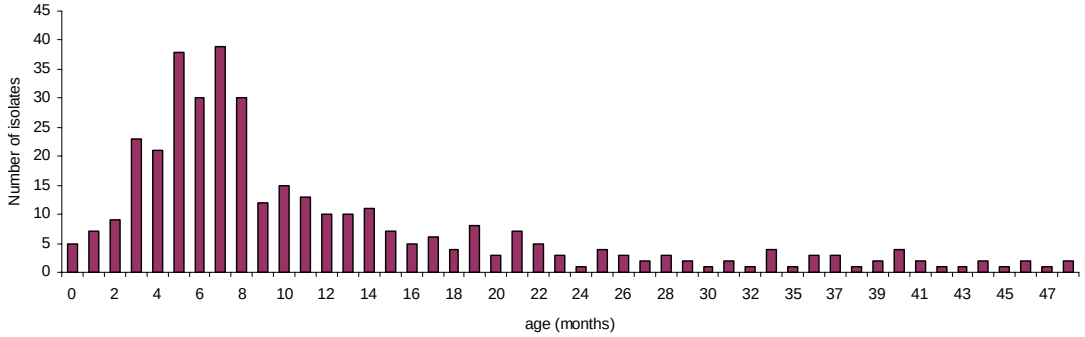

Figure 7. Age specific (age in months) number of isolates from CSF or CSF and blood in 2001-2005

International perspectives

The Netherlands is among the first European countries to include PCV7 in their childhood immunization program. Norway has included PCV7 in their childhood immunization program at the beginning of 2006.[58] The UK has introduced the immunization in September 2006.[59] In the UK, PCV is given routinely in the primary schedule at two and four months of age with a subsequent dose at thirteen months of age, since a two-dose primary course followed by a booster has been shown to offer immunogenicity comparable to a three-dose course and booster and this will reduce the costs by 25%.[60] The UK will also implement a pneumococcal vaccination catch-up program for children under two years of age who have already received their regular primary vaccinations.

In July 2006, vaccination against meningococcal C and pneumococcal disease is also added to the routine childhood immunisation programme in Germany. The Standing Committee on Vaccination (‘Ständige Impfkommission’ (STIKO)) at the Robert Koch-Institut recommends vaccination with 7-valent conjugate pneumococcal vaccine at the earliest possible opportunity, which means at the same time as tetanus, diphtheria, pertussis, polio, *Haemophilus influenzae* b and hepatitis B vaccine at the age of two, three, four, and eleven-fourteen months.[44]

Recommendations for vaccination, surveillance and research

Data on the number of cases of invasive pneumococcal disease in the Netherlands are 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 intensifying the routine surveillance. Medical microbiological laboratories throughout the country are asked to send *all* their pneumococcal strains isolated from CSF or blood from children < 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 9 large laboratories that cover approximately 20% of the Dutch population. It is also important to obtain information on the clinical

manifestations and underlying disease of invasive pneumococcal disease. Therefore, this information will be obtained using questionnaires that will be filled out by students interviewing physicians by phone. This will be done in collaboration with the Children's Hospital (WKZ) of the University Medical Centre Utrecht.
Aims of this enhanced surveillance are:

- to monitor changes in incidence and disease burden of invasive pneumococcal disease in children after introduction of PCV7;
- to identify vaccine failures of PCV7;
- to monitor changes in the serotype distribution after introduction of PCV7;
- to monitor the incidence and disease burden in the general population and to assess possible herd-immunity effects after the introduction of PCV7.

The surveillance will become more complete and reliable if invasive pneumococcal disease would become a notifiable in the Netherlands. Introduction of a notification system for invasive pneumococcal disease in the Netherlands in 2008 is now under discussion.
There has been much debate on the number of doses of Prevenar that should be used in the NIP to provide sufficient protection against pneumococcal disease. The Health Council has advised to use four doses as no evidence exists to show that three doses will protect as well as four doses. However, several European countries, among which the UK, have introduced a three dose regime in their NIP. We recommend comparing the clinical data, immunological data and the impact on the serotype distribution in the Netherlands and the UK in a collaborative study between the CIb and the Health Protection Agency (HPA). Such a study should also be used to design tests to study correlates of protection (COP) and to assess the COP in both immunization schedules.
In the report on the NIP in 2005, the question whether it would be desirable to vaccinate the elderly against pneumococcal disease was raised.[1] An analysis with regard to cost-effectiveness of pneumococcal vaccination of elderly persons in international literature is given in a report on the economic evaluation of prevention.[10] No new evidence has become available to decide to introduce such a vaccination since the report on the NIP in 2005. However, it remains an important question to answer, and we recommend to perform a randomised clinical trial to assess the desirability of offering pneumococcal vaccination to the elderly in the Netherlands.

3. Programmatic vaccination outside the NIP

3.1 Influenza

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

Vaccine

Current target groups

Following the 1998 advice from the Dutch Health Council, vaccination in the Netherlands is currently recommended for all people aged 65 and above, and for people with certain medical conditions (e.g. chronic pulmonary conditions, cardiac conditions, diabetes mellitus, kidney failure, immunocompromised conditions), based on an increased risk of severe morbidity following influenza infection in these groups. The Dutch Association of Nursing Home Physicians in 2004 recommended vaccination for all nursing staff in nursing homes as well.[61] At present the Dutch Health Council is preparing an update of the advice on target groups for annual vaccination. This could include an advice on modifying the age range (also because targeting by age might be more effective than targeting by indication), modifying recommended medical conditions, and including groups such as health care workers in order to reduce transmission to high-risk groups currently targeted. Cost-effectiveness of vaccinating healthy adults based on international models is discussed in a report on economic evaluation of prevention.[10] In view of this overall limited morbidity and limited effectiveness on absenteeism,[62] this is currently not a contemplated policy in the Netherlands.

For the 2005-2006 season, 83.5% of those aged 65 and above (with and without medical indication) accepted vaccination, and 72.3% of younger people with a medical indication, which is in line with acceptance in previous years.[63]

In June 2006 the European Vaccine Manufacturers have reported delays in the production of the 2006-2007 season due to the low yield of one of the three recommend strains (the H3N2 component). Therefore, availability of influenza vaccines is expected to be limited for 2006-2007, and distribution to be delayed by a few weeks. VWS has ensured that vaccines will be available first to those for whom it recommends annual vaccination. It is expected that the NVI will have sufficient doses of vaccine available for those for whom vaccination is recommended.

Vaccine effectiveness

There is as of yet no monitoring of seasonal VE in the Netherlands. In 2007 data collected within the sentinel surveillance system will be used to obtain estimates of the actual effectiveness.[64] In 2006 a new Cochrane review was published on the efficacy and effectiveness of influenza vaccination of health-care workers in reducing cases of influenza-like illness (ILI), influenza, complications from influenza, death from influenza, and death from all causes among the elderly people they care for in institutions. The authors concluded that staff vaccination had a significant effect on ILI when patients were vaccinated but did not protect against influenza or against

pneumonia. However, deaths from pneumonia and from all causes were reduced. The authors warn that these findings must be interpreted in the light of possible selection, performance, attrition, and detection biases.[65]

Adverse events

Influenza vaccination is considered to be a very safe intervention, serious or systemic side-effects are rarely reported. Recently, it was pointed out that few data on safety collected in randomised controlled trials have been reported.[66] During the 2006 vaccination rounds, unexpected deaths following vaccination in Israel triggered extensive evaluation of a potential association. This analysis showed that such an association was very unlikely.[67] A similar conclusion was reached in the Netherlands in an in-depth medical and statistical analysis of unexpected deaths following vaccination. Such events support the need to develop and maintain a strong surveillance of all potential side-effects following vaccination.

Availability of new vaccines and other new developments

If an influenza pandemic would occur, the Netherlands plan to vaccinate the whole population once a vaccine has become available. The Dutch Health Council has advised on the priority groups for vaccination (health care professionals, followed by those at highest risk for morbidity and mortality). The Netherlands currently do not consider using a pre-pandemic avian influenza vaccine as part of a prime-boost strategy (see International perspectives).

Epidemiology of infection and disease

The incidence of ILI among patients consulting general practitioners (GP) with respiratory complaints (sentinel surveillance) in the 2005-2006 season was 161 per 10,000 inhabitants. The weekly incidence was above baseline (3/10,000) between week 1 and week 15 of 2006. The peak weekly incidence was reached in week 7 with 14.5/10,000. Incidence was highest in the north of the country, in rural areas, and among young children aged 0-4 years. At the peak of the epidemic, 45.9% of ILI in the sentinel practices was associated with influenza virus infection.

Over the past decade, based on the sentinel surveillance data collected by the Netherlands Institute for Health Services Research (NIVEL), the number of people who consult their GP for an ILI during the season has gradually declined from 484/10,000 in 1993 tot 161/10,000 over the past year. The number of deaths where influenza was directly indicated as a cause of death in 2005-2006, 100, was the lowest of the past five years (Statistics Netherlands).[68]

Pathogen

During the 2005-2006 season, the influenza epidemic in the Netherlands was dominated by influenza B first, and later by influenza A H3N2. Influenza A H1N1 was only observed in a few patients who had most likely contacted the infection abroad.

The NIC-EMC (‘Nederlands Influenza Centrum - Erasmus Medisch Centrum’) receives viral isolates through both the sentinel surveillance and from virological laboratories for further characterisation; this information is used by the WHO to advise on the composition of the vaccine for the following season. This year, characterisation showed that the circulating

influenza B strains in 2005-2006 differed significantly from the vaccine strain. The influenza A (H3N2)-viruses showed a good match with the vaccine strain; only a few of these strains showed some minor differences.[69]

International perspectives

For the coming 2006-2007 influenza season, the WHO has updated her recommendation for the northern hemisphere replacing the current influenza B strain with the B/Malaysia/2506/04 strain. The influenza A (H3N2) and A (H1N1) strains have not been changed.

For nearly ten years now, avian influenza A (H5N1) has been causing incidental human infections with a high case fatality rate. In the past year, many countries in Europe have experienced proven influenza A (H5N1) infections among birds or sometimes poultry. No human infections with influenza A (H5N1) virus have occurred in the Netherlands so far. The Netherlands experienced an outbreak of a low pathogenic avian influenza A (H7N7) virus on a single poultry farm in 2006, without known transmission to humans.

In spite of generally poor antibody responses, several pharmaceutical companies are working on the development of a human H5N1 influenza vaccine, which could be stockpiled prior to a pandemic. A mathematical modelling study suggested that with a 30% efficacy, such a vaccine could still have a significant impact,[70] but concerns remain regarding safety, as well as the impossibility to determine the likelihood of an H5N1 pandemic and the financial risks involved.[71] The vaccine industry is actively lobbying to promote such a prime-boost strategy. In August 2006, the WHO, although not necessarily recommending investing in prepandemic vaccines, has recommended 3 H5N1 candidate vaccine viruses for piloting: A/Indonesia/6/2005-like virus; A/Bar headed goose/Qinghai/1A/2005-like virus; A/Anhul/1/2005-like virus.

Recommendations for vaccination, surveillance and research

The Dutch Health Council is currently evaluating whether changes are indicated in the groups for which annual seasonal influenza vaccination should be recommended.

Surveillance of uptake of influenza vaccination among those for whom it is recommended is currently limited to those (the majority) who receive their vaccine through their GP. It would be advisable to extend this surveillance to include other specific high-risk groups, in particular nursing-home residents. At the same time, surveillance of potential side-effects needs to be strengthened and it should be explored if actual VE estimates can be obtained during each season within the current sentinel surveillance.

Surveillance of ILI and influenza among GPs can be further strengthened by linked surveillance of pneumonia, as the most important direct complication of influenza infection. This will also support pandemic preparedness planning.

Further developments with respect to effectiveness, safety and availability of a prime-boost strategy need to be monitored closely and evaluated scientifically on potential merits.

3.2 Tuberculosis

M.A.B. van der Sande, K. Kremer, M.R. Klein, C.G.M. Erkens (KNCV Tuberculosisfoundation), D. van Soolingen

Vaccine

Current target groups

BCG is still the only vaccine available for the prevention of *Mycobacterium tuberculosis* infection. It has been in use since 1921 and protects against miliairy tuberculosis (TB) and TB meningitis in children. In the Netherlands, the current target group consists of children of immigrants from high prevalence countries. This target group is contacted via the Municipal Health Services. In 2006, the RIVM/CIb in collaboration with the KNCV Tuberculosisfoundation and the National Health Council developed a mathematical model to evaluate the cost-effectiveness of this selective vaccination approach. Based on the available National Tuberculosis Registry (NTR) data, the model showed that 5,900 (95% CI 3,000-15,400) children need to be vaccinated to prevent one case of miliairy TB or TB meningitis. These data suggested that a selective vaccination policy targeting children from immigrants would be a cost-effective approach and should be continued.[72] Further analysis with more data is continuing.

Vaccine effectiveness

With more and more mycobacterial genome sequences becoming available and with the introduction of new molecular techniques, it is clear that the genetic variation in *M. tuberculosis* isolates from high-prevalence settings is far less than in low-prevalence settings. This may indicate an ongoing selection towards genotypes with a higher ability to circumvent BCG-induced immunity.[73,74]

Recent data regarding the effect of different BCG strains and route of administration on VE come from an ongoing large-scale phase-IV vaccine trial with BCG conducted by the South African TB Vaccine Initiative. The first results show that BCG Danish 1331 given intradermally gave overall equal protection against TB in children, as compared with BCG Tokyo 172 BCG given percutaneously, but that the former regime significantly reduced the proportion of children with disseminated disease.[75,76]

Besides the reported effects on TB disease it is now also observed that BCG vaccination protects against *M. tuberculosis* infection.[77] However, these results are still controversial and debated in the literature.[78,79]

Availability of new vaccines and other new developments

As the current BCG vaccine does not offer protection against adult pulmonary TB, in particular in high incidence countries, there is a clear need for a more effective vaccine. Novel TB vaccine strategies that are currently being developed include live attenuated (mycobacterial) vaccines and subunit vaccines in combination with adjuvants.[80,81]

The pivotal question to address is whether or not to replace BCG or to improve it? Evidently there are beneficial effects of BCG vaccination in young children. It will therefore be a tour de force to tackle the ethical issues around clinical trials designed to withhold a (partially) effective vaccine and test experimental vaccines with unknown efficacy.

Novel live-attenuated mycobacterial vaccines that are being developed are planned to replace BCG, since they are not likely to be effective as booster vaccines.[82,83] These live-attenuated vaccines include mutant strains of *M. tuberculosis*, but also recombinant BCG strains with either overexpression of immunodominant TB antigens[84] or with improved features to enhance immunogenicity.[85]

Before these live vaccines may be implemented, in particular the mutant *M. tuberculosis* strains, it will be necessary to address the safety concerns. It is known that the otherwise non-virulent BCG is capable of inducing disseminated disease in people with genetic defects in their cellular immune response.[86]

Of note, BCG is still the gold-standard vaccine in animal models of TB. Novel vaccine candidates have in general not been able to surpass the efficacy of BCG. However, the most impressive results to date have been obtained with a recombinant BCG strain expressing listeriolysin and which is deficient in Urease C.[85]

The other major approach to develop novel TB vaccines includes strategies to improve the efficacy of BCG vaccination: 1) complementing immunity by redirecting immune responses to TB antigens that are not ordinarily targeted by the immune system after BCG vaccination; 2) boosting the pre-existing immunity by enhancing immune responses to TB antigens that are shared with BCG. These approaches comprise mainly subunit TB vaccine candidates, e.g. recombinant protein(s) in combination with experimental adjuvants and using attenuated viral/bacterial vectors.

Candidate TB vaccines that are in phase-I/II testing include: 1) modified vaccinia Ankara (MVA) overexpressing Ag85A (Oxford University);[87,88] 2) Mtb72f (recombinant fusion protein of Rv0125 and Rv1196) in ASO2A adjuvant (GSK); and 3) Hybrid-1 (recombinant fusion protein of Ag85B and ESAT-6 in IC31 adjuvant (Statens Serum Institute, Intercell).[80,81] Of note, the heterologous prime-boost strategy with BCG and MVA-Ag85A appears to be a very powerful way to enhance immune responses to immunodominant TB antigens.[87,88] The most advanced, albeit also rather controversial, is a heat-killed *M. vaccae* preparation (SRL172) that is currently tested in a phase-III efficacy trial in Tanzania.[89]

In partnership with the Aeras Global TB Vaccine Foundation and with tremendous financial support of the Bill and Melinda Gates Foundation (among others), new initiatives have started that are expected to further accelerate the development of novel TB vaccines.[81]

To accelerate the development of new vaccination strategies, there is an urgent need to develop biomarkers of protective immunity that will be important for optimizing vaccine strategies during phase-II testing. In addition, well-defined biomarkers of TB disease are urgently needed as they could serve as surrogate clinical endpoints to shorten follow-up time during phase-III testing.[80] The first effective prophylactic TB vaccines are expected to reach the market in the next five-ten years; a new post-exposure and/or therapeutic TB vaccine will take longer to emerge.

Epidemiology of infection and disease

In the Netherlands, the incidence of new *M tuberculosis* infections decreased in 2005 with 14% compared to 2004. In total, 1157 TB patients were reported, among whom 1,076 new cases and 81 patients who had been reported with a previous episode of TB. Of all new patients, 682 (58.9%) were male. Median age was 37 years (IQR 27-55). For 33 deaths TB was recorded as the cause of death, which was comparable to previous years. The decline in the number of patients for whom a positive sputum culture was confirmed in the RIVM national reference laboratory in 2005 compared to 2004 was less marked with a 4% reduction (882 versus 851).

Pathogen

M. tuberculosis isolates in low-prevalence settings like Europe and the USA generally reveal a high degree of DNA polymorphism. This presumably reflects the 'frozen' genetic diversity of endogenous reactivations of remote infections from an extended period of time, the import of cases from very different areas and the effective prevention of spread of individual strains. In high-prevalence settings like Africa and Asia, a high degree of conservation has been observed among *M. tuberculosis* isolates. It has been postulated that this may be due to selective advantages of successful genotypes regarding the ability to resist treatment by anti-tuberculosis drugs and to circumvent BCG-induced immunity.

Currently, much international research is oriented on the explanation of the successful spread of conserved genotypes of *M. tuberculosis* such as the Beijing genotype. In an earlier study in a mouse model Beijing strains appeared hyper virulent in comparison to less prevalent strains.[90] The pathology caused by infection with the Beijing strains differs from that of other strains.

So far, not much is known on DNA repair mechanisms in *M. tuberculosis*, whereas mutator genes play a major role in the pathogenesis of other bacteria like the gram-negatives. A few years ago, it was found that Beijing bacteria, in contrast to other *M. tuberculosis* genotypes, carry a wide variety of mutations in putative mutator genes.[91] This may be associated to a higher virulence and a more developed ability to gain resistance. Mouse model studies in several international institutes have pointed out that protection of BCG against infections by Beijing genotype strains is far less than against other strains.[90]

The latest developments are that two lineages of the Beijing genotype have been distinguished; the typical and atypical strains. The typical Beijing strains are far more prevalent, genetically more conserved, correlated with BCG vaccinated patients in Vietnam, and carry mutations in putative mutator genes.[74] The difference between typical and atypical Beijing strains may shed more light on the (re) current worldwide tuberculosis epidemic.

International perspectives

There are indications that the worldwide population structure of *M. tuberculosis* may be changing towards selection of genotypes with particular selective advantages, like in case of the Beijing genotype.[92] More large, representative studies are needed to confirm this picture. The emergence of the Beijing genotype has also been associated with reduced BCG effectiveness.[73] Although the Beijing genotype bacteria may be responsible for in between 20-40% of the worldwide case with a focus on Asia, not much is known on the situation in Africa and Latin

America. On the basis of preliminary studies in Central Africa it is expected that selection of more adapted genotypes may also play a major role over there. Since a few years, groups working on the development of vaccines have more interest in findings in the molecular epidemiology of tuberculosis.
In 2006, a large worldwide survey (on basis of almost 30,000 cases) was published on the worldwide spread of the Beijing genotype of *M. tuberculosis*.[92] It was found to be wide spread, and correlated with drug resistance in some, but not all regions. Furthermore, the Beijing genotype was found to be emerging in several settings.
Another development which is causing great concern is the spreading of multidrug resistant (MDR) TB, and in particular the recent emergence of extensively drug resistant TB (XDR).[93] This strain is virtually untreatable as neither the standard drugs nor at least three of the six classes of more toxic and less effective second-line treatments are effective. Until recently, only isolated cases of XDR-TB had been identified, but in 2006 an outbreak of XDR among over 100 patients (all HIV-positive) in South-Africa gave cause to great alarm. Prevalence of these strains in the Netherlands is still very low, but alertness towards the possibility of introduction from affected regions needs to be high.

Recommendations for vaccination, surveillance and research
At present, a selective BCG vaccination strategy, targeting children from high prevalence countries, could be continued. The further development of molecular typing techniques gives new insights in transmission patterns, which will assist a strategy aimed at elimination. Alertness towards the possible introduction of MDR or XDR *M. tuberculosis,* however, remains vital.

Acknowledgement: J.F.R. Thole, ASG, Lelystad

4. Future NIP candidate vaccines

4.1 Hepatitis A

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Vaccine

Effectiveness

The effectiveness of a hepatitis A vaccination program for migrant children in Amsterdam from 1992-2004, using a retrospective population based data analysis, was evaluated by Sonder et al.[94] The overall hepatitis A incidence in Amsterdam declined after a paediatric vaccine was introduced in 1997. This decline was seen in migrant children travelling to hepatitis A-endemic countries, contacts with hepatitis A patients, primary school students, injecting drug users (IDU), and persons with unknown source of infection, but not in MSM or in travellers to endemic countries other than migrant children. They concluded that the Amsterdam vaccination coverage of Turkish children, combined with the current level of hepatitis A virus (HAV) endemicity in Turkey, is high enough to stop import of Turkish cases of HAV in the Netherlands. However, this is not the case for Moroccan children, possibly because the incidence of HAV is estimated to be higher in Morocco than in Turkey.[94] According to Dijkshoorn et al. there is no difference in the degree of vaccination between Turkish and Moroccan migrant children in the Netherlands.[95]

Adverse events

In 2006 a study of reported adverse events after combined hepatitis AB vaccine is published. The adverse events were extracted from the Vaccine Adverse Events Reporting System (VAERS), the passive safety surveillance system of the USA. Assessing causality in VAERS is difficult because of incomplete information in many reports. The adverse events reported to VAERS were in greater part similar to those seen after the monovalent HAV and HBV.[96]

There are few studies on the immunogenicity of hepatitis A vaccines in children under two years of age.[97,98,99] Infants under one year of age show a good response to vaccination when the mother is negative for antibody to hepatitis A virus. In children from anti-HAV positive mothers there was also a protective level of antibody, although there were significant differences in geometric mean titre (GMT) of anti-HAV in both groups.[97,99]

Disease

Epidemiology

The number of notified cases of hepatitis A in the Netherlands increased from 375 in 2003 to 447 in 2004. An outbreak of hepatitis A among homeless people in Rotterdam and a rise of travel-related hepatitis A due to a food-related outbreak in Egypt contributed to this increase in 2004. Also there was an increase of hepatitis A notifications in MSM.[100] However, the number

of notifications in 2005 (215) is again corresponding with the long-term decreasing trend since the early nineties.

Economic aspects

Apart from the study of Navas et al.[101] no new economic studies have become available. Navas et al. studied the efficiency of the hepatitis A vaccine as a combined A and B vaccine in pre-adolescents in Catalonia (Spain), compared to the current hepatitis B vaccination programme in that area. They suggested that the addition of a hepatitis A vaccine to an already existing hepatitis B vaccination scheme would not only be cost-efficient, but even cost-saving. However, the base incidence in Catalonia was 15 per 100,000, while in the Netherlands the annual incidence ranges between 1 and 3 per 100,000. Sonder et al.[94] suggest that the most effective way to improve the vaccination coverage would be to implement HAV vaccination in the current routine NIP for children from immigrants. Endemic countries for hepatitis B largely overlap with countries endemic for hepatitis A. Consequently, they recommend offering children with at least one parent originating from a hepatitis B-endemic country not only hepatitis B vaccination, which is current policy in the Netherlands, but two A and B vaccine doses in their second year of life, six months apart. This would give lifelong protection against hepatitis B, and possibly lifelong protection against hepatitis A.[94] This would probably be cost-effective, as the additional costs for the combination vaccine are marginal. One dose of Havrix Junior (for ages one-fifteen years) costs € 28.10 and one dose of Twinrix costs € 41.86.[102]

However, a combined hepatitis A and B vaccination would not fit into the NIP of the Netherlands. According to the current vaccination schedule, migrant children receive a hepatitis B vaccination in the form of the hexavalent vaccine Infanrix Hexa (GSK) (diphtheria, pertussis, tetanus, hepatitis B, poliomyelitis and Hib) at two, three, four and eleven months. Moreover, the Havrix Junior vaccine can only be administered at the age of one to fifteen years, which also contradicts with the current hepatitis B vaccination scheme within the first year of life.

International perspectives

Since licensure of effective hepatitis A vaccines in the mid-1990s, USA hepatitis A rates have fallen precipitously, particularly since 1999, when routine childhood vaccination was recommended in states with consistently elevated rates. By 2004, the overall rate had declined to 1.9/100,000 population, the lowest rate ever recorded and 79% lower than any previously recorded lowest point. These marked declines occurred, with relatively modest vaccination coverage, suggesting that strong herd immunity accompanies the initiation of routine vaccination programs. Routine childhood vaccination induced similar results in Israel and selected regions of Italy, Spain, and Australia.[103]

Recommendations for vaccination, surveillance and research

The previous report concluded that hepatitis A vaccination would probably not be cost-effective, regarding the low incidence of hepatitis A in the Netherlands. The further decrease in incidence of hepatitis A in 2005 does not lead to different recommendations than those made in the previous report.

A new option could be to administer the hepatitis A and B vaccine combined; studies of Sonder et al. and Navas et al. suggest that combination of the hepatitis A and B vaccine would be beneficial, especially with regard to cost-effectiveness. However, no analysis has been done in the Netherlands to study the cost-effectiveness of combined hepatitis A and B vaccination for migrant children in the Netherlands. Moreover, a combined vaccine such as Havrix Junior (for ages 1-15), would not fit into the current NIP, because of the dissimilarities in vaccination scheme.

4.2 Rotavirus

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Vaccine

Availability and new developments

Two live oral rotavirus vaccines are available, which both have completed large scale clinical trials. The monovalent vaccine RotaRix (GSK) is derived from an attenuated human rotavirus strain P[8]G1 (RIX 4414). RotaTeq (Merck & Co. Inc., USA, in joint venture with SP) is a pentavalent vaccine which combines the five bovine-human reassortant strains G1, G2, G3, G4, and P[8].[104] RotaRix was licensed in the Netherlands in March 2006, and the licensure for RotaTeq was approved by the European Union (EU) in June 2006.[105] Several vaccine manufacturers in developing countries are working on their own rotavirus vaccines, resulting in several other vaccine candidates in earlier stages of testing.[104,105,106,107,108,109,110]

The former RotaShield vaccine (Wyeth Lederle Vaccines, unit of American Home Products, USA) may be reintroduced on the market.[111,112] The risk of intussusception (IS) appeared to be smaller than originally estimated, after correction of age effects of the recipients. RotaShield is being upgraded to a hexavalent vaccine.[107]

Effectiveness

RotaRix is administered in two oral doses (month 2 and 4) to infants and for RotaTeq three oral doses are required (month 2, 4, 6). Both vaccines are intended to be given to infants at the same time as their immunizations for diphtheria, pertussis and tetanus, and so far no observation is made that either of the two vaccines would affect the immune response of simultaneously administered infant vaccines.[104,113] Results from phase III trials demonstrated that both vaccines are effective against rotavirus gastroenteritis in vaccinated infants in comparison to unvaccinated infants of the same age during the first season after vaccination.[114,115] RotaTeq vaccine was estimated to reduce in the first season after vaccination office visits to a physician or clinic visits for G1-G4 rotavirus gastroenteritis by 86.0% (95% CI 73.9 - 92.5%), G1-G4 rotavirus gastroenteritis of any severity by 74.0% (95% CI 66.8 - 79.9%). In the second season the RotaTeq vaccine efficacy against G1-G4 rotavirus gastroenteritis of any severity was 62.6% (95% CI 44.3 - 75.4%).[115] Vaccine efficacy for RotaRix against rotavirus gastroenteritis induced

hospitalization for at least one night was estimated to be 85.0% (95% CI 69.9% - 93.5%) and for severe rotavirus gastroenteritis vaccine efficacy was estimated to be 84.7% (95% CI 71.7% - 92.4%) in the first season.[114] No information was available for the second season for this vaccine. However, the waning effectiveness of both vaccines during the second and following seasons, and its consequences for the recommended frequency of vaccination can be estimated by modelling.

A comparison between both vaccines is difficult due to: a) differences in classification of disease severity due to different use of the Vesikari scale; b) different populations studied; c) not always including all rotavirus types. Ruiz-Palacios et al.[114] and Vesikari et al.[115] also report vaccine efficacy for serotype-specific rotavirus gastroenteritis for any severity (Table 6).

Table 6. Serotype-specific efficacy of vaccines against severe rotavirus gastroenteritis of any severity in the first season after vaccination

Serotype	RotaRix % (95% CI)	RotaTeq % (95% CI)
G1/G1P[8]	91.8 (74.1 – 98.4)	95.1 (91.6 – 97.1)
G2/G2P[4]	41.0 (<0 – 82.4)	87.6 (<0 – 98.5)
G3/G3P[8]	87.3 (64.1 – 96.7)	93.4 (49.4 – 991.1)
G4/G4P[8]	87.3 (64.1 – 96.7)	89.1 (52.0 – 97.5)
G9/G9P[8]	87.3 (64.1 – 96.7)	100.0 (67.4 – 100.0)
G12	Not reported	100.0 (<0 – 100.0)

Adverse events

For both RotaTeq and RotaRix it was proven by extended clinical trials (> 31,000 and 34,000 children) that there is no increased risk for IS after rotavirus vaccination nor for any other severe side-effects.[104,114,116,117,118] No difference in the occurrence of IS between the vaccines recipients and the placebo groups has been detected. The schedule was strictly adjusted to starting at an early age, thus minimising the risk of chance association of coincidental IS and the vaccination. For more common adverse events no differences of consequence were detected between the vaccine and the placebo recipients and between the two vaccines. Adverse interactions between the rotavirus vaccines and the concomitant immunisation schedule vaccines did not occur. Safety for special groups as immune-compromised children has not yet been evaluated. Neither has the risk of IS for catch up schedules in older infants been decided.[119,120] The adverse effect of vaccination on natural rotavirus infection with non-vaccine strains (and vice versa) has been discussed. Adverse effects were considered unlikely however.[121]

The ACIP has recommended uptake of the vaccine in the USA infant vaccination schedules.[122] Several South and Middle American countries have already introduced routine rotavirus vaccination.[114] For all rotavirus vaccines the approved/recommended schedules require the first dose to be administered from 6 weeks to three months of age, with no catch-up vaccinations for older infants.[122,123] Recommendation is to install a sensitive safety surveillance for the post-marketing period to detect hitherto unsuspected rare severe adverse events (with the IS experience in mind).[104,118,122,124]

Pathogen

The current vaccines target the prevention of severe rotavirus illness caused by the 'common' rotavirus serotypes G1-G4. Since the start of rotavirus strain surveillance, these strains have been found as causes of the majority of rotavirus episodes for which medical care was sought.[125] In the past decade, however, other rotavirus serotypes have emerged, especially the G9 rotaviruses. In the Netherlands a new rotavirus strain G12[P8] was identified as one of the causative agents of an outbreak in a nursing home, which occurred between January and April 2006. Apparently, this strain was not documented in Europe before, and it was identified in the USA only once before. The G12 strain is commonly found in Asia and South America. It is unknown whether this strain was introduced into the Dutch nursing home from abroad.[126] The strong similarity with sequences of recently detected G12 strains in South America, USA, and Asia suggested a relative recent introduction of this strain to people in the Netherlands.[127]

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 compared with previous years; 1,324 diagnoses were registered by the virological weekly returns compared to 946 – 1,079 in the previous years. In 2005 56% of the hospital admissions of children aged younger than five years was estimated to be caused by rotavirus. In the previous five years this ranged between 48% and 56%. According to laboratory based surveillance, the majority of rotavirus infections is found in children aged younger than five years (94%), especially in infants and mostly in boys (58%). The incidence of laboratory-confirmed rotavirus infections is very low in people aged older than five years.[128] However, more outbreaks were reported in 2005 and 2006 than in the previous years, of which the majority occurred in nursing homes and one in a day-care centre. The number of outbreaks even doubled from eight outbreaks in 2005 to 17 outbreaks in 2006.[126,128] Besides, also internationally there is increasing evidence of severe rotavirus infections in adults.[129,130,131]

Burden of disease

Based on Dutch data[132,133,134,135] the annual number of rotavirus infections in the Netherlands was estimated to be equal to 190,000 rotavirus gastroenteritis infections (range 110,000 to 325,000), whereof 58,000 would occur in children younger than five years.[136,137] However, most cases recover without requiring medical help. Nevertheless, rotavirus is responsible for about 3,400 hospitalized rotavirus gastroenteritis cases (range 2,800 to 4,000), whereby the rotavirus infection is either community-acquired and results in hospital admission, or nosocomial-acquired, resulting in a prolongation of the hospital stay.[136,137]About 95% of the hospitalised cases are children younger than five years. Based on international literature it was estimated that each year for about 2.9 hospitalised children (range 2.3 to 3.5) the rotavirus infection would be fatal.[137,138,139] The associated annual disease burden was estimated to be equal to 500 Disability

Adjusted Live Years (DALY). About 45% of the total disease burden is due to years of life lost (YLL).[137]
Over the last two decades there have been sporadic reports of children with acute or fatal cases of rotavirus gastroenteritis testing positive for rotavirus antigen and/or nucleic acid in various extraintestinal locations such as serum, liver, kidney, bladder, testes, nasal secretions, CSF and the central nervous system.[140] Clinically, rotavirus has been associated with complications such as prolonged diarrhoea, convulsions, pancreatitis and respiratory symptoms,[141,142,143,144] the causal role of rotavirus in these syndromes has not been systematically evaluated and therefore, remains inconclusive. However, recent studies have shown that extraintestinal spread of rotavirus occurs in animals (mice, rats and rhesus macaque) and humans. In humans, it has been shown that antigenemia commonly occurs during natural infection, suggesting the potential for further spread.[145,146,147] In view of these developments, the possible associations of rotavirus with other clinical syndromes is being studied.[148,149,150]

Economic aspects

Rotavirus infections in the Netherlands, both community-acquired cases and nosocomial-acquired cases, were estimated to result each year in about € 8.1 million direct health care costs (range € 6.8 million to € 9.2 million) and in € 15.6 million indirect non-health care costs (range € 6.3 million to € 33.4 million), resulting in total cost-of-illness of € 23.7 million (range € 14.3 million to € 41.7 million) for the year 2004.[137] Previous conducted cost-effectiveness studies[151,152] were based on the old RotaShield vaccine. And apart from Fischer et al.[153] and Podewils et al.,[154] who estimated the cost-effectiveness for the new available rotavirus vaccine(s) in Vietnam and in Asian children, respectively, no other cost-effectiveness studies have been published so far. Given the higher rotavirus fatal rate in Asia, an extrapolation to the Netherlands cannot be made. A cost-effectiveness study was applied in order to determine if the introduction of rotavirus vaccine in the Dutch NIP might be cost-effective or not. More detailed information on cost-effectiveness studies published in international literature on rotavirus vaccination are given in a report on economic evaluation of prevention.[10]
Based on the scarce information on rotavirus vaccine cost prices - a reported cost price of $69 per dose for RotaTeq in the USA[119] - we estimated that the vaccine related costs would be equal to € 187 per vaccinated child. Assuming that rotavirus vaccine induced protection is only in children younger than five years, with highest vaccine protection in the first year of vaccination, both rotavirus vaccines would be effective in reducing the annual number of rotavirus infections in children aged younger than five years (reduction of about 34,000 rotavirus infections, of which 2,150 hospitalisations and 2.5 fatal rotavirus cases per year). However, the introduction of rotavirus vaccine in the Dutch immunization program would not be cost-effective, neither from the social perspective (€ 144,000 per DALY) nor from the third payer perspective (€ 148,000 per DALY). With the underlying assumptions rotavirus vaccination would only be cost-saving at vaccine-related costs of less than € 24 per vaccinated child.[137] Cost-effective would the programme run for vaccine-related costs of less than € 46 per vaccinated child. The cost per vaccinated child is lower than the recently published (Augustus 2006) vaccine costs estimate of $66 per child at which vaccination is likely to be cost-saving in the US, using the health-care

perspective.[122] Vaccine related costs, discount rate, and life-age at which protection is assumed to wane, are the major factors that determine whether a rotavirus vaccination program is cost-effective or not.[137]

International perspectives

June 2006, RotaRix is licensed in approximately 35 countries and the EU. It has been introduced into national vaccination programs in Brazil, Panama, and Venezuela. A licensure application has not yet been submitted in the USA.[104] RotaTeq was licensed in the USA in February 2006, and two weeks later routine immunisation of children in the USA was recommended by the ACIP of the Centre for Disease Control and Prevention (CDC). In an analysis that used estimates of current rotavirus disease burden, vaccine efficacy, vaccine coverage rates, and health costs, investigators of the CDC estimated that a national rotavirus vaccination program in which 3 doses of RotaTeq are administered at ages two, four, and six months would be cost-saving or at least cost-effective.[104,122]

Recommendations for vaccination, surveillance and control

Taking the published cost price of $69 per dose of RotaTeq into account, the introduction of rotavirus vaccine in the Dutch vaccination program would not be cost-effective, neither from the social perspective nor from the third payer perspective. A significant decrease in the vaccine-related costs would be necessary before the introduction of rotavirus vaccines in the Dutch vaccination program would become cost-effective. However, the introduction of the vaccine would be practically feasible and could probably reduce the burden of disease substantially.[137] Another important, but missing aspect in the consideration of including rotavirus vaccination in the NIP of the Netherlands would be information about circulating rotavirus strains in the Netherlands, and about possible extra-intestinal clinical syndromes caused by rotavirus. This information is incomplete at the present time. Although information about circulating strains could be obtained through intensive surveillance, collaboration of primary diagnosing laboratories to obtain strains for typing is a prerequisite.[155]

4.3 Varicella Zoster Virus (VZV) infection

H.J. Boot, H.E. de Melker, C. Wesselo

Vaccine

Availability and new developments

Recently (autumn 2006) the first four-fold combination vaccine, which contains the live vaccine viruses of measles, mumps, rubella and varicella (MMRV) (ProQuad®, SP MSD) has obtained a European marketing license. It is expected that a comparable vaccine of GSK (Priorix-tetra®) will obtain a European license in 2007. The feasibility of universal VZV vaccination in the Netherlands with these new MMRV combination-vaccines has recently been assessed using a

structured checklist.[156,157] In the USA a vaccine against herpes zoster (Zostervax®, Merck & Co USA) has obtained a marketing license in 2006 for people above 60 years of age.

Effectiveness

Universal varicella vaccination, applied from 1995 onwards as a single-shot vaccination with the monovalent Oka-vaccine, has led to a profound decline in varicella associated burden of disease (hospitalization and GP visits) in the USA.[158] Also a first report about universal varicella vaccination in Taiwan shows a profound decline in number of severe varicella cases.[159] Furthermore, also decline in hospitalization due to secondary bacterial infections, often found to be followed after primary VZV infection (i.e. invasive group A Streptococcus), is temporarily linked to the introduction of varicella vaccination USA.[160]

To reduce breakthrough infections which may occur with single vaccination, the CDC-ACIP has recently advised to expand VZV vaccination in the USA with a second dose. This second dose should preferably be given in combination with the second MMR vaccination (i.e. as MMRV) at four-six years of age.[161]

Adverse events

The safety profile of MMRV is expected to be comparable to the safety profile of measles, mumps and rubella vaccine. The most common side effects found in clinical trials are: injection site complaints, fever and rash (including measles-like rash and varicella-like rash).

Recommendations for vaccination, surveillance and control

Introduction of universal VZV vaccination in the Dutch NIP will prevent most of the GP-visits, hospitalizations and death that occur due to varicella zoster virus.[156] However, burden of disease is only moderate for a primary varicella infection, and chickenpox is generally seen as a benign childhood disease. With regard to desirability to implement MMRV in the NIP two major uncertainties are:[156] 1) the impact of universal varicella vaccination on the incidence of herpes zoster, as it is suggested that VZV transmission in the population stimulates the immune system of adults/elderly which might prevent or delay herpes zoster; 2) the cost-effectiveness ratio (CER) for the Dutch situation[10]. More specific insight into the varicella-related burden of disease in the Netherlands is desirable, as often not varicella but a secondary bacterial infection is the reason for hospitalization. In a joined effort with the paediatricians (‘Nederlands Signaleringscentrum Kindergeneeskunde’), the RIVM is currently gathering more information on the health care related cost and burden of disease of severe varicella-related disease. Furthermore, a dilemma is the implementation in the NIP since at present MMR is given at fourteen months and nine years. For MMRV it is likely that the second vaccination will be given in the second- fourth year of life.

4.4 Meningococcal serogroup B disease

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

Vaccine

Availability and new developments

Currently there is no vaccine available to prevent meningococcal serogroup B disease in Western Europe.

Disease

Burden of disease

Since 2002 the number of patients with meningococcal B disease has been decreasing, as can be seen in Figure 8 and Table 7. In 2005 the number of cases has decreased to 212, and until October 124 patients have been reported in 2006. This decreasing trend may be explained by natural fluctuation in the occurrence of the bacteria. Nevertheless, the nearly twofold unexplained decrease in incidence since 2000 is considerable and merits further investigation.

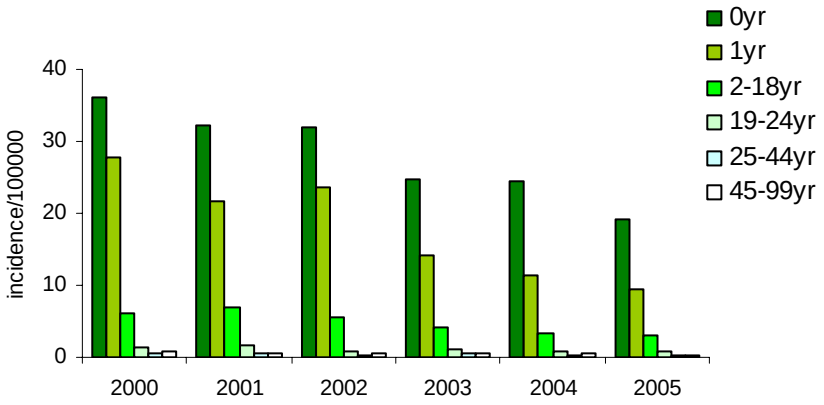

Figure 8. Age-specific incidence of meningococcal B disease by year, 2000-2005

Table 7. Absolute number of patients with meningococcal B disease

	2000	2001	2002	2003	2004	2005
0yr	73	67	65	50	49	37
1yr	56	44	49	29	23	19
2-18yr	198	233	189	142	110	102
19-24yr	17	18	11	13	10	11
25-44yr	30	22	20	23	14	16
45-99yr	43	36	39	36	32	27
Total	417	420	373	293	238	212

International perspectives

In Ireland the incidence of meningococcal B disease has also decreased, from 8.1/ 100,000 in 1999 to 4.1/100,000 in 2004.[42] In contrast, in the UK the incidence and predominance of serogroup B disease continuously increased until 2001 and only slightly decreased since then. The increase in the UK was in conjunction with an increase in B:4 isolates. However, the latter may be partly due to the availability of a better discriminating anti-serotype 4 monoclonal antibody.[162]

Despite changing trends, serogroup B remains the predominant meningococcal serogroup in Western Europe and at present there is no vaccine available to prevent the disease. A monovalent vaccine (MeNZB™) has been introduced for universal vaccination in New Zealand since 2004. The vaccine is given to all 6 weeks to nineteen year olds and only targets the epidemic strain PorA type P1.7-2,4. Among all young New Zealanders less than twenty years old, about 80% or about 949,000 have now completed three doses of the MeNZB™ vaccine. For Maori, the figure is about 72% or about 201,000. In 2005 group B meningococci continued to dominate throughout New Zealand causing 77.9% of all cases that could be typed. However, the proportion among all typed cases of the epidemic strain decreased from 73% (184/252) in 2004 to 59.5% (113/190) in 2005.[163] The vaccination schedule in New Zealand is now 3 vaccinations plus a booster dose in infants and 3 vaccinations in children until twenty years of age. The vaccine efficacy is 79.7% (95% CI 63-89%). Sofar they had 25 cases of vaccine breakthrough defined as >28 days post third dose (11 cases under the age of five years; 14 cases over the age of five years (including 1 death). New Zealand reports no safety concerns and so far 3 million doses are given (www.immune.org.nz).

During the 15th International Neisseria Conference in Cairns, Australia, there were quite a few reports on new NmenB vaccine development. Several vaccine companies are now performing phase-II clinical trials using protein vaccines other than PorA. Wyeth is testing a lipoprotein vaccine, Novsartis uses a 5 components protein vaccine and GSK is testing a vaccine composed of four minor outer membrane components.

Recommendations for vaccination, surveillance and research

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

M.A.B. van der Sande, W. Luytjes, T.G. Kimman

Vaccine

Availability and new developments

Since the withdrawal in the 1960s of a formaldehyde-inactivated alum-precipitated RSV vaccine due to disastrous worsening of disease during subsequent natural infection, developments towards a safe and effective vaccine have only again accelerated over the past few years. The young age of infection, the immunological immaturity, the interference of maternal antibodies, and the incomplete immune response to natural RSV are all major challenges. Currently, subunit, live attenuated, recombinant and polypeptide vaccines are being evaluated as well as plasmid vaccines coding for parts of the F and G surface glycoproteins and vaccinia vector.[164]
NVI is currently 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. 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 A was more prevalent in the Netherlands.
The pathogenesis of RSV is still not fully understood. Direct damage of the airways may result in airway dysfunction, while inflammatory processes are associated with severe disease as well. The relative importance of these two mechanisms in the severity of disease still remains unclear. For successful vaccine development, a clear understanding of the role of T-cell responses to primary and later exposure is essential.[165]

Disease

Burden of disease

Epidemiological data on trends in RSV in the Netherlands are available through the Virological Weekreports, in which laboratories report virological diagnosis. Based on these reports, the previous RSV season started in week 46 of 2005 and lasted till week 16 of 2006. Therefore, this year the RSV season was relatively short, and preceded the influenza season. The peak of notifications occurred in week 51.[166]
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 6.1% of patients presenting with an ILI, 5.4% of patients presenting with

another upper respiratory tract infection and in 9.4% of the patients presenting with a pneumonia or bronchiolitis.[68]
RSV disease is most serious among premature infants, infants with chronic lung disease or congenital heart disease, and the elderly. Apart from virological and patient-related determinants, also socioeconomic background and differences in host genetic background are likely to contribute to the variability in disease severity.
In the absence of an effective vaccine, palivizumab is still the mainstay for prevention among young children, although other antibodies such as MEDI-524 are still being tested for there effectivity.

Economic aspects
The University of Groningen has performed a study for the NVI to determine which vaccine prices would result in cost-saving vaccination. Cost of vaccination lies in acceptable ranges (below € 80 per doses). The study is based on child hospitalisations only, and may therefore underestimate the economic impact of RSV. Furthermore, the calculations depend on still unknown factors such as vaccine efficacy. Data on such factors will become available after clinical trials have started, planned at the end of 2007/beginning of 2008.

Recommendations for vaccination, surveillance and control
The prospects for a new RSV vaccine to be proven safe and effective appear to be good. 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

H.J. Boot, A.A.M. Gerritsen, M.J.J. Mangen, N.A.T. van der Maas, H.E. de Melker

Vaccine
Availability and new developments
Two HPV-subunit vaccines have been developed. The quadrivalent Gardasil®, which has been developed by SP MSD and has recently (September 2006) obtained a European marketing license, contains viruslike particles (VLPs) of HPV-6,-11,-16,-18 and an aluminium adjuvant. HPV-6 and -11 are the causative agents of most (80-95%) genital warts. The bivalent Cervarix®, which has been developed by GSK and is expected to gain access to the European market early 2007, contains only the HPV-16/18 VLPs, but is adjuvated with a new and more potent adjuvant (AS04) containing next to aluminium also monophosphoryl lipid (MPL) A.[167]

Effectiveness

In 2006 two reports on the effectiveness of HPV-vaccination have been published.[168,169] The presented results are in line with earlier reports: i.e. 100% efficacy in preventing persistent HPV-16/18 infection of the cervix and against HPV-16/18 induced pre-stages of cervical cancer. The efficacy against transient HPV-16/18 infection is, however, not complete (80-90%). Transient infection will not induce cervical cancer, but will allow circulation and hampers the establishment of herd-immunity. Long-term efficacy data are not available yet, as the clinical trials with these vaccines are only ~five years underway.[168,169] Cross-protection against incident HPV-45 (vaccine efficacy of 94%) and HPV-31 (vaccine efficacy of 55%) infections has been reported for Cervarix®.[168] Gardasil® was reported to induce antibodies that recognize HPV-31, -45, -52, and -58, which is indicative for cross-protection.[170]

Adverse events

The results of clinical trials did not show any serious adverse event that was causally related to vaccination. Furthermore, there were no large differences in common adverse events between vaccine recipients and placebo controls. In trials of the quadrivalent vaccine nine cases of possible autoimmune disorder were found in the patients (0.76/1,000; 95% CI 0.44-1.31), compared to three in the controls (0.31/1000; 95% CI 0.11-0.91). It must be stated that there is not enough information to address causality to these cases. The reported incidence of autoimmune disorders after Gardasil® vaccination appear to be consistent with natural incidence.[171] Active surveillance of adverse events like arthritis can be done in collaboration with NSCK ('Nederlands Signaleringscentrum Kindergeneeskunde').

About 90% of all subjects had injection site reactions, which were all causally related. Systemic adverse events were reported in 69-86% of all cases, only in part causally related. No effect of vaccine-related adverse events was found on compliance with completion of the vaccination course.[168,169] Monitoring of (long-term) adverse events will have to be conducted. For Cervarix® this is also relevant, because this vaccine contains the new, MPL-containing, adjuvant.[167]

Pathogen

More than 80 different HPV genotypes have been identified, of which ~40 can infect the female genital tract and ~15 genotypes are regarded as high risk genotypes, which can induce cervical cancer.[172] 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,[173,174] probably resulting in a stronger selection pressure. The consequences of new antigenic or virulent variants are, however, expected to be minor. Strains of one genotype but belonging to different lineages and with different pathogenic features are found to co-circulate.[175]

Disease

Epidemiology

A persistent (5-25 years) infection with a high risk HPV-strain is a prerequisite for developing cervical cancer. In Europe ~75% of the cervical cancer cases are caused by either HPV-16 (~60%) or -18 (~15%). HPV is highly transmissible, and it is estimated that ~80% of the sexual-active women are infected at least once during life time. Most infected women spontaneously clear the HPV-infection. In developed countries cervical cancer screening programs are in place which reduces the burden of disease due to HPV-infection by detection of cervical lesions and pre-stage of cancer. Despite the screening program ~600 cases of cervical cancer are reported each year in the Netherlands, and this is fatal for ~200 of these women.

There are no data available on the incidence of HPV-16 and -18 in the Netherlands, and prevalence data are only available for women from the screening population and not for the general population. A study among 21,996 women recruited from the regular screening program (aged 30-60 years) found that 1.6% of all women had a single or multiple infection with HPV-16 and 0.4% with HPV-18 (PROBASCAM: Bulkmans, personal communication).[176] A study among 83 patients with squamous cell carcinoma showed that 74% of the patients with a single infection were infected with HPV-16 and 11% with HPV-18. In patients with adenocarcinoma (n=70) these figures were 34% and 55%, respectively.[177] Because Dutch data on HPV-16/18 prevalence are largely missing for the 15-30 years-old cohort of the general population, the (cost-) of effectiveness of catch-up vaccination and male vaccination is difficult to predict. Data on HPV-16/18 incidence in this group, for example by a serologic survey for HPV-16/18 antibodies,[178,179] should be gathered.

Burden of disease

The disease burden in DALYs is composed of YLL and YLD (years lived with disability). On average 610 cervical cancer cases and 215 fatal cervical cancer cases per year are reported (2001 to 2003).[180] Fatality due to cervical cancers results on average in 20.5 YLL per case, resulting in a total estimate of 4,400 YLL per year. Assuming that morbidity is valued with 1.6 YLD per average fatal cervical cancer case and with 1.8 YLD per average non-fatal cervical cancer cases,[179] YLD due to morbidity is estimated at 1,000 per year. The disease burden is thus estimated at 5,400 DALY per year. Not considered in this estimate are the disease burden due to the different cervical intraepithelial neoplasia (CIN) grades, genital warts, as well as the reduced quality of life of partners and children of cervical cancer patients.

Economic aspects

With the help of a Markov model[181,182] that simulates the natural history of cervical cancer for a cohort of women the direct (static) effect of vaccination in the Dutch female population was modelled and crude CER, expressed in net cost (€) per life years gained (LYG), were estimated.[183] In these calculation it was assumed that only girls would be vaccinated at the age of ten to twelve years. Using the third payer perspective the direct health care costs were estimated according to the Dutch guidelines. Costs were discounted at 4% and effects at 1.5%. Assuming life-long protection a total of 400 cervical cancer cases would be avoided, whereof 107 fatal

cases. Assuming a cost price of € 100 per dose and no booster vaccination, the estimated CER would be € 24,000 per LYG, if life long protection is assumed. If however, one additional booster would be required, than the CER would be € 28,000, assuming life-long protection. The results were strongly depending on: a) the vaccine cost price assumed; b) the duration of protection; c) the level of protection, although not explicitly modelled, and d) the discount rate chosen. Not considered in this analysis were, given the static nature of the model, indirect effects due to reduced transmission of HPV in a partially vaccinated population. Despite all uncertainties and using conservative estimation (i.e. vaccine efficacy of 80%, no impact on the screenings program, no reduced transmission, no cross-protection and no impact on non-cervical cancers), the analysis indicates an acceptable cost-effectiveness ratio for HPV-vaccination of pre-adolescent girls for all plausible scenarios. More information with regard to international cost-effectiveness studies could be find in a report on the economic evaluation of prevention.[10]

International perspectives

Gardasil® has already obtained a marketing license in several developed countries (including the USA, Mexico, Canada, New Zealand and Australia). This vaccine is generally licensed for girls between 9-26 years of age. Europe and Australia have, however, also granted permission for vaccination of boys/men, although effectiveness of male vaccination has not been proven.[184] Large scale vaccination of all females of 10 to 26 year of age with Gardasil® is expected to start in 2007 in the USA.

Recommendations for vaccination, surveillance and control

A lot of international data on HPV-prevalence, cervical cancer incidence and clinical trials of HPV-vaccination has been published in recent years (e.g. monograph of Vaccine (supplement 3 of volume 24, 2006)). The RIVM/CIb is currently assessing a possible introduction of universal HPV of pre-adolescent girls in the Netherlands, by using a recently developed model for introduction of a new vaccine in an NIP.[185] One of the most important issues concerning the introduction of HPV-vaccination is its long-term efficacy. Overall HPV-VE might be influenced by waning immunity, cross-protection, reduced transmission, and genotype replacement. Although VE over time is a major factor for all vaccines, this is especially important for HPV-vaccination of pre-adolescent girls with an anticipated time-lag of >fifteen years before the first effects can be expected, and >5 decades before full impact will be reached.

HPV-vaccination will, in time, 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. In order to get a better insight in the direct and indirect effects of HPV vaccination programs, it is necessary to develop mathematical models that combine the effect of vaccination, reduced HPV transmission, and screening programs to optimize the most (cost-) effective reduction of cervical cancer. Such a model can be used to evaluate potential changes in the cervical cancer screening program and introduction of screening for high-risk HPV infections.[186]

A joined workshop by the Medicines Evaluation Board (CBG), Health Council (Gezondheidsraad) and RIVM was held in November 2006 to address issues related to introduction of HPV vaccination and cervical cancer screening in the Netherlands. Items of this

workshop were: HPV incidence/prevalence in young women, vaccination of men, desirability and extent of a catch up campaign, changes in the screening program (including high-risk HPV testing), need for (dynamic) modelling studies, and monitoring of adverse events and vaccine efficacy.

5. Discussion

In this chapter we address several broader issues of current interest in the field of routine vaccination into a NIP which include: considering impact on effectiveness due to changes in the NIP, vaccination of other age groups, acceptance of vaccination, discounting in economic evaluation studies and the role of notification in surveillance of vaccine preventable diseases.

Considering impact on effectiveness due to changes in the NIP

The NIP has been adjusted several times in 2006 with the introduction of vaccination against a new target disease (pneumococcal disease), a change in schedule for a vaccination already included (hepatitis B), replacement of one vaccine by another (e.g. Infanrix-IPV+Hib by Pedicacel) and combination of previously given separate vaccines (DT-IPV with aP at four-years). All changes – also if only temporary – need careful consideration not only because of (practical) implementation into the NIP but also because of (future overall) effectiveness and safety of the NIP. For example the addition of pneumoccocal vaccine required the change to a hexavalent vaccine (DTaP-HBV-IPV/Hib) for children of immigrants, since this is the only available combination vaccine including HBV and because only two injections should be given at one time (advice Health Council). This could affect the immune response to various NIP components, including pertussis, Hib and hepatitis B. Therefore, we plan to study the immunogenicity of the different components among children of immigrants to monitor the effects of this change. The impact of adding pneumococcal vaccine on DTaP-IPV/Hib will also be studied. Thus, in general, in any decision for a change in the NIP, the potential impact on (effectiveness of) the programme should be taken into account.

Vaccination of other age groups

The NIP at present covers the age range from infants to nine year-olds. The annual influenza vaccination programme is the only vaccination programme currently targeting other age groups (i.e. individuals aged 65 years and over, and individuals at increased risk of morbidity and mortality following an influenza infection). However, in the near future possibly newly developed vaccines as well as already available vaccines could be offered to (pre-) adolescents and/or adults. These vaccines include acellular pertussis vaccine, hepatitis B vaccine, HPV vaccine and zoster vaccine. Vaccination of these age groups raises the question on how to achieve and preserve successful vaccination programmes. Many factors should be taken into account such as vaccination approach, how to organize – i.e. inside or outside the NIP – such programmatic vaccination programmes, acceptance of vaccination (e.g. against sexually transmitted infections like HPV), the need for information, education and/or communication depending on various target groups (e.g. parents, health care professionals). While any change in NIP (see above) needs to be prepared, this is even more the case for those vaccinations that target age groups outside the historical age frame of the NIP.

Acceptance of vaccination

Vaccine uptake is a key factor for the success of a vaccination programme. In general vaccine coverage is very high in the Netherlands. Despite this very good achievement several topics need further attention.

Firstly, there are pockets of unvaccinated individuals, in particular geographically clustered orthodox reformed individuals, which poses a continuous threat of new epidemics such as observed recently for rubella. Efforts to increase uptake in these groups remain necessary. Also, monitoring should be performed every now and then of the number of individuals that belongs to these groups and the proportion that accepts vaccination, to be able to specify the risk for new epidemics.

Secondly, high vaccination coverage can not be guaranteed per se on the long term. Insight into reasons and characteristics for compliance and non-compliance (also outside the orthodox reformed groups) is relevant in particular to develop effective information for both parents and professionals. The new vaccination coverage database offers opportunities to study vaccination uptake in more detail and specific studies on vaccine acceptance could further address this.

Finally, for new vaccines knowledge on acceptability in the population of the vaccine preceding any decision regarding extension of the NIP is desirable. On the one hand to be able to predict the impact of vaccination on disease burden, and on the other hand to develop good communication tools to optimize uptake. As mentioned previously in the decision to add any new vaccine or vaccine combination to the NIP the potential influence on the total effectiveness (interference with other components, influence on uptake of other vaccinations in the NIP) should also be kept in mind.

Discounting costs and health effects and its impact on the results of economic evaluation studies

Public health economic analyses are a relevant part of the broad evaluation with respect to potential vaccine candidates for a NIP. In the Netherlands, the Dutch guidelines for public health economic evaluation recommend the use of a common so-called discount rate, i.e. to account that the financial costs and revenues occur at different points in time. Until mid-2005, this discount rate was 4% for both costs and health effects.[187,188] Other countries and other analysts use slightly different discount rates, but in general the recommended rate is within the 3% to 5% range. Since mid-2005, however, the Dutch guidelines for public health economic evaluation have changed. Now it is recommended to use a discount rate of 1.5% for health effects and 4% for costs.[189] The main reason to change the recommendation was to reduce the disadvantage in economic evaluations of preventive interventions (due to the fact that their benefits occur in the (far) future) compared to curative interventions. Especially in the evaluation of interventions with health benefits in the far future, such as infectious diseases-related interventions or changes in lifestyle, the practice of discounting these future benefits at a 4% discount rate resulted in relatively unfavourable cost-effectiveness ratios (Table 8).

Table 8. Example: estimated CERs expressed in euro per LYG for an avoided premature death of an infant with a life-expectancy of 80 years for which net costs of € 1 million were made, using different discount rates for health effects.

Net costs	*Remaining life-years*	*Remaining years if discounted at … %*		*Estimated CER*
		Discount rate	Years that count in the denumerator of the CER	
€1.000.000	80 years	0%	80	€12.500/LYG
€1.000.000	80 years	1.5%	46.6	€21.459/LYG
€1.000.000	80 years	4%	24	€41.667/LYG

Using the new Dutch guidelines results, in general, result in more favourable cost-effectiveness ratios for preventive interventions compared to the previous situation. The consequence may be that some of the previously evaluated and cost-ineffective programs might become cost-effective if an update of the previous analysis is made, only because a lower discount rate would be applied. Therefore, we recommend that for each cost-effectiveness study an extensive scenario analysis is conducted. Here, costs and consequences should be presented in undiscounted as well as discounted figures, and different discount rates should be used. Such a scenario analysis allows users of cost-effectiveness research to investigate the impact of discounting easily.

The role of notification in surveillance of vaccine preventable diseases

Currently the list of notifiable diseases is being reviewed. The most important consideration with regard to the inclusion of a disease in the new infectious diseases law (‘Wet Publieke Gezondheid’) is the need and possibility for disease control measures. Routine vaccination in the NIP is an important disease control measure to reduce the burden of vaccine preventable diseases in our population. Surveillance of vaccine preventable disease is a prerequisite to monitor the impact of a large scale health intervention by a vaccination programme launched by the government. It is therefore important that all diseases targeted by the NIP are notifiable diseases. At present this is not the case for tetanus, mumps, Hib and invasive pneumococcal disease, while surveillance for these diseases is lacking or suboptimal. Therefore we recommend that these diseases should be included in the future list of notifiable diseases.

6. Recommendations

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

Vaccination

- Measles vaccination strategy during an outbreak needs to be addressed given that a new outbreak in areas with low vaccine uptake is expected in the coming years.
- Taking into account the results of economic evaluations, an universal immunization vaccination strategy of hepatitis B needs to be reconsidered.
- The selective BCG vaccination strategy targeting children from countries with a high tuberculosis prevalence should be continued.
- Given the low incidence of hepatitis A, the dissimilarities in vaccine and vaccination schedule for hepatitis A and B, and the unknown cost-effectiveness of hepatitis A/B vaccination, routine vaccination against hepatitis A is not (yet) recommended.
- The inclusion of rotavirus vaccination in the NIP should be considered. A substantial reduction in burden of disease could be reached with vaccination. However, a significant decrease in vaccine related costs would be necessary before universal rotavirus vaccination will become cost-effective.
- When further information on burden of severe varicella-related disease becomes available from paediatric surveillance, the desirability of routine varicella vaccination needs to be reconsidered.
- Given the severity of disease, ongoing development of RSV and meningococcal B disease candidate vaccines is recommended. The prospects for a new RSV vaccine to be proven safe and effective appear good.
- The recent marketing license for the first HPV-vaccine necessitates a decision on the uptake of HPV as part of the NIP. Various issues – in particular long-term VE, safety and integration with the screening programme – need to be addressed before such a decision can be made.

Surveillance

- For pertussis and rotavirus a surveillance system should be set up to allow systematic collection of circulating strains.
- Making tetanus, mumps, Hi(b) and invasive pneumococcal disease mandatory notifiable diseases is essential to obtain more insight in the epidemiology of these diseases and the effectiveness of the programme in the Netherlands.
- During outbreaks, systematic laboratory testing of cases of rash illness (measles, rubella) is an important tool for outbreak investigation. In inter-epidemic periods, rash illness surveillance may contribute to certification of elimination and early warning.
- For mumps, enhanced surveillance, including appropriate laboratory confirmation, is recommended.

- For invasive pneumococcal disease the intensified surveillance should be continued to monitor the effects of the introduction of pneumococcal vaccination in the NIP.
- For influenza it would be advisable to extend the surveillance of uptake of vaccination to include other high-risk groups. Furthermore, surveillance of ILI and influenza among GPs can be further strengthened by linked surveillance of pneumonia.
- Ongoing surveillance is required for meningococcal serogroup C disease to be able to detect vaccine failures.

Research

- To obtain insight in the most effective pertussis vaccination strategies which protect 0-6 month old infants which are too young to be (fully) immunized, further development of dynamic pertussis models, based on the results obtained in the transmission study is desirable.
- We recommend the further characterization of the pertussis 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.
- Since it is not clear whether the recently introduced acellular pertussis vaccine (aP) also confers some protection against *B. parapertussis*, we advice to study the efficacy of the acellular vaccine against *B. parapertussis* in a mouse model.
- The availability of new national seroprevalence data following the current PIENTER 2 study will allow study of the seroprevalence of the (future) target diseases of the NIP. Specific recommendations were made in this report with regard to tetanus (evaluate the Dutch guideline for tetanus prophylaxis), polio virus (examine possible waning in immunity in elderly) and MMR in infants (information on a change of the first MMR vaccination to an earlier age).
- It is necessary to renew the Dutch contingency plan in case of a polio outbreak, and also for measles an action plan for outbreak investigation and control is needed.
- To examine the risk of the emergence of cVDPVs we recommend to analyze whether enteroviruses circulating in the Netherlands can recombine with polioviruses and give rise to virulent strains.
- Further research is required to determine the role of the differences in the capsular gene cluster on effectiveness of the Hib vaccine.
- Field studies to assess the effectiveness of the mumps component of the MMR vaccine are recommended.
- A next measles outbreak would offer opportunities for research. Areas to be looked at include field evaluation of VE, risk factors for vaccine failure, risk factors for non-vaccination, effects of waning immunity and correlates of protection.
- Currently a study on antenatal screening for rubella is performed at the RIVM to come to an evidence-based advice.
- We recommend to investigate the opportunities to study hepatitis B vaccination and MS in the Netherlands.

- The effect of the combination vaccines on antibody responses to the different components (e.g. D, T, aP, HBV, IPV, Hib) should be studied.
- To determine the number of doses of Prevenar to provide sufficient protection against pneumococcal disease, the clinical and immunological data, and the impact on serotype distribution in the Netherlands (four doses) and the UK (3 doses) should be compared.
- To assess the desirability of offering pneumococcal vaccination to the elderly in the Netherlands, a randomised clinical trial should be performed.
- The further development of molecular typing techniques gives new insights in transmission patterns of *M. tuberculosis*, which will assist a strategy aimed at elimination.
- In order to get better insight in the direct and indirect effects of HPV vaccination programs, it is recommended to develop mathematical models that combine the effect of vaccination, reduced HPV transmission, and screening programs to optimize the most (cost-)effective reduction of cervical cancer. Such a model can be used to evaluate potential changes in the cervical cancer screening program and introduction of screening for high-risk HPV infections.

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Annex 1. Overview changes in the NIP since 2000

Table A.1: NIP 1st July 2001 – 31st August 2002
(change: aP added at four 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 A.2: NIP 1st September 2002 – 28th February 2003
*(change: Men C added at fourteen 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 A.3: NIP 1st March 2003 – 31st December 2004
(change: Hib given combined with DTwP-IPV at two, three, four and eleven months of age, for all children born on or after 1st April 2002; and HBV added for infants in specified risk groups at two, three, four and eleven 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 A.4: NIP 1st January 2005 – 31st December 2005
(change: wP replaced by aP at two, three, four and eleven 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 MS
3 months	**DTaP-IPV/Hib**	**Infanrix IPV+Hib/GSK**		
4 months	**DTaP-IPV/Hib**	**Infanrix IPV+Hib/GSK**	HBV**	HBVAXPRO/SP MS
11 months	**DTaP-IPV/Hib**	**Infanrix IPV+Hib/GSK**	HBV**	HBVAXPRO/SP MS
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 A.5: 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 two, three, four and eleven 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 A.6: NIP from 1st June – July/August 2006
(change: pneumococcal vaccination added at two, three, four and eleven months of age, for all children born on or after 1st April 2006; and introduction of combined vaccine DTaP-HBV-IPV/Hib at two, three, four and eleven months of age for children in specified risk groups born on or after 1st April 2006 [as a consequence a HBV vaccination at three months of age is added])

In general:

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

Specified risk groups:

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

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

Table A.7: NIP from July/August 2006 onwards
(change: in July/August 2006 a combined DTaP-IPV vaccine will be introduced at four 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.

Annex 2. Composition of vaccines used in 2006

Vaccine	Composition
Pediacel/SP MSD RVG 32118 Diphtheria, tetanus, 5 component acellular pertussis vaccine, inactivated poliomyelitis vaccine and conjugated *Haemophilus influenzae* type b-vaccin (adsorbed) 0.5 ml	Purified diphtheria toxoid ≥ 30 IU Purified tetanus toxoid ≥ 40 IU Purified pertussis toxoid (PT) 20 µg Purified filamentous haemagglutinin (FHA) 20 µg Purified fimbrial agglutinogens 2 and 3 (FIM) 5 µg Purified pertactin (PRN) 3 µg Inactivated type 1 poliovirus (Mahoney) 40 DU Inactivated type 2 poliovirus (MEF-1) 8 DU Inactivated type 3 poliovirus (Saukett) 32 DU *Haemophilus influenzae* type b polysaccharide (polyribosylribitol phosphate) 10 µg conjugated to tetanus toxoid (PRP-T) 20 µg absorbed to aluminium phosphate 1.5 mg
BMR vaccine/NVI RVG 17654 Mumps, measles and rubella vaccine 0.5 ml	Mumps virus (Jeryl Lynn) ≥ 5000 p.f.u. (plaque forming unit) Measles virus (Moraten) ≥ 1000 p.f.u. Rubella virus (Wistar RA 27/3) ≥ 1000 p.f.u.
DT-IPV vaccine/NVI RVG 17641 Diphtheria (adsorbed), tetanus (adsorbed) and inactivated poliomyelitis vaccine 1 ml	Diphtheria-toxoid* ≥ 5 IU Tetanus toxoid* ≥ 20 IU Inactivated poliovirus type 1 ≥ 40 DU Inactivated poliovirus type 2 ≥ 4 DU Inactivated poliovirus type 3 ≥ 7.5 DU *adsorbed to aluminium phosphate 1.5 mg Al^{3+}
Prevenar/Wyeth EU/1/00/167 Pneumococcal saccharide conjugated vaccine (adsorbed) 0.5 ml	Pneumococcal polysaccharide serotype 4* 2 µg Pneumococcal polysaccharide serotype 6B* 4 µg Pneumococcal polysaccharide serotype 9V* 2 µg Pneumococcal polysaccharide serotype 14* 2 µg Pneumococcal oligosaccharide serotype 18C* 2 µg Pneumococcal polysaccharide serotype 19F* 2 µg Pneumococcal polysaccharide serotype 23F* 2 µg * Conjugated to the CRM_{197} carrier protein and adsorbed to aluminium phosphate 0.5 mg
NeisVac-C/Baxter RVG 26343 Conjugated meningococcal C saccharide vaccine (adsorbed) 0.5 ml	Neisseria meningitidis (C11-strain) Polysaccharide O-deacetylated 10µg Conjugated to tetanus toxoid 10-20 µg Adsorbed to aluminium hydroxide 0.5 mg Al3+
Acellulair pertussis vaccine/GSK RVG 22335 3 component acellular pertussis vaccine 0.5 ml	Pertussis toxoid (PT) ≥ 25µg Filamentous haemagglutinin (FHA) ≥ 25µg Pertactin ≥ 8µg Adsorbed to aluminium phosphate

HBVAXPRO/ SP MSD EU/1/01/183 Hepatitis B vaccine for children and adolescents 0.5 ml	Hepatitis B-virus surface antigen, recombinant* (HBsAg) 5µg Adsorbed to amorphe aluminiumhydroxyphosphatesulphate 0.25mg *yeast strain Saccharomyces cerevisiae (2150-2-3)
Infanrix Hexa/GSK EU/1/00/152 Difteria, tetanus, pertussis (acellular component), hepatitis B (rDNA), inactivated poliomyelitis vaccine and conjugated *Haemophilus influenzae* type b-vaccine (adsorbed) 0.5 ml	Adsorbed diphtheria toxoid $\geq$ 30 IU Adsorbed tetanus toxoid $\geq$ 40 IU Adsorbed pertussis toxoid (PT) 25 µg Adsorbed filamentous haemagglutinin (FHA) 25 µg Adsorbed pertactin (PRN) 8 µg Adsorbed recombinant HBsAg protein 10 µg Inactivated type 1 poliovirus (Mahoney) 40 DU Inactivated type 2 poliovirus (MEF-1) 8 DU Inactivated type 3 poliovirus (Saukett) 32 DU Adsorbed purified capsular polysaccharide of Hib (PRP) 10 µg covalently bound to tetanus toxoid (T) 20-40 µg
Triaxis Polio/SP MSD RVG 27569 Difteria, tetanus, pertussis (acellular component) and inactivated poliomyelitis vaccine (adsorbed) 0.5 ml	Purified diphtheria toxoid $\geq$ 2 IU Purified tetanus toxoid $\geq$ 20 IU Purified pertussis toxoid (PT) 2.5 µg Purified filamentous haemagglutinin (FHA) 5 µg Purified fimbrial agglutinogens 2 and 3 (FIM) 5 µg Purified pertactin (PRN) 3 µg Inactivated type 1 poliovirus (Mahoney) 40 DU Inactivated type 2 poliovirus (MEF-1) 8 DU Inactivated type 3 poliovirus (Saukett) 32 DU adsorbed at aluminium phosphate 0.33 mg
MMR Vax /SP MSD RVG 17672 Mumps, measles and rubella vaccine 0.5 ml	Mumps virus (Jeryl Lynn) $\geq$ 5000 $TCID_{50}$ (tissue culture infectious doses) Measles virus (Schwartz) $\geq$ 1000 $TCID_{50}$ Rubella virus (Wistar RA 27/3) $\geq$ 1000 $TCID_{50}$
Priorix/GSK RVG 22052 Mumps, measles and rubella vaccine 0.5 ml	Mumps virus (RIT 4385) $\geq 10^{3.7}$ $CCID_{50}$ (cell culture infectious doses) Measles virus (Schwartz) $\geq 10^{3.0}$ $CCID_{50}$ Rubella virus (Wistar RA 27/3) $\geq 10^{3.0}$ $CCID_{50}$

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