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The national immunisation programme in the Netherlands: current status and potential future developments

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Rapport in het kort

Het Rijksvaccinatieprogramma in Nederland: huidige situatie en ontwikkelingen

Het Rijksvaccinatieprogramma in Nederland is zeer effectief en veilig. Vaccinatie van een aantal andere (leeftijds)groepen zou het succes en de effectiviteit van het vaccinatieprogramma kunnen vergroten, en is aan te bevelen. Uitbreiding van het programma met nieuwe doelziekten kan voor een aantal ziekten aanzienlijke gezondheidswinst opleveren. Voortdurende bewaking van de effectiviteit van het programma is van groot belang. Handhaven van de hoge vaccinatiegraad is essentieel om terugkeer van de ziekten te voorkómen.

De ziekten waartegen wordt gevaccineerd zijn grotendeels onder controle. Vaccinatie van (jong) volwassenen nu (kinkhoest) of in de toekomst (bof, mazelen, rodehond, hepatitis B) zal verder verbetering kunnen geven. Ook andere vaccinatiestrategieën verdienen aandacht, zoals vaccinatie van pasgeborenen of aanstaande ouders. De vervanging van het huidige difterie, tetanus, poliomyelitis, hele-cel kinkhoest en *Haemophilus influenzae* vaccin (DKTP/Hib) door een combinatievaccin met een a-cellulaire kinkhoestcomponent (DK_ATP/Hib) ingevoerd begin 2005 moet nauwkeurig worden gemonitored, zowel voor kinkhoest als de overige vaccincomponenten.

Het Rijksvaccinatieprogramma kan met vaccins tegen andere ziekten uitgebreid worden. Pneumokokken-vaccinatie van kinderen levert belangrijke gezondheidswinst op. De wenselijkheid om waterpokken-vaccinatie te introduceren - mogelijk in een combinatievaccin met bof, mazelen en rodehond - moet bestudeerd worden. Als tegen meningokokken B, respiratoir syncytieel virus en humaan papillomavirus effectieve en veilige vaccins op de markt komen, is uitbreiding van het vaccinatieprogramma naar verwachting raadzaam. Dit geldt (nog) niet (of in mindere mate) voor de al beschikbare vaccins tegen influenza, hepatitis A en tuberculose. Voor deze ziekten is continuering van het huidige beleid nodig met mogelijke verlaging van de leeftijd voor influenzavaccinatie van 65 jaar naar 50 jaar. De wenselijkheid van vaccinatie van kinderen tegen influenza is een punt voor nader onderzoek, evenals pneumokokken-vaccinatie van ouderen. Vaccinatie tegen herpes simplex virus-2 en rotavirus is nog niet mogelijk. Vaccinatie levert naar verwachting relatief beperkte gezondheidswinst op voor herpes simplex virus-2. Als een rotavirus vaccin beschikbaar komt is een kosten-effectiviteitsanalyse aangewezen.

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

Abstract

The national immunisation programme in the Netherlands: current status and potential future developments

The national immunisation programme in the Netherlands is very effective and safe. Vaccination of some other (age)groups may, however, improve the success and effectiveness of the programme and is recommended. Extension of the programme with new target diseases may result in considerable health gain. Monitoring the effectiveness of the programme remains important. Maintaining high vaccine uptake is vital to prevent (re)emergence of disease.

The target diseases are largely under control. Vaccination of (young) adults now (pertussis) and in the future (mumps, measles, rubella, hepatitis B) may give further improvement. Also, other vaccination strategies need attention such as maternal or newborn vaccination for pertussis. The switch to a DTPa-IPV/Hib combination vaccine in 2005 should be monitored carefully both for pertussis and other components.

The national immunisation programme could be extended with new target diseases. Pneumococcal vaccination for children is expected to give important health gain. The desirability to introduce varicella vaccination – possibly in combination with mumps, measles and rubella – needs further study. When effective and safe vaccines become available for meningococcal serogroup B, respiratory syncytial virus and human papillomavirus, extension of the immunisation programme might be advisable. Extension of the programme with available vaccines for influenza, hepatitis A or tuberculosis is not (yet) recommended. For these diseases the current policy needs to be continued, possibly with lowering the age of influenza vaccination from 65 years to 50 years of age. The desirability to vaccinate children against influenza and elderly against pneumococcal infection needs further investigation. Vaccination against HSV-2 or rotavirus is not possible yet. The health gain is expected to be limited for HSV-2. When a vaccine for rotavirus comes available a cost-effectiveness analysis is needed.

Key words: National immunisation programme, MMR, DTP/IPV/Hib, hepatitis B, meningococcal serogroup C.

Preface

The National Institute for Public Health and the Environment was asked to inform the Ministry of Health, Welfare and Sports on developments with regard to vaccine-preventable disease that are relevant for the Netherlands, in particular with respect to epidemiology and (cost)effectiveness.
In this report, we aim to produce an overview of the status of the programme mainly based on disease, vaccine coverage, safety, immuno- and pathogen surveillance. We make recommendations to improve the control now and in the future of the current target diseases. Furthermore, the aim of the report was to address the need and possibility for extension of the programme with new target diseases. We draw conclusions and make recommendations with regard to extension of the national immunization programme in the Netherlands based on the current available knowledge with regard to vaccine, disease, pathogen and cost-effectiveness. Furthermore, we address what information is lacking to found such a decision. We hope that this report will contribute to the decision making process on the composition of the National Immunisation Programme.

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Abbreviations

ACIP	Advisory Committee on Immunisation Practices
AIDS	Acquired Immunodeficiency Syndrome
AFP	Acute flaccid paralysis
Anti HBc	antibody against hepatitis B core protein
Anti HBs	antibody against hepatitis B surface protein
ARIEL	Acute Respiratoire Infecties in de Eerste Lijn (Acute Respiratory Infections in Primary Care)
BCG	Bacil Calmette Guerin
CBS	Central Bureau for Statistics
CDC	Center for Disease Control
CI	Confidence interval
CIE	Centrum voor infectieziekten Epidemiologie (Centre for Infectious diseases Epidemiology)
CJD	Creutzfeld Jacob Disease
CNS	Central Nervous System
CRS	Congenital Rubella Syndrome
CSF	Cerebrospinal fluid
cVDPV	virulent circulating vaccine-derived polioviruses
DALY	Disability-adjusted Life Year
DISC	Disabled infectious single cycle
DNA	Desoxyribo Nucleic Acid
DOT	Directly observed treatment
DPSU	Dutch Paediatric Surveillance Unit
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
ELISA	Enzyme linked immunosorbent assay
ESEN	European Sero epidemiology network
EU	European Union
FDA	Food and drug administration
GGD	Gemeentelijke gezondheidsdienst (Municipal Health Service)
GG&GD	Gemeentelijke gezondheidsdienst (Municipal Health Service)
GP	General Practitioner
GR	Gezondheidsraad (Health Council)
GSK	Glaxo Smith Kline
HAV	Hepatitis A virus
HIB	Hepatitis B immunoglobulines
HBsAg	hepatitis B surface protein antigen
HBV	Hepatitis B virus
HD	Human Dose
HepB	Hepatitis B
Hib	*Haemophilus Influenzae B*
HIV	Human Immunodeficiency Virus
HPV	Human papilloma virus

HSV	Herpes Simplex Virus
ICER	Incremental Cost Effectiveness Ratio
IDU	Injecting Drug User
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IGZ	Inspectie voor de gezondheidszorg (Inspection of Health Care)
ILI	Influenza like illnesses
IOU	International opacity units
IPV	Inactivated Polio Vaccine
ISIS	Infectious diseases Surveillance Information System
IU	International Units
JL	Jeryl Lynn strain
LAIV	Life attenuated influenza vaccine
LIS	Laboratorium voor infectieziektesurveillance (Laboratory for Infectious diseases Surveillance)
LPS	lipopolysaccharide
LTR	Laboratorium voor Toetsing van het Rijksvaccinatieprogramma (Laboratory for Vaccine-preventable Diseases)
LVE	Landelijke Vereniging voor Entadministraties
Men B	Meningococci B
Men C	Meningococci C
MHS	Municipal Health Service
ml	millilitre
MLST	Multilocus Sequence Typing
MMR	Combination of Measles, Mumps and Rubella vaccines
MMRV	Combination of Measles, Mumps, Rubella en Varicella vaccines
mo	months
MPL	monophosphoryl lipid
MR	Combination of measles and rubella vaccine
MSM	Men who have sex with men
MV	Measles Virus
NDR	National Disease Registry
NIP	National Immunisation Programme
NPG	Nationaal programma griepppreventie (National programme influenza prevention)
NRBM	Nederlands Refentielaboratorium voor Bacteriële meningitis (Netherlands Reference Laboratory for Bacterial Meningitis)
NVI	Netherlands Vaccine Institute
NVVA	Netherlands association of nursing home physicians
OMV	Outer membrane vesicles
OPV	Oral Polio Vaccine
P_A	Acellular pertussis vaccine
PCR	Polymerase Chain Reaction
PFP	purified protein
PIENTER	Peiling Immunisatie Effect Nederland Ter Evaluatie van het Rijksvaccinatieprogramma (Assessing the immunisation effect of the Netherlands to evaluate the NIP)

PorA	Porin A
PorB	Porin B
PRP	Polyrisylribitol Phosphate Polysaccharide
P_W	Whole cell pertussis vaccine
py	person years
QALY	Quality Adjusted Life Years
RGI	Rubella Genotype I
RIVM	Rijksinstituut voor Volksgezondheid en Milieu (National Institute for Public Health and the Environment)
RNA	Ribonucleic Acid
RSV	Respiratory Syncytial Virus
RV	Rubellavirus
SOA	Seksueel overdraagbare aandoening (Sexual Transmitted Disease)
STD	Sexual Transmitted Disease
STDEV	Standard Deviation
STI	Sexual Transmitted Infection
TB	Tuberculosis
Th	T helper cell
TIG	Tetanus Immunoglobulin
TT	Tetanus Toxoid
UK	UK
USA	United States of America
VAERS	Vaccine Adverse Event Reporting System
VAP	Vaccine associated paralysis
VAPP	Vaccine associated paralytic polio
VFC	Vaccines For Children
VLP	Virus Like particle
VTV	Volksgezondheid toekomstverkenningen (Public Health Status and Forecast)
VZV	Varicella Zoster Virus
WHO	World Health Organisation
WHO/EURO	World Health Organisation, Regional Office for Europe

Keywords

National immunisation programme, diphtheria, tetanus, pertussis, poliomyelitis, haemophilus influenzae, measles, mumps, rubella, meningococcal disease, hepatitis b virus, pneumococcal disease, influenza, hepatitis a virus, rotavirus, varicella zoster virus, respiratory syncytial virus, human papilloma virus, herpes simplex virus, tuberculosis.

Contents

Samenvatting

Het Rijksvaccinatieprogramma is een van rijkswege bekostigd, landelijk vaccinatieprogramma. Dit brengt de plicht mee tot continue bewaking van de effecten van het programma, inclusief eventuele gevolgen op de lange termijn. Regelmatig komen (vernieuwde) vaccins tegen huidige en nieuwe doelziekten beschikbaar. Ook kunnen zich wijzigingen voordoen op het gebied van epidemiologie, immuunstatus, microbiologie en kosten-(effectiviteit). Deze veranderingen kunnen aanleiding geven tot (her)overweging van samenstelling van het Rijksvaccinatieprogramma.

Het doel van dit rapport was ten eerste om inzicht te geven in mogelijkheden voor verbetering van effectiviteit van het huidige Rijksvaccinatieprogramma. Evaluatie van het huidige programma (difterie, kinkhoest, tetanus, poliomyelitis, *Haemophilus influenzae* type b, bof, mazelen, rode hond, meningokokken C, hepatitis B) is uitgevoerd met behulp van surveillance van ziekte, vaccinatiegraad, immuunstatus, kiem (antigene variatie) en bijwerkingen.
Daarnaast had dit rapport als doel vast te stellen voor welke ziekten uitbreiding van het programma wenselijk zou kunnen zijn. Voor pneumokokken, influenza, hepatitis A, rotavirus, varicella zoster, meningokokken B, respiratoir syncytieel virus, humaan papillomavirus, herpes simplex virus-2 en tuberculose werd dit nagegaan. De afweging werd gebaseerd op informatie over vaccin, pathogeen, ziekte en kosten-effectiviteit. Met uitzondering van respiratoir syncytieel virus zijn deze vaccins beschikbaar of tenminste in fase III onderzoek. De verwachting is dat voor respiratoir syncytieel virus binnen 10 jaar een vaccin beschikbaar is.

De ziekten waartegen momenteel wordt gevaccineerd zijn grotendeels onder controle. Vaccinatie van (jong) volwassenen nu (kinkhoest) of in de toekomst (bof, mazelen, rodehond, hepatitis B) zal verder verbetering kunnen geven. Ook andere vaccinatiestrategieën verdienen aandacht, zoals vaccinatie van pasgeborenen of aanstaande ouders tegen kinkhoest. De vervanging van het huidige difterie, tetanus, poliomyelitis, hele-cel kinkhoest en *Haemophilus influenzae* vaccin (DKTP/Hib) door een combinatievaccin met een a-cellulaire kinkhoestcomponent (DK_ATP/Hib) in 2005 moet nauwkeurig gemonitored worden zowel voor kinkhoest als overige vaccincomponenten.

Het Rijksvaccinatieprogramma kan met andere ziekten uitgebreid worden. Pneumokokken-vaccinatie van kinderen levert belangrijke gezondheidswinst op. De wenselijkheid om waterpokken-vaccinatie te introduceren - mogelijk in een combinatievaccin met bof, mazelen en rodehond - moet bestudeerd worden. Als tegen meningokokken B, respiratoir syncytieel virus en humaan papillomavirus effectieve en veilige vaccins op de markt komen, is uitbreiding van het vaccinatieprogramma naar verwachting raadzaam. Dit geldt (nog) niet (of in minder mate) voor de al beschikbare vaccins tegen influenza en hepatitis A. Voor deze ziekten is continuering van het huidige beleid nodig met mogelijke verlaging van leeftijd voor influenzavaccinatie van 65 jaar naar 50 jaar. De wenselijkheid van vaccinatie van kinderen tegen influenza is een punt voor nader onderzoek, evenals pneumokokken-vaccinatie van ouderen. Vaccinatie tegen herpes simplex virus-2 en rotavirus is nog niet mogelijk. Naar verwachting levert vaccinatie tegen herpes simplex virus-2 relatief beperkte gezondheidswinst op. Voor rotavirus is een kosten-effectiviteitsanalyse raadzaam als een vaccin beschikbaar komt.

Het huidige Rijksvaccinatieprogramma is effectief en veilig. Vaccinatie van een aantal andere leeftijdsgroepen dan de huidige groepen is raadzaam om de effectiviteit van het programma te

verbeteren. Uitbreiding van het programma met een aantal nieuwe doelziekten kan aanzienlijke gezondheidswinst opleveren. Continue bewaking van de effecten van het Rijksvaccinatieprogramma blijft nodig. Handhaven van de hoge vaccinatiegraad is van uiterst belang om terugkeer van de ziekten te voorkómen.

Summary

The national immunisation programme in the Netherlands is a government-funded programme. It is therefore the government's duty to evaluate its effectiveness; this includes monitoring long-term effects. In addition, regular reconsideration of the national immunisation programme is needed as new vaccines become available and changes occur in the epidemiology, immune status, microbiology and (cost)-effectiveness.

This report aimed firstly to identify opportunities to improve the control of current target diseases of the national immunisation programme. Evaluation of the current programme (diphtheria, pertussis, tetanus, poliomyelitis, *Haemophilus influenzae* type b, mumps, measles, rubella, meningococcal serogroup C and hepatitis B) was performed using surveillance data on disease, vaccination coverage, immune status, pathogen (antigenic variation) and adverse events.
Secondly, this report aimed to determine whether extension of the programme with other diseases is desirable. For pneumococcal disease, influenza, hepatitis A, rotavirus, varicella zoster, meningococcal serogroup B disease, respiratory syncytial virus, herpes simplex virus-2 and tuberculosis the desirability of extension of the programme was determined. For these diseases vaccines are available or at least phase III clinical trials are performed, with the exception of respiratory syncytial virus. The expectation is that a respiratory syncytial virus vaccine will be available within 10 years. The assessment was based on information with regard to vaccine, pathogen, disease and cost-effectiveness.

The diseases targeted in the NIP are largely under control. Vaccination of (young) adults now (pertussis) and in the future (mumps, measles, rubella, hepatitis B) may give further improvement. Also, other vaccination strategies, such as maternal or newborn vaccination for pertussis, need consideration. The effects of the switch to a DTP_a-IPV/Hib combination vaccine in 2005 should be monitored carefully, both for pertussis and other components.
The national immunisation programme could be extended with new target diseases. Pneumococcal vaccination for children will give important health gain. The desirability to introduce varicella vaccination – possibly in combination with mumps, measles and rubella – needs further study. When effective and safe vaccines become available for meningococcal serogroup B, respiratory syncytial virus and human papillomavirus, extension of the immunisation programme might be considered. Extension of the programme with available vaccines for influenza, hepatitis A or tuberculosis is not (yet) recommended. For these diseases the current policy needs to be continued, possibly with lowering the age of influenza vaccination from 65 years to 50 years of age. The desirability to vaccinate children against influenza and the elderly against pneumococcal disease needs additional investigation. Vaccination against HSV-2 or rotavirus is not possible yet. The health gain is expected to be limited for HSV-2. When a vaccine against rotavirus becomes available, a cost-effectiveness study is advised.

The national immunisation programme in the Netherlands is very effective and safe. Vaccination of some other (age)groups may, however, improve the success and effectiveness of the programme and is recommended. Extension of the programme with new target diseases may result in considerable health gain. Monitoring the effectiveness of the programme remains important. Maintaining high vaccine uptake is vital to prevent (re)emergence of disease.

Introduction

1.1 Background

In the Netherlands, the National Immunisation Programme (NIP) has been a government-funded programme since 1957. The NIP aims to provide high quality service of vaccination against vaccine preventable diseases. To do so, the NIP responded to changes in both vaccine availability and the epidemiology and disease burden associated with vaccine-preventable infections.

Changes in the NIP aimed to improve the programme in two main ways. Firstly, the quality of the immunisation programme as already implemented within the current NIP could be improved. Secondly, the group of diseases and the micro organisms targeted in the programme could change. New vaccines have been added as they became available and their inclusion was deemed justifiable. Smallpox vaccination ceased as the disease was eradicated, the ultimate aim for many vaccine-preventable diseases.

The Ministry of Public Health, Welfare and Sports (VWS) decides on the vaccination policy in the Netherlands. The Netherlands Vaccine Institute (NVI) is responsible for delivering all vaccines used within the NIP and produces most of the vaccines for the NIP. The RIVM, the National Institute of Public Health and the Environment, has an advisory role towards VWS. The RIVM was asked to evaluate the current immunisation programme and assess potential future opportunities to improve the programme by additional vaccines or expansion of current vaccines to other groups. This report addresses both aspects.

1.2 Aim

This report aims to identify opportunities to improve the control of vaccine-preventable diseases in the Netherlands, by evaluating the current NIP and assessing the need for inclusion of new vaccines.

1.3 Outline of the report

In **Chapter 2** recent changes in current NIP (DTP_w-IPV/Hib, MMR, Men C, hepatitis B) as well as the vaccination schedule are described. The methods of surveillance used to evaluate the effectiveness of the NIP are given and the vaccine uptake in the Netherlands is discussed. The chapter summarizes conclusions and recommendations regarding the current NIP that are mainly based on the in-depth information for each of the target diseases (Chapter 4).

In **Chapter 3** criteria for selecting candidate vaccines for the NIP are given, as well as general considerations regarding extension of the NIP. In the present report, the following diseases were considered for inclusion in the national immunisation programme: pneumococcal disease, influenza, hepatitis A, rotavirus, varicella zoster, meningococcal disease serogroup B, respiratory syncytial virus, human papilloma virus, herpes simplex virus-2 and tuberculosis. Chapter 3 gives conclusions and recommendations regarding extension of the NIP for the potential vaccine-candidates discussed in Chapter 5. Furthermore, an overview is given for the disease burden and cost-effectiveness of the potential vaccine-candidates.

Chapter 4 gives a detailed description of the vaccines that are currently used in the NIP. For every disease the availability and history of vaccines, current epidemiology- immunology- and pathogen-surveillance methods and results and international perspectives are described.

Chapter 5 describes potential target diseases for the NIP. For these diseases available vaccines, epidemiology, disease burden, cost-effectiveness, international perspectives and alternative prevention methods are presented. Finally based on this in-depth information considerations regarding inclusion in the NIP are given.

2. Current National Immunisation Programme

2.1 Recent changes in the National Immunisation Programme and current vaccination schedule

In the Netherlands, vaccination of a large part of the population against diphtheria, tetanus and pertussis vaccination (DTP) was introduced in 1952. The National Immunisation Programme (NIP) was implemented in 1957 offering DTP and poliomyelitis vaccination (IPV) to all children born from 1945 onwards. Nowadays vaccination against measles, mumps, rubella, *Haemophilus influenzae* type b (Hib), meningococci serogroup C and hepatitis B (for risk groups only) are included in the programme. The injections that are currently administered are specified in Table 1 together with the age of administration and schedule. In addition to diseases included in the NIP, influenza vaccination is offered to individuals aged 65 years and over and individuals at risk in the Netherlands influenza prevention programme (Chapter 3 and 5).

In 2000, a review on the NIP and its possible future composition by 2010 was written.[1] From March 1999 onwards immunisations in the NIP begin at age 2 months, whereas before they started at age 3 months. Since then the NIP has been adapted several times (Appendix I). In 2001 (around October), a booster vaccination with acellular pertussis vaccine was introduced at 4 years of age (birth cohort 1998 onwards). In response to the increased incidence of meningococcal serogroup C disease observed in 2002, the Minister of VWS decided to include Men C vaccination in the NIP for children of 14 months of age from September 2002 onwards (birth cohort 1st June 2001 onwards). In the same year, a catch-up campaign was carried out to protect children aged 1 to 18 years against meningococcal serogroup C disease. In January 2003, hepatitis B vaccination was added to the NIP for children born to parents from middle or high endemic countries (birthcohort 1st January 2003 onwards). Since March 2003, the Hib-component is given mixed with DTP_w-IPV vaccine. Finally, in January 2005 the DTP_w-IPV combination vaccine was replaced by a combination vaccine including an acellular (instead of the whole-cell) pertussis component.

Table 2-1: Vaccination schedule of the NIP in 2005

Episode	Age	Injection 1	Injection 2
Episode 1	2 months	DTP_a-IPV/Hib	Hep B *
	3 months	DTP_a-IPV/Hib	
	4 months	DTP_a-IPV/Hib	Hep B *
	11 months	DTP_a-IPV/Hib	Hep B *
	14 months	MMR	Men C
Episode 2	4 years	DT-IPV	P_a
Episode 3	9 years	DT-IPV	MMR

* 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 is hepatitis B carrier.
Source: http://www.rivm.nl/rvp/rijks_vp/vac_schema/

2.2 Methods to evaluate effectiveness and safety of the current NIP in he Netherlands

The assessment of the effectiveness and safety of the NIP is based on five main surveillance methods.

Disease surveillance is important since the reduction of incidence achieved after a vaccine has been introduced into routine use is the ultimate measure of success of the programme. In the Netherlands, most information on the incidence of vaccine-preventable disease is derived from notifications, laboratory reports, data on hospital admissions and registration of deaths.

Surveillance of vaccination coverage is performed to identify risk groups or regions in which coverage is lower. Vaccination coverage is an indicator for effectiveness of control provided the vaccine has a high efficacy. In addition, data on vaccination coverage is useful to predict the existence of herd immunity. In the Netherlands, provincial immunisation administrations maintain a database of vaccination records for all children younger than 13 years of age. This offers the opportunity for a detailed monitoring of the vaccination coverage for the various target diseases. In paragraph 2.3 general information is presented regarding the vaccination coverage in the Netherlands.

Serological surveillance as an epidemiological method for the evaluation of the NIP is essential to obtain insight into immunity of the population, identify subpopulations at risk and to assess risk for (re)emergence of disease. Serological surveillance offers the opportunity to study secondary effects in the long-term of mass vaccination because the epidemiological dynamics of infectious diseases change. In 1995-1996 a large population-based seroprevalence study was performed to obtain insight into the immune status of the general population.[2] In 2005-2006, a new population-based serosurveillance study will start with a similar design.

Pathogen surveillance, i.e. surveillance of the phenotypic or genotypic characteristics of a pathogen, is important to study whether the pathogen has changed, especially vaccination (pressure) leads to changes in the pathogen and whether this leads to a reduction in vaccine effectiveness.

Finally, *safety of the vaccine* is monitored. In the Netherlands an enhanced passive surveillance system for monitoring adverse events following vaccinations, with a 24-hour telephone service is available. The interval between vaccination and the event is established, and the likelihood of causality with the administered vaccine is assessed for all reported adverse events.[3] In addition, active surveillance of adverse events is conducted in 2004 and 2005.
Surveillance results based on these methods given above are described in Chapter 4 in detail for the diseases currently included in the NIP.

2.3 Acceptability and uptake of vaccination in the Netherlands

2.3.1 Vaccine uptake in the Netherlands

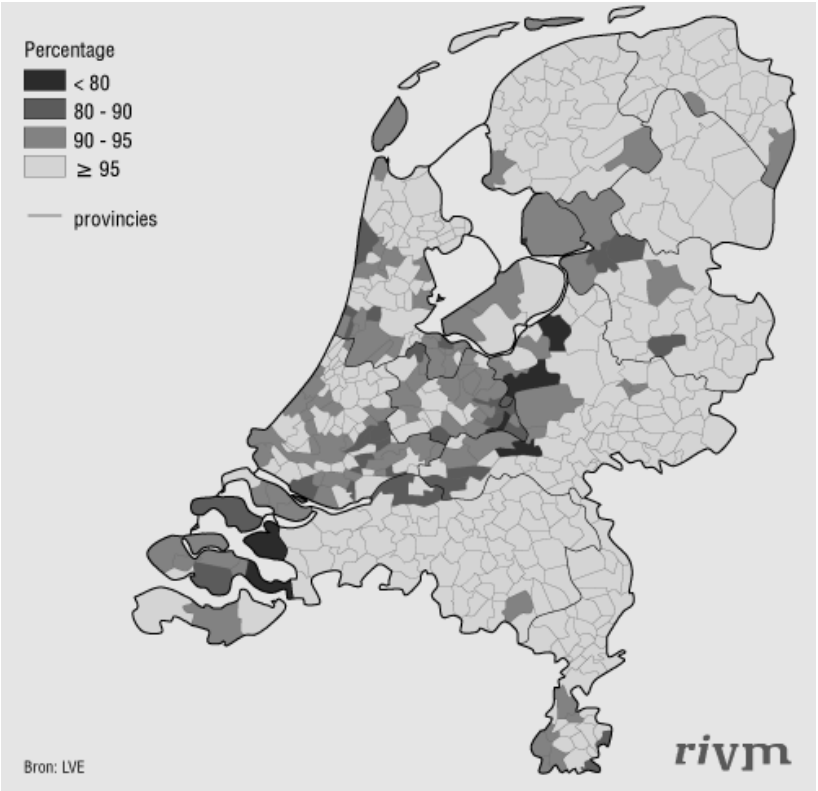
Vaccination coverage in the Netherlands is high and amounts to 95.3% for all 12-month-old children for the first re-vaccination against DTP_w-IPV/Hib and 95.8% among 2-year-old children against MMR.[4] Over the last five years there has been a slight decrease in vaccination coverage among infants. However, the coverage per 1-1-2004 showed a small rise. The political and public (media) attention for pertussis might have negatively affected vaccine uptake. High vaccination coverage is necessary to prevent infectious micro-organisms from circulating in the population. The percentage that is required for herd immunity varies between vaccines and between micro-organisms, but is on average between 90 and 95%.

2.3.2 Regions and groups with lower vaccine uptake

The percentage of vaccinated children differs between regions. Particularly regions with large groups of people that reject vaccination for religious or philosophical reasons have low vaccination coverage. In addition, communities with a large number of people that are very critical towards vaccination have a decreased percentage of vaccinated children. In an area that stretches from the Southwest to the Northeast of the country, many municipalities have a vaccination coverage less than 95%.

Figure 2-1: DTP-IPV vaccination per 1st January 2004 by municipality. The first revaccination of infants of the birth cohort of 2001.

Source: LVE



This area is sometimes referred to as the Bible belt, because a relatively large proportion of their inhabitants have religious objections against vaccination. Some regions within this area have a vaccination coverage below 80%.
Objections against vaccination on religious grounds are common for some groups of protestants (orthodox reformed groups). These groups reject vaccination because they believe it is inconsistent with their faith in divine providence.
Objections on philosophical grounds come from followers of the anthroposophy and homeopathy. Anthroposophists believe that it is useful for children to experience childhood diseases. In this, they discriminate between 'dangerous' and 'less dangerous' diseases and recommend to vaccinate against 'dangerous' diseases (diphtheria, tetanus, polio, pertussis, and rubella), but not against 'less dangerous' diseases (measles, mumps and Hib-diseases). Followers of the homeopathy do not give univocal advice on vaccination. Both homeopathic remedies as alternative for vaccines and homeopathic remedies supplementary to vaccines are advised. Sometimes alternative vaccination schedules are suggested.
During the last years, an increasing aversion against vaccinations has risen amongst some parents. In 1994, concerned and critical parents founded the 'Nederlandse Vereniging Kritisch Prikken' (NVKP). According to this society, children receive too many vaccinations at a too young age. They demand better information about illnesses, the risks of illnesses and the risks of vaccination. The 'Stichting Vaccinatieschade' founded in 2003 has the same objections.
As stated before, participation in the NIP is not mandatory. For public health sake, the government tries to promote high vaccination coverage. To achieve this, the government informs parents about vaccinations, the risk of infectious diseases, but also about the risks of vaccination. Recently, efforts have been made to improve the information about the NIP. Now, a small-scale study performed among critical parents has to shed light on why precisely these parents object to vaccination of their child. The public information about the NIP will be improved as a response to the results of the study.

2.4 Conclusions and recommendations regarding the current NIP

2.4.1 Disease-specific conclusions and recommendations

In this paragraph, conclusions and recommendations are presented, based on detailed information presented in Chapter 4, regarding the diseases currently included in the NIP.

Diphtheria

Surveillance data (mainly based on notifications and laboratory surveillance of *Corynebacterium diphtheriae* isolates) show that there is no evidence of circulation of *C. diphtheriae* in the Netherlands. No information is available currently on toxin alleles. Therefore, it is recommended for toxin genes of all clinical isolates to be sequenced to study whether these genes are adapting to vaccination. A new serosurveillance study (Pienter II) will give insight into population immunity against diphtheria. In particular, waning immunity and the lack of immunity in adults born before introduction of vaccination are causes for concern.

Depending on the results of the serosurveillance, (re)vaccination of adults might be reconsidered.

The replacement of the DTP_w-IPV/Hib vaccine with a DTP_a-IPV/Hib vaccine could result in a reduction of immunogenicity of the diphtheria component. Although the amount of diphtheria component could be increased to improve immunogenicity, this will probably not increase duration of memory immunity.

The resurgence of diphtheria in the former Soviet Union illustrates the fragile balance between population immunity and epidemics. Although the incidences of diphtheria in most of the Baltic States and the Newly Independent States has significantly reduced, the values are still high compared to most Western European countries. Thus, introduction of diphtheria from these countries remains a cause for concern, especially in view of the presence of large groups in the Netherlands with low or absent anti-diphtheria toxin antibodies.

Tetanus

Tetanus vaccination is very effective. Only a few cases per year are observed that occur among unvaccinated individuals, mostly born before routine vaccination was introduced and thus lack tetanus antibodies. Surveillance of tetanus is based on requests for human tetanus immunoglobulin and requests for diagnostic tests when tetanus is considered. Tetanus was removed from the list of mandatory notifiable diseases in 1999 since is not communicable but acquired through environmental exposure to the spores of *Clostridium tetani*. In the UK, a cluster of tetanus cases occurred in injecting drug users (IDUs) in 2003/'04. One fatal case of tetanus in an IDU occurred in 2004 in the Netherlands. To allow timely detection of possible re-emergence of tetanus it might be needed to re-introduce it to the list of notifiable disease.

Recently the policy of tetanus immunoglobulin (TIG) and tetanus revaccination after injury have been re-formulated. Thanks to the success of the NIP and the persistence of high antibody levels many years after tetanus vaccination it is therefore now justified to limit the administration of TIG to those who are at the highest risk i.e. those who are known to be unvaccinated, women born before 1950 and men born before 1936.

The replacement of the DTP_w-IPV/Hib vaccine by the DTP_a-IPV/Hib vaccine in 2004 for infant vaccination could have (small) effect on the immunogenicity and duration of memory immunity.

Pertussis

Several surveillance sources are used to estimate the incidence of pertussis, i.e. notifications, hospital admissions and seroprevalence studies. With the latter we can estimate the incidence of all *B. pertussis* infections, both clinical and subclinical. Notification data and hospital admissions show that pertussis is still endemic in the Netherlands with epidemic peaks every 2-3 years. Of all diseases which are part of the NIP, pertussis has the highest incidence per person year. Such a high incidence compromises the health of babies too young to be vaccinated and causes significant morbidity among adolescents and adults. Hopefully, this situation will improve with the replacement of the whole cell vaccine by an acellular pertussis vaccine which took place in January 2005. The effects of this major change in the NIP on the incidence of pertussis will probably not be evident in the short term: No catch-up vaccination will take place, and it will take long before a considerable part of the population is immunised with this vaccine. After the introduction of the booster vaccination for 4-year-olds, all surveillance sources showed a decrease in the incidence among the 3 and 4 year-olds compared with previous years. A similar, immediate, effect may be expected within 1-4 year after the switch to the acellular vaccine.

The switch to an acellular vaccine involves a number of uncertainties. The immunity induced by acellular vaccine is much narrower compared to the whole cell vaccine. This may result in increased infections by *B. parapertussis* or *B. bronchiseptica* and the emergence of *B. pertussis* escape variants. Thus, pathogen surveillance remains of utmost importance. A system for the collection of clinical *Bordetellae* isolates is not in place and we highly recommend the implementation of such a system.

It is not clear what the short and long-term effects of the removal of lipopolysaccharide from the NIP will be. This molecule has many activities such as adjuvancy and Th1-polarization of the immune response, but is also the cause of adverse events. Introduction of combination vaccine with an acellular pertussis component in 2005 is expected to lead to a decrease in adverse events. This introduction may require changes in the criteria or antigens used for serodiagnosis of pertussis.

Waning immunity is one of the causes of the re-emergence of pertussis and may be countered by booster vaccinations. To develop an optimal booster regime, tools must be developed to quantify immunity and memory. Maternal immunisation should be considered, as it may be the most cost-effective way to protect newly born infants in populations with much circulation of the pathogen.

Poliomyelitis

No cases of polio have been reported in the Netherlands since the outbreak among orthodox reformed persons in 1992-1993. In 2002, the European region has been declared Polio-Free. Both environmental surveillance (2004) and surveillance of acute flaccid paralysis (2002) has been stopped. Therefore, documentation of the absence of poliovirus circulation in the Netherlands is only based on a rapid and adequate response on notification of suspected cases, and on the results of enterovirus surveillance project. The recent re-emergence of polio in Africa demonstrates that a high state of alertness is still required as long as wild-type poliovirus in not eradicated.

Despite the enormous success of the Global Polio Eradication Initiative, there is still an urgent need to continue vaccination against poliovirus. There are still areas of poliovirus circulation from which virus may be imported into the Netherlands. A considerable part of the elderly population would be at risk for infection in the event of reintroduction of poliovirus. Vaccination of elderly during an outbreak should be considered. Furthermore, orthodox reformed individuals have insufficient immunity to prevent circulation of poliovirus after import of virus in this community that refuse vaccination on religious grounds.

Almost all developed countries have replaced OPV for IPV. However, most developing countries still use live Sabin-derived OPV (live attenuated). The use of OPV brings the risk of the emergence of virulent circulating vaccine-derived polioviruses (cVDPVs). The emergence of these cVDPVs is a major threat for the worldwide eradication campaign and urges a good 'exit' strategy for OPV. Definition of the genetic changes that lead to cVDPVs is important to combat these strains.

Haemophilus influenzae serotype b

Vaccination against *Haemophilus influenzae* serotype b (Hib) has been very successful and has nearly eradicated the disease caused by Hib among children. However, recently there has been an increase in the number of cases of invasive Hib disease. Among children in age groups eligible for vaccination virtual all cases were true vaccine failures. In addition, the number of cases among adults has increased as well and the incidence among adults is now back at pre-vaccination levels.

Genotyping of the strains isolated from cases of vaccine failures has shown that the increase is not caused by a single clone. Thus, there is no indication that escape variants of Hib have emerged. In fact, genetic diversity of the Hib strains seems to have increased considerably after introduction of the Hib vaccine in the NIP. This indicates that vaccination has had a major impact on the composition of the circulating Hib strains causing invasive disease in the Netherlands.

From data obtained in the UK, it is clear that acellular pertussis vaccine reduces the response compared to whole cell vaccine to the Hib vaccine component and this probably has contributed to the considerable increase of invasive Hib disease in the UK. The Netherlands introduced acellular pertussis vaccine in January 2005 and therefore careful surveillance of Hib cases and the genotypic distribution of the Hib strains are required.

Another factor that may have contributed to the considerable increase in the number of cases of invasive Hib disease in the UK is a short duration of immunity due to a vaccination schedule. In the UK, children are vaccinated at 2, 3, and 4 months of age. The Netherlands is using the same schedule but in addition, Hib is included in the booster vaccination at 11 months. This may prevent waning immunity in the age group at risk. It is recommended to maintain the current immunisation schedule with the booster vaccination at 11 months. This may prevent the need for a catch up campaign like the issued in the UK in the summer of 2002 in which all children younger than 4 years of age were re-vaccinated. Continued monitoring is required to follow and explain the presumed increase.

Measles, Mumps, Rubella

Despite mandatory notification, the reported incidence of measles is not reliable. Clinical symptoms resembling measles may be caused by pathogens other than measles and rubella viruses. Therefore, laboratory confirmation of suspected cases is clearly needed.

Because of low vaccination coverage within socio-graphically clustered religious communities in the Netherlands, epidemics will continue to occur, almost exclusively within these communities despite the high national vaccination coverage and population immunity. These communities remain at risk for outbreaks. In the light of the initiatives of WHO to eliminate measles in Europe (target date 2010), initiatives in enhancing the vaccination coverage within these specific communities and maintaining high vaccination coverage in the total population should be encouraged.

There are no objective reports on the incidence rate of mumps, as it is not notifiable. Recent outbreaks of mumps have been described in several European countries including the Netherlands (2004), mostly in older children and young adults who only received one dose of the vaccine. This underlines the importance that children receive at least two doses of the mumps vaccine, preferably in combination with measles. Laboratory diagnosis of clinical mumps (parotitis) is essential.

Despite mandatory notification (of laboratory confirmed cases only), the reported incidence of rubella is not reliable. Notified cases within unvaccinated religious clusters, both at present (rash disease surveillance) as well as in the past (serological surveillance) indicates extensive circulation of the virus within these communities. In 2004, a large outbreak of rubella in unvaccinated individuals (mainly orthodox reformed) commenced.
Analysis of measles virus (and rubella virus) strain variation is part of the measles surveillance, recommended by WHO to monitor the elimination status of measles in different European countries. For mumps, strain variation is considerable and might constitute a problem in the near future.
A future population-based serosurveillance study (Pienter II) will give valuable information about unvaccinated susceptible groups, population immunity, persistence of antibodies after the second vaccination (waning immunity), levels of maternal antibodies passed on to babies by vaccinated mothers and the possible interference of Men C vaccination with MMR vaccination. The decrease of maternal antibodies might necessitate additional efforts to protect children from contracting measles before 14 months of life, possibly by earlier vaccination with MMR vaccine. Development of a measles vaccine that can be administered before 6 months of age is particularly relevant for developing countries. Furthermore, waning immunity increases in populations where the circulation of the virus has stopped, i.e. the vaccinated population in the Netherlands. This also might demand for a solution in the nearby future to protect the elderly vaccinated persons. In these instances, insight in the protection level of the population provides a rational for changes in vaccine schedules.
The immunogenicity of the currently used measles and rubella vaccine strains (Moraten and RA 27/3) is good, although reinfection of previously vaccinated persons has been reported for both viruses. In contrast, the immunogenicity of the mumps vaccine strain (Jeryl Lynn) is debated. Recently, a number of mumps outbreaks have been described which might be related to the use of particular mumps vaccine strains. The Jeryl Lynn vaccine contains two strains (JL2 and JL5), one of which may be less immunogenic. Other used mumps vaccine strains have similar problems, the Swiss Rubini vaccine being far too less immunogenic and the Japanese Urabe vaccine being too reactogenic. If mumps continues to be a problem, giving further boosters should be considered.

Meningococci C

Vaccination against *Neisseria meningitidis* serogroup C (Men C) has been introduced in the NIP in 2002, accompanied with a catch-up programme for all children below 18 years. It has led to a dramatic decrease of the number of cases of invasive disease caused by Men C and no vaccine failures have been reported yet. The increase of the number of cases of invasive Men C disease in 2001 has accelerated the introduction of the vaccine, but the reasons for the increase have remained unexplained. To be able to intervene rapidly in case of other sudden shifts in the serogroup distribution, further study to find explanations for this sudden increase is necessary.
The current vaccine seems to be very effective and there seems to be no need to alter its formulation. However, the vaccine is directed against the capsular antigen of Men C only. Meningococci have been shown to exchange genetic information extensively including the information required for the capsule. This could potentially lead to meningococcal strains with the genetic make up and virulence factors of Men C and the capsule of Men B. Therefore, careful genotyping of the meningococcal strains isolated from Dutch patients is required.

Hepatitis B

Hepatitis B vaccination in our NIP is targetted, unlike all other NIP-vaccines which are given universally. It is given to only those children that are born to parents, of whom at least one originates from a country where chronic hepatitis B infections are moderately (2-8%) or highly (>8%) endemic,

and to children born to chronically HBV-infected mothers.
All acute and chronic hepatitis B cases are mandatory reported (Osiris), but as most HBV infections are sub-clinical, the actual incidence of HBV can only be estimated. On basis of the screening of pregnant women, it is estimated that ~70,000 people are chronically infected with HBV in the Netherlands. A joined project of RIVM and GG&GD Amsterdam (started in 2004) on the molecular-epidemiology of acute hepatitis B aims to determine the most likely source of infection and genotype of each viral isolate. These data are an indispensable tool to gather information on transmission networks of hepatitis B, and to determine whether our NIP-HBV targeted immunisation programme, in addition to vaccination of other persons with elevated risk, is indeed (cost-) effective in the long run.
Reports concerning vaccine-escape mutants in countries where hepatitis B is given as a universal childhood vaccine indicates a potential threat of reduced effectiveness of vaccination. Monitoring changes in antigenic composition of the circulating hepatitis B strains is therefore desirable.
New six-in-one combination vaccines, in which the hepatitis B vaccine is mixed with DTP_a-IPV/Hib components, are available within Europe, and in use in e.g. France and Belgium. Currently (since 1.1.2005) the 5-fold DTP_a-IPV/Hib combination vaccine (Infrarix-penta, GSK) is used as the universal childhood vaccine in our NIP. A (cost-) effectiveness study that compares the current hepatitis B vaccination policy with universal childhood vaccination using a 6-component vaccine (i.e. Infrarix-hexa, GSK) is recommended.

2.4.2 Final remarks and conclusions

In table 2-2, an overview is given of recommendations for the current target diseases. For details, we refer to Chapter 3. The conclusions are summarized:

The Dutch immunisation programme is highly effective and safe
Target diseases are largely under control in the Netherlands because of an effective and safe immunisation programme with a high vaccine coverage.

Maintain high vaccine uptake
Maintaining high vaccine uptake in the Netherlands is of utmost importance to prevent (re)emergence of any of the target diseases.

Continue and improve surveillance
Firstly, although for most of the target diseases included in the current NIP, disease surveillance is sufficient, improvements are recommended for several diseases (i.e. diphtheria, tetanus, and mumps). Repeating the population-based serosurveillance study performed in 1995-1996 will be of considerable value, in particularl to study persistence of immunity after vaccination and natural immunity (i.e. measles, rubella, diphtheria, and poliomyelitis). Surveillance of the pathogen should be stressed because of the (possible) effect of vaccination pressure on changes of the pathogen, which might lead to vaccination being less effective (Hib, hepatitis B, meningococcus C, mumps, pertussis).

Extend vaccination to other (age) groups
While the current NIP is targeting infants and children - vaccinations sessions are performed between two months and nine years of age – surveillance results strongly indicate that extension to other age groups are necessary to maintain and to improve the effectiveness of the programme. In addition to considering adult/adolescent (re)vaccination strategies now (e.g. pertussis) and in the future (e.g.

measles, mumps, rubella, hepatitis B), other vaccination strategies need attention such as maternal (e.g. pertussis) or newborn vaccination (e.g. pertussis).

Consider change in vaccination (schedule)

The switch to a DTP_a-IPV/Hib combination vaccine could possibly in the long run have consequences on both pertussis epidemiology and on the protection against other target diseases, in particular *Haemophilus influenzae* type b and on Th_2-mediated diseases. Lowering the first age of MMR-vaccination should be considered when protection by maternal antibodies is shorter and results in a period before the first vaccination in which children are susceptible to infection.

Table 2-2: Overview of recommendations regarding target diseases of the current NIP.

Target disease	Disease surveillance	Safety surveillance	Vaccination Coverage	Serological surveillance	Pathogen	Current changes in vaccination (schedule) or indications	Future changes in vaccination (schedule) or indication
Diphtheria	Continue	Continue; To watch: switch to DTP_a-IPV/Hib	Continue	To watch: Immunity in adults; lmmunogenicity DTP_a-IPV/Hib; Insufficient herd immunity in orthodox reformed individuals.	Strengthen, sequence toxin alleles		Consider (re)vaccination of adults
Tetanus	Strengthen, re-consider notification	Continue; To watch: switch to DTP_a-IPV/Hib	Continue	To watch: Immunity in adults born before introduction of vaccination; lmmunogenicity DTP_a-IPV/Hib?	--	Limit re-vaccination to those at highest risk	
Pertussis	Continue; To Watch: Sources of infection Effect of switch to DTP_a-IPV/Hib	Continue; To watch: switch to DTP_a-IPV/Hib	Continue	To watch: Infection frequency in population; Change criteria serosurveillance as result of switch to DTP_a-IPV/Hib	Continue Surveillance other *Bordetella* species	Consider booster vaccination in adults (caregivers)	Consider maternal or newborn vaccination
Polio	Strengthen: genetic changes in cVDPV strains	Continue; To watch: switch to DTP_a-IPV/Hib	Continue	To watch: Immunity in elderly; Insufficient herd immunity in orthodox reformed individuals		Consider (re)vaccination elderly in case of outbreak	Consider (re)vaccination elderly in case of outbreak
Hib	Continue; To watch Effect of switch to DTP_a-IPV/Hib	Continue; To watch: switch to DTP_a-IPV/Hib	Continue	lmmunogenicity DTP_a-IPV/Hib?		Continue four dose schedule	

Table 2-2. Continued.

Target disease	Disease Surveillance	Safety Surveillance	Vaccination Coverage	Serological surveillance	Pathogen	Current changes in vaccination (schedule) or indications	Future changes in vaccination (schedule) or indication
Mumps	Strengthen	Continue	Continue	To watch: Persistence vaccine-induced antibodies; Maternal antibodies; Immunity in adults; Risk of outbreak in orthodox reformed individuals	To watch: Virus strain variation	Continue 2-dose schedule	Consider dropping age of first dose Consider dropping age of second dose Consider (re)vaccination of adults
Measles	Strengthen: Rash disease surveillance	Continue	Continue	To Watch: Persistence vaccine-induced antibodies Maternal antibodies Immunity in adults Risk of outbreak in orthodox reformed individuals	To watch: Virus strain variation in view of elimination	Continue 2-dose schedule	Consider dropping age of first dose Consider dropping age of second dose Consider (re)vaccination of adults
Rubella	Strengthen: Rash disease surveillance	Continue	Continue	To watch: Persistence vaccine-induced antibodies; Maternal antibodies; Immunity in adults; Risk of outbreak in orthodox reformed individuals	To watch: Virus strain variation	Continue 2-dose schedule	Consider dropping age of first dose Consider dropping age of second dose Consider (re)vaccination of adults
Men C	Continue	Continue	Continue		To watch: Genotyping in view of possibility of change of genetic information	Continue 1-dose schedule at 14 months of age	
Hepatitis B	Continue	Continue	Continue	To watch: Immunity in risk groups; Infection frequency	To watch: Antigenic variation	Consider adolescent and/or universal vaccination	Combine with hepatitis A (Chapter 3 and 5)

3. Extension of the National Immunisation Programme

3.1 Methods for selecting candidate vaccines for the National Immunisation Programme

Criteria for inclusion of vaccine candidates in this review were the following. Those diseases – with public health relevance in the Netherlands - were included for which the Jordan Report (2002) stated that results for phase III clinical trials were available or being carried out.[5] Furthermore the scope of NIP was taken, i.e. it should be a potential candidate for routine vaccination. Based on these criteria pneumococcal disease, influenza, hepatitis A, rotavirus, varicella zoster and meningococcal disease serogroup B were reviewed. Human papilloma virus and herpes simplex-2 were added to the list since phase III clinical trial data became available after the composition of Jordan report (2002).[5] Respiratory syncytial virus (RSV) was added because it is expected that RSV vaccine will become available in the next 10 years and phase II trials are far advanced. Finally, it was decided to discuss tuberculosis in the present chapter because of the (possible) emergence of multiresistant strains.
In addition to the above mentioned diseases, the disease burden of *Helicobacter pylori*, *Chlamydia trachomatis*, *Neisseria gonorrhoea*, cytomegalovirus and hepatitis C were described in the report 'Towards a Dutch national vaccination programme for the 21st century'.[1] Potential vaccines for these diseases did not meet the above mentioned criteria for inclusion in this review because vaccine development is in an early stage. They were therefore not included in the present report.

3.2 Evaluation of the candidate vaccines for inclusion in the national immunisation programme

To make a rational judgement on possible extension of our NIP, disease-specific information is needed with regard to vaccine, pathogen, disease and cost-effectiveness. In Appendix II a diagram containing these four key elements is given. The field of *vaccine* describes information on availability of vaccines, effectiveness, adverse events and cost of the vaccine and immunisation programme. Subsequently, *pathogen* information is needed on pathogenicity, infectiveness, transmission route and antigenic variation. In the field of *disease,* information on disease burden, care and cost, work loss and school absenteeism is essential. Furthermore, mainly based on the information from the three fields, vaccine, pathogen and disease, insight into cost-effectiveness is generated. In general, in the Netherlands a threshold of €20,000 per QALY is applied in cost-effectiveness evaluations. Information of the four elements and their interactions are used to come to considerations regarding adaptation of our NIP. The focus of this Chapter is on scientific information. This in-depth information could be used in considering extension of the NIP. Other issues shall and will play a role to come to a final decision on extending the NIP. In the next paragraph, ethical principles for collective immunisation programmes published by Verweij et al. (2004) and the Health Council (2002) are given.[6,7]

3.3 General considerations regarding extension of the NIP

Recently, Verweij et al. published ethical principles for collective immunisation programmes.[6] These principles were and will be used (advice on meningococcal and pneumococcal vaccination for infants) by the Dutch Health Council to decide on inclusion of a vaccine in the NIP.[6,7] In his paper Verweij mentions seven principles for collective immunisation programmes.

1. Collective immunisation programmes should target serious diseases that are a public health problem. An infectious disease can be regarded as a public health problem when the incidence is high or when there is a chance of a large outbreak.
2. Each vaccine, and the programme, as a whole must be effective and safe.
3. The burden and inconvenience for participants should be as small as possible. This refers to the decision mentioned by the Health Council to limit the number of injections given in one session. By minimising the burden and inconveniences and by taking them seriously, this will contribute to willingness to participate and thereby high vaccine coverage.
4. The programme's burden/benefits ratio should be favourable in comparison with alternative vaccination schemes or preventative options. Verweij et al. mention that cost-effectiveness analysis is an important aspect with regard to this principle
5. Collective immunisation programmes should involve a just distribution of benefits and burdens.
6. Participation should generally be voluntary unless compulsory vaccination is essential to prevent a concrete and serious harm.
7. Public trust in the immunisation programme should be honoured and protected

This report, in particular chapter 5, addresses (a part of the) scientific information needed to fill in the above-mentioned ethical principles.

3.4 Conclusions and recommendations regarding extensions of the NIP

3.4.1 Disease-specific conclusions and recommendations

In this paragraph, disease-specific conclusions and recommendations are described. Considerations regarding surveillance, cost-effectiveness and inclusion in the NIP are given.

Pneumococcal disease

Data on the number of cases of pneumococcal disease in the Netherlands is obtained by the surveillance performed by the Netherlands Reference Laboratory for Bacterial Meningitis and the RIVM. This system covers about 80% of all cases of pneumococcal meningitis in the Netherlands and forms a reliable source for epidemiological data. Data for other non-invasive forms of pneumococcal disease (pneumonia and otitis media) is incomplete due to the absence of a specific reporting system.
The incidence of pneumococcal disease has been more or less constant during recent years in the Netherlands. In 1999, the highest age-specific incidence was observed in children <5 years of age (8.2/100,000), and a second peak occurred among people aged over 65 years (2.4/100,000). The Health Council estimated that yearly 160 cases of septicaemia, 7500 cases of pneumonia and around 200,000 cases of otitis media occur in the Netherlands in children younger than 10 years of age. The Dutch Health Council has advised in 2001 to include vaccination of infants with Prevenar in the NIP.

Although the incidence and burden of disease of invasive pneumococcal disease justify uptake in the NIP, due to high costs it has not yet been implemented..
As it seems only a matter of time before pneumococcal vaccination for infants is implemented, it is important to be prepared to monitor the effects of vaccination on the composition of the circulating pneumococci. Shifts in serotype distribution and replacement may reduce the vaccine effectiveness.
The cost-effectiveness of vaccination in infants with a 7-valent conjugate vaccine has been estimated at €30,800 to €88,300 per QALY gained, assuming vaccine costs per dose of €15.88 and € 40, respectively. Including indirect costs in the model will improve cost-effectiveness.
There has been much debate on effectiveness of vaccination in the elderly. Recently the Dutch Health Council decided not to alter their previous advice and thus decided against the pneumococcal vaccination in the elderly. Based on an review of scientific evidence, the Committee has, because of insufficient knowledge, concluded that pneumococcal vaccination in ≥65 year olds is not justified under the present circumstances. The Council did advise that further research on the effectiveness of vaccination in elderly is required. A carefully planned randomised clinical trial to determine the effects of pneumococcal vaccination in the elderly may be required.

Influenza
Since 1992, the Netherlands influenza sentinel surveillance network (RIVM, NIVEL, and NIC) provides sufficient epidemiological and clinical information about circulating influenza strains. Despite the representativeness of the sentinel surveillance network, underestimation of the influenza incidence during the season occurs; not all patients with an acute respiratory infection visit the general practitioner (GP) and some GPs of the network report patients with acute respiratory infections (ARIs) more frequently than others do.
In the Netherlands, much information is already available about care and costs of influenza. In addition, a recent study on cost-effectiveness of the present Dutch influenza prevention programme provided insight in the cost-effectiveness of influenza vaccination in high risk children, adults and elderly. This study suggested that for high risk adults and elderly influenza vaccination is clearly cost-effective. However, for high risk children vaccination appeared to be costly.
With respect to healthy children, a scenario-analysis has estimated that in people younger than 19 years old, assuming a normal influenza attack rate, 118,499 GP consultations would be required, 62 patients would require hospitalisation and about 9 would die of influenza.[6] Foreign studies show that universal influenza immunisation of healthy children can be cost-effective, dependent on factors such as attack rate and direct and indirect costs of vaccination. Studies on cost-effectiveness of vaccinating healthy children have not been conducted in the Netherlands. The results of the Dutch economic analysis in high-risk children suggest that vaccinating healthy children may also not be cost-effective. However, when considering the above-mentioned disease-burden of healthy children due to influenza and the possible beneficial effects of vaccinating all children on morbidity in the community, vaccinating healthy children might well be cost-effective. Further analyses on this are necessary. Data on morbidity and mortality may convince parents who may be reluctant to have their children vaccinated annually, of the benefits of annual influenza vaccination for their children, their families and the community.

Hepatitis A
The incidence of hepatitis A in the Netherlands is decreasing. Most infections occur in high-risk groups, for whom vaccination policies are available. However, the uptake of these targeted programmes is not yet optimal. Currently, we consider HAV vaccine not valuable for inclusion in the NIP. The expected public health profit in terms of gained DALYs is estimated to be very low.

Continuing (and optimizing) the current targeted vaccination policy is more appropriate. This includes vaccination of travellers, 2nd and 3rd generation migrants, MSM and active control of outbreaks. For the long term, attention is needed for the decreasing immunity in the adult population, as this might lead to an increasing number of symptomatic infections at adult age. An increase in disease burden and increased health cost would require a new evaluation.
For future evaluations, some crucial information is lacking. HAV infections are notifiable to the Inspectorate of Health, so fairly adequate information about incidence of symptomatic disease is available. However, asymptomatic infections are not notified and there is some underreporting of cases, especially of secondary cases. Besides, linking of related cases must be done manually, as cases are reported individually. Consequently, outbreaks are not recognised very well. It is also unknown how often outbreak-associated costs are assessed. Data on absence from work is not specifically available for hepatitis A (only available for all hepatitis combined). Hence, a valid measure of the indirect costs associated with HAV infection cannot be provided.
There has only been a cost-effectiveness study on vaccination of children of ethnic minorities in one urban region. For this targeted policy, vaccination would only be cost saving if the vaccine price would be lowered, but probably has a favourable cost-effectiveness. A cost-effectiveness study on vaccination of all newborns has not been performed.
Finally, if vaccination with hepatitis A would be implemented in the NIP an ethical question raises. Children, in whom disease primarily is asymptomatic, would be vaccinated to prevent disease in adults.

Rotavirus
At this moment, inclusion of rotavirus vaccine in the NIP is not feasible as no vaccine is registered in the Netherlands. We expect a vaccine to be registered within the next 5 years. The public health profit of vaccination in terms of gained DALYs is intermediate. So, when a vaccine comes available uptake must be evaluated by a (cost-)effectiveness study for the Dutch situation. To be cost saving, the vaccine price should be lower than the price for Rotashield, the vaccine that has been registered in the US, but taken from the market because of very rare but severe adverse effects (intussusception). If rotavirus vaccination was to be included, newborns should be the target population because of the high infection rate at very young age. For future evaluations, some data are missing. Mortality data specific for rotavirus are lacking. In addition, there are emerging genotypes of rotavirus circulating worldwide, which are not included in the currently developed vaccines. It is not clear which rotavirus genotypes predominantly circulate in the Netherlands. Therefore, a study of circulating genotypes of rotavirus must be carried out for estimation of the effectiveness of the vaccine. One vaccine was licensed in Mexico very recently: Rotarix, but data about the cost of this vaccine are not available. Besides, in our country we lack detailed insight in the use of laboratory tests and costs of these tests. There has been an economic evaluation of rotavirus vaccination (with Rotashield), but costs of implementation of rotavirus vaccination into the NIP were not taken into account. If the vaccination schedule does not fit the current schedule, additional cost calculations are needed.

Varicella Zoster
Chickenpox is an almost universally acquired childhood disease caused by Varicella Zoster Virus (VZV): It is estimated that 97% of the children of >5 years in the Netherlands have serologic proof of a VZV infection.
Although chickenpox is generally seen as a benign disease, the estimated disability-adjusted life years associated with chickenpox is estimated at about 1200 DALYs. More than 2/3 of these DALYs are estimated to be preventable by childhood vaccination. Data on disease burden due to chickenpox

indicated that the costs in the Netherlands are probably lower than other countries (e.g. USA and Germany). However, cost-calculations are complicated by the fact that most VZV-related hospital admissions are due to superinfections. Some western countries (e.g. USA and Germany) have introduced universal varicella vaccination. Combination vaccines in which the varicella vaccine is combined with the existing Measles-Mumps-Rubella components will soon be licensed in Europe. Mathematical modelling of a mass childhood immunisation strategy against VZV predicted that this would lead to a period of significant rise in herpes zoster morbidity (shingles). However, in the long run the incidence of shingles is expected to decrease compared to pre-vaccination levels. Before introducing VZV vaccination, a feasibility/cost-effectiveness study of the replacement of current MMR with MMRV in our NIP is recommended. In addition suitable surveillance mechanisms for herpes zoster should be established.

Meningococcal disease group B

Since many years, data on *Neisseria meningitidis* is being obtained by the surveillance performed by the Netherlands Reference Laboratory for Bacterial Meningitis and the RIVM. This system covers about 80% of all cases of invasive meningococcal disease in the Netherlands and forms a reliable source for epidemiological data. *Neisseria meningitidis* serogroup B (Men B) is the most frequently isolated serogroup from patients with invasive meningococcal disease in the Netherlands. The incidence of Men B disease amounted to 2.9/100,000 in the period 1993-2003. The incidence and serious nature of invasive Men B disease justify uptake in the NIP.

An economic evaluation of meningococcal B vaccination in infants in the Netherlands estimated that the cost-effectiveness is €15,720 per QALY gained (€21,420 per life-year gained). In this study, it was assumed that the total number of cases per year was 306. However, in 2003 only 138 Men B cases occurred in children between 0 and 4 years. Using this incidence doubles the the costs per QALY gained.

The currently available Men B vaccines are monovalent and therefore cannot be used in countries such as the Netherlands, where many different serotypes are present. Several vaccine manufactures are developing and testing different Men B vaccines. One of the mostly like candidates for inclusion in the Dutch immunisation programme is the multivalent PorA based vesicle vaccine that the NVI has developed. PorA vaccines have been shown to provide good protection against Men B. However, its licensing for use in the Netherlands will take at least another 5 years. Furthermore, there are many different PorA antigens. Vaccination with a subset of these PorA antigens may select Men B strains with other PorA antigens. As a result, the vaccine may have to be frequently modified to include other PorA types.

Inclusion in the current schedule would be feasible if the Men B vaccine is combined with Men C and/or a pneumococcal conjugate vaccine.

Respiratory syncytial virus

Since 1970, the Netherlands influenza sentinel surveillance network (RIVM, NIVEL, and NIC) provides epidemiological information on RSV. Despite the representativeness of the sentinel surveillance network, underestimation of the RSV incidence during the season occurs; not all patients with an acute respiratory infection visit the GP and some GPs of the network report patients with ARIs more frequently than others do.

In addition to the sentinel surveillance, the Dutch working group of clinical virological laboratories, which includes laboratories from all over the country, report their diagnoses to the RIVM. Furthermore, some medical microbiology laboratories daily report the positive and negative results of diagnostic tests to the Infectious diseases Surveillance Information System (ISIS). By means of

diagnosis criteria, ISIS determines the number of RSV-associated illnesses, which serve as an early warning. A disadvantage of the latter system is that the area covered by the reporting laboratories represents a small part of the Dutch population. Information on hospital admissions is available.
No economic evaluations for the Dutch situation are yet available about vaccination against RSV. A Dutch study concerning passive immunisation estimated an efficacy of 75% for infants at the highest risk. It seems reasonable to expect that a future vaccine will have similar efficacy. It is important to realize that the passive immunisation is very expensive, at €4,500 per child. It is unlikely that a vaccine will cost anywhere near such price; a price around €100-200 seems more likely. In that situation, vaccination will be cost-saving for the infants with the highest risk, whilst vaccination of all infants will probably be cost-effective. Currently, the Netherlands Vaccine Institute (NVI) is conducting a study on cost-effectiveness of RSV vaccination.
The above points out that inclusion of the RSV vaccine in the NIP is an important step in the prevention of infant hospitalisations and morbidity and mortality. Hopefully, RSV vaccines will be available within 5 years. Maternal and intranasal vaccines are the most prominent candidates for RSV vaccines, since these vaccines could evade the inhibiting effect of maternal antibodies. An essential criterion for the implementation of the future RSV vaccine is safety: the future vaccine should e.g. not induce enhanced disease upon a subsequent infection with RSV and should not exacerbate asthma. This will be a difficult issue since mechanisms underlying vaccine-enhanced disease are unclear.

Human papilloma virus
Prevention of human papilloma virus infections, which are the causative agent of cervical cancer, has a high priority as ~6000 DALYs are lost due to high-risk HPV-genotype infections. Data on incidence, prevalence and transmission of HPV-16 and 18 (the most carcinogenic HPV-genotypes) in the Netherlands is incomplete, or lacking at all. Currently, our national screening programme considerably reduces the incidence of cervical cancer.
The prophylactic HPV subunit vaccines for pre-adolescent girls (12-year of age), which are currently being evaluated in large-scale phase 3 clinical trials by Merck and GSK, show great promises to reduce the burden of cervical cancer. It is expected that these vaccines will be licensed in Europe within 3 years. However, the duration of protection, which is important for an accurate (cost-) effectiveness analysis of these HPV-vaccines, is largely unknown. A cost-effectiveness analysis should include the anticipated impact of HPV-vaccination on the (costs of) our national cervical cancer screening programme.

Herpes simplex virus-2
Seroprevalence studies indicate that ~8% of our population is latently infected with HSV-2. Although many people are infected (only 1/3 of the infected people have clear genital herpes-like symptoms), the burden due to HSV-2 is expected to be relatively small (i.e. ~ 87 DALYs) and the need for universal vaccination less urgent. The only subunit HSV-2 vaccine that is currently being tested in a phase 3 clinical trial is not suitable for universal vaccination, as it is only partially effective (~75%) in female adolescents that have not been infected by HSV-1 at that age. In the Netherlands, ~45% of the 12-year girls are serological positive for HSV-1. It is unlikely that a suitable and cost-effective HSV-2 will be available for our NIP within the coming 10 years.

Tuberculosis

We consider tuberculosis vaccination not valuable for uptake in the NIP. The only available vaccine is BCG-vaccine. This vaccine does not protect against disease but only against its severe forms. Furthermore, efficacy of BCG is not clear and ranges from 0-80% in different studies. In Japan, a country with low incidence, universal TB vaccination has shown not to be cost-effective. Data on TB are adequate to monitor the incidence in the Netherlands. About 1400 new cases are registered each year in the Netherlands of which more than half has a non-Dutch nationality. Parts of these are asylum seekers who were infected in their home country. In this situation, vaccination does have no effect.

In the Netherlands, a good treatment procedure, especially for asylum seekers, exists: Directly Observed Treatment (DOT). Cases are followed during the period they use antibiotics. Treatment works quite well, if there is no resistance. With the increasing number of migrants from Eastern Europe, the chance of spread of multi-resistance TB is increasing. If multiresistant TB will rise in the Netherlands in the next few years, general TB vaccination should be reconsidered.

3.4.2 Overview of comparison between disease burden and cost-effectiveness

In the present paragraph both estimates of the disease burden measured in disability-adjusted life years (DALYs) and cost-effectiveness (when available measured in costs per quality adjusted life year gained) are compared for the diseases for which potential vaccine candidates are considered in Chapter 5. The incremental cost-effectiveness ratios (ICERs) of various vaccinations inform policy-makers and others about the balance between costs and health effects, which may aid decision-making. The estimates of burden of disease are valuable to policy-makers since one is often willing to pay more to prevent a disease with high disease burden. Estimations of both DALYs and ICERs are based on many assumptions and thus have a large uncertainty. Most assumptions are described in detail in a previous review of the NIP.[1] Furthermore, several ICERs presented in this report are not derived from cost-effectiveness analyses for the Dutch situation, since they are often not available. In addition, an important aspect regarding estimations of the cost-effectiveness is that usually there is no underlying infectious-disease specific (dynamic) model; i.e. the fact that we deal with an infectious agent is often neglected. In contrast to the previous report (van der Zeijst et al.), not for all diseases estimations of the ICER in terms of costs per QALY were available.[1] In the previous report, these costs per QALY were based on a report from the Institute of Medicine 'Vaccines for the 21st Century; a tool for decisionmaking'.[8] Their QALY estimations were rough and based on US situation. In the present report, sometimes other outcome-measures had to be used since no QALY information was available. The table below gives three categories of cost-effectiveness. 'Cost-effective' refers to less than €20,000 per QALY gained. This limit is based on the often-cited limit for the cost-effectiveness ratio of €20,000 per life year saved, which is regarded as acceptable for preventive medicine.[9] 'Uncertain cost-effectiveness' refers to €20,000 to about €50,000 per QALY gained, whilst the last category 'Not cost-effective' refers to at least €50,000 per QALY gained. For those diseases for which costs per QALY estimations were not available and other outcome-measures had to be used, a cost-effectiveness expert based the category on evaluation.

Table 3-1: Summary of Disease burden and cost-effectiveness

	Disease burden (DALYs)			
	0-300	300-1000	1000-3000	3000-10000
Cost-effective			Varicella(*),*** RSV Pneumococcal 65+ years	
Uncertain cost-effectiveness	HSV-2		Meningococcal B(*)	Influenza** HPV Pneumococcal 0-4 years*
Not cost-effective	Hepatitis A		Rotavirus* Tuberculosis*	

* When presenting preventable disease burden the disease would move to one lower category. For meningococcal B disease and varicella, the preventable disease burden is just below 1,000 DALYs. This is indicated by (*) . For rotavirus and tuberculosis, a range is given for the preventable disease burden, i.e. 673-1,010 and 537-1,073 DALYs, respectively.
** Cost-effective for elderly (50+), but cost-effectiveness is unknown for healthy children. The preventable disease burden is based on universal vaccination.
*** The effect on zoster is not taken into account

Using DALYs and cost-effectiveness to summarize whether or not inclusion in the NIP is desirable, one might conclude that vaccination against hepatitis A and HSV-2 are not suited for inclusion in the NIP. The cost-effectiveness is rather unfavourable, while the disease burden is relatively low in comparison to other candidates. Rotavirus and tuberculosis vaccination is expected to be 'not cost-effective', but the disease burden is considerably higher than for hepatitis A and HSV-2. Vaccination against varicella, RSV and pneumococcal disease (65+) might be desirable since the disease burden is relatively high and vaccination is expected to have a favourable cost-effectiveness ratio. For meningococcal B and more particularly for pneumococcal disease (4+), HPV and influenza the disease burden is relatively high, which could justify the expectation of a somewhat less favourable cost-effectiveness. As discussed above comparisons remain difficult because of the many uncertainties.

3.4.3 Final remarks and conclusions

In table 3-2, an overview is given of the conclusions and recommendations regarding potential vaccine candidates. For detailed information, we refer to disease-specific paragraphs of Chapter 5. The main conclusions and recommendations are summarized:

Inclusion of pneumococcal vaccine for children in the NIP

Considering the high burden of disease, we conclude pneumococcal vaccine for children needs to be included in the NIP. This was previously advised by the Health Council.

Extension of the current NIP with available vaccines for influenza, hepatitis A or tuberculosis is not (yet) recommended

For influenza, hepatitis A and tuberculosis based on the current knowledge (epidemiology, effectiveness vaccine, cost-effectiveness) there is insufficient evidence to justify extension of the NIP

with vaccines against one of these diseases. For influenza and hepatitis A, the ethical issue of vaccinating children to prevent disease in adults needs attention, as well as cost-effectiveness analysis. For TB inclusion in the NIP could be reconsidered when epidemiology (multi resistant TB) changes.

Extension of the current NIP with the available varicella zoster vaccine might become feasible when combined with MMR

Inclusion of varicella zoster vaccine in the current NIP might be considered, although concerns regarding the effect of mass childhood varicella vaccination on the incidence of zoster in the adult population need to be addressed. Cost-effectiveness (and acceptability) will be more feasible when varicella zoster vaccine can be given in combination with MMR (i.e. MMRV). Such a vaccine will be available in the near future.

Meningococcal B, respiratory syncytial virus and human papilloma virus are suitable to include in future NIP when effective vaccine(s) become available

At this moment, no effective vaccines are available yet against meningococcal serogroup B disease, RSV or HPV. Extension of the NIP with such vaccine(s) could be recommended, when such vaccines become available. For HPV, it is expected that an effective vaccine will be licensed in Europe within 3 years.

Rotavirus and herpes simplex virus-2 are less likely to be candidates for a future NIP at this moment

At this moment, no effective vaccines are available against rotavirus or HSV-2. Given the current situation, inclusion in the NIP of future HSV-2 vaccine candidate has less priority. For rotavirus a cost-effectiveness study is needed when a vaccine comes available.

Table 3-2: Overview of recommendations regarding potential vaccine candidates for the NIP (detailed information in Chapter 5)

Target disease	Vaccine available	Vaccine available within 5 years	Surveillance	Cost-effectiveness	Include in current NIP	Include in future NIP (within 10 yrs)	Other (vaccination) strategies
Pneumococcal infection	Yes	Combination vaccine pneumo-men C	Monitor incidence and distribution by sero- and genotyping (serotype replacement)	Include herd-immunity and serotype replacement	Yes.	Combination with Men B/C	Consider elderly vaccination depending on results randomized controlled trial Continue vaccination of risk groups
Influenza	Yes	Intranasal vaccine Live attenuated vaccine Vaccines that induce heterosubtypic immunity will take more than 5 years	Continue sentinel network (RIVM, NIVEL, NIC)	Determine for high-risk children Determine for healthy children	No	Possibly for healthy children, but also need ethical consideration	Vaccinate 50+ (in stead of 65+) Continue vaccination of risk-groups, also health care workers and household contact
Hepatitis A	Yes, also combination hepatitis A/B		Insight into outbreaks. Measure decrease in adult immunity.	Determine for newborns	No	Possibly, in combination with hepatitis B and depending on adult immunity Needs ethical consideration	Continue vaccination of certain groups (travellers, MSM, 2nd and 3rd generation migrants, active prevention outbreaks) Consider vaccination of Turkish and Moroccan parents (in combination with hepatitis B)?
Rotavirus	No	Yes	Insight into mortality Genotyping Safety	Not a priority	Not possible yet	Possibly, but public health profit is intermediate	

Table 3-2: Continued.

Target disease	Vaccine available	Vaccine available within 5 years	Surveillance	Cost-effectiveness	Include in current NIP	Include in future NIP (within 10 yrs)	Other (vaccination) strategies
Varicella zoster	Yes	Combination vaccine with MMR (i.e. MMRV)	Continue sentinel surveillance GP Consequence of earlier 2-dose of MMR(V)	Determine for combination with MMR	Possibly	Possibly as MMRV combination	Vaccination of adults
Meningococcal B	No	At least five years Combination vaccine pneumo-men B/C Serogroup independent meningococcal vaccine in (far) future	Monitor incidence Monitor distribution of PorA types.	Determine particular when changes occur in incidence	Not possible yet	Yes, when an effective vaccine is available	
RSV	No	Unlikely	Determine risk groups	Determine*	Not possible yet	Yes, for those with high or intermediate risk if an effective vaccine is available	Passive immunisation
HPV	No	Possibly	Occurrence of HPV-16 and 18	Determine for various vaccine strategies	Not possible yet	Yes, if an effective vaccine is available	Cervix screening programme
HSV-2	No	Unlikely		Not a priority	Not possible yet	Unlikely	
TB	Yes, effectiveness BCG unknown for TB		Monitor multiresistant TB		No	Depending on occurrence of multiresistant TB	Continue good treatment procedure

* A cost-effective analysis is currently being made by Netherlands Vaccine Institute (NVI)

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4. Diseases currently included in the National Immunisation Programme

4.1 Diphtheria

F.R. Mooi, P.E. Vermeer-de Bondt, F. Abbink

4.1.1 Introduction

Diphtheria is an acute infectious disease of the upper respiratory tract and occasionally of the skin. It is caused by local and systemic action of the diphtheria toxin, produced by toxigenic *Corynebacterium diphtheriae*, *Corynebacterium ulcerans* and *Corynebacterium pseudotuberculosis*.[1] Disease caused by the toxin of these bacteria is indistinguishable.[2,3,4] The toxin genes are carried by a bacteriophage.

The incubation period of diphtheria is two to five days. The disease is characterized by pseudomembranous inflammation of the upper respiratory tract, usually in the pharynx but sometimes in the posterior nasal passages, larynx and trachea. This may lead to respiratory obstruction. In addition, widespread damage to other organs (including myocarditis and polyneuritis) can occur. A cutaneous form of diphtheria also exists.[5] Diphtheria can be subclinical, but fast fatal outcomes also occur, especially in very young children and older persons. Disease can be milder in vaccinated individuals.

Infectiveness in patients with untreated disease may last for up to four weeks. Carriers, who may be asymptomatic, can potentially transmit the infection for longer. Humans are the only reservoir for *C. diphtheriae* and transmission occurs through aerosol and close contact. Cattle are the normal reservoir for *C. ulcerans*, and humans can acquire infection through the consumption of raw dairy products and contact with animals. Between 1986 and 1993, 8% of the 215 *Corynebacterium* isolates received by the PHLS in the UK were *C. ulcerans*.[6] Person-to-person spread of *C. ulcerans* is probably uncommon.

Immunity depends primarily on the presence of antibodies to the toxin, and an effective vaccine has been available since the 1930s. Disease can be treated by passive immunisation with horse anti-toxin antibodies. Transmission of diphtheria can be prevented by chemoprophylaxis and immunisation of contacts.[7]

4.1.2 Diphtheria vaccine

Diphtheria toxoid is one of the oldest vaccines used. It is obtained by inactivation of the purified toxin with formaldehyde according to a procedure, which was developed in the 1930s.[8] For the NIP, two vaccines, which include diphtheria, are available: DTP-IPV/Hib and DT-IPV, containing 15 and 2.5 Lf, respectively. Immunisation schedules are shown in paragraph 2.2. The adjuvant used to increase immunogenicity is aluminium phosphate or aluminium hydroxide. Combination vaccines used in the Netherlands have phenoxyethanol as preservative and aluminium phosphate as adjuvant. There are no strict contra-indications for diphtheria vaccine.[9]

4.1.3 Adverse events following diphtheria vaccine

Over forty years ago, it was noticed that the diphtheria vaccine was less well tolerated, especially in people who had natural infection previously. Further purification, the precipitation with aluminium salts and lowering the amount of toxoid have considerably reduced adverse effects. Nowadays severe local and systemic reactions are rare. Local reactions and systemic events following diphtheria-vaccines and tetanus-vaccines are comparable in severity and rate and do not differ from those of the combined product with or without added IPV vaccines.[10] The rate of adverse events may be somewhat higher but lower than the total number of adverse events if the vaccines are given at a separate site or at a different time.

In the Netherlands, diphtheria toxoids are only available in combination products with tetanus and polio, with or without pertussis components. See for the adverse events following DT-IPV under tetanus and DTP_w-IPV under pertussis. There is insufficient evidence for the existence of a so called 'hyperimmunisation reaction' to diphtheria vaccine components with the modern/current vaccines. Diphtheria toxoid vaccines have not been implicated as a cause of lasting disability or chronic illnesses.[11] There are no signals that including diphtheria-vaccine in a combination vaccine simultaneously with other vaccines, deteriorates effectiveness of other vaccine-components. CRM197 (variant of diphtheria toxoid) containing vaccine, as carrier protein of several polysaccharide vaccines, may benefit from simultaneous or prior diphtheria-vaccination.[10]

There are no strict contra-indications for the diphtheria component. Severe anaphylaxis has not been observed after diphtheria vaccination.[12]

4.1.4 History of diphtheria and diphtheria vaccination in the Netherlands

Prior to vaccination, respiratory diphtheria commonly affected pre-school and school age children. Large epidemics occurred in Europe during and after the Second World War, with an estimated one million cases. In the Netherlands, the last epidemic occurred during World War II with 222,000 cases reported between 1940 and 1946. Diphtheria vaccination was introduced in the Netherlands in 1957, when it was offered to all those born since 1945. Vaccination had a dramatic impact on reducing the incidence of infection, and in 1963, the last fatal case of diphtheria in the Netherlands was registered.[13] Currently, children are vaccinated at the ages of 2, 3, 4 and 11 months with a combination vaccine comprised of diphtheria toxoid, tetanus toxoid, killed whole cells of *Bordetella pertussis*, inactivated poliovirus and *Haemophilus influenzae* type b polysaccharide (DTP_w-IPV/Hib vaccine). Booster doses are given at age 4 and 9 years with DT-IPV. Before 1999, the first series of DTP_w-IPV/Hib vaccinations were given at the age of 3, 4, 5 and 11 months. The coverage for receiving at least three vaccinations by age 12 months has been 97% in the past decades.[14,15]

In addition to routine infant immunisation, diphtheria vaccination is also advised for persons at increased risk for exposure (e.g., travellers to endemic-disease countries and those who work with injection drug users and alcoholic patients and laboratory workers).

4.1.5 Epidemiology of diphtheria in the Netherlands

Surveillance of diphtheria in the Netherlands is based on notifications and laboratory surveillance. In addition, hospital admission statistics are analysed yearly. No formal system for laboratory surveillance is in place, but current practice is that isolates of *Corynebacterium* are sent to the RIVM where the identity of the strain and its capacity to produce toxin (toxigenicity) are determined.

Notifications

After the epidemic in the 1940s, notifications decreased significantly (Fig. 4-1). Between 1997 and 2003, two cases of cutaneous diphtheria were notified, both were vaccinated individuals.[16] From one of these a non-toxigenic strain of *C. diphtheriae* was isolated, while for the other no laboratory results are available. Nobody died of diphtheria in this period.

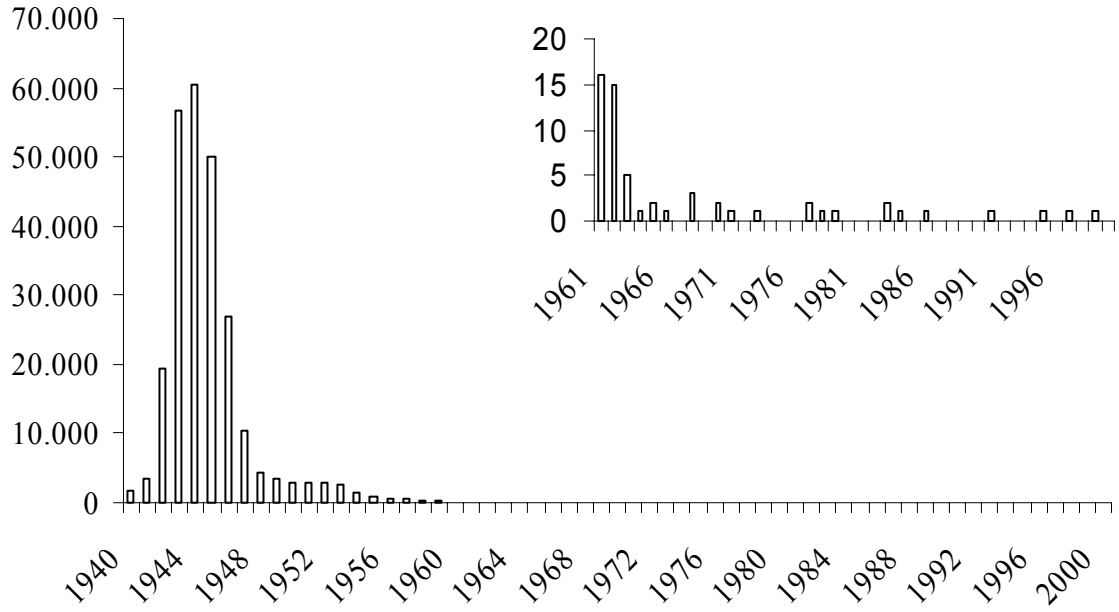

Figure 4-1: Notifications of diphtheria since 1940 (source Inspectorate of Health)

Laboratory surveillance

Since 1990, 29 human isolates of *C. diphtheriae* have been sent to the RIVM; none of these was toxigenic.[17] In 2002, a toxigenic *C. ulcerans* was isolated from an unvaccinated patient with diphtheria symptoms and in 2004 from a rhesus monkey.[18]

Hospital admission statistics

Between 1997 and 2003, three patients were admitted to hospital with diphtheria as the main diagnosis.[19] No laboratory diagnosis for these cases was available.

From the surveillance data, it can be concluded that there is no evidence of circulation of toxigenic *C. diphtheriae* in the Netherlands.

4.1.6 Levels of immunity against diphtheria in the Netherlands

Immunity against diphtheria in the general Dutch population and in persons refusing vaccination was assessed in a large population-based study carried out in 1995-'96.[20] Consensus is lacking about the exact antitoxin level needed for complete protection.[21-24] However, according to international standards <0.01 IU/ml, 0.01-0.1 IU/ml and >0.1 IU/ml refer to, no, basic and full protection.[25] The Dutch study showed that 88% of individuals had a level higher than this minimum threshold (0.01 IU/ml); for 58% the level was >0.1 IU/ml. Twelve percent of the population was not protected against diphtheria. These estimates and the geometric mean titre (0.12 IU/ml) are within the range of findings for other European countries.[1,26-32]

Two main clusters of (potential) unprotected individuals were identified. Firstly, over 60% of the socio-geographically clustered religious (orthodox reformed) community had antibody levels lower

than the minimum threshold of 0.01 IU/ml. Inadequate herd immunity to diphtheria may allow introduction of diphtheria into this group, and subsequently spread through the population. A similar situation for poliomyelitis caused an outbreak of poliomyelitis in the Netherlands in 1992-93.[33] For poliomyelitis, the solution may be eradication of the causative agent. For diphtheria, the WHO has not yet formulated such a goal.

Second, about one third of adults aged 50 to 79 years lack antibodies against diphtheria. These individuals were born before the introduction of diphtheria vaccination in the Netherlands, and their immunity was not boosted due to low circulation of *C. diphtheriae* in the population. As in other industrialized countries, lack of immunity in older persons is a cause for concern.[34-36] It is unknown whether these individuals are protected by memory immunity. The observation that the epidemic in the Newly Independent States did not lead to transmission to the Netherlands is reassuring and suggests that diphtheria immunity in the Netherlands – as well as in other countries – will suffice. The Health Council in the Netherlands also reviewed the potential impact of the resurgence of diphtheria in the former Soviet Union in 1996, and advised at that time that changes in the Netherlands diphtheria immunisation programme – such as booster vaccinations among adults - were not necessary.[37]

Insight into the current seroprevalence of the general population would give information on waning immunity and [lack of] immunity in adults born before introduction of vaccination. Furthermore, the persistence of antibodies after complete vaccination could be studied further. In the previous seroprevalence study in 1995-1996, a decrease in antibody level was observed with increasing age among individuals who were completely vaccinated according to the NIP. When these data were interpreted longitudinally, this corresponded with a continuous decline of vaccine-induced antibodies. Only a small part of those aged 30-34 years (i.e. about 25 year after vaccination) had low antibody levels. However, with continuous decline of antibody levels the proportion of adults that has critical antibody levels has increased. Depending on the results of seroprevalence, (re)vaccination of adults could be considered or the existence and effectiveness of memory studied.

4.1.7 *C. diphtheriae* strain variation in the Netherlands

Clinical protection against diphtheria is based on neutralisation of toxin by antibodies. Variation occurs in the diphtheria toxin, both at the DNA and protein level. Toxin variants, which are less well neutralized by vaccine-induced antibodies, will confer a selective advantage since the toxin plays an important role in the ecology of *C. diphtheriae*. Such toxin variants can spread quickly through the *C. diphtheriae* populations, as the toxin genes are carried by a bacteriophage.

No information is available on the toxin alleles, which circulate in Western Europe or the Netherlands.[38] Thus, it is not clear whether the toxin genes are adapting to vaccination. Therefore, we recommend that toxin genes of all clinical isolates be sequenced.

4.1.8 Diphtheria vaccine developments

In 2005, the DTP_w-IPV/Hib vaccine currently used for infant immunisation will be replaced by a DTP_a-IPV/Hib vaccine. Combination vaccines with a whole cell pertussis component are more immunogenic than those containing acellular pertussis components due to the presence of lipopolysaccharide, a known adjuvant. DTP_w-IPV/Hib vaccines induce higher levels of anti-diphtheria toxin levels compared to DTP_a/Hib vaccines.[39] Indeed, in the UK, a switch from DTP_w-IPV/Hib to DTP_a-IPV/Hib has been associated with the re-emergence of *Haemophilis influenzae* type b infections.[40]

Another concern is the effect on memory when switching vaccines. The content of diphtheria vaccine can be increased to improve immunogenicity. However, this will probably not increase duration of memory.[41] The necessity for vaccination of adults with low or no antibody titres to diphtheria toxin has been discussed in several reports of the Dutch Health Council. In the most recent report, it is concluded that there is currently no need for vaccination or revaccination of elderly.[42] For travellers to regions where diphtheria is still a problem, vaccination with a monovalent diphtheria vaccine is recommended, however.

4.1.9 International perspectives of diphtheria vaccination

The resurgence of diphtheria in the former Soviet Union illustrates the fragile balance between population immunity and epidemics. Several factors have probably contributed to the diphtheria epidemic, but it is assumed that waning immunity in adults played an important role. The introduction of an improved public health strategy of prevention and control has significantly reduced diphtheria in most of the Baltic States and Newly Independent States. However, compared to most Western European countries, diphtheria incidence in a number of East European countries remains high (incidence per 100,000 in 1999-2003: Georgia 0.63, Latvia 4.2, Ukraine 0.6, Russian Federation 0.55).[43,44] Thus introduction of diphtheria from these countries remains a cause for concern, especially in view of the presence of large groups in the Netherlands with low or absent diphtheria toxin antibodies.

References of diphtheria

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4.2 Tetanus

F. Abbink, P. Vermeer-de Bondt, H.E. de Melker

4.2.1 Introduction

Tetanus is the only vaccine-preventable disease that is not communicable but acquired through environmental exposure to the spores of *Clostridium tetani*. The disease is caused by a potent neurotoxin produced during the anaerobic growth of the bacterium in necrotised tissues such as dirty wounds, from the umbilicus following non-sterile delivery, or following injecting drug use. The incubation period is between 4 and 21 days (most commonly about ten days).

Clinical symptoms of tetanus are muscle spasms, initially muscles of mastication causing trismus or 'lockjaw', which results in a characteristic facial expression – 'risus sardonicus'. Trismus can be followed by spasms of other muscles, such as sustained spasm of back muscles – 'opisthotonus'. Finally, mild external stimuli may trigger generalized tonic tetanic seizure-like activity, which contributes to the serious complications of tetanus (dysphagia, aspiration pneumonia) leading to death unless intense supportive treatment is rapidly initiated.[1] Diagnosis is most often only based on clinical symptoms.

In developed countries, most cases of tetanus occur in unvaccinated elderly, born before introduction of tetanus in the NIP. However, in the US, up to 18% of cases of tetanus are in younger individuals who inject illicit drugs.[2] Tetanus in injecting drug users (IDUs) was uncommon in Europe up to 2003. This situation changed when a cluster of over 20 cases was identified in the UK in 2003.[3] In the Netherlands, one fatal case of tetanus in an IDU occurred in 2004.[4] Natural infection with tetanus does not provide immunity, and recurrent infections have been described.[5] Tetanus can very effectively be prevented by active and passive immunisation.

4.2.2 Vaccines available against tetanus

The vaccine used in the NIP is tetanus toxoid (TT). The toxoid is formaldehyde-inactivated toxin, adsorbed onto aluminium salts to increase its immunogenicity. TT induces the formation of specific antibodies, which neutralize the toxin.

The current preparations in the Netherlands are DTP-IPV, for primary vaccination of infants and preschool children with normal D-content, DT-IPV with decreased content of D-toxoid and single T-vaccine. Tetanus can almost completely be prevented by vaccination.

4.2.3 Adverse events following tetanus vaccine

Local reactions are rather common and seem to be very much dependent on combination, age, dose number/age and of course also on case definitions and case ascertainment scenarios.[6] Also differences in lots and not only in manufacturers are present. Pain or tenderness is reported in up to 85% of booster doses with in up to 30% redness and swelling. More severe local reactions are reported in less than 2%. There is no conclusive evidence for the existence of the so-called hyperimmunisation reaction and no consistent association with increasing dose numbers or pre- and post-vaccination titres. Moreover the donors of human-tetanus-immunoglobulin who are vaccinated at the time that antibody levels are high repeatedly, hardly ever have severe local reactions. However, extensive local reactions do happen, for which the pathophysiology is unclear and recurrence after further

vaccinations is not predictable. There is also no direct link with pre-existing antibody titre levels (unpublished data RIVM, Vermeer-de Bondt). Although rates of adverse events are a little higher when T-vaccine is combined with D, with or without IPV, the frequency and severity are not increased compared to separate administration of the vaccines.
For DT-IPV, the most commonly used vaccine containing Tetanus-toxoid (apart from DTP_w-IPV), the safety profile is as follows: Local reactions to the DT-IPV vaccine (with adult formulation of the diphtheria-component) are rather common and usually mild to moderate. 30-70% of recipients report to have some local reaction, depending on the age, schedule, injection site and technique, applied case definitions and methods of case ascertainment. Usually these local reactions resolve in one or two days and rarely interfere with normal activities. Low-grade fever is reported in up to 30% of recipients. Higher fever of over 39°C is rare, also depending on age. Occasionally very high fever, extensive local reactions or swollen limp, or in susceptible children collapse reactions or febrile convulsions occur. As with all vaccinations syncope may follow and very rarely abscess formation occurs.[7-9]
DT-IPV vaccines have not been identified as a cause of lasting disability or chronic illnesses.[10] Association with plexus neuritis is speculative, since only based on open case series with unknown denominators. These designs tend to overestimate rates. The experience in the Netherlands is favourable. There is no link with seizures or Guillain Barré syndrome. Evidence favours these to be unrelated chance occurrences. Tetanus-containing vaccines do not seem to have adverse effects on antibody response to other components. They may enhance response to polysaccharide vaccines that use tetanus-toxoid as carrier protein.[6] There are no contra-indications for the T-component or DT-IPV vaccine. Severe anaphylaxis appears not to exist. Reports stem mainly from the time that impurities in the formulation may have played a role and or combinations with (heterologous) immunoglobulines.

4.2.4 History of tetanus and tetanus vaccination in the Netherlands

Tetanus vaccination was introduced in the Netherlands in 1957 and was offered to all those born in 1945 and thereafter. This has dramatically reduced the incidence of tetanus.[11,12]

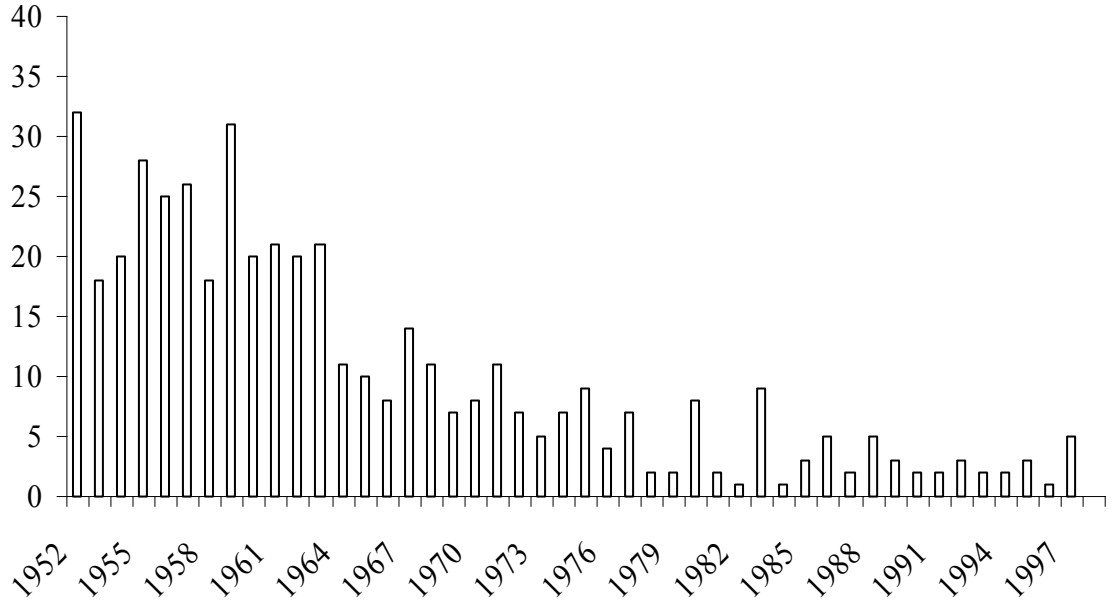

Figure 4-2: Notifications of tetanus (Source: Inspectorate of Health)

Currently children are vaccinated at the ages of 2, 3, 4, and 11 months with diphtheria, tetanus, pertussis, inactivated polio vaccine and *Haemophilus influenzae* type b (DTP-IPV/Hib combined) and at ages 4 and 9 years with DT-IPV. Before 1999, the first series of DTP-IPV/Hib vaccinations were given at the ages of 3, 4, 5 and 11 months.
The coverage for at least three vaccinations by age 12 months has been 97 % in the past decades.[13,14]
Tetanus prevention following trauma consists of passively providing antitoxic antibody (human tetanus immunoglobulin) for some groups, and of simultaneously inducing active immunity by starting active vaccination for everybody. Until recently, tetanus immunoglobulin (TIG) was advised for unvaccinated persons and those with an unclear vaccination status as well as those vaccinated more than 15 years ago. However, a recent study demonstrated that this policy is inefficient.[15] The number of patients needed to treat to prevent a tetanus case is very high. Thanks to the success of the NIP and the persistence of high antibody levels many years after tetanus vaccination it is therefore now justified to limit the administration of TIG to those who are at the highest risk i.e. those who are known to be unvaccinated, women born before 1950 and men born before 1936.[16]

4.2.5 Epidemiology of tetanus in the Netherlands

Mandatory notification for tetanus was abolished in 1999. Since then, tetanus surveillance is performed by the RIVM, based on requests for human tetanus immunoglobulin and requests for diagnostic tests when tetanus is considered.
No neonatal tetanus cases have been reported since 1984.[17,18] Between 1999 and 2003, 11 cases of tetanus were registered, all in unvaccinated individuals. In 2004, a fatal case of tetanus in an injecting drug user in Amsterdam was registered.[15] Re-introduction of tetanus notification also in view of possible contamination of drugs is recommended. This would be useful since diagnosis in IDUs could be missed, when they are considered as an overdose.

4.2.6 Levels of immunity against tetanus in the Netherlands

Immunity against tetanus in the general Dutch population and in persons refusing vaccination was assessed in a large population study carried out in 1995/96.[19]
More than 95% of those born after the introduction of routine vaccination had tetanus antitoxin levels above the minimum protective level. After the sixth vaccination, a gradual decrease in tetanus antitoxin levels occurred. Nevertheless, immunisation in accordance with the routine programme induces protection for at least two decades but probably much longer. Not only many members of religious groups who refuse vaccination, but also many adults born before the introduction of vaccination lack tetanus immunity. The lack of immunity in these groups is associated with the occurrence of tetanus. The higher risk of tetanus infection in these age groups explains that of the 34 tetanus patients reported in 1984 to 1996, 30 patients (88%) was born before 1945, i.e. before the introduction of routine vaccination. However, the Dutch Health Council concluded in her advice in 2001 that because of the low tetanus incidence there is no urgent indication to advice vaccination of persons aged 50 years and above.[20] The Health Council concluded that in individual cases it could be desirable that older people, particularly those born before 1950, are aware that their immunity against tetanus (and diphtheria) may be limited.

4.2.7 Strain variation of tetanus in the Netherlands

Tetanus is unique among the vaccine-preventable diseases in that it is not communicable. Tetanus spores are ubiquitous in the environment. Furthermore, the resulting absence of herd immunity means that every unvaccinated individual is at risk of tetanus.

4.2.8 Tetanus vaccine developments

As mentioned earlier, in 2005, the DTP_w-IPV/Hib vaccine currently used for infant immunisation will be replaced by a DTP_a-IPV/Hib vaccine. Combination vaccines with a whole cell pertussis component are more immunogenic than those containing acellular pertussis components due to the presence of lipopolysaccharide, a known adjuvant. The clinical relevance is unclear. For tetanus, the boosting effect of lipopolysaccharide is smaller than for diphtheria. Another concern is the effect on memory when switching vaccines. The content of tetanus vaccine can be increased to improve immunogenicity. This will probably not increase duration of memory.[21]

4.2.9 International perspectives of tetanus vaccination

The WHO has stated the aim to eliminate neonatal tetanus worldwide. Turkey was the only country in the WHO European region still reporting cases in 2002.[22]

In Western Europe, most cases of tetanus occur in unvaccinated elderly, similar to the situation in the Netherlands.[23] In 2003, however, a cluster of over 20 cases of tetanus occurred in IDUs in the UK.[3] This led UK Public Health authorities to recommend tetanus immunisation for all IDUs with incomplete or uncertain immunisation status.[24] In the US, a considerable proportion of tetanus cases (up to 18%) occurs in IDUs.[2]

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4.3 Pertussis

F.R. Mooi, P.E. Vermeer-de Bondt, S.C. de Greeff

4.3.1 Introduction

Pertussis ('whooping cough') is a highly contagious disease of the respiratory tract caused by members of the *Bordetella* genus. In the Netherlands, 95% of pertussis cases are caused by *Bordetella pertussis*, while 5% are caused by *Bordetella parapertussis*. Pertussis was a major cause of child mortality before the introduction of vaccination.

Pertussis is preceded by an incubation period of 6 to 20 days.[1] The disease is characterised by a catarrhal phase followed by a phase with paroxysmal coughs, which lasts for at least two weeks.[2] The paroxysmal coughs can be accompanied by cyanosis, apnoea and fever. The most prevalent complications of pertussis are secondary infections, such as otitis media or pneumonia, and encephalopathy and seizures. Particularly among young unvaccinated infants, pertussis can cause severe symptoms and complications. In vaccinated (older) children and adults, the disease most often occurs with milder and/or unrecognised symptoms.[3]

Transmission of the infection is by aerosol droplets, which is most efficient when there is close (less than 5 feet) contact. Cases are infectious from six days after exposure to three weeks after the onset of typical paroxysms, and are most infectious during the early catarrhal phase.

4.3.2 Pertussis vaccine

A whole cell vaccine containing two pertussis strains is currently used in the Netherlands (table 4-1), but will be replaced in 2005 by an acellular pertussis vaccine.

Table 4-1: Characteristics of the two strains used in the Netherlands whole cell vaccine.

Strain	Pertussis toxin type	Pertactin type	Serotype
134	PtxA2	Prn1	$Fim2^{+/-}$, Fim3
509	PtxA4	Prn7	Fim2, $Fim3^{+/-}$

From ref [4]

4.3.3 Adverse events following pertussis vaccination

Vaccination with whole cell pertussis-containing vaccines is often followed by local and systemic reactions. Verschoor and Wildschut found 13-30% redness (>2 cm) and 49-73% pain at the site of injection.[5] In the Rotterdam study in 1993, the percentages of local reactions were 55-75% for any inflammatory symptom. (Unpublished data, RIVM, Vermeer-de Bondt) In this study, reported incidences for toddlers were 50% for redness, 30% for swelling and 90% for pain.[6]

Fever, crying, sleeping problems, drowsiness, irritability and listlessness are also common adverse events. These symptoms occur in over half the recipients in the two studies, with different presentation and rates for different doses and ages. The percentages of children who showed persistent screaming was strongly dependent on age, case definition and level or method of case ascertainment and varied from a few percent to 1 promille.[5,6]

Acknowledged more severe adverse events are collapse reactions, occurring predominantly in the youngest infants after the first dose, with a rather small risk of recurrence after subsequent vaccinations.[7,8] These occur in approximately 1 per 1,000 infants. Discoloured leg syndrome was first recognised in 1993 and since then reported consistently to the enhanced passive surveillance system. The syndrome is age- and possibly dose-dependent and has an estimated occurrence of 1 per 1,500 children. There is some risk of recurrence (currently under study).[9] Febrile seizures occur in approximately 5% of children between 6 months and 4 years of age with the median around one years of age. Because DTP_w-IPV often causes fever, some predisposed children may have a febrile seizure after DKTP, mainly after the fourth dose (frequency approx 1: 5,000-10,000).[10,11]
Despite earlier allegations, pertussis whole cell vaccine has not been proved to cause lasting disabilities in controlled or systematic studies.[12] No relation has been established between pertussis whole cell vaccination and epilepsy, encephalopathy, diabetes mellitus, autism, retardation, sudden infant death syndrome or chronic neurological diseases. The risk of common airway, gastro-intestinal infections or of invasive bacterial infections is not increased following vaccination with pertussis whole cell vaccine. If anything, the risk appears to be decreased and there is no sign of any immune suppression.[13]
The age at which DTP_w-IPV is given is also the age that several of these serious conditions occur or become apparent which might explain the association with vaccination .
Since the 80s, acellular pertussis vaccines have been developed, mainly because of the rather high rate of adverse events after whole cell pertussis vaccination. Acellular vaccines containing only pertussis proteins (with 2, 3 or 4 components) have been compared in a small study in the Netherlands before introducing the acellular pertussis booster at 4 years of age in 2002. Fever and crying were significantly more prevalent in the whole cell vaccine group compared to the acellular vaccine group.[6]
Safety and efficacy of acellular vaccines have been investigated in large trials in Sweden, Italy and Germany.[14] The studies differed with respect to design, schedules, case definitions and method and level of case ascertainment resulting in statistical and clinical heterogeneity. Reviewing the different studies reveals certain trends, however.[15] Compared to the whole cell vaccines, acellular pertussis vaccines were generally less reactogenic.
This difference in reactogenicity between whole cell and acellular vaccines concerns the frequency of common minor adverse events (local reactions, fever, crying, irritability, pallor, drowsiness e.g.). Whole cell vaccines have a 3-5 times higher rate of adverse events compared to acellular vaccines. Ranges for collapse reaction were 0-0.47 per 1,000 children with acellular vaccines versus 0.06-0.67 per 1,000 for whole cell recipients.[16] The so-called extensive limp swelling (ELS), as adverse event following the fifth dose of acellular pertussis vaccines needs further study.[17]
For the acellular pertussis vaccines, there is no epidemiological link with serious adverse events with lasting or chronic defects. Vaccination with acellular vaccines may be followed by unrelated serious events, like diabetes mellitus, autism, sudden infant death syndrome, mental retardation, West syndrome, etc, in the same frequency as with the whole cell pertussis vaccines, just by chance alone.
It is necessary to follow these new vaccines in the programme intensively, both in passive as in active designs.[18-22]

4.3.4 History of pertussis and pertussis vaccination in the Netherlands

Pertussis vaccines have been used in the Netherlands on a large scale. Initially [1952-1957] as a single vaccine, and later in combination with diphtheria, tetanus, polio and Hib (Table 4-2). Vaccination with pertussis whole cell vaccine has been very successful in reducing morbidity and mortality due to pertussis.

Both pertussis vaccines and vaccination schedules have been changed frequently since the introduction of pertussis vaccination in 1952 (Table 4-2). Most relevant are the changes implemented since 1997. In 1997, the criteria for release of the vaccine were enhanced, in that lots were required to contain at least seven International Units [IU] instead of 4 IU. Estimations of vaccine-efficacy indicated an increase in 1998-2002 compared to 1996-1997, suggesting that these changes have been effective.[23] In 1999, the vaccination schedule was changed so that the first vaccination was given at two instead of 3 months. No effect has [yet] been observed of this change.[23] In 2001, a booster vaccination with a three component acellular vaccine at the age of 4 yrs was introduced which has resulted in a decrease in the incidence of pertussis in this age category.[24]

Table 4-2: Changes in the pertussis vaccines and vaccination schedules.

Period	Vaccine combination	Characteristics pertussis component	Vaccination schedule
1952-1959	DTP_w	20 IOU/HD	3,4,5 mo, 4 yr
1959-1962	DTP_w	16 IOU/HD, ≥ 4 IU/HD	3,4,5 mo, 4 yr
1962-1975	DTP_w –IPV	16 IOU/HD, ≥ 4 IU /HD, second strain	3,4,5, 11 mo
1975-1984	DTP_w –IPV	10 IOU/HD, ≥ 4 IU/HD	3,4,5, 11 mo
1985-1992	DTP_w –IPV	16 IOU/HD, ≥ 4 IU/HD	3,4,5, 11 mo
1993-1996	DTP_w -IPV – Hib	16 IOU/HD, ≥ 4 IU/HD	3,4,5, 11 mo
Dec 1997	DTP_w -IPV – Hib	16 IOU/HD, ≥ 7 IU/HD	3,4,5, 11 mo
Jan 1999	DTP_w -IPV – Hib	16 IOU/HD, ≥ 7 IU/HD	2,3,4, 11 mo
Nov 2001	DTP_w -IPV – Hib	16 IOU/HD, ≥ 7 IU/HD	2,3,4, 11 mo, P_a at 4 yr.
Mar 2003	DTP_w -IPV /Hib	16 IOU/HD, ≥ 7 IU/HD	2,3,4, 11 mo, P_a at 4 yr.
Jan 2005	DTP_a-IPV/Hib	Ptx, FHA and Prn	2,3,4, 11 mo, P_a at 4 yr.

Abbreviations: DTP_w, diphtheria toxoid, tetanus toxoid and whole cell pertussis vaccine. IPV, inactivated polio. Hib, Haemophilis influenzae b vaccine. IOU, international opacity units. HD, human dose. IU, international units. P_a, acellular pertussis vaccine. Source.[25]

Current vaccination against pertussis

Until the 1st of January in 2005, children were vaccinated intramuscularly at the ages of 2, 3, 4 and 11 months with a combination vaccine produced by NVI, comprised of diphtheria toxoid, tetanus toxoid, pertussis whole cells and inactivated polio [DTP_w-IPV]. A vaccine against *Haemophilus influenzae* type b [Hib], produced by Aventis-Pasteur, is mixed with DTP_w-IPV before injection. A booster vaccination with a three component acellular vaccine from GlaxoSmithKline (GSK) containing pertussis toxin, pertactin and filamentous hemagglutinin is given at 4 years of age.

The coverage for at least three vaccinations by age of 12 months has been 97% in the past decades.[26,27] It must be noted however, that in the national registration no difference can be made between DTP_w-IPV and DT-IPV vaccinations, so vaccination coverage levels for pertussis may be somewhat lower than for DT-IPV. Details on the coverage levels for acellular booster vaccination given at the age of four are not available yet.

4.3.5 Epidemiology of pertussis in the Netherlands

The surveillance of pertussis in the Netherlands is mainly based on notifications, hospital admission data and death registration. As in many developed countries, pertussis has remained endemic in the Netherlands. A sharp increase in notifications was observed in 1996.[28] The current incidence

according to notifications is still higher in comparison to the years before the 1996-1997 epidemic. Based on various surveillance sources epidemic peaks have been revealed every two to three years (in 1996, 1999, 2001 and 2004). In the last decade, the incidence of notified cases varied between 50.2/100,000 in 2001 and 16.0/100,000 in 1998. Yearly age-specific incidences are highest for the 5-9 year olds.[29] In 2001, 2002 and 2003, respectively, 8030, 4487 and 2847 cases were notified.[30] In figure 4-3 notifications and hospitalisations for pertussis are displayed.

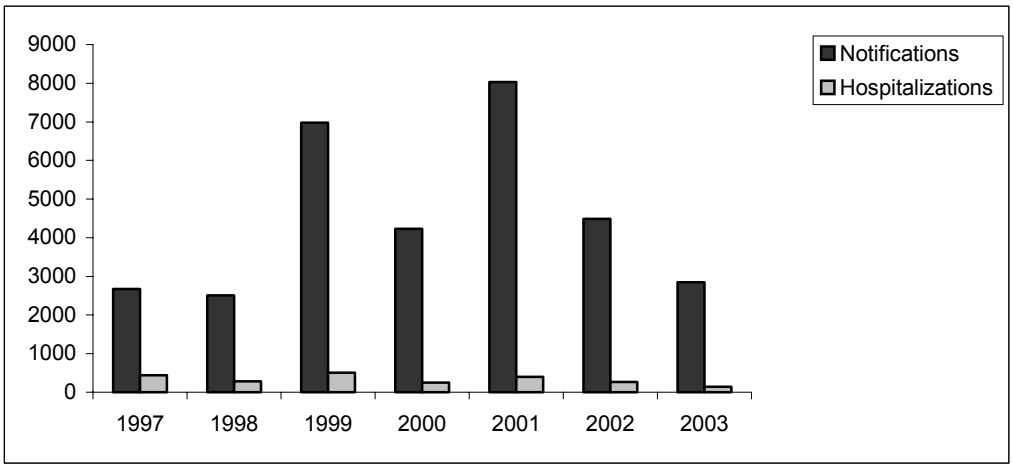

Figure 4-3: Notifications and hospitalisations for pertussis since 1997. Source [23].

Based on a cross-sectional, sero-epidemiological study, conducted in 1995 the actual incidence of infections with *B. pertussis* in the Netherlands was estimated at 6.6%, with highest incidence reported for the 20-24 year olds.[31] Similar results where reported for England and Wales.[32] Although most of the infections in older adolescents and adults are mitigated or subclinical, they contribute to the transmission of pertussis to the high-risk group, such as neonates, which have not yet been sufficiently vaccinated. Furthermore, there is evidence that the high circulation of *B. pertussis* among adolescents and adults results in significant economic damage.[33,34]

Notification based on clinical symptoms underestimates the incidence of pertussis, as many infections are mild or subclinical. Notifications based on hospitalisations are less affected by factors such as awareness for the disease, diagnostic methods and criteria. Hence, hospitalisation data are especially suitable to compare the pertussis epidemiology between different countries. Like notifications, incidences of hospitalisation for pertussis show peaks every 2-3 years. In recent years, the highest incidence was reported in 1996 (3.3/100,000) and the lowest in 2003 (0.9/100,000).[23] Most hospitalisations due to pertussis [circa 40%] are among children less than 1 year and especially among those younger than 3 months of age, i.e. those too young to be protected by vaccination. Yearly 50 (in 2003) to 250 (in 1996 and 1999) children younger than 3 months are admitted to hospital because of pertussis. In the last decade, eight deaths due to pertussis have been reported (2 in 1996, 2 in 1997, 1 in 1998 and three in 1999). All eight patients were children less than 1 year of age.[35]

In 2002, 1 year after introduction of the booster vaccination for 4-year-olds, all surveillance sources showed a decrease in the incidence of the 3 and 4 year-olds compared with previous years. Besides, small increases in the number of patients older than 5 years were seen.[29]

4.3.6 Levels of immunity against pertussis in the Netherlands

Immunosurveillance plays an important role in estimating the true circulation of *B. pertussis* [see above], in confirmation of clinical diagnosis and in estimating the susceptibility to *B. pertussis* [re-]infection. Confirmation of clinical diagnosis is based on high IgA or IgG titres against *B. pertussis* cell wall components and pertussis toxin, respectively.[36,37] The introduction of an acellular vaccine in 2005 may require changes in the criteria or antigens used for serosurveillance of pertussis. Furthermore, the current serosurveillance does not detect other *Bordetella* species associated with whooping cough such as *B. parapertussis*. Estimation of the susceptibility for [re-]infection is problematic since no clear correlates of protection have been defined, as for tetanus and diphtheria. High titres against pertactin, fimbriae and pertussis toxin are associated with protection against clinical disease.[38,39] However, minimum titres required for protection have not been established. Waning immunity has been suggested to be one of the causes for the re-mergence of pertussis, and assays to measure memory should be developed to study immunity at the population level.[40] T-cell mediated immunity is important for protection against pertussis. However, no correlates of T-cell immunity protection have been defined.[41]

4.3.7 *B. pertussis* strain variation in the Netherlands

Strain surveillance is important for the detection and monitoring of escape variants, for the monitoring of population immunity, and serves as an early warning system. There is no sentinel system in place for the systemic collection of B. [para]pertussis strains. Clinical isolates are sent to the RIVM for confirmation or classification on an ad hoc basis. At the RIVM, strains are serotyped en genotyped. Serotyping characterizes the fimbrial [sero]types produced by the bacteria. This is relevant since fimbriae are important protective antigens and are used in a number of acellular pertussis vaccines.[42-44] Furthermore, there is evidence that Fim2 strains are more virulent than Fim3 strains.[45] Finally, changes in frequencies of fimbrial serotypes are associated with changes in population immunity and may serve as an early warning system.[46]

Genotyping is used to detect shifts in the B. [para]pertussis population, which may reflect changes in population immunity. In addition, genotyping is used to characterize the genes for proteins, which are part of pertussis vaccines. This allows the detection and monitoring of escape variants.[47]

Strain surveillance has revealed major shifts in the Netherlands *B. pertussis* population.[47-50] In general vaccine-type surface proteins have been replaced by novel types. Strains used for the production of acellular vaccines originate from the 1940s to 1950s and consequently there is a mismatch between acellular vaccines and circulating strains. Several studies have indicated that strain variation affects vaccine efficacy in the mouse model.[51-53] The mismatches between vaccine strains and circulating strains are relatively minor, and may be less relevant in recently immunized individuals. However, strain variation may be important in individuals with waning immunity. In fact, there is a very direct temporal relationship between the most recent shift in the *B. pertussis* population and the current pertussis epidemic.[50] In summary, strain surveillance has provided evidence that the emergence of escape variants has played an important role in the pertussis epidemics in the Netherlands.[54,55]

The current system to collect 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 PCR in many medical laboratories, and this has resulted in a dramatic decrease in the number of strains sent to the RIVM. It is highly recommended that a [sentinel] system is set up that allows the systematic collection of *Bordetella* strains. This system can also be used for the collection of other pathogens relevant for the NIP.

4.3.8 Pertussis vaccine developments.

A number of important changes to pertussis vaccination have and will be implemented. In 2005, the current DTP_w-IPV/Hib vaccine was replaced by DTP_a-IPV/Hib (a GlaxoSmithKline Beecham vaccine, including a 3 component pertussis vaccine, comprised of pertussis toxin, pertactin and filamentous hemagglutinin. In 2006, this will be replaced by the acellular vaccine from Aventis-Pasteur (a 5 component vaccine, comprised of pertussis toxin, pertactin and filamentous hemagglutinin, Fim2 and Fim3). Finally, in 2007, a DTP_a-IPV/Hib combination vaccine will be introduced, which is very similar to the Aventis-Pasteur 5 component vaccine but produced by the NVI.

It is possible that the pertussis whole cell vaccine, which is currently used, is less efficacious than the three or five component acellular vaccines. In that case, a further improvement may be expected in the age category 1-4 yrs after the switch to DTP_a-IPV/Hib. The developments in Canada, where a switch from a weak whole cell vaccine to a more potent five component acellular vaccine has occurred in 1997-1998, may be particularly relevant for the Netherlands. In Canada, vaccine doses for the primary series are given there at 2, 4, and 6 months of age, with booster doses at 18 months and again at 4–6 years of age.[56] In the Canadian state of British Columbia, the switch in vaccines coincided with a decline in the proportion and absolute incidence of infant [<1 yr] and preschool [1-4 yr] pertussis. Furthermore, hospitalisations and deaths due to pertussis also declined overall and particularly in infants and preschool children. However, the incidence of pertussis in infants and preschool children and the total population remain at unacceptable high levels [respectively, 197/100,000. 80/100,000 and 44/100,000 in 2000 which was an epidemic year]. The incidence in the age category 1-4 yrs is significantly lower compared to the Netherlands (Table 4-3). It should be noted that comparison of pertussis incidences between countries is problematic due to differences in diagnostic criteria and coverage. Further, booster immunisations at the age of 4-6 years of age were introduced in Canada in 1996, 5 years earlier than the Netherlands.[57] Since only a small fraction of the total population is vaccinated with pertussis vaccines each year [in the Netherlands, ~ 4% of the population], population effects will take some time to emerge. The extent of these effects will depend on the contribution of the vaccinated age categories to transmission, and the degree of memory induced by the vaccine.

Another issue which should be followed closely is the incidence of infections by *Bordetella* species against which acellular vaccines confer little or no protection, such as *B. parapertussis*, *B. bronchiseptica* and *B. holmesii*. The NVI whole cell vaccine confers some cross protection against *B. parapertussis*, and a switch to an acellular vaccine with less, or no, cross-protection may result in an increase in *B. parapertussis* infections.[58] *B. bronchiseptica* is isolated from pertussis patients and *B. holmesii* may represent an emerging pathogen.[59,60]

The switch to an acellular vaccine will remove *B. pertussis* lipopolysaccharide [LPS] from the childhood NIP. LPS is a potent immunogen and is known to polarize the immune response towards the Th1 arm. In contrast acellular vaccine pertussis vaccines induce a mixed Th1/Th2 response.[61] The long-term effects of these changes remain to be determined. LPS is able to enhance the immune response against co-administered antigens, and removal of this adjuvant may affect the immune response against other components of DTP-IPV/Hib. Indeed, this has been observed in the UK, where a switch from DTP_w-IPV/Hib to DTP_a-IPV/Hib has been associated with the re-emergence of *Haemophilis influenzae* b infections.[62] In the UK and the Netherlands, respectively, three and four Hib immunisations are given and the lower frequency of immunisations in the UK may have contributed to the re-emergence of Hib disease.

Table 4-3: Comparison of pertussis notifications per 100,000 in British Columbia and the Netherlands in epidemic years. [1]

	< 1 yr	1 to 4 yrs	Total population
British Columbia	197	80	44
the Netherlands	166	211	50

[1] The epidemic years 2000 [British Columbia] and 2001 [the Netherlands] were compared.[56,57]

4.3.9 International perspectives of pertussis vaccination

As yet, it is difficult to assess the long-term effect of the introduction of acellular vaccines on pertussis disease since only a small part of the population will be targeted. Furthermore, although data on short-term [0-5 years] efficacies are available, it is not clear how well acellular vaccines are able to induce long-term immunity, which is of crucial importance to decrease the circulation of the pathogen. In addition to strain variation, waning immunity is one of the major causes of the resurgence of pertussis.[55] In some countries, [e.g. the UK and France] [slightly] less effective acellular vaccines have replaced very effective whole cell vaccines. The resulting decrease in immunity may be compensated by booster immunisations, however.

The type of acellular vaccine and vaccination schedules used, differ significantly between countries. Thus, it is extremely useful and important to follow the trends in pertussis outside the Netherlands. The RIVM has participated in an EU-funded project in which the epidemiology of pertussis in five EU countries [Finland, Sweden, Germany, the Netherlands and France] was studied in relation to vaccination policies.[63,64] It is our aim to apply for extension in 2005 and include more countries.

4.3.10 Other developments of pertussis vaccination

The primary aim of pertussis vaccination is the protection of the age group of 0-4 years and, within that group, especially the unvaccinated neonates in which morbidity and mortality is highest. In principle, several strategies are open to attain this: significantly reducing the circulation or even eradication of the pathogen, immunisation of groups important for transmission to infants, neonatal immunisation and maternal immunisation. *B. pertussis* is very contagious and its basic reproductive rate is estimated to be in excess of 14.[65] This implies that very high, sustained, population immunity is required to eradicate the pathogen or even to significantly reduce its circulation.[66] This will require many booster vaccinations, as immunity induced by natural infection and immunisation wanes to levels allowing re-infection after 5 to 7 years.[67] Instead of increasing the number of boosters, scarce resources could be focused on reducing exposure of infants or increasing their immunity. Decreasing exposure can be attained by vaccination of parents, newborn children, health care workers, etc. However, perhaps the most effective way to protect the [unvaccinated] infants is, by maternal immunisation. This approach has been highly effective in reducing neonatal tetanus. Although maternal immunisation is fraught with difficulties, we highly recommend a feasibility study.[68]

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4.4 Poliomyelitis

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4.4.1 Introduction

Poliomyelitis (polio) is a highly infectious, viral disease. Poliovirus is a member of the enterovirus subgroup, family Picornaviridae and three poliovirus serotypes (p1, p2 and p3) can be distinguished. Poliovirus can invade the nervous system, and can cause total paralysis in a matter of hours. The virus enters the body through the mouth and multiplies in the intestine. Initial symptoms are fever, fatigue, headache, vomiting, and stiffness in the neck and pain in the limbs. One in 100 – 1.000 infections leads to irreversible paralysis (usually in the legs). Among those paralysed, 5 –10 % die when their breathing muscles become immobilised. Humans are the only known reservoir of poliovirus, which is transmitted most frequently by persons with asymptomatic infections. Person-to-person spread of poliovirus via the faecal-oral route is the most important route of transmission, although the oral-oral route may account for some cases.[1]

4.4.2 Vaccines available against poliomyelitis

The Dutch polio vaccine is the inactivated (IPV) or Salk vaccine based on the poliovirus strains Mahoney (type1), MEF-1 (type 2), and Saukett (type 3). Live oral polio vaccine (OPV or Sabin) is not used routinely in the Netherlands, and will be used in outbreak situations only.

4.4.3 Adverse events following poliomyelitis vaccination

Single trivalent polio vaccines are well tolerated with low rates of local reactions in both children and adults. Redness, swelling and tenderness are reported in 0.5-1.5%, 3-11% and 14-29%, respectively.[2,3] Systemic adverse events are also mild and non-specific and occur infrequently. Single IPV vaccination may also be followed by collapse reactions but the incidence rate is unknown since this is a rare event and IPV usually is administered combined with other components. This applies also for febrile convulsions or persistent screaming. Severe local or systemic adverse events attributable to the IPV-vaccine are extremely rare.

IPV is not followed by acute flaccid paralysis, as is a known adverse event of the live polio vaccines (OPV). The only time this happened was in the Cutter Incident when the vaccine was inadvertently not fully inactivated. Improved manufacturing procedures have made this impossible since.[4]

In the current schedule, IPV is given combined in the DTP_w-IPV/Hib or DT-IPV vaccines. Adverse events are dominated by the other components in both combination vaccines. DT-IPV is less reactogenic as the whole cell pertussis containing vaccine. See for those adverse events under pertussis. Adding IPV to the vaccines did not change the safety profile of the other components.[5] Adverse events following the combined DTP_w-IPV/Hib are mentioned in the pertussis paragraph and for DT-IPV in the section on tetanus.

The change to Vero Cell lines from the currently used MK cell lines is not to be expected to change the safety profile.[3,6] Up until now no specific adverse events have been identified however. The expected change to the attenuated Sabin viruses for the seed lots will diminish the risk of accidental spread of polio.

4.4.4 History of polio and polio vaccination in the Netherlands

Poliovirus vaccination was introduced in the Netherlands in 1957 and was offered to all those born in 1945 and thereafter. Currently children are vaccinated at the ages of 2, 3, 4, and 11 months with diphtheria, tetanus, pertussis, inactivated polio vaccine and *Haemophilus influenzae* type b (DTP-IPV/Hib combined) and at ages 4 and 9 years with DT-IPV. The vaccine used in the NIP is IPV, which is administered intramuscularly. Most developing countries in the world use the Oral Polio Vaccine (OPV or Sabin-vaccine), a live attenuated vaccine, which is known to sporadically cause vaccine associated paralytic polio (VAPP). In the Netherlands, this vaccine is only used in epidemic conditions when wild poliovirus is circulating, because it rapidly infects the gastrointestinal tract, thus blocking the spread of virus. The uptake for at least three vaccinations by age 24 months has been 97 percent in the past decades.[7-9]

Since the implementation of polio vaccination incidence of polio decreased to almost zero, except for some outbreaks (see figure 4-4).

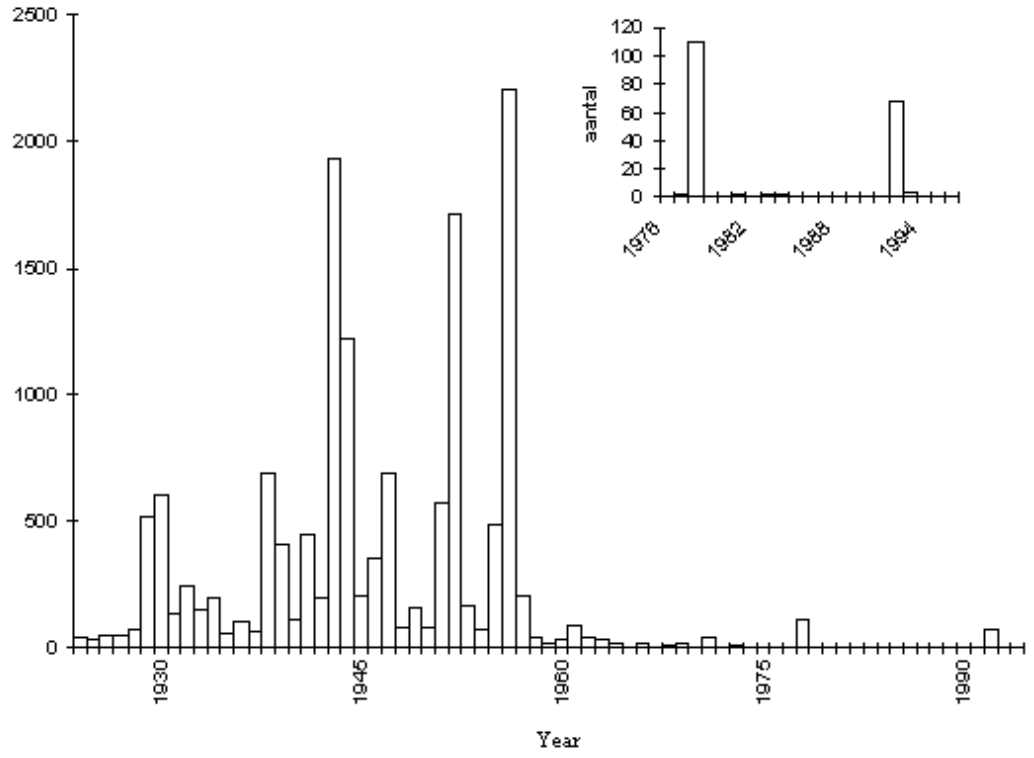

Figure 4-4: Absolute number of poliomyelitis cases in the Netherlands. (Source: Infectious Diseases Bulletin 9(5) 1998).

4.4.5 Epidemiology of poliomyelitis in the Netherlands.

Polio surveillance in the Netherlands is currently based on clinical and virological surveillance. Clinical surveillance consists of mandatory notification of suspected patients. Surveillance of patients with acute flaccid paralysis (AFP) has been stopped in 2002 because the European Region has been declared Polio-free.

Despite high vaccination coverage, three larger poliomyelitis outbreaks occurred in the Netherlands in recent decades (1971, 1978, 1992–1993), with consequent exportation to polio-free countries (Canada and the USA).[10,11] The last two outbreaks were confined to Orthodox Reformed persons who refused

vaccination. These outbreaks occurred in 1978, with 110 reported cases of disease caused by poliovirus type 1, and in 1992–1993, with 71 cases caused by poliovirus type 3.[12] Between these two outbreaks, three imported cases of poliomyelitis were reported in persons who acquired the disease abroad; no cases have been reported since the 1992–1993 outbreak. Major outbreaks similar to those that developed in the previous decades did not occur in the 1960s and early 1970s. Smaller outbreaks did occur in the first 10–15 years after vaccination began in communities with a high percentage of Orthodox Reformed persons not vaccinated for religious reasons.

Most unvaccinated persons in the Netherlands have not been vaccinated for various reasons, but they are protected against poliomyelitis because of previous infection or herd immunity. However, the Orthodox Reformed minority of at least 275,000 persons is insufficiently protected by herd immunity since they form a socio-geographically closely knit network.[13] Vaccination is accepted to some degree among even the Orthodox Reformed groups; about a third of the Orthodox Reformed persons reported that they had been vaccinated.[13,14]

Until eradication of poliomyelitis is established throughout the world, countries certified free of endemic polio remain at risk of importing wild polioviruses from regions of the world in which they still circulate. Reintroduction of the virus might also arise from laboratory stocks, vaccine production facilities, environmental samples, or deliberate release.[15,16] Moreover, recent unexpected findings in Hispaniola and Egypt have shown that outbreaks can be caused by revertant OPV (Sabin)-derived strains, known as cVDPVs (circulating Vaccine-Derived Polio Virus).[17,18]

4.4.6 Levels of immunity against poliomyelitis

In general the Dutch population is well protected against poliomyelitis.[19] However, despite high antibody prevalences (often exceeding 90%) and a vaccination coverage rate in the NIP of 97 percent, the threat of a poliomyelitis outbreak in the Netherlands is still real, especially because of the socio-geographically clustered group that is unvaccinated for religious reasons. Furthermore, the cohort born between 1925 and 1945 has low(er) seroprevalence levels.[19] The latter group was ineligible for the routine immunisation programme and might have escaped natural infection due to reduced poliovirus circulation. In addition, natural or vaccine induced immunity may have waned. A recent study, addressing memory immunity in elderly people, showed that a considerable part of the elderly population would be at risk for infection in the event of reintroduction of the virus. Proportions of at least 6% (type-1 poliovirus) and 15% (type-3 poliovirus) of the elderly population of the Netherlands were found to be at risk for infection.[20] Vaccination of this cohort during an outbreak should be seriously considered.

4.4.7 Strain variation of poliomyelitis in the Netherlands

Currently poliovirus does not circulate in the Netherlands. However, when wild-type virus is isolated, it will be characterized molecularly and antigenically to determine whether the virus will be neutralized by IPV-induced immunity. Previous experience indicates that altered antigenic properties of wild-type poliovirus together with impaired herd immunity may be epidemiologically important.[21] The strains isolated from the last outbreaks in the Netherlands (1971, 1978, 1992–1993) were neutralized by vaccine-derived immunity.

In the Netherlands, polio is a notifiable disease. Every isolate of poliovirus is characterised to determine the origin of the virus, i.e. wild type or vaccine-derived. Many isolates, however, have an intermediate genotype, i.e. they are drifted Sabin or recombinant strains. Virulence and transmissibility is determined for relevant, suspected strains. When wild-type virus is isolated, the

virus will be sequenced to determine the routes and duration of transmission, information that is relevant for the eradication of poliovirus.
In addition to clinical surveillance, the following actions are taken to monitor the polio-free status of the Netherlands:

- Every poliovirus isolated by peripheral labs is sent to RIVM and characterized (see above)
- Non-typed enteroviruses are sent to RIVM to exclude the presence of poliovirus
- All peripheral labs report the number of faecal samples that have been tested for enteroviruses
- All peripheral labs participate in a yearly quality control system.

4.4.8 Poliomyelitis vaccine developments

As mentioned above, the genetic instability of the currently used Sabin-derived OPV is a great concern during the next stages of the eradication process. Therefore in the USAthe National Institutes of Health is funding fundamental research to make better vaccines that will be genetically stable and not revert to a more neurovirulent form, and that are more efficient and efficacious, especially when used in tropical and developing regions of the world.[22]
Many western countries recently replaced OPV in their immunisation programmes for IPV, to eliminate concerns regarding vaccine-associated paralysis (VAP) and the emergence of cVDPVs.

4.4.9 International perspectives of poliomyelitis vaccination

Overall, in the 15 years since the Global Polio Eradication Initiative was launched, the worldwide number of cases has fallen by over 99%, from an estimated number of more than 350,000 cases in 1988 to 783 laboratory-confirmed cases in 2003. In the same period, the number of polio-infected countries was reduced from 125 to 7. However, despite these achievements, the Polio Eradication Initiative faced an increase in global cases in 2002 over 2001. In 2002, 1919 cases were reported (as of 16 April 2003), compared to 483 in 2001. This increase can be attributed to an epidemic in India, and a further increase in cases in Sub-Sahara Africa. Further progress includes the certification of polio-free regions. In 1994, the World Health Organization (WHO) Region of the Americas
(36 countries) was certified polio-free, followed by the WHO Western Pacific Region (37 countries and areas including China) in 2000 and the WHO European Region (51 countries) in June 2002. Widely endemic on five continents in 1988, polio is now found only in parts of Africa and south Asia (1).
Despite the enormous success of this initiative, there is still an urgent need to continue vaccination against poliovirus for the following reasons. Locally there are still areas of poliovirus circulation. From these hot spot areas, the virus may be imported into the Netherlands. The Netherlands are vulnerable to infection because of its large cohort of non-vaccinating persons. This cohort has now been free of natural infections for more than 10 years, leading to an estimated cohort of at least 60,000 – 70,000 children <10 years of age that is vulnerable for infection. Hence, it is particular important to recommend vaccination of travellers to and from these areas. In addition to non-vaccination, it appears that a cohort of elderly, previously infected or vaccinated persons gradually becomes more vulnerable for infection because of waning immunity. Although these persons may have some ‘memory immunity’, it appears that memory immunity (especially in seronegative elderly) may not be sufficient to stop virus replication and transmission. It is therefore important to continue monitoring the immunity of elderly, for example in a next immunosurveillance project, and to develop an immunisation protocol of these elderly before a next polio outbreak. Worldwide live Sabin-derived OPV strains are still widely used, predominantly in developing countries. Especially when

vaccination coverage declines, the use of OPV brings the risk of the emergence of virulent circulating vaccine-derived polioviruses (cVDPV). The genetic changes leading into cVDPV should be characterized in order to allow risk assessment of newly isolated strains. The emergence of these cVDPVs is the major threat for the word-wide eradication campaign and urges a good 'exit' strategy for OPV, for example by replacing OPV for IPV word-wide, the use of 'stable' live polio vaccine, or other strategies. With the ongoing success of wild-polio eradication, the risk of escape of virulent poliovirus from laboratories or vaccine factories becomes relatively more important.
With the elimination of poliovirus coming in sight, relevant questions relating to the worldwide eradication are:

- Whether reintroduction of poliovirus is possible from persistently infected immuno-deficient individuals that persistently excrete virus.
- The contribution of antiviral drugs in the late stages of the eradication, for example to control persistent shedding of virus.
- The choice of vaccine in the post-eradication stage and if re-emergence occurs.
- The threat of poliovirus reintroduction from laboratories, vaccine factories, or bioterrorist attacks.
- The threat of emergence of cVDPV/s from Sabin vaccine.

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4.5 *Haemophilus influenzae* serotype b

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4.5.1 Introduction

Before the availability of a vaccine, *Haemophilus influenzae b* was the leading cause of meningitis in the Netherlands. Isolates of the Gram-negative bacterium *Haemophilus influenzae* can be separated in two distinct groups: nonencapsulated (nontypable) and encapsulated strains. Encapsulated strains can cause serious invasive disease, such as meningitis, septicaemia, epiglottitis, cellulitis and arthritis. Encapsulated strains express capsular polysaccharides and based on their ability to react with antiserum are designated as serotypes a-f. Serotype b is responsible for the vast majority of invasive infections.

Nonencapsulated strains are usually commensal organisms found in the human nasopharynx. However, they also are a frequent cause of otitis media and bronchitis, but very rarely cause invasive disease.[1,1]

4.5.2 Vaccines available against *Haemophilus influenzae b*

The first vaccine that was licensed in 1985 was a polyrisylribitol Phosphate Polysaccharide (PRP) Vaccine. This vaccine is of limited importance since the development of new vaccines. In 1979 PRP polysaccharide conjugate vaccine was developed. In this vaccine, an immunogenic carrier protein (like diphtheria and tetanus toxoids, oligosaccharides) is used. The Hib-vaccine used in the Netherlands has tetanus-toxoid as carrier protein (PRP-T). It is non-adjuvated and contains no preservatives. In the current schedule, Hib is given mixed with DTP-IPV. Efficacy was 95% to invasive Hib disease in some clinical trials in Africa. In western countries, PRP-T has proved to be effective as well.[2]

4.5.3 Adverse events following *Haemophilus influenzae b* vaccine

Local reactions following single Hib vaccination are usually short-lived and mild. Depending on case definitions and methods of case ascertainment, percentages given are 7-15% in the younger infants and increasing with age and dose to around 32%. Fever occurs in 5-10% of cases on the day of or the day after the vaccination.[3-6] Single Hib-vaccination may also be followed by collapse reactions, but the incidence rate is unknown since this is a rare event and Hib usually is administered simultaneously or mixed with other vaccines. This applies also for febrile convulsions or persistent screaming. Severe local or systemic adverse events attributable to the Hib vaccine are extremely rare.[7]

Of the currently available conjugated Hib vaccines, none are suspected to be followed by early-onset disease as has been known to occur after several unconjugated vaccines. There are no studies reporting that including Hib in the schedule was followed by a decrease in efficacy of other vaccine components [3]

Adverse events are dominated by the other components of the combined vaccine, in particular by the whole cell pertussis vaccine component. Adding Hib does not alter the severity of the adverse events but may be followed by a small increase in number of adverse events. However, this is lower than when the vaccines are given separately (injection site or in time). The recently introduced mixed administration of Hib with DTP_w-IPV has not altered the type and frequency of passively reported

adverse events compared with DTP-IPV alone. [8] A field trial in 1993 did not reveal significant differences in the more common local or systemic adverse events between simultaneous or mixed administration compared to the control vaccine DTP_w-IPV only (unpublished data trial RIVM DKTP-Hib, 1993 Vermeer-de Bondt). No severe anaphylactic reactions have been reported since the introduction of Hib in the Netherlands schedule in July 1993. In addition, no epidemiological links have been shown between Hib vaccine and other rare severe events, like DM, SIDS or Guillain Barré syndrome.[3,8,9]

Currently there are no contra-indications to the Hib-vaccine. Furthermore, the so-called theoretical hypersensitivity to tetanus-toxoid, used as protein carrier in the Hib vaccine, has not posed a problem in the Netherlands schedule.[10]

4.5.4 History of Hib and Hib vaccination in the Netherlands

The introduction of a Hib vaccine in the NIP in 1993 has nearly eliminated invasive Hib disease in the Netherlands.[11] Currently, children are vaccinated at the ages of 2, 3, 4, and 11 months with a mixed vaccine against diphtheria, tetanus, pertussis, polio and *H. influenzae* type b (DTP-IPV/Hib). The vaccine used in the NIP is PRP-T) and is administered intramuscularly. Before the introduction of a combined vaccine in 2003, DTP-IPV and Hib vaccines were administered simultaneously but in two separate limbs. The uptake for at least three vaccinations by the age of 12 months has been somewhat lower for Hib than for DTP-IPV which has been stable for decades at around 97%.[12,13] Hib coverage levels for the last 10 years are 1-1.5% lower than DTP-IPV levels indicating postponement of Hib vaccination.[13] However, this problem has now been solved with the introduction of the combined DTP-IPV/Hib vaccine.

4.5.5 Epidemiology of invasive Hib disease in the Netherlands

Surveillance of *H. influenzae* is mainly based on serotyping of isolates by the Netherlands Reference Laboratory for Bacterial meningitis (NRBM).

In 2002 nearly 29% of *H. influenzae* isolates sent for typing to the NRBM were of serotype b.[11] Before the introduction of the vaccine, 1-5% of the Netherlands children aging 0-4 years carried type b strains asymptomatically. Hib carriage prevalence was lowest in adults and young infants and highest in pre-school children. A recent prevalence study carried out in the UK showed that the prevalence of Hib carriage was reduced to 0% in the 1997-2000.[14]

Before the introduction of the Hib vaccination approximately 800 invasive Hib infections occurred annually in the Netherlands (incidence: 78/100,000), 90% among children below 5 years of age. Half of these infections resulted in meningitis, mainly among very young infants (median age of 6-12 months) and 15-30% resulted in epiglottitis (median age of patients was 2-3 years). The overall mortality from *H. influenzae* meningitis is less than 5%, but sequelae like hearing loss and seizure disorder occured.[15] As a result of vaccination against Hib since 1993 the number of invasive infections of Hib has decreased dramatically (Figure 4-5).[16]

However, in 2002 and 2003 an increase was noticed (17 isolates in 2001, 31 in 2002 and 33 in 2003). Although much lower than before introduction of vaccination incidence reached the same level as in 1996. In 2002 and 2003, half of the cases occurred in patients 0-4 years of age. The percentage of vaccine failures among the cases of invasive Hib disease in children eligible for vaccination fluctuated, but increased from 50% in 2001 to reach levels 88% in 2002 and 76% in 2003.

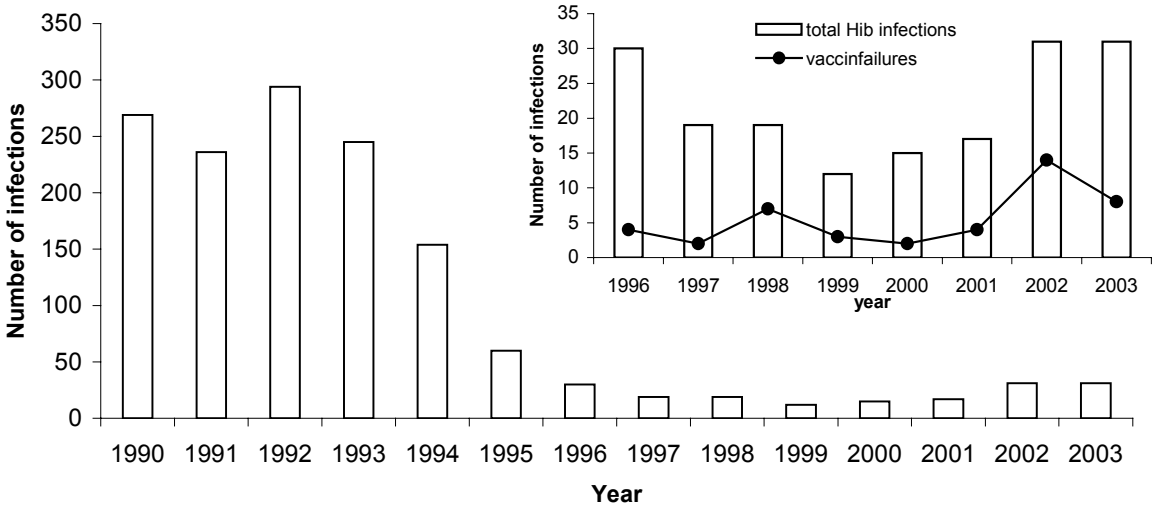

Figure 4-5: Number of cases of invasive disease with H. influenzae type b in 1990-2003. Vaccine failures among all cases of invasive Hib disease in 1996-2003 are depicted in the insert.
Source: NBM.

4.5.6 Levels of immunity against Hib

As part of a serosurveillance study performed in 1995, the RIVM assessed the antibody level to the Hib capsular polysaccharide in the Dutch population, after introduction of mass vaccination from 1993 onwards.[17] The prevalence of antibodies at protective levels of ≥0.15 μg/mL was 99.4% at 0-2 months after the fourth vaccination and 100% at 3-5 months after the fourth vaccination and after that it declined to 83.3% at 27-29 months. A relatively low seroprevalence among older children (3-7 years) was explained by a decreased circulation of bacteria and hence a decrease in natural boosting after introduction of vaccination. In adults, the prevalence of antibody levels ≥0.15 μg/mL declined with increasing age but remained high: from 94.0% in the 20-24 year age group it declined to 83.7% in individuals aged 75-79 years. Based on these results and the sharp decrease in invasive Hib disease after introduction of vaccination, it was concluded that the overall immunity against Hib in the Dutch population is satisfactory. Key questions for the future are whether Hib will circulate sufficiently to provide natural re-exposure, and if not how long memory immunity will persist after vaccination without re-exposure.[17]

4.5.7 Strain variation of Hib in the Netherlands

The routine characterization of *H. influenzae* is based on the pioneering work by Pittman who developed a serotyping method to distinguish six serotypes among the encapsulated strains.[18] In the Netherlands, the NRBM performs serotyping on virtually all isolates from patients with Hib meningitis and many isolates from other cases of invasive Hib disease. No further subtyping is performed. Prior to the introduction of Hib vaccination virtually invasive disease caused by *H. influenzae* was in 0-4 year olds and was caused by Hib. After the vaccination in 1993 the number of Hib cases dropped considerably and there was an increase in the number of cases of caused by non-encapsulated and serotype f of *H. influenzae*. This was particularly true in individuals older than 4 years of age; 10 cases caused by non-encapsulated *H. influenzae* in 1992 and 52 in 2001.
Compared to 1999 the number of cases of invasive Hib disease in 2002 had more than doubled in both the age group of 0-4 years and those older than 4 years. Only few studies have described subtyping *H.*

influenzae and these have shown a rather clonal character of Hib.[19-21] Subtyping of Netherlands Hib strains isolated in the pre-vaccination era and after the introduction of the vaccine is now being performed. This may provide insight in changes in the composition of the circulating Hib population and the possible emergence of vaccine-escape variants. Preliminary data suggest an increase of genetic diversity of Hib strains after the introduction of the vaccine in 1993.

4.5.8 Hib vaccine developments

The currently used Hib vaccine in the Netherlands and many other countries is composed of the capsular polysaccharide, the polyribosylribitolphosphate, which is coupled to the tetanus toxoid (PRP-T). The polysaccharide is extracted and purified from cultured *H. influenzae* serotype b and chemically coupled to the protein carrier to form the glycoconjugate. A recent study from Cuba described the construction of a synthetic vaccine in which synthetically constructed oligomers of ribosylribitolphosphate were coupled to tetanus toxoid.[22] The vaccine has successfully been used in phase I and phase II trials. This development may lead to a safer and cheaper vaccine and may be of major interest for the development of other glycoconjugate vaccines such as those used for immunisation against *S. pneumoniae*.

4.5.9 International perspectives of Hib vaccination

In the UK, an increase in invasive Hib disease incidence has coincided with the distribution of combination vaccines that contain acellular pertussis (DTP_a/Hib). The combination with acellular pertussis has shown to reduce immunogenicity of the Hib component. The relevance on protection against disease was shown in a UK study in which more cases with invasive Hib than controls had received three doses of DTP_a/Hib.[23] In the Netherlands, the current whole cell pertussis vaccine will be replaced in 2005 by an acellular pertussis vaccine. This may have an impact on the incidence of invasive Hib disease in the Netherlands.

In the Netherlands, children are vaccinated at the ages of 2, 3, 4 and 11 months. Several other countries, like the UK, do not vaccinate at 11 months. This may lead to a waning immunity during an age when children are highly susceptible for Hib infection. In the UK, this is seen as a major cause for the upsurge of invasive Hib disease in the past few years. For this reason, a catch up vaccination for all children between 6 months and 4 years of age has been used in the UK in 2003.[24]

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4.6 Measles

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4.6.1 Introduction

Measles is an acute viral illness transmitted via respiratory droplets. The average incubation period is ten days and a person is infectious two days before prodromal stadium until four days after start of exanthema. Clinical features include fever, Koplik Spots, coryza, conjunctivitis, bronchitis and rash. In industrialized countries, the most common complications are otitis media (7-9% of cases), pneumonia (1-6%), and encephalitis (0.05-0.1%).[1] The introduction of a live attenuated measles vaccine has largely abrogated endemic circulation of the measles virus (MV) in many of these countries, although isolated cases and small outbreaks continue to occur due to importation of the virus.

Measles virus belongs to the most contagious viruses of man, associated with 30-40 million infections and an estimated global mortality of about 750,000 cases each year. Measles remains endemic in many African and Asian countries due to insufficient vaccination coverage and lower efficacy of the vaccine as a result of different environmental factors (secondary infection, vitamin A deficiency, immune suppression).[2,3] Measles may be ultimately responsible for most child deaths, because of complications from pneumonia, diarrhoea and malnutrition. Target dates of 2000, 2007 and 2010 for its elimination were established for the Americas, the European Region and the Eastern Mediterranean Region, respectively. The aim in the African Region, the South-East Asia Region and Western Pacific Region is to reduce measles mortality.[2] To interrupt virus transmission 95% of a population must be protected.[4]

4.6.2 Vaccines available against measles

Measles vaccines, which are, now in active use worldwide are cell-line passaged attenuated viruses derived from Edmonston measles virus, isolated from a measles patient in 1954. The virus has been propagated and attenuated on different cell lines, resulting in several strains (AIK-C, Schwarz, Moraten, Edmonston-Zagreb) that are currently used as a vaccine. The Moraten-type measles vaccine was introduced in the Netherlands in 1976. Since 1987, the vaccine (licensed from Merck & Co.) is administered subcutaneously together with attenuated mumps virus vaccine (Jeryl Lynn strain) and rubella virus vaccine (Wistar RA27/3 strain).

4.6.3 Adverse events following measles vaccination

Adverse events following single measles vaccine are usually mild en transient.[5]

The rate and severity are comparable in single vaccines and combined measles, mumps and rubella vaccines (MMR), apart from some specific events of the two other components. See below.

Local reactions following MMR are rare, except for instant stinging pain of short duration and sometimes a local flare.[5,6] Systemic adverse events are limited to susceptible vaccinees and occur between 6-12 days after the vaccination, with fever of >39.5^{o}C in 5-15% of 14 months old children. This occurs with a median of 7-9 days after the vaccination, lasting 1-2 days. In 3-12%, some sort of rash occurs 7-10 days after the vaccination (median) which lasts 1-3 days. Sometimes this rash is atypical (urticarial i.e.). A study in twins showed only an increased incidence rate for fever on day 9

and 10.[7] For rashes, often other causes could be established like 5th or 6th disease. Very high fever (>40,5°C) is reported rarely and sometimes the rash is very impressive.[8,9]
Febrile convulsions have a relative risk of 3 for the period 8-14 days after the vaccination and are estimated to occur in 1 in 5000-10000 of 14 month olds.[8,10] Severe immediate anaphylactic reactions have not been reported since the vaccine was introduced in the Dutch programme, so this risk seems only theoretical.[5,11-13]
Occasionally more severe adverse events have been reported. Idiopathic thrombocytopenic purpura appear to occur in 1 per 30000-50000 first doses.[14-16] This may be attributed to both the M- and the R-component as this a known complication in natural disease. Acute post infectious cerebellar ataxia is very rarely reported following MMR. The relation with the vaccine is speculative. In a current active surveillance through NSCK, no substantiation for vaccine causality could be found (unpublished data, RIVM, Vermeer-de Bondt).
Arthritis may follow rubella-vaccines and therefore also MMR vaccine.[5,14] This occurs mainly in susceptible older girls and women, as is the case with the natural infection (much more frequently). There are no permanent sequelae.
Orchitis is very rarely reported following mumps vaccine, but causal relation could not be substantiated. This is, if at all, only to be expected in susceptible older boys and men, and with the current two doses schedule are therefore extremely rare. Aseptical meningitis has been shown to occur after vaccination with the Urabe mumps strain. This is not the case with the mumps strain (Jeryl Lynn) used in the Netherlands.
No epidemiological links have been found between MMR vaccination and diabetes mellitus, postinfectious encephalopathy/encephalitis, SSPE, autism, GB syndrome, asthma, Reye syndrome, optic neuritis or autoimmune diseases.[5,14,17,18]
Current scientific evidence does not support the hypothesis that measles-mumps-rubella (MMR) vaccine, or any combination of vaccines, causes the development of autism, including regressive forms of autism. Independent groups of experts have extensively reviewed the question about a possible link between MMR vaccine and autism. The largest study to date has been conducted in Denmark and involves 537,303 children born from January 1991 through December 1998; 440,655 of the children were vaccinated with MMR and 96,648 were not. The researchers did not find a higher risk of autism in the vaccinated than in the unvaccinated group of children.[19]
MMR has few contra-indications.[9] Being a live vaccine, MMR should not be administered to patients with severe immunodeficiency because it may lead to persistent progressive infection. Pregnancy is also a contraindication for MMR vaccine, but after inadvertent vaccination, there seems to be no link with congenital anomalies. Children with severe allergic reactions to chicken eggs may be vaccinated in the normal setting without precautions.[20]

4.6.4 History of measles and measles vaccination in the Netherlands

In 1976, measles vaccination was introduced in the NIP of the Netherlands with a plain live attenuated measles vaccine offered to toddlers of 14 months. Since 1987, it is a component of the MMR-vaccine and given at the age of 14 months and 9 years of age.[21] This second dose was introduced with the purpose of providing a second chance of immunisation for persons who did not receive the first dose and for persons in whom the first vaccination did not lead to immunity. A catch-up campaign during the first 3 years with MMR for 4-year-old girls and boys was carried out. For years, the coverage for the MMR at 14 months has been around 95%, and at 9 years somewhat higher at 96%.[22,23] However, it is likely that the total protection for MMR for these children is somewhat lower because it is known that a fraction of parents decide to skip the first MMR vaccination at 14 months. When the child did

not develop these diseases at the age of 9 years, some parents convert to vaccination mainly to protect the child against rubella.

4.6.5 Epidemiology of measles

Surveillance of measles in the Netherlands is based on mandatory notifications In 2001, 2002 and 2003 17, 3 and 4 cases were notified, respectively.[24] Notifications are displayed in figure 4-6.

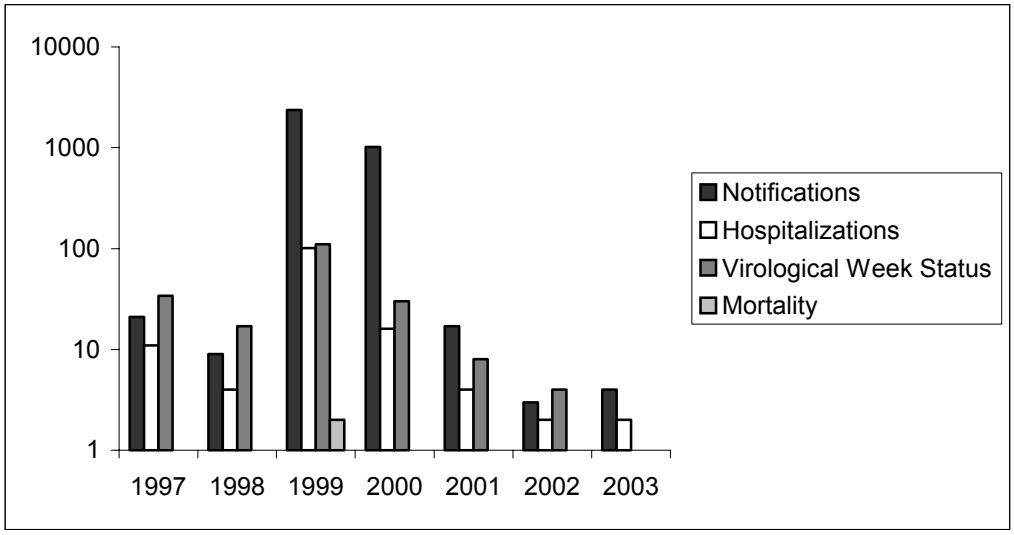

Figure 4-6: Notifications, hospitalisations, positives in Virological Laboratory Reports and mortality of measles since 1997 (source: Abbink et al. RIVM report 2003)[23]

The reported measles incidence rates decreased to one of the lowest in Europe (<1 per million in 1998), suggesting that measles is no longer endemic in the Netherlands. However, because of low vaccination coverage within socio-geographically clustered religious communities, epidemics may still occur almost exclusively within these communities, despite the high national vaccination coverage and population immunity. Indeed, notification data show that measles epidemics have occurred every 5-7 years within these communities since the introduction of the NIP in 1976.[22] During the last epidemic in 1999/2000, 3292 cases were reported. 94 Percent of the affected patients had not been vaccinated and only one patient received two doses of vaccine. Three patients died and 16% suffered from complications.[21]

Although all cases of measles should be notified in the Netherlands, a considerable underreporting has been determined. Suspected measles cases are sometimes confirmed by the detection of specific serum antibodies.[25] However, the need for venous blood samples keeps physicians and patients from laboratory investigation, especially when it concerns uncomplicated measles cases. The reported incidence of measles may therefore not be reliable. Clinical symptoms resembling measles can be caused by other viruses (e.g. human parvovirus B19, human herpes virus type 6), leading to a high degree of misdiagnosis.[26,27] This finding emphasizes the need to perform laboratory confirmation and epidemiological investigation of clinically suspected measles cases, especially when measles incidence rates are low. Mild or asymptomatic MV infections may occur in immune individuals.[28]. To improve the surveillance of measles (and rubella) in the Netherlands, especially during inter-epidemic periods, the National Institute for Public Health and the Environment started a diagnostic programme to discriminate erythematous exanthema in 2003.[29]

4.6.6 Levels of immunity against measles

In the Netherlands, vaccine coverage against measles now exceeds 95%. Immunity against measles in the general Dutch population and in persons refusing vaccination was assessed in a large population based study carried out in 1995/96.[22] The results suggest that wild measles virus may still circulate in municipalities with low vaccine coverage; the circulation in the general population seems to have decreased significantly right after the introduction of mass vaccination. The overall prevalence in the general population was high (95.7%, 95% confidence limits 95.3–96.2%); Age-specific results showed seroprevalences of 94.6% (95% confidence interval (CI) 93.3–96.0%) in the once vaccinated 2–9-year-old group, 89.2% (CI 86.2–92.2%) in the mainly twice vaccinated 10–21-year-old group, and 98.5% (CI 97.9–99.1%) in the unvaccinated 22–49-year-old group. The seroprevalence in the age groups offered two vaccinations was lower than the level believed to be necessary for the elimination of measles. However, the recent measles epidemic (1999/2000) that started among orthodox reformed individuals hardly led to cases among the general population. This shows that in contrast to orthodox reformed individuals, the herd immunity among the general population is sufficient to prevent circulation of measles.[22]

4.6.7 Strain variation of measles in the Netherlands

The detection of sources of infection and epidemiological chains of measles virus transmission by means of phylogenetic analysis of isolated measles viruses has become an essential part in monitoring the effectiveness of immunisation programmes. Single cases and outbreaks in countries with high vaccination coverage were thus found to be caused by the importation of genetically heterogeneous viruses from areas with inadequate measles control. Measles viruses are currently divided into 8 classes, comprising 22 genotypes based on a minimum nucleotide sequence divergence of 2.0% for the hemagglutinin protein (H) and 2.5% for the N-terminal part of the nucleoprotein (N). Some genotypes (E,F,G1, D1) are considered inactive because no representative viruses from these genotypes have been isolated in the past 15 years.[30]

Most clinical specimens obtained between 1990 and 1997 in Western Europe harboured genotype C2, which includes a number of isolates from the Netherlands outbreak in 1991.[31] Genotype D6 is now more widely distributed in many European countries and this genotype was responsible for the latest measles outbreak in the Netherlands in 1999.[28] Recent observations have shown the rapid replacement of genotype D6 by a new endemic genotype (D7) in central Europe.[32]

Measles virus is considered an antigenically stable virus, despite the genetic differences. Vaccine strains that are in use worldwide belong to a single genotype but are expected to protect against genetically disparate measles virus strains. However, resistance of certain wild-type isolates to the neutralizing activity of antibodies raised against the measles vaccine has been described, which suggests a reduced protection against certain measles virus strains.[33] Other studies describe the emergence of new genotypes, which rapidly replace others and which even coincides with antigenic changes in the H envelope protein.[32] Whether these antigenic alterations are intrinsic for immune escape from the vaccine remains to be investigated.

4.6.8 Measles vaccine developments and WHO strategy

Live attenuated measles vaccines derived from the Edmonston strain are highly effective and expected to induce a protection comparable to that induced after natural infection. With the price of US$ 0.15 for one measles vaccine dose, children in developing countries can survive exposure to measles without sequelae. Coverage could be greatly enhanced if administration could be carried out

without a needle and syringe. The coverage with measles vaccine is low in many countries due to limited resources.[34] This is currently stimulating the development of novel vaccines, which can be administered without the use of a needle.[34] The most straightforward approach would be a live attenuated measles vaccine administered by aerosol. This vaccination route was recently shown to be highly effective for measles and tested in large-scale booster campaigns with good public acceptance.[35] Current projects managed as a partnership between WHO, CDC and the American Red Cross, with funding from the Bill & Melinda Gates Foundation now support an aerosolized measles vaccine to be licensed in 2007 and introduced in practical use in 2009. Studies are also in progress to develop new measles vaccines effective for immunisation of infants before 6-months of age. Infants are refractory to conventional measles vaccines in the presence of maternal anti-measles antibodies and the need to delay immunisation until passively acquired antibodies have declined has been impediment to the global control and eradication of measles. Live vaccines, given intranasally, are not directly hindered by maternal antibody interference and could be a good alternative. To reach this objective several technologies are currently being tested, including DNA vaccines and viral vectors such as highly attenuated poxviruses, both of which were shown highly effective in inducing immune protection against measles in the macaque model, both in the absence and presence of maternal antibodies.[2]

4.6.9 International perspectives of measles vaccination

The WHO Global Strategic Plan for Measles, published in 2001, provides a broad agenda and framework to ensure a sustainable reduction in measles mortality and to make significant progress towards interrupting measles transmission in regions and countries with elimination objectives. Health21, the health policy framework prepared by WHO Regional Office for Europe and endorsed by the WHO Regional Committee for Europe in 1998, identified a number of targets for communicable disease control in the European Region, including elimination of measles and controlling CRS and mumps by 2010.[2] As the current measles target for 2007 is being recognized as difficult to achieve and combined antigen vaccines containing measles and rubella are being used extensively in the Region, the operational target for measles is now aligned with the Health21 CRS target. Countries undertaking measles elimination should consider taking the opportunity to eliminate rubella as well, through use of MR or MMR vaccine in their childhood immunisation programmes, and in measles campaigns. The overall objective of the Strategic Plan for measles is to interrupt the indigenous transmission of measles by 2010.

4.6.10 Other developments

Vaccinated persons who develop clinical symptoms upon exposure to measles were previously shown to have reached a critical antibody titre (0.2 units of IgG antibody per ml serum).[36] On basis of this criterium, anti-measles antibody titres have waned in a significant percentage of vaccinated young adults in the Netherlands.[22] Whether such individuals are at risk for measles is difficult to determine as they are not readily exposed to the virus nor epidemiologically clustered. Also, the serological analysis could either over- or underestimate the number of susceptible persons, depending on the type of serological tests (e.g. ELISA, Neutralization Test) and the virus strain (vaccine-type, wild type) used.[33,37] Such differences are in part related to the properties of different measles viruses to bind to different cellular receptors.[38,39] Thus, it is not yet clear to what extent the measles vaccine is capable of retaining its protective effect against emerging heterologous measles virus strains.

Although mass vaccination has led to a dramatic reduction in the number of reported measles cases, vaccination may have undesirable secondary effects. Several studies have shown that vaccine-induced antibody levels are lower than naturally acquired antibody levels.[40,41] Thus, waning immunity can be envisaged in a population where the circulation of wild type measles virus has largely stopped because of an efficient immunisation programme, such as is the case in the Netherlands.[37] This may have consequences for women approaching childbearing age. Their infants will be protected by maternal antibodies for a shorter time due to lower titres.[40,42,43] This will demand for either early vaccination with MMR, the effect of which will be difficult to interpret with respect to the efficacy and safety of all MMR components, or a strategy based on the boosting of the immune response in the general population, especially of individuals who are at childbearing age.

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4.7 Mumps

R.S. van Binnendijk, G.A.M. Berbers, F. Abbink, P.E. Vermeer-de Bondt

4.7.1 Introduction

Mumps ('parotis epidemica') is a viral infection of primarily the salivary glands. Its classical symptoms are unilateral or bilateral parotitis, although approximately a third of all infections are asymptomatic.[1,2] Orchitis is a complication mainly found in puberty, in 20-30% of clinical cases.[3] Four to six percent of infections can be more serious because of neurological complications (aseptic meningitis, deafness). The incubation period of the disease varies from 15 to 21 days.
Mumps is spread from person to person by aerosols and it is highly contagious.
In most parts of the world, the annual incidence of mumps is in the range 100–1000 per 100,000 inhabitants, and epidemics occur at intervals of two to five years. The incidence of the disease peaks among children aged five to nine years.[4] Natural infection with mumps virus is thought to confer lifelong protection, although rare cases of reinfection have been documented.[5] Theoretically, the disease could be eradicated, but public health efforts to control it are given low priority. However, it is particularly important in reducing the disease acquired in adulthood, when the complications may be comparatively severe.[4] It is also important to note that clinical symptoms such as parotitis can be caused by para-influenza virus type 1 and 3 and coxsackievirus, leading to a high degree of misdiagnosis. This finding emphasizes the need to perform laboratory confirmation and epidemiological investigation of clinically suspected mumps cases, especially when mumps incidence rates are low.
Recent outbreaks of mumps in several European countries have raised questions about the efficacy of several vaccine strains in use, in combination with both primary and secondary vaccination failures due to inadequate vaccination schedules.[6,7]

4.7.2 Vaccines available against mumps

Mumps vaccine is administered in combination with measles and rubella vaccine (MMR). The Jeryl Lynn strain of mumps virus is part of the trivalent combination vaccine used in the Dutch immunisation programme, as in most other European countries today. Efficacy was estimated to be 91% to 96% in several studies.[8]

4.7.3 Adverse events following mumps vaccine

Adverse events following mumps vaccine are generally mild and transient.[1] Fever is infrequent and peaks 10-14 days after the vaccination. Rash is uncommon. Parotitis appears to occur in up to 3% of vaccine recipients. Orchitis may rarely follow vaccination, as does arthritis. These events are very rare however, and an epidemiological association has not been found.[1,9,10] Severe mumps vaccine-linked adverse events are very rare and there is no indication that the vaccine causes lasting disabilities or chronic illness. Aseptic meningitis appeared to be a vaccine strain specific complication and did not follow the vaccines in use in the Netherlands. Encephalitis within 30 days of vaccination is not more frequent than the background rate.
Mumps vaccine is administered in combination with measles and rubella vaccine components (MMR). The measles vaccine, except for a few mumps specific adverse events and some that may be

rubella specific events, dominates the adverse events following MMR. Adverse events and contra-indications for MMR[11] are described under measles.

4.7.4 History of mumps and mumps vaccination in the Netherlands

In the Netherlands, before introduction of vaccination, 300-800 mumps cases were hospitalised annually, mostly for meningitis. A two-dose mass immunisation programme with a combined vaccine against measles, mumps and rubella (MMR) was adopted in the Netherlands in 1987. A catch-up campaign during the first 3 years with MMR for 4-year-old girls and boys was carried out. For years, the coverage for the MMR at 14 months has been around 95%, and at 9 years somewhat higher at 96%. However, it is likely that the total protection for MMR for these children is somewhat lower because it is known that a fraction of parents decides to skip the first MMR vaccination at 14 months. When the child did not develop these diseases at the age of 9 years, some parents convert to vaccination mainly to protect the child against rubella.
After introduction of MMR, the number of hospitalisations decreased rapidly to less than 10 cases annually (8).[12]

4.7.5 Epidemiology of mumps in the Netherlands

Surveillance is based on hospitalisation data and mortality data. In 2001, 2002, and 2003 two, five and three hospitalisations for mumps were registered. Mumps is not notifiable in the Netherlands.

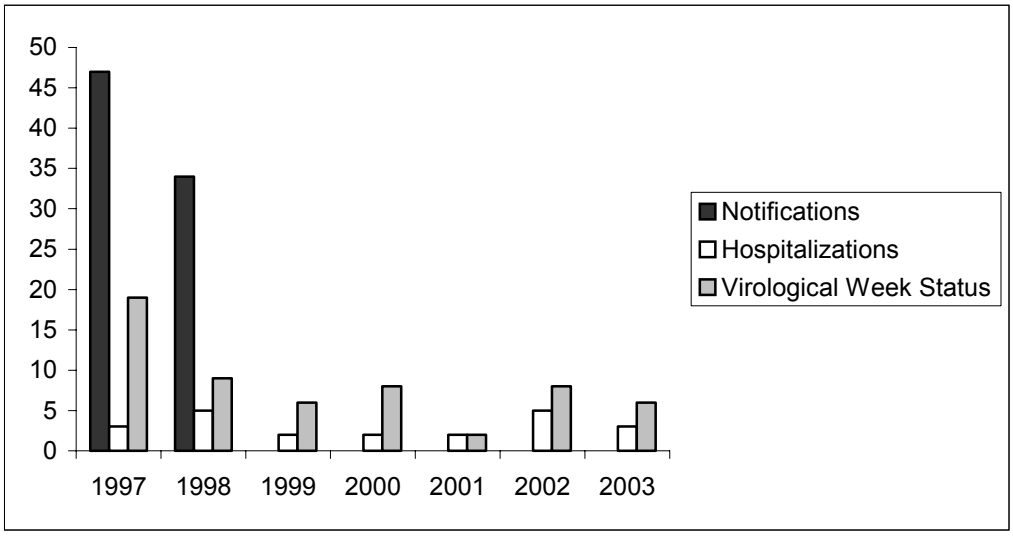

*Figure 4-7: Notifications, hospitalisations and positive mumps in Virological Laboratory Reports of Mumps in the Netherlands *Notifications mandatory until 1998.*

In most recent years, the annual reported incidence of mumps cases has been less than one per 100,000 of the population in the Netherlands. These results were obtained from a large study comparing data from six countries (Denmark, England and Wales, France, Germany, Italy and the Netherlands) that conducted large serological surveys for mumps, in the mid-1990s, as part of the European Sero-Epidemiology Network (ESEN). The assay results were standardized and related to the schedules and coverage of the immunisation programmes and the reported incidence of mumps.

Low incidence of disease and few susceptibles amongst adolescents and young adults were observed in countries with high mumps vaccine coverage (e.g. the Netherlands).[13]

4.7.6 Levels of immunity against mumps

Immunity against mumps in the general Dutch population and in persons refusing vaccination was assessed in a large population based study carried out in 1995/96 .[12] In the national sample, the seroprevalence for mumps in vaccinated cohorts-particularly those with only one dose- was lower than in the unvaccinated, natural immune cohorts. The level of population immunity required to block transmission of mumps has been estimated using mathematical models to be between 85 and 90%.[14-16] In the Netherlands, a country with high vaccine coverage levels, the proportions of older children and adolescents with antibodies to mumps virus were above these levels. Overall seroprevalence in the adult age groups in the national sample was 96.2%. Seroprevalence was somewhat lower in the vaccinated age groups, but still sufficient to maintain herd immunity. After the first dose of vaccine, an increase up to age three years to 93.2% and a subsequent decline in prevalence to 88.9% at age 7 was seen. Seroprevalence in those eligible for two vaccinations was 94.4%. It should be envisioned that waning immunity increases in populations where the circulation of the virus has stopped, such as principally is the case in the vaccinated population in the Netherlands. This also demands for a solution in the nearby future to protect the elderly vaccinated persons. Immunological surveillance and insight in the protection levels is needed to rationalize changes in vaccine schedules. Recently (2004), a cluster of mumps patients among adolescents (students) was observed in the Netherlands.
In the religious groups, seroprevalence was generally lower in the age group1-4 years than in the national sample but for the older age groups seroprevalences were similar.[14] Immunity in the orthodox reformed age groups born after introduction of vaccination is expected to have become too low to prevent outbreaks. A large part of these children will reach adulthood without immunity against mumps.

4.7.7 Strain variation of mumps in the Netherlands

Mumps virus is an enveloped negative-strand RNA virus and member of the family Paramyxoviridae, a genus that also includes e.g. human parainfluenza virus types 2 and 4. Mumps virus is serologically monotypic but serologic cross-reactivity exists between mumps virus and the human parainfluenza viruses, which poses problems in the diagnosis of mumps. Post vaccine meningitis has been documented in individuals vaccinated with the Urabe mumps strain. This neurovirulency was found to be associated with a wild type substitution of A for G in nucleotide position 1081 of the HN protein, which is within the major neutralizing domain of mumps virus.[17,18]
Strains have been differentiated by amplification and sequencing of segments of the F-gene, the HN-gene and the SH-gene, the latter being the most variable gene and used to characterize mumps isolates for clinical diagnosis, outbreak description, confirmation of vaccine-induced adverse events, and to identify new virus strains. More than 300 mumps cases linked to secondary-school outbreaks in the UK between 1995 and 2002 have thus been described. From these and other studies, genotypes A-K have now been proposed for mumps virus.[19] None of the genotypes could be clearly linked with mumps-associated meningitis, pancreatitis or orchitis. None of the strains were genetically close to the Jeryl Lynn (JL) vaccine strain (genotype A), and this applies both for strains analysed before and after the introduction of vaccination.[19] This raises the question whether the JL-type vaccine would protect populations from infection by genetically disparate mumps viruses, though it is expected that it will. However, recent observations contradict this assumption, as genotype A virus was shown to be

endemic in Sweden between 1971 and 1999 and was more difficult to neutralize by sera raised against the JL-type vaccine.[20] Emergence of disparate mumps virus strains under selective immune pressure of the vaccine has also been suggested for certain cases of mumps re-infection, which might contribute to the resurgence of mumps.

4.7.8 Mumps vaccine developments

There are no plans to improve or to change the mumps vaccine. All commercially available mumps vaccines are based on live, attenuated strains of the virus. Of these, the Rubini strain was recently shown to have poor efficacy, while the Urabe Am9 strain has been withdrawn because of vaccine-associated meningitis. WHO recommends that these vaccines should no longer be used. Most countries now use the attenuated Jeryl Lynn isolate. Extensive use of the mumps vaccines in industrialized countries has proved them safe and efficacious; so far, about 500 million doses have been administered. Approximately 120 countries are using mumps vaccine in their national immunisation programmes.

Recent outbreaks of mumps have been described in several European countries, particularly in older children and young adults who have only received one dose of the vaccine.[6,7] These and other observations have underlined the importance of children having received at least two doses of the mumps vaccine, preferably in combination with measles. However, there is limited information on the effectiveness of a second dose of mumps vaccine.[8] Also, the low vaccine efficacy of the Rubini strain, widely implemented in universal immunisation programmes, could be a major reason for the recent mumps resurgence and failure of mumps immunisation in many countries.

4.7.9 International perspectives of mumps vaccination

The International Task Force for Disease Eradication identified mumps as a potential target for eradication, and recommended that this should be linked to the policy of combined vaccination against measles and rubella.[4] The World Health Organisation, Regional Office for Europe (WHO/EURO), established a control target of an annual incidence of less than one case of mumps notified per 100,000 of the population to be achieved by its member countries by 2010.[5] With national and regional measles and rubella elimination efforts now underway in the Americas and Europe, programmes may be established that could lead to the elimination of mumps if MMR vaccine is used.

4.7.10 Other developments

Recent molecular analysis of mumps virus strains in different European countries has pointed to the genetic and antigenic differences between the Jeryl Lynn vaccine strain and circulating wild type strains.[19] A direct consequence of the vaccine to elicit lesser protection against particular strains has been reported.[20] Emergence of disparate mumps virus strains under selective immune pressure of the vaccine has been suggested by others.[21] Ongoing mumps surveillance is therefore necessary, yet this has to be initialized in most European countries, including the Netherlands.

An important note, relevant for those countries who have adopted the Jeryl Lynn vaccine strain is that this particular vaccine contains two different isolates, termed JL2 and JL5. Their proportion in the different vaccine lots is not a static event, yet wild type mumps viruses (including genotype A) antigenically matches JL-2 more closely than JL-5 and it is therefore possible that JL-2 will give better protection than JL-5.[20]

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4.8 Rubella

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4.8.1 Introduction

Rubella was considered a relatively benign infection, but became prominent after 1941 when an ophthalmologist discovered an unusual number of children with cataracts related to a large rubella outbreak and the consequence of maternal infection during pregnancy. Rubellavirus infects the placenta in pregnant women, leading to entrance of virus in the fetal circulation. It then infects many fetal organs, resulting in congenital rubella syndrome or CRS.[1] The first 12 weeks of pregnancy is clearly the most dangerous time for the fetal outcome if the mother contracts an infection. When acquired between the 16th and 20th weeks of gestation, deafness has been reported as a complication. However, the damage caused by congenital rubella infection does not stop at birth. CRS survivors may suffer from progressive hearing loss, visual impairment and late cataracts and a variety of syndromes thought to be autoimmune, including diabetes mellitus and thyroïditis.[2]

Rubella is predominantly a childhood disease, endemic throughout the world, although a comprehensive immunisation programme in most industrialized regions, including the USA, Europe, Japan, and Australia, has reduced the incidence of disease to low levels in these areas. Rubella is only moderately contagious. Incubation period is about ten days. The disease is most contagious when the rash is erupting, but virus may be shed from 7 days before to 5-7 days or more after rash onset. Infants with CRS shed large quantities of virus from body secretions for up to one year and can therefore transmit rubella to persons caring for them who are susceptible to the disease.[3]

A safe and effective vaccine against rubella is available. The primary purpose of rubella vaccination is to prevent the occurrence of congenital rubella infection including CRS. The approaches are to prevent CRS through immunisation of adolescent girls and/or women of childbearing age or to eliminate rubella as well as CRS through universal vaccination of infants and young children with or without mass campaigns, surveillance, and assuring immunity in women of childbearing age.

Vaccination is not carried out in many of the developing countries, however, and therefore most of the world's population is still infected naturally and is susceptible to epidemics of rubella that occur in irregular cycles at about 6- to 10-year intervals.[4] Cost-benefit studies in developed as well as developing countries have demonstrated that, when combined with measles vaccine in countries with coverage of over 80%, the benefits of rubella vaccination outweigh the costs.[5]

4.8.2 Vaccines available against rubella

The currently licensed rubella vaccines in wide international use are based on the live attenuated RA 27/3 strain of the virus, proven to be safe and efficacious. In clinical trials 95%–100% of susceptible persons aged 14 months and older developed rubella antibodies by 21–28 days after vaccination. Vaccination even at nine months of age results in seroconversion rates of more than 95%. Vaccine-induced immunity is generally assumed to last lifelong, although rubella antibodies may fall below detectable levels. The rubella vaccine is implemented in the Dutch NIP.

4.8.3 Adverse events following rubella vaccine

Adverse events following single rubella vaccines are generally mild and transient. Rash and fever occur less frequently than following measles vaccine and appears a little later.[2] As with measles vaccine, girls appear to have a higher rate of adverse events than boys do.

Specific events following rubella vaccines are lymphadenopathy, up to 7.5% and arthralgias or arthritis in up to 15% of vaccinees.[6] There are no permanent sequelae. Rates are highest in seronegative older girls and women, and very rare in 14 months old children.[7] When given as combined vaccine the adverse events are dominated by the measles component, except for those rubella specific events above and possibly some rare mumps specific events. See for adverse events following MMR under measles.

There are only few contra-indications for rubella containing vaccines.[8] Being a live vaccine, it should not be given to severely immunocompromised persons. Administration in pregnancy is also contra-indicated, but after inadvertent vaccination there seems to be no link with congenital anomalies.[9-11] Severe anaphylactic reactions to the rubella component have not been reported.

4.8.4 History of rubella and rubella vaccination in the Netherlands

A two-dose mass immunisation programme with a combined vaccine against measles, mumps and rubella (MMR) was adopted in the Netherlands in 1987, replacing the selective schoolgirl vaccination strategy introduced in 1974. The combination vaccine is administered at the age of 14 months and 9 years. It may also be administered to older children, adolescents, students, childcare personnel, health care workers, military personnel and adult men in contact with women of childbearing age. The selective vaccination strategy attempted to eliminate the risk of rubella infection amongst women of childbearing age only to prevent congenital rubella syndrome (CRS). However, mathematical models showed that a universal two-dose vaccination schedule would be more effective.[12,13] In contrast to selective vaccination, this strategy might interrupt rubella virus transmission and eventually be more effective in reducing the incidence of CRS. Since 1987, a combined vaccine of measles, mumps and rubella (MMR) has been given to boys and girls at the age of 14 months and 9 years. A catch-up campaign during the first 3 years with MMR for 4-year-old girls and boys was carried out.[14] For years, the coverage for the MMR at 14 months has been around 95%, and at 9 years somewhat higher at 96%.[15] However it is likely that the total protection for MMR for these children is somewhat lower because it is known that a fraction of parents decide to skip the first MMR vaccination at 14 months. When the child did not develop these diseases at the age of 9 years, some parents convert to vaccination mainly to protect the child against rubella.

4.8.5 Epidemiology of rubella in the Netherlands

Surveillance of rubella is based on mandatory notifications and hospitalisations data. In 2001, 2002 and 2003 four, three and one cases were notified.[16] Notifications are displayed in figure 4-8. [17]

In 2004, a large outbreak of rubella started among individuals who had declined vaccination on religious grounds. By the time this report was produced, the outbreak was ongoing.[17a]

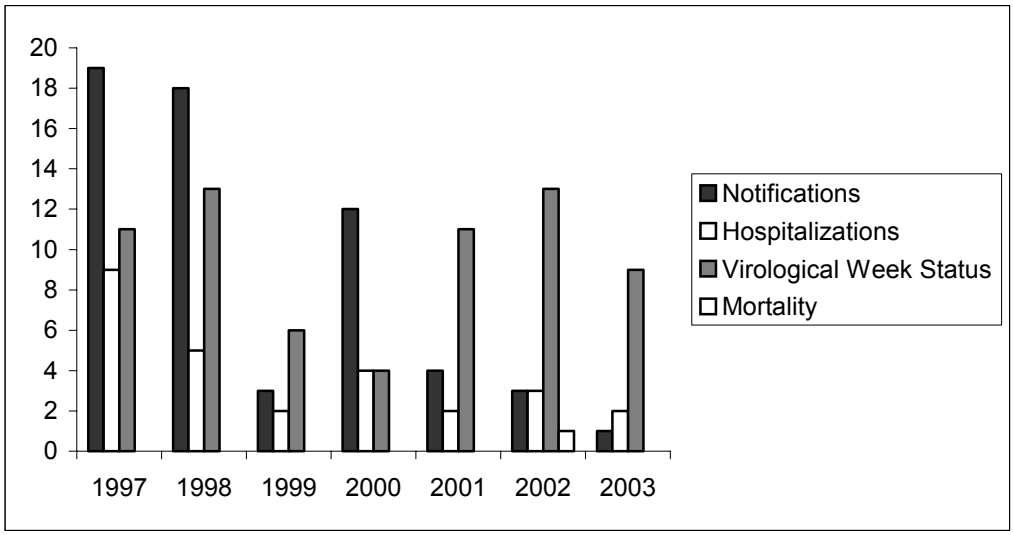

Figure 4-8: Notifications, hospitalisations, positives in Virological Laboratory Reports and mortality of rubella in the Netherlands (source: Abbink et al. RIVM report 2003)

The reported annual number of rubella cases in the European Region has increased 75% during the last decade. While the number has declined in Western Europe and in Central Eastern European countries, in the Newly Independent States rubella continues to circulate freely in most countries, with a large epidemic in 1999–2001. In the Netherlands, the success of vaccination is evident from the fact that the number of reports of rubella infections and CRS in the post vaccination era have decreased considerably.[17,18] Mortality has been very low since 1950 (0-2 cases/year) with the last death due to rubella seen in 1985. The number of notifications for rubella and CRS as well as the number of hospital admissions has both decreased drastically since1987.
Rubella diagnosis without laboratory confirmation is quite unreliable. Many rash illnesses may mimic rubella infection and up to 50% of rubella infections may be subclinical. Asymptomatic reinfections in persons previously immunized against rubella have been documented.[1] Reliable evidence of acute rubella infection is the presence of rubella-specific IgM antibody, demonstration of a significant rise in IgG antibody from paired acute and convalescent sera, or a positive detection of rubella virus by culture or by RT-PCR (CDC data sheet). It should be noted that false positive serum rubella IgM tests have occurred in persons with parvovirus infections, with a positive heterophile test for infectious mononucleosis, or with a positive rheumatoid factor.

4.8.6 Levels of immunity against rubella

Immunity against rubella in the general Dutch population and in persons refusing vaccination was assessed in a large population based study carried out in 1995/96 .[19] In the national sample, the seroprevalence for rubella in vaccinated cohorts-particularly those with only one dose- was lower than in the unvaccinated, natural immune cohorts. However, the (high) prevalence for rubella (96.5%) was above the level needed to prevent epidemics. Furthermore, no indications for rapidly waning immunity after vaccination were found. There are indications of low virus circulation in the last few years. The very high seroprevalence in women at childbearing age is consistent with the few reported cases of congenital rubella syndrome (CRS) at present. However, individuals in the age group of
1±9 years who are not vaccinated for religious or other reasons have a considerably lower seroprevalence and thus there is a potential risk of a CRS outbreak or single cases. In the coming

years, serosurveillance studies should focus on high-risk populations such as young individuals who are unvaccinated because of religious objections.

4.8.7 Strain variation of rubella in the Netherlands

Rubellavirus (RV) is the only member of the genus Rubivirus in the family Togaviridae. The virus is a small enveloped negative-strand RNA particle composed of about 10 Kd with two embedded envelope proteins, E1 and E2 and one structural protein(C) composing the capsid. Virus neutralizing antibodies are primarily directed against E1. Rubella is antigenically stable and consequently antigenic variation is not expected to pose a risk in the use of rubella vaccines or for serological diagnosis. However, sequencing studies concentrating on the E1 open reading frame for the viruses isolated from 17 countries from 1961 to 2000 confirmed the existence of at least two genotypes on basis of E1. Rubella genotype I (RGI) isolates, predominating in Europe, Japan, and the Western hemisphere, segregated into discrete subgenotypes; international subgenotypes present in the 1960s and 1970s were replaced by geographically restricted sub genotypes after approximately 1980. The emergence of a new international subgenotype since 1997 has been documented. This subgenotype apparently originated in Asia and spread to Europe and the USA.[20-22]

4.8.8 Vaccine developments

Except for some new rubella vaccine strategies under assessment, including the development of subunit vaccines and the use of recombinant DNA technology, there are no serious plans to improve or to change the rubella vaccine, despite the possible dangers associated with vaccination of pregnant women or immunocompromised individuals.[4]

4.8.9 International perspectives of rubella vaccination

Measles and rubella remain important causes of vaccine-preventable disease and death in the European Region of WHO. Although an increasing number of Member States provide highly effective vaccines to prevent both of these diseases as part of their routine Expanded Programme on Immunisation, challenges remain to improve coverage in the countries currently using the vaccines and to introduce rubella vaccine in the countries that have not yet implemented a programme. Countries undertaking measles elimination (target 2007) should consider taking the opportunity to eliminate rubella as well (<1 CRS per 100, 000 live births, target 2010), through use of MR or MMR vaccine in their childhood immunisation programmes, and also in measles campaigns.[23] Progress towards meeting these targets will be reviewed in 2005 in accordance with the 2005 global assessment of measles control.[24]All countries undertaking rubella elimination should ensure that women of childbearing age are immune and that routine coverage in children is sustained at over 80%. This is to prevent a paradoxical increase of CRS as predicted in mathematical models and also experienced in Greece, where low-level introduction of MMR in infants was followed by an decreasing seroprevalence among women of childbearing age and an outbreak of CRS in 1993.[1]

4.8.10 Other developments

Symptomatic and asymptomatic reinfections of persons vaccinated against rubella are common. The danger of reinfection with fetal transmission is a fact, in the presence of both natural and vaccine-induced immunity, but the risk is probably less than 5% in the first trimester of pregnancy compared with at least 80% in primary infection. Reinfection may be most frequent in individuals with low titres

of virus neutralizing antibodies (< 15 IU/ml). Yet the presence or absence of neutralizing antibodies does not always correlate with the likelihood of reinfection, because infants with CRS have been born to mothers who have antibody levels of 15 IU/ml or greater.[1] Other immunologic factors, including cellular immune responses, mucosal immune responses and presence of certain epitope specificities in the antibody repertoire have been reported of significance, but their contribution in reducing the risk of maternal transfer of the virus and eliminating the viral excretion in CRS has yet to be determined.
Rubella vaccination has been contraindicated during pregnancy because of the theoretical (but never demonstrated) teratogenic risk. Based on data collected by the CDC in the Vaccine in Pregnancy Registry, no evidence of CRS occurred in offspring of the 321 susceptible women who received rubella vaccine and who continued pregnancy to term. Since the risk of the vaccine to the foetus appears to be extremely low, if it exists at all, routine termination of pregnancy is not recommended (CDC website, rubella datasheet). It now also appears that no cases of CRS have been reported in pregnant women in Brazil, who have been inadvertently vaccinated against rubella during a rubella vaccination campaign in 2002.
Maternal immunisation could be an interesting future alternative, instead of attempts to reduce the age of primary MMR vaccination in very young children.

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4.9 Meningococcal disease caused by *Neisseria meningitidis* group C

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4.9.1 Introduction

Meningococcal disease is caused by the Gram-negative bacterium *Neisseria meningitidis*. Based on the antigenic properties of the capsular polysaccharide several serogroups of *N. meningitidis* can be distinguished. The predominance of particular serogroups seems to depend on geographic location and composition of the population. Meningococci are found as commensal organisms in the throat of 5% to 20% of children and adolescents. Carriage is lower in adults. In sub-Saharan Africa group A meningococci are responsible for endemic disease, but this serogroup has nearly completely disappeared from Europe and the USA. In the Netherlands, as in most other countries in Europe, meningococcal meningitis is mainly caused by serogroup B and C (Men B and Men C. Before 1999, serogroup B predominated in the Netherlands, but subsequently, an alarming and unexplained rise in the incidence of Meningococci C was seen. This has led to the introduction of the polysaccharide conjugate vaccine in the Dutch NIP in 2002. The most important clinical presentations of meningococcal disease are meningitis and severe sepsis. Despite availability of proper treatment, overall mortality is around 5% to 10%.

4.9.2 Vaccines available against meningococcus C

The current Men C-vaccines are conjugated capsular poli- or oligosaccharides, which are linked to a carrier-protein assuring effectiveness in the very young by T-cell dependent immune response leading to immunologic memory. The vaccines are adjuvated to aluminium salts, in the case of the vaccine used in the Netherlands alluminumhydroxide (NeisvacC). This vaccine contains no preservatives.
Efficacy is age dependent and ranges from 12% among 6 to 23 months old children to 83% in adults. Duration is based on found persistence of antibodies in 2 to 5 years after vaccination. If persistence of antibodies is found in two or more years after vaccination, duration is expected to be 10 years.[1]

4.9.3 Adverse events following meningococcal C vaccine

Adverse events following Men C in the campaign have been followed intensely by monitoring tolerability and by registration of acute paroxysmal events. Infrequent and the more severe events have been surveyed by the enhanced passive surveillance system of the RIVM.
Men C vaccines are usually well tolerated. Local reactions are generally transient and mild. Their presentation and rate of occurrence depends on the age of the vaccinees. Percentages given are 7-15% in the younger children and increase with age to approximately 60% (self reported), depending on case definition and methods of case ascertainement.[2-6] Fever of >38^{o}C and malaise occur in 5-10% of the cases on the same day or on the first day after vaccination. Malaise is expressed differently in different age groups. This ranges from lethargy, increased fussiness and crying in the very young, to bellyache in the toddlers, and headache and dizziness in the older schoolchildren or pain in all limbs.
A follow-up among 870 children who received both Men C-vaccine and MMR at the age of 14 months yielded the same percentages.[7]

Severe adverse events following Men C-vaccination are extremely rare. Single Men C-vaccination may also be followed by collapse, but the incidence rate is unknown since this is a rare event and Men C in the infants is usually administered simultaneously with other vaccines. This is also true for persistent screaming. In the Men C campaign in 2002, three reported febrile convulsions were attributed to the vaccination, as were seven so-called 'atypical attacks' in which no definite diagnoses could be made.[3] The other major reactions reported following Men C-vaccination in the campaign were local reactions (14 children) and very high fever (>40.5^{o}C), also in 14 children. Three children were admitted to the hospital for minor events following the vaccination. Of the 1512 reported children, only 2.8% (41) had severe adverse reactions and all children recovered completely. The other reported severe events were judged coincidental events, not caused by the vaccination. The campaign with nearly 3 million vaccinations was therefore very safe and successful.
No early-onset disease has been reported following Men C-vaccination, and so far vaccine-failure has not been observed. In addition, there is no suspicion of interference with decrease in efficacy of other vaccine-components given simultaneously with the Men C-vaccine. In the current schedule, Men C is given simultaneously with the MMR at 14 month of age.
Because of the different nature of the two vaccines it is in most cases possible to attribute the event to the specific vaccines.[8]Adverse events are not expected to increase in number and severity by giving these vaccines simultaneously. This is documented by comparing the rates of MMR alone and Men C alone in the relevant age groups.[9] both for common and rare, more severe events.[8] No severe anaphylactic reactions have been reported since the introduction of Men C in the Netherlands vaccination schedule in July 2002. Also there are epidemiological links between Men C vaccine and other rare severe events.[10-12]
No reliable safety results are yet available of the Men C and Pneumococcal combination vaccines currently under trial.

4.9.4 History of meningococcal C disease and meningococcal C vaccination in the Netherlands

Vaccination against invasive disease caused by Men C was introduced in the NIP in the Netherlands in September 2002 following a nationwide vaccination campaign targeted at all children from 12 months to 18 years of age.[13] Vaccination was introduced after a steep rise in meningococcal C disease. The Men C conjugated vaccine is administered simultaneously, but in another limb, with the MMR vaccine in the Netherlands at the age of 14 months. Details on routine vaccine coverage levels are not available yet. However, with the nationwide vaccination campaign organized in 2002 94% of the children targeted for vaccination were reached.[14]

4.9.5 Epidemiology of Meningococcal C disease in the Netherlands

Surveillance of Men C disease in the Netherlands is based on mandatory notification and submission of disease isolates to the NRBM, where isolates of meningitis cases are serotyped.
Traditionally serogroup B was the most common serogroup (80-90% of all isolates) of meningococcal disease in the Netherlands, followed by serogroup C (10-15%). However, in 1999 to 2001 a rise in the incidence of serogroup C occurred and the incidence had increased to 1.7/100,000 in 2001 and therewith accounted for 38% of all isolates sent to the NRBM.[15] The incidence of meningococcal C disease increased in all age groups. In 2002, the NRBM typed 221 isolates of patients as meningococcal C disease, while in 2003 only 42 patients with meningococcal C disease were reported. Hence, the incidence of meningococcal C disease decreased from 1.7/100,000 in 2001 to

0.3/100.000 in 2003. In 2001, the year before introduction of the vaccine, the highest incidence of Men C disease was reported for children under 1 year of age (9.7/100,000), a second peak was found among the 1-5 year-olds (6.0/100,000) and in the group of 15-18-year olds incidence amounted 8.3/100,000. After introduction of vaccination, in 2003, the incidence/100,000 for these groups amounted 5.4, 0.6 and 0, respectively (figure 4-9). Since the introduction of Men C conjugate vaccine, no cases of Men C disease have been reported in previously vaccinated children

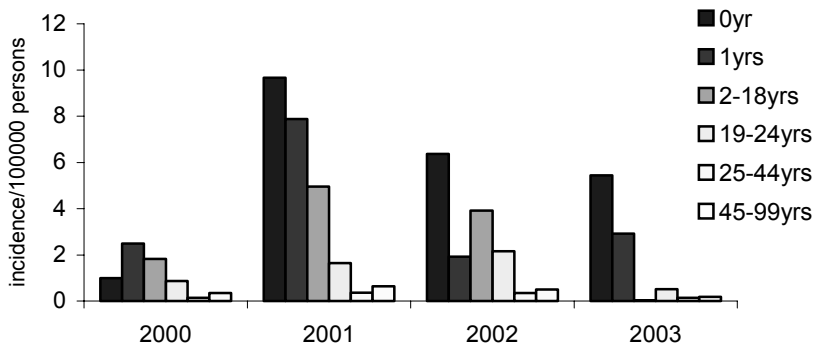

Figure 4-9: Incidence of meningococcal C-disease by age group 2000-200. Source: NRBM and Osiris notifications.

From January 2003, onwards intensified surveillance was started to monitor the effects of the vaccination campaign as well as the introduction of the vaccine in the NIP. In 2003, 348 patients with meningococcal disease were notified and for 280 patients the intensified surveillance questionnaire, attached to the notification-form after introduction of vaccination against meningococcal C-disease, was completed. According to this questionnaire 15% (5) of serogroup C cases (n=33) presented symptoms of meningitis and septic shock at hospital admission, 15% (5) demonstrated septic shock without meningitis, 42% (14) presented meningitis without septic shock and for the presentation of symptoms was different or unknown.
Presence of septicaemia is associated with a higher case-fatality rate.[16,17] Mortality by serogroup in the Netherlands is only known for 2002 and 2003, based on the intensified surveillance. In 2002, at least 10 persons died from meningococcal-C disease. In 2003 only one of the 39 reported serogroup C-patients died.
Of the survivors of meningococcal disease, 10-20% has sequelae, like hearing loss, neurological disability, or loss of limb.[16,18] The percentage of survivors with sequelae is higher for survivors of serogroup C- than for those with serogroup B-disease.[19]

4.9.6 Levels of immunity against meningococcus C

Protection against meningococcal disease (including Men C) for newborns is provided by serum bactericidal antibodies that are transplacentally acquired from the mother. These antibodies persist only a few months. Normally in the pre-vaccination era, low levels of bactericidal antibodies are present in children below 2 years of age, the age group with the greatest disease risk. In the years thereafter, natural acquisition of these antibodies is inversely related with age, which is accompanied with a decrease of incidence of meningococcal disease.[20]

After the nation wide vaccination campaign in 2002 the immune status for anti-Men C antibodies in the Netherlands must have changed dramatically. Considering the immunogenicity of the Men C conjugate vaccine at least 95% of the vaccinees is expected to have developed serum bactericidal titres above the threshold necessary for protection (>1 : 4) when measured with human complement. Moreover, the quality of the antibodies, in particular the bactericidal activity, elicited by conjugate vaccines is superior to that elicited by polysaccharide vaccines. In addition, up until now this complement-mediated bactericidal antibody response is considered the best serologic correlate of protection.[21] The overwhelming majority of children and adolescents up until 20 years of age are expected to be well protected. This is corroborated by the dramatic decrease in incidence of Men C cases after the mass vaccination campaign. There are no data available yet to confirm the new situation in the Netherlands, but a second large-scale immunosurveillance project is being planned now and will provide insight in the present immune status of the Dutch population for Men C.

4.9.7 Strain variation of meningoccoccus C in the Netherlands

Based on the composition of their polysaccharide capsule at least 13 distinct serogroups can be distinguished among meningococci. However, virtually all cases of meningococcal disease are caused by serogroups A, B, C, W135 and Y. For epidemiological purposes, strains are further classified in serotypes and serosubtypes.

The serotype is based on the reactivity of specific antiserum with an outer membrane component, a porin designated PorB. Serosubtyping is based on reactivity of monoclonal antibodies with the porin PorA. This results in a nomenclature listing serogroup, serotype and serosubtype separated by colons e.g. B:4:P1.4.[22] Genosubtyping, in which the DNA sequence encoding for two variable loops of PorA (VR1 and VR2) are determined, may gradually replace the serosubtyping.[23] In addition, variation in the core of LPS can be used to classify immunotypes.[24] Multi-locus sequence typing (MLST) is currently seen as the golden standard for typing meningococci and has identified particular sequence types associated with hypervirulent properties of meningococci.[25] However, MLST is a very costly typing technique and is not used as a standard typing technique in the NRBM.

Since 1994, when the NRBM started reporting serotyping of Men C, the most frequently isolated Men C serotype has been serotype 2a and this accounted for 80% of isolates.[15] Similarly, the predominant serosubtypes of Men C serosubtypes over the last decade have been P1.5 and P1.2. However, there have been temporal fluctuations in the distribution of these serosubtypes either apart or in combination with each other. Over the last decade the most frequently isolated types of Men C have been C:2a:P1.5 and C:2a:P1.2,5, which attributed for 41% and 25% of all Men C isolates typed by the NRBM in 2002. PorA genotyping of the Netherlands strains is being performed since 2000. Only minor changes in the distribution have been observed. The predominant genotypes had VR1,VR2 combination 1.5,2 and 1.5-1,10-8 accounting for 40% and 38% of the typed Men C isolates. There have been no published reports on MLST of Netherlands meningococci yet.

4.9.8 Meningococcal C vaccine developments

The three currently used polysaccharide conjugate vaccines seem to confer good protection and have only recently been introduced in routine vaccinations schedules. There seems to be no need to alter the present vaccine formulation.

4.9.9 International perspectives of meningococcal C vaccination

The UK was the first country to implement routine scheduled vaccinations with Men C conjugate vaccine in 1999 and conducted a catch-up programme for older children. This resulted in an immediate fall in disease incidence occurred and reducing the number of cases with Men C meningococcal disease with more than 95%. Moreover, the vaccine showed also an indirect protective effect as the attack rate in the unvaccinated population in the cohorts targeted for vaccination, was reduced by 67%.[26] Spain and Ireland introduced the vaccine in 2000 with a catch-up programme for older children. Both countries witnessed an impressive decline in number of Men C cases reducing incidence from 3.7/100,000 in 1999 to 0.1 in 2003 in Ireland. Belgium and Iceland introduced the vaccine at the same time as the Netherlands in 2002. There are considerable differences in the vaccination schedules used in these countries (Table 4-4).

Table 4-4: Vaccination schedules of meningitis C in different countries.

	Vaccination at
UK	2, 3 and 4 months
Ireland	2, 3 and 4 months, single dose for 1-22 year olds
Belgium	12 months
Iceland	6 and 8 months
Spain	2, 3 and 4 months
Netherlands	14 months

The study of data from England and Wales estimated the direct protection from both catch-up and routine vaccination schedules and confirmed that the vaccine provides high levels of direct protection in most age groups.[27] However, young infants who have undergone the routine vaccination have high protection for the first year but then experience a decline and may indicate the need for a booster vaccination.

4.9.10 Other developments

The current Men C vaccine is a single component vaccine protecting against infection with Men C only. However, the majority of cases of meningococcal disease in the Netherlands is caused by serogroup B meningococci. Meningococci have the capability to exchange genetic material and this may cause an important problem: capsular switch. Strong, vaccine-induced, immune pressure against the Men C polysaccharide capsule may cause selection of Men C strains that have exchanged the genes encoding for the capsule with that of Men B strains. This could lead to a wolf in sheep's clothing: hypervirulent Men C strains with the Men B capsule. Such capsule switch has been observed before.[28] To monitor for possible changes in the virulence of Men C including capsule switch it is important to genotype meningococcal strains causing invasive disease.

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4.10 Hepatitis B virus

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4.10.1 Introduction

Hepatitis B virus (HBV) is one of the viral causes of hepatitis. Following infection, acute symptomatic disease occurs in less than 10% of children and about 30% of adults.[1] Incubation period is variable with four weeks to six months. Symptoms can range from abdominal discomfort with or without jaundice to acute liver necrosis. HBV infection can resolve, but 85% of infected newborns and 2-7% of infected adults become chronically infected, which eventually can lead to cirrhosis and hepatocellular carcinoma. Hepatitis B is a common viral infection of humans, and in some countries over 50% of the population has serological proof of a past infection (i.e. Southeast Asia and sub-Sahara Africa), and worldwide ~300 million people are chronically HBV infected. HBV transmission occurs by percutaneous or permucosal exposure to infective body fluids, or perinatally.[2]
Prevalence of chronic hepatitis B in the Netherlands is generally low (~0.4%, i.e. ~70,000 people), but is higher in risk groups such as injecting drug users, homosexual man, and prostitutes (~0.8%) and is alleviated in certain ethnic minorities descendent from high or intermediate endemic countries (e.g. Moroccans and Turks).[3,4]

4.10.2 Vaccines available against Hepatitis B

Effective plasma-derived hepatitis B vaccines have been available since the early 1980's. Recombinant (yeast-derived) vaccines, containing different parts of the hepatitis B (pre)-Surface protein (HBsAg), have replaced nowadays the plasma-vaccines. These recombinant sub-unit vaccines are very effective (~95%), and are used in large-scale newborn vaccination campaigns in countries were hepatitis B is moderate to high-endemic (>2% carriers).[5] Immunisation of infants born to hepatitis B-infected mothers can prevent chronic infection in >90% of cases when immunisation is started within 48 hours of birth. Different hepatitis B vaccines can contain different amounts of antigen. Engerix (GSK) for example contains 20 micrograms of HBsAg (full dose = 1.0 ml), while HBPROVAX (AP-MSD) contains 10 micrograms of HBsAg (full dose = 1.0 ml). Children are vaccinated with only half a dose (0.5 ml) and usually receive three vaccinations within the first year of live. In the NIP children which are eligible for Hep B vaccination (see further on) receive 0.5 ml of HBPROVAX (= 5.0 microgram of HBsAg in 0.5 ml) at 2, 4, and 11 months of age.

4.10.3 Adverse events following HBV vaccine

Adverse events following hepatitis B vaccination are usually mild and of short duration and appear to be no more frequent than in placebo recipients.[6] Pain occurs in 3-30%, and fever, mainly low grade, in less than 10%, depending on age and case definitions. Severe local or systemic adverse events are extremely rare.[7,8] Single HepB-vaccine may, depending on age, be followed by collapse reactions, but the incidence rate is not known since this is a rare, age specific adverse event and the vaccine is often given simultaneously or combined with other components. [7] The same applies for febrile convulsions or persistent screaming. Neonatal vaccination is safe with very low rate of fever.[9]
If hepatitis B vaccine is given simultaneously with DTP_w-IPV/Hib, the adverse events are dominated by the pertussis component. Addition of the hepatitis B vaccine does not alter the severity of the

adverse events. A small increase in number of adverse events may be present, but this is lower than when these vaccines are given time spaced.[6]

4.10.4 History of HBV vaccination in the Netherlands.

In 1992, the World Health Organisation (WHO) recommended that all countries implement universal immunisation against HBV by 1997, and over 100 countries have done so. The Netherlands has, however, continued a policy of selective immunisation of those at highest risk of infection.[10] On 1st March 2003, routine immunisation of children with at least one parent born in a country with a moderate (2-8%) or high prevalence (>8%) of chronic hepatitis B infected people was started. This means that currently ~16% of infants in the Netherlands are being vaccinated for hepatitis B in the NIP.

Next to this targeted childhood immunisation programme, three additional hepatitis B immunisation programmes are in place. The first programme (since 1989) aims to reduce the vertical transmission. Around the 12th week of pregnancy each woman is invited to take part in a serum screening which, among other tests, determines the presence of major surface antigen of hepatitis B antigen (HBsAg). If a woman is found positive, the child is scheduled to receive hepatitis immunoglobulin within 24 hours after birth, and will additionally receive a complete hepatitis B vaccination within its first year. Although, over 95% of the children of identified HBsAg-positive mothers receive both the passive immunisation (HBIG) and at least three active immunisations (HBsAg), it was found that about ¼ of all vaccination was untimely.[4]

The second special programme (initiated in 2000) is targeted at people who have an elevated risk of close and intimate contact with potentially hepatitis B-infected people, either due to their profession (e.g. dentists, nurses), or due to their housing facility (e.g. mentally disabled people).

The third special programme is targeted at IDUs, prostitutes, MSM and heterosexual persons with multiple sexual contacts. Eligible people are recruited at places, which they frequently visit such as methadone care, municipal health services, and STI-outpatient clinics. A blood sample is taken at the time of the first dose of the hepatitis B vaccination, and depending on the status, (negative for hepatitis B markers, i.e. ~85%) participants will receive the two additional vaccinations. In the period November 2002 to November 2004 18.738 persons have been vaccinated, and 82% and 51% received a second and third vaccination, respectively. [3]

4.10.5 Epidemiology of hepatitis B in the Netherlands

Acute viral hepatitis B has been a notifiable disease in the Netherlands from 1976. Over the past 10 years the mean yearly incidence of acute hepatitis B was 229 cases (STDEV = 43). In 2003, 319 cases of acute hepatitis B were diagnosed. The estimated incidence of acute hepatitis B in 2003 was 3.1 per 100,000 male inhabitants and 0.9 per 100,000 female inhabitants. In 2002, these numbers were 2.6 and 0.7, respectively.[11] The increase in incidence of acute hepatitis B in 2003 (n=319) compared to 2002 (n=247) and 2001 (n=197) may be attributed to a better surveillance system or a more active pre-vaccination screening in the vaccination campaign of IDUs, prostitutes and MSM since November 2002.

The most reliable data on the prevalence of chronic hepatitis B infections in the Netherlands can be deduced from the serologic screening of pregnant women. Over the years chronic hepatitis B infection prevalence is found to be ~0.4% in pregnant women.[4] This might be an underestimation, as the HBsAg prevalence in pregnant women who are not participating in this screening (estimated to be up to 15% [4]) is probably higher (Steenbergen, Pers. Com. 2003). In the large population-based sero-

epidemiology study from 1995 in the Netherlands (PIENTER), only the prevalence and level of antibodies against the core protein (anti-HBc) were determined as marker for a past or present infection (seroprevalence=2.1%).[12]

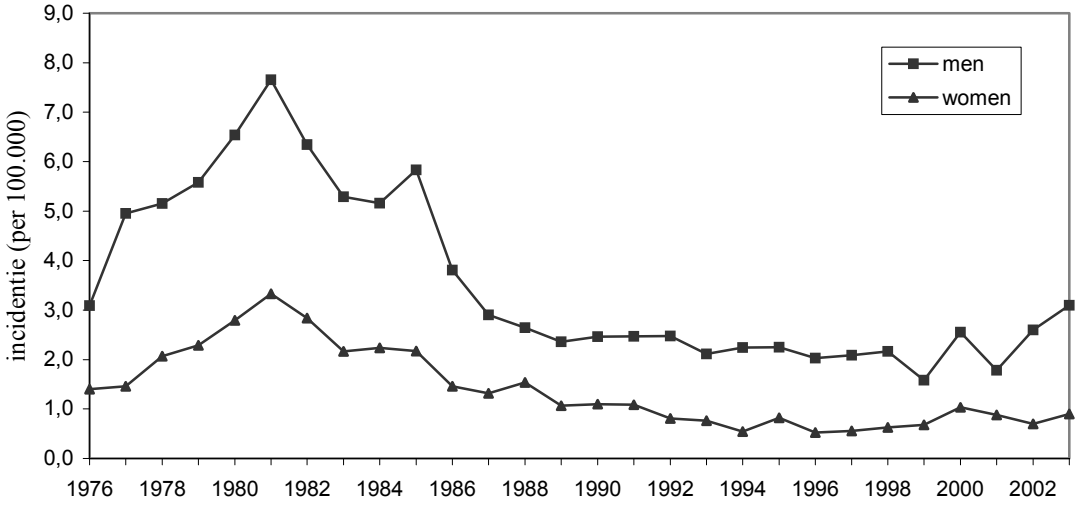

Figure 4-10: Incidence of acute hepatitis B in the period 1976-2003, by sex (Source: Osiris notifications)

4.10.6 Levels of immunity against hepatitis B

Due to the only recent introduction of the targeted childhood vaccination of hepatitis B, the vast majority of the Dutch population is not protected against hepatitis B. A new immunosurveillance study (planned for 2005-2006) should preferably be used to determine the prevalence of past HBV infections (anti-HBc), the prevalence of chronic infected (HBsAg) people, and the prevalence of HBV-protected people (anti-HBs) in our general population.

Based upon clinical trials and data form countries where general childhood immunisation programmes have been established a long time ago (e.g. Taiwan, 1984), it is anticipated that the targeted immunisation programmes as handled in the Netherlands (childhood dose hepatitis B at 2, 4 and 11 month of age), will induce protection for a long time (>15 years), and probably life-long in those who are participating.[13-15]

4.10.7 Strain variation of hepatitis B virus in the Netherlands

Until recently, no general surveillance of hepatitis B strains has been performed in the Netherlands. Molecular data from a limited surveillance study (n=54) in Amsterdam among acute hepatitis B cases revealed 3 main clusters of hepatitis B strains: IDU strains (genotype D, n=16), Moroccan strains (genotype D, n=12) and MSM strains (genotype A, n=20).[16] Because these data represents a period (1992-1997) before the larger immunisation programmes were initiated, and because Amsterdam has a different population in comparison to the remaining part of the Netherlands, these data only give an indication of the circulating strains in the population.

In January 2004, a national acute hepatitis B surveillance study has been initiated by RIVM and GG&GD Amsterdam, to type each acute hepatitis B strain reported in the Netherlands, at molecular level. Preliminary data from this study show that most acute hepatitis B cases are caused by strains which are predominantly found among MSM (genotype A), while the strains found normally

associated with IDU (genotype D) are now only found sporadically (RIVM, GG&GD Amsterdam, Unpublished data).
The appearance of vaccine escape mutants in high prevalence countries that have (universal) childhood immunisation has been described.[17,18] What the long-term effect of these vaccine-escape mutations is on vaccine efficacy is however unclear.

4.10.8 HBV vaccine developments

Major hepatitis B vaccine companies have developed combination vaccines in which the hepatitis B vaccine is combined with DTP_a-IPV/Hib. These six-in-one vaccines are already in use in Germany, France and Belgium.
The 6-component GSK Infanrix Hexa (DTP_a-HBV-IPV/Hib) vaccine contains a 3-component (PT [25 microgram], FHA [25 microgram], and Pertactin [8 microgram]) acellular pertussis vaccine, and 10 microgram HBsAg. Before application, the Hib antigen of Infanrix Hexa has to be reconstituted.
A comparable vaccine (Hexavac) is being marketed by Aventis-Pasteur. This vaccine (DTP_a HBV-IPV-Hib) is ready to use, and contains only two pertussis components (PT [25 microgram], FHA [25 microgram]), and 5 microgram HBsAg. An alternative multicomponent vaccine (Pediacell of Aventis, which contains a 5-component acellular pertussis vaccine (i.e. $DTP5_a$-IPV/Hib) is not available as a hexavalent (i.e. +HBV) vaccine, nor are their plans to register such a vaccine (APMSD, Pers. Com., July 2004).
Following the Health Council advice the Minister of Health has decided that a five-in-one vaccine (without the HBV) replaced the current DTP_w-IPV/HIB from 01-01-2005 onwards.

4.10.9 International perspectives of HBV vaccination

Several low-prevalence countries have started to reduce the incidence of acute hepatitis B by targeted vaccination of high-risk groups. However, following the WHO advice of May 1992, most of the western countries have now implemented universal childhood immunisation programmes with generally good (>85%) and excellent (>95%) reported vaccination coverage. [19] Many countries, including most European (10/17), have complemented the universal infant vaccination with a universal adolescent catch-up immunisation programme. [16] In Europe two countries have chosen for adolescent vaccination only (i.e. Switzerland (reported coverage ~60%) and Slovenia (reported coverage ~98%)). Clinical studies indicate that a 2-dose regime of hepatitis B vaccination (in combination with a stronger adjuvant) also yield excellent sero-conversion rates in adults and adolescents.[20,21] A 2-dose regime is anticipated to increase cost-effectiveness and compliance rates of adolescent vaccination considerably. A cost-effectiveness calculation of only a universal (2-dose) adolescent hepatitis B vaccination, or a universal infant vaccination accompanied by a catch-up adolescent programme is currently being performed for the Dutch situation by the RIVM.
Universal childhood vaccination has been shown to be very effective in several countries. Taiwan was the first country that started mass vaccination in 1984. There the average annual incidence of hepatocellular carcinoma in children has dropped significantly from 0.70 per 100,000 children between 1981 and 1986 to 0.36 between 1990 and 1994.[22] Also for Italy, the first European country that adopted universal childhood hepatitis B vaccination accompanied by catch-up adolescent vaccination in 1991, a profound decrease in acute hepatitis B and hepatitis B-induced liver disease has been reported.[23]
On basis of questionnaires, homo- (~35%) and hetero- (~25%) sexual contact are the most likely route of transmission of HBV resulting in acute hepatitis B in the Netherlands, while in ~30% of the cases

the source of infection is unknown.[11] Like other Northern European countries (e.g. UK, Norway and Denmark) the Netherlands has not chosen for universal vaccination. Given the increasing mobility of the (Netherlands) population, and the increase of heterosexual transmission, it is uncertain whether the current targeted immunisation programmes will succeed in reducing the incidence of acute hepatitis B in the Netherlands in the (near) future.

4.10.10 Other developments

The vaccination strategy for targeted infant vaccination in the Netherlands has only started in January 2003. As a result, it is difficult to determine whether this vaccination strategy is successful at this moment. Furthermore, because there is a long period between the acquisition of a chronic infection and clinical manifestations like cirrhosis and hepatocellular carcinoma, it will take a long period before a decline in prevalence of (chronic) hepatitis B will become apparent.

The transmission of HBV is largely dependent on importation from foreign countries, as it has been calculated that transmission without import is too low for continuing circulation.[24] Several factors that influence the importation of HBV are difficult to predict. One of these factors that can change drastically within a few years is the number of immigrants from a particular part of the world. Furthermore, (holiday) visits of Netherlands people in combination with (unprotected) sex appears to account for a considerable number of acute HBV cases, and this number will be hard to reduce.

Recently, it was shown that the prevalence of chronically hepatitis B among the known risk groups such as IDU, MSM and prostitutes is, in the Netherlands, is only twice as high (i.e. ~0.8%) as in the general population (i.e. ~0.4%, general screening of pregnant women).[3] The impact of this data (in combination with the increased of heterosexual transmission) on the (cost-) effectiveness of the current hepatitis B immunisation programmes will be subject of further study at the RIVM.

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5. Diseases with potential for inclusion in the national immunisation programme by 2010

5.1 Pneumococcal vaccine

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5.1.1 Introduction

Streptococcus pneumoniae is a Gram-positive bacterium and a normal inhabitant of the human upper respiratory tract. The pneumococcus can be regarded as an opportunistic pathogen frequently causing mucosal infections such as sinusitis and otitis media. However, it can also cause invasive diseases such as meningitis, septicaemia and pneumonia, which usually are associated with bacteraemia. Morbidity and mortality are high and annually approximately 3 million people die worldwide of pneumococcal infections. About one third of these casualties are children under the age of five. The high mortality is not restricted to the developing countries. In the USA, pneumococcal disease kills more people annually than all other vaccine-preventable diseases combined.

Pathogenicity

S. pneumoniae is a bacterial pathogen that affects children and adults worldwide. It is a leading cause of illness in young children and causes illness and death among the elderly and persons who have certain underlying medical conditions. The organism that colonizes the upper respiratory tract can cause disseminated invasive infections, including bacteraemia and meningitis. More often, the pathogen causes pneumonia and other lower respiratory tract infections. Frequently occurring upper respiratory tract infections are otitis media and sinusitis. The susceptibility of infants and young children probably reflects the initial exposure of an immature immune system. In contrast, susceptibility of elderly people depends on several factors, which are not restricted to the immune system. The pneumococcus carries a wide variety of virulence factors that facilitate adherence and entry into the host. The polysaccharide capsule is the most important virulence factor of the pathogen. It protects the bacterium from phagocytosis by blocking the deposition of complement. Non-encapsulated pneumococci are non-virulent and antibodies against the capsule are protective. Remarkably, only a limited number of capsular serotypes account for disease in man. The reasons for this capsule type-dependent virulence are unknown, but have been suggested to be related to their capability to resist phagocytosis and ability to induce antibodies.[1,2]

Infectiveness and transmission route

Infection with pneumococci can be achieved through transmission of respiratory droplets from one individual to the other. In most cases, the pneumococcus will colonize the individual without apparent symptoms and disease will develop in only a small proportion of the infected persons. Carriage rates of 30% among young children are unusual.[3]

Antigenic variation

Currently, the pneumococcal vaccines are based on the capsular polysaccharides of the pneumococcus. There are at least 90 different serotypes and this poses a problem in designing multivalent vaccines. It has led to a selection of the polysaccharides of the most prevalent serotypes in the vaccines. However, there are marked differences in serotype distributions in the various geographic regions in the world and thus efficacy may differ from country to country. In addition, *S. pneumoniae* is a natural competent organism that is capable of horizontal transfer of genes, including those encoding the capsular polysaccharides.[4,5] Immune pressure due to vaccination with polysaccharides may lead to shifts in the distribution of the prevalent capsular types and is known as serotype replacement. These potential difficulties may require the development of new vaccines based on immunogenic pneumococcal proteins that are less variable and may provide a universal pneumococcal vaccine. The surface proteins PspA, PsaA, the cytolytic toxin pneumolysin (Ply) and neuraminidase are produced by all pneumococci and display only a limited polymorphism. Some of these proteins may be used in a vaccine to induce protective immunity.[6]

5.1.2 Vaccines available against pneumococcal disease

Availability

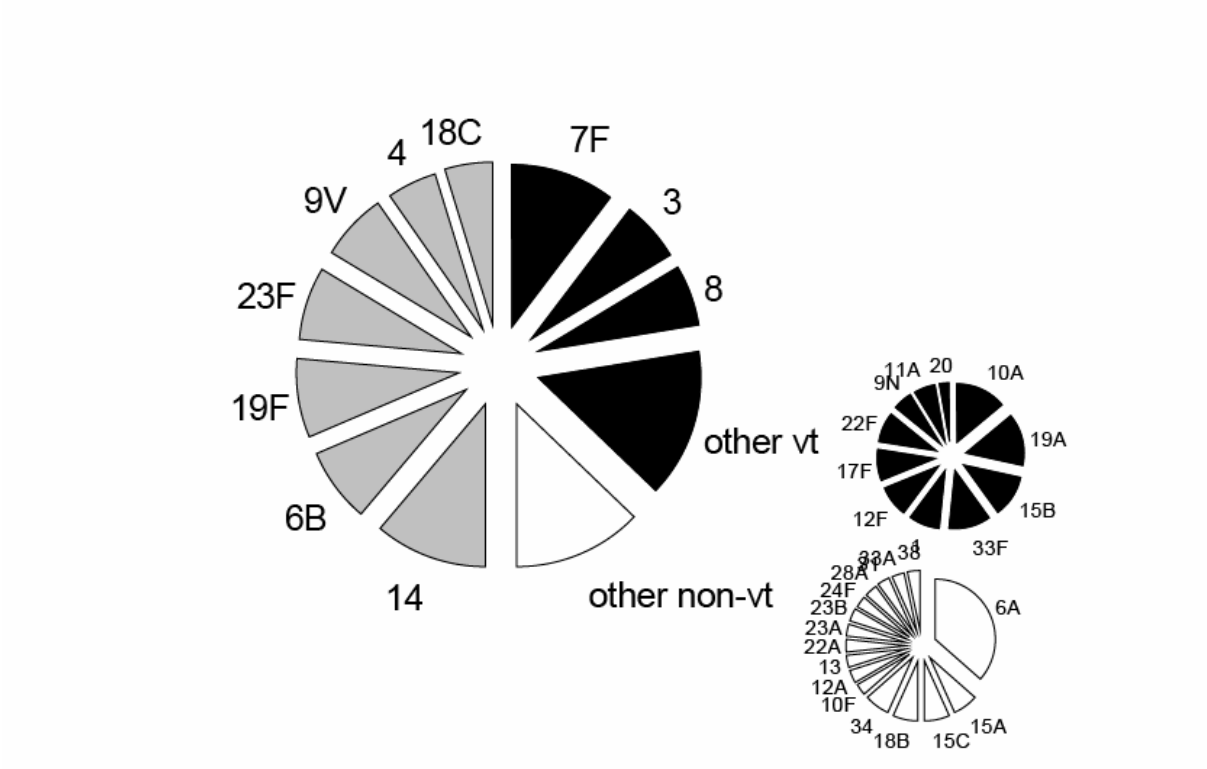
There are two types of vaccines licensed for prevention of pneumococcal infections. The first type of vaccine is composed of the purified capsular polysaccharide of 23 different pneumococcal serotypes covering the majority of the serotypes causing disease in adults. This vaccine, supplied by several companies, is poorly immunogenic in children under 2 years in age. It does not induce sufficient immunological memory, necessitating revaccination five years after the initial vaccination.

For protection of infants and young children currently, only single licensed pneumococcal conjugate vaccine is available. This vaccine, named Prevnar in the USA and Prevenar outside the USA, is manufactured by Wyeth and contains the capsular polysaccharides from serotype 4, 6B, 9V, 14, 18C, 19F and 23F coupled to CRM_{197}, a non-toxic variant of diphtheria toxin. The vaccine prevents invasive infection by the seven most prevalent serotypes, which are responsible for at least 60% of pneumococcal infections in infants and toddlers. Wyeth is developing a 9-valent vaccine adding serotypes 1 and 5 to the cocktail. GSK and Aventis Pasteur included serotypes 1, 3, 5 and 7 in their candidate 11-valent conjugate vaccines. The candidate vaccines are now being tested in clinical trials.

In the Netherlands, neither the 23-valent polysaccharide vaccine nor the 7-valent conjugate vaccine has been included in the NIP. However, the 23-valent polysaccharide vaccine is advised for individuals who are at substantially increased risk of pneumococcal infection. These include asplenic patients, people with low immunity and those suffering from Hodgkin's disease.

Effectiveness

The available pneumococcal vaccines would cover a large proportion of the serotypes that are causing meningitis in the Netherlands. Of all meningitis cases that occurred in 2003 in the Netherlands 50% is covered by the 7-valent Prevenar conjugate vaccine and more than 85% by the 23-valent polysaccharide vaccine (Figure 5-1).



The grey slices denote the serotypes that are covered by the 7-valent conjugate vaccine Prevenar and the 23-valent polysaccharide vaccine. The black slices indicate the serotypes covered by the 23-valent polysaccharide vaccine only. The white slice denotes serotypes not included in the vaccines. The smaller pie charts indicate the distribution of the serotypes represented as 'other' in the main pie chart (vt=vaccine types). Data were obtained from NRBM.

Figure 5-1: Pie diagram representing the distribution of pneumococcal serotypes of 236 strains isolated from cerebral spinal fluid in the Netherlands in 2003.

There is considerable controversy on the use of the pneumococcal vaccine for all individuals over 65 years of age. In a recent report the Dutch Health Council stated: 'On the basis of an assessment of the scientific evidence undertaken for the Health Council by the Dutch Cochrane Centre, the Committee has concluded that extension of the indication for pneumococcal vaccination is not scientifically justified under the present circumstances'.[7] The meta-analysis by the Dutch Cochrane Centre revealed that the efficacy in the various randomized clinical trials varied between 0 and 100%. The Centre concludes that the efficacy studies often had considerable flaws in methodology and the outcomes mostly had large reliability intervals hampering interpretation. In contrast, the CDC recommends to use the vaccine in all adults 65 years of age or older and in persons over 2 years in age belonging to risk groups.

An evaluation of the use of Prevenar in the Northern California Kaiser Permanente has shown that the conjugate vaccine yielded more than 87% reduction in invasive disease caused by the vaccine serotypes in children under 1 year of age.[8] The reduction was approximately 60% for children between 1 and 5 years of age. The impressive decrease in invasive pneumococcal disease demonstrates the high efficacy of the vaccine. In addition, the Kaiser Permanente study suggested strong herd immunity, providing protection to non-vaccinated children. Although Prevenar is effective in preventing invasive disease, pneumonia and acute otitis media caused by the vaccine types, it does not seem to prevent recurrent acute otitis media.[9] Although nasopharyngeal carriage of pneumococci of serotypes included in the conjugate-vaccine was greatly reduced after vaccination, immediate and

complete replacement by non-vaccine pneumococcal serotypes took place. Therefore, pneumococcal conjugate vaccination does not seem to be effective to prevent otitis media in children with a history of recurrent acute otitis media.

Adverse events

Adverse events following conjugated pneumococcal vaccines were usually mild and transient.[10]Local reactions were common, usually mild and self-limiting with a frequency of reported pain ranging from 20-56%. Swelling and induration were equal in vaccine recipients and controls. According to one study, the local reactions were less frequent in children younger than 2 year of age than in older children receiving conjugated Men C vaccine, but investigators had opposite results. Higher rates of systemic adverse events were found compared to participants receiving HepB control vaccine. However, in a later study all children also received DTP with whole cell pertussis component simultaneously, making interpretation difficult. The rates of crying and fever were higher in the vaccine recipients than in the control group. It is unclear how much of this is attributable to the study vaccine or to the concomitant administered vaccines. In a post-licensure study in which children were followed for a period of up to two months after vaccination only the risk of fever was increased within two days after immunisation.[10]The rates in which adverse effects occur depend very much on the vaccination schedule and the child's age at the time of vaccination. The use of single PneumC vaccines may be followed by collapse reaction, persistent screaming and other more severe adverse events. However, the incidence rates are unknown and this will have to be studied when the vaccine is used in large groups. It is not to be expected that the severity of adverse events will increase if PneumC vaccine is administered simultaneously with other infant vaccines. There are no strict contra-indications against Pneumococcal vaccination.

5.1.3 Epidemiology of pneumococcal disease

The number of cases of pneumococcal meningitis in the Netherlands can be determined through a clinical microbiology laboratory-based national surveillance of cerebrospinal fluid isolates. Because the laboratories send their isolates of patients to the NRBM on a voluntary base, the actual number of patients with pneumococcal meningitis is underestimated by approximately 20%. For the other disease manifestations, the available information is less reliable due to underreporting (septicaemia) and due to the absence of a specific reporting system (pneumonia and otitis media).

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 80 are in children aged 10 years and younger. In 1999 the highest age-specific incidence was observed in children <5 years of age (8.2/100,000), and a second peak occurred among people aged over 65 years (2.4/100,000).[11] Otitis media is by far the most frequent clinical form of disease among children. The Health Council estimated yearly 160 cases of septicaemia, 7,500 cases of pneumonia and around 200,000 cases of otitis media in the Netherlands in children aged 10 and younger.[12]

5.1.4 Burden of pneumococcal disease

Disability-adjusted life years (DALYs) lost due to pneumococcal disease are estimated to be 3417, of which 1273 will be preventable by vaccination of children (appendix III). These estimations are 2000 and 1280 DALYs for individuals of 65 years and above.

On average, 11% of patients with invasive disorders die from them. Pneumococcal meningitis causes a mortality rate of 15-20% and another 27% have sequelae such as mental retardation, epilepsy and spasticity.[11,12] The mortality rate for invasive pneumococcal disease without meningitis is around 6%.[12] Mortality rate increases to around 17% when symptoms of meningitis and septic shock occur.[13]

Care and costs

Data on hospitalisation in the Netherlands (Prismant; revised by VTV, RIVM) shows that the average number of in-hospital days for pneumococcal meningitis and septicaemia between 2000 and 2003 was about 16 days. This number differs by age. For patients from 0 to 4 years old the average length-of-stay is about 10 days, for patients over 65 years, this is about 20 days. Besides the costs of in-hospital days, pneumococcal meningitis and septicaemia are associated with minor direct medical costs such as GP visit, follow-up visits with specialist, diagnostic procedures etc. A detailed account of resource use is provided by Bos et al., and these estimates have been combined with recent unit costs.[13,14] In total, the direct medical costs for pneumococcal meningitis and septicaemia amount to €4.7 million per year, of which 14% is related to patients between 0-4 years, 3% to patients between 5-9 years, and 46% to patients over 65 years.

In addition to these direct medical costs, the costs for long-term care for neurological sequelae and hearing loss should be included. In their paper, Bos et al. presented cost estimates for these types of care, which have been adjusted by the price index.[15] The total costs amount to between €5 - 12 million, depending on assumptions made about long-term care for elderly patients.

Of the estimated 7,500 pneumonia cases, on average 2,050 per year are hospitalized (VTV, 2001-2003), with an average length of stay of 14 days. Combining this with the estimated resource use for pneumococcal pneumonia for patients who are not hospitalized as estimated by Bos et al., the total costs per year are approximately €11.6 million.

Using the information in Bos et al. about resource use for otitis media and using current unit costs, it is estimated that these costs amount to an additional €2.5 million. Thus, the total costs per year associated with pneumococcal disease amount to €23-40 million per year.

Work loss and school absenteeism

Little information is available about work loss and school absenteeism due to pneumococcal disease. On average, each year 20 cases of meningitis and septicaemia and 78 cases of pneumonia requiring hospitalisation occur in children between 5 and 20 years. In these cases, at least about 1 month of school will be missed.

In adults between 20 and 65 years, 133 cases of meningitis and septicaemia and 834 cases of pneumonia requiring hospitalisation occur. Here, at least 1 month of work will be lost. However, parents of children with pneumococcal disease will also miss work due to visits to GP and specialist, and for hospital visits. In the study by Bos et al., it was assumed that three days of work are missed when a child is hospitalized, versus 6 hours for patients with uncomplicated pneumonia and otitis media.

5.1.5 Cost-effectiveness of pneumococcal vaccination

The cost-effectiveness of vaccination against pneumococcal infections has been studied both for children and for people older than 65 years.[12,16] It has been estimated that vaccination of children with a 7-valent pneumococcal vaccine (assuming that the cost per vaccine dose is €40) leads to a cost-effectiveness ratio of €88,300 per QALY gained. When a lower vaccine price of €15.88 is assumed, the ratio decreases to €30,800 per QALY gained. In these estimates, indirect costs such as

productivity losses are not taken into account. Including these indirect costs will decrease the ratios. Note that the costs per dose of a 7-valent pneumococcal vaccine in a Canadian and Swiss study were estimated at €37 and €65, respectively.[17]
Including the herd immunity effect in the analysis, will probably result in more favourable estimates of cost-effectiveness, while considering serotype replacement will have the reverse effect. However, the total effect is unclear.[18]
In the economic evaluation of vaccination of people over 65 years, a cost-effectiveness ratio of €10,100 per life-year gained was found. This estimate was based on a vaccine price of €17. Increasing the age at which the vaccine is administered increases the cost-effectiveness ratio.
The NVI has re-calculated cost-effectiveness in 2003. In their calculations, they have included the effect of herd immunity, an observation made in a large USA study by Whitney et al..[18] The inclusion of this effect of herd immunity increased the acceptable costs per dose from €16 to €19. Furthermore, the NVI considered the possible effect of serotype replacement. Their conclusion was that serotype replacement does not play a role in invasive pneumococcal disease and thus will not influence the vaccine costs. This needs further study.

5.1.6 Alternative prevention and intervention measures for pneumococcal disease

With the exception of particular risk groups, pneumococcal vaccines are not yet used in the Netherlands. There are no alternative preventative measures available. Patients can be treated with antibiotics, but care should be taken to prevent the development of antibiotic resistance.

5.1.7 Considerations regarding uptake of pneumococcal vaccine in the NIP

Recently the Dutch Health Council decided not to alter their previous advice and thus decided against the pneumococcal vaccination in the elderly.[7] On the basis of an assessment of the scientific evidence undertaken for the Health Council by the Dutch Cochrane Centre, the Committee has concluded that extension of the indication for pneumococcal vaccination is not scientifically justified under the present circumstances. This decision was made because the various studies described in literature yielded conflicting results and that many of the studies described in literature had flaws in design. Although the scientific evidence currently available does not suggest that combined influenza and pneumococcal vaccination is advisable for over-sixty-fives, the Council wishes to see comparative research conducted to shed more light on this matter. This should urge Netherlands scientists to determine the effects of pneumococcal vaccination in the elderly in a carefully planned randomised clinical trial. The results of such a trial will provide the data to assess whether pneumococcal vaccination in the elderly will yield enough gain in health to justify introduction of the vaccine.
Although the Dutch Health Council has advised to include vaccination of infants with Prevenar in the NIP, this has not yet been implemented.[12] The Council has considered inclusion this vaccine based on two principles: its positive effect on public health and the possibility to fit the vaccine into the current immunisation program. The gain in public health by pneumococcal vaccination in newborn is obvious. Now that Hib vaccination is combined with DTP-IPV since 2003, there is space for an additional injection and therefore the second prerequisite has been fulfilled. The Council suggested implementing vaccination against group C meningococci and pneumococci when the combined Men C/pneumococcal vaccine would be available which they estimated to be in 2005. The minister of VWS has decided not to implement vaccination with pneumococcal vaccine of infants until the price

of the vaccine has become cost-effective or until a combined Men C/ pneumococcal vaccine becomes available.

5.1.8 International perspectives of pneumococcal vaccination

Despite the availability of the vaccine, there are only few countries that have implemented the pneumococcal vaccination for newborns in their NIP. Since 2000, it has been used routinely in the USA and it is now offered routinely in Canada and Austria as well. Similarly to the Netherlands, the high costs associated with vaccination with the conjugate vaccine have withheld most other countries from introduction in the national immunisation programmes.

Until now, only the USA has used pneumococcal vaccination in the elderly on a large scale. This was done in compliance with the recommendations of the Advisory Committee on Immunisation Practices (ACIP). Many researchers have questioned the validity of the 1997 recommendation to use the pneumococcal polysaccharide vaccine in all persons aged ≥65 years.

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5.2 Influenza

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5.2.1 Introduction

Influenza epidemics occur once a year during winter in temperate areas of the northern and southern hemisphere. During an epidemic, about 20% of children and 5% of adults develop symptomatic influenza A or B. It causes a broad range of illness, from asymptomatic infection through various respiratory syndromes, disorders affecting the lung, heart, brain, liver, kidneys and muscles, to fulminant primary viral and secondary bacterial pneumonia.
Influenza viruses are variable with respect to their pathogenicity. For instance, influenza seasons in which influenza A (H3N2) predominates are associated with higher mortality than influenza A H1N1 seasons. [1,2] Bacterial superinfections are the most important complications of influenza, with Staphylococcus aureus causing the highest morbidity and mortality.[2]

Infectiveness and transmission route

Most influenza virus infections are spread by virus-laden respiratory droplets. The incubation period of influenza ranges from 1 to 7 days, but is commonly 2-3 days. In adults the duration of virus shedding after onset of illness is usually 3 to 5 days. In children virus shedding at high titres is generally more prolonged and virus can be recovered from up to 6 days before to 21 days after the onset of symptoms. [2]

Antigenic variation

Influenza viruses show great antigenic diversity. Influenza A viruses are classified into subtypes based on their antigenic differences between two surface proteins, hemagglutinin (15 subtypes) en neuraminidase (9 subtypes). Three hemagglutinin subtypes (H1, H2, H3) and two neuraminidase subtypes (N1 en N2) have established stable lineages in humans. The two surface proteins amongst others determine influenza virus epidemiology. During antigenic drift, strains of virus evolve by accumulation of point mutations in the surface proteins. Humans can still be partly protected against the drifted strain by existing antibodies against the predecessor of the drifted virus and T-cell immunity to non-structural proteins. T-cell immunity is only seen with natural infection or live vaccines. Antigenic shift occurs with the emergence of a new virus containing a new hemagglutinin alone or a new combination of hemagglutinin and neuraminidase. This new virus is antigenically distinct from earlier human viruses and earlier human immunity gives limited (due to T-cell cross-reactive immunity) or no protection (due to absence of humoral protection) against infection. [3]

5.2.2 Vaccines against influenza

Availability

The influenza vaccines currently used are predominantly inactivated influenza vaccines, produced from virus grown in embryonated hens' eggs. They consist of whole virus, detergent-treated split product or purified hemagglutinin and neuraminidase surface antigen formulations of three strains according to recent WHO recommendations. All split inactivated influenza vaccines are approved for persons aged ≥6 months, except for persons with hypersensitivity to egg protein or other vaccine

compounds. In children, dosage recommendations for inactivated influenza vaccine vary according to age group. In children aged <6 years, two doses (0.5 ml) of vaccine are recommended with an interval of at least 4 weeks. Among adults, a second dose administered during the same season caused limited or no improvement in antibody response.[4] [3,5]Cell-culture vaccines avoid the risk of contaminated eggs, take a shorter time to produce vaccine and the vaccine-virus more closely resembles viruses present in clinical samples than egg-grown viruses. Cell-culture vaccines have been licensed in the Netherlands, but are not yet commercially available.

Live attenuated influenza vaccines (LAIV), which consists of viruses with genes for hemagglutinin and neuraminidase antigens of the current wild-type virus and genes of an attenuated influenza virus, mimic a natural infection because of intranasal delivery and due to the natural replication process of the vaccine-strain after administration. The 'cold adapted'-characteristic of this vaccine provides a good replication at temperatures found in the nasopharynx, but not at temperatures found in the lower airways. The advantage of this vaccine is that it triggers a broader immune response and a more durable protection. In addition, it is easy to apply in children. LAIV was approved by the USA FDA for use in healthy persons aged 5-49 years.[3,4] Persons with chronic pulmonary and cardiovascular disorders, metabolic or immunodeficiency diseases, history of Guillain Barré syndrome, hypersensitivity to eggs, pregnant women and health care workers caring for severely immunosuppressed patients should abstain from LAIV. [6]

In the Netherlands, the following vaccines were registered for the season 2003/2004: Influvac (RVG 22289, split virus vaccine), Vaxigrip (RVG 22306 en RVG 23880, split virus vaccine).

Because of the antigenic drift of the influenza viruses, every influenza vaccine needs to fulfil the season-specific recommendations of the WHO and the European Union with respect to their virus-content. Therefore, influenza vaccines are registered per year and annual vaccination is required.[6]

Effectiveness

The antigenic match between the vaccine strain and the circulating strain, but also the age and immunocompetence of the vaccine recipient determines the efficacy and effectiveness of the annual vaccine. With respect to effectiveness, many cohort and case-control studies have shown lower rates in vaccinees than in controls regarding hospital admissions for pneumonia and influenza (low risk status: 40-49%; intermediate risk status: 32%; high risk status 30%, elderly: 20-79%), all respiratory disorders in the elderly (17-32%), all respiratory admissions and heart failure in the elderly (20%), pneumonia and influenza deaths (high risk status 33%; elderly: 54-64%) and all cause mortality in the elderly (39-75%).[3] Results on vaccine-efficacy are summarized in table 5-1[3].

Table 5-1: Efficacy of inactivated influenza vaccine in various populations.

Population	Vaccine/dose	Study	Outcome	Efficacy (%;95% CI)
Children	Split product + surface antigen, 15 µg	Random-effects meta-analysis of RCTs	Symptomatic lab-confirmed influenza	80 (74-90)
Adults working age	Split product, 15 µg	Random-effects meta-analysis of RCTs	Symptomatic lab-confirmed influenza; lab-confirmed influenza	77 (66-85)
Community-dwelling elderly	Surface antigen, 15 µg	RCT	Lab-confirmed influenza	52 (29-67)
Elderly people in welfare nursing homes	Split product, 15 µg	Prospective cohort study	Symptomatic lab-confirmed influenza	60 (CI absent)

RCT = randomised control trial

Adverse events

Local reactions following Influenza-vaccinations are usually mild and of short duration and do rarely prohibit daily activities.[7-12] Percentages reported are up to 65% and vary depending on case-definitions and level of case-ascertainment, but also on age en vaccination schedule. Systemic events as fever, muscle ache, arthralgia and headache vary also and occur in up to 15% of the vaccinees, most frequently in the younger children without prior doses.[13]Severe local or systemic reactions appear to be rare.[14] Other severe adverse events following immunisation with the Influenza-vaccines could not be ascribed to the vaccine. There is no increased risk of asthma attacks in children and adults.[15] Re-analysis made the previously reported increased risk of Guillain Barré syndrome that seemed to be associated with a particular influenza campaign in 1976 (swine fever) less certain and estimations are now less than one additional/extra case per 100,000-1,000,000 vaccinations.[16-19]

Vaccination rate

In the Netherlands, according to the National Programme Flu Prevention (Nationaal Programma Grieppreventie (NPG)) target groups for influenza vaccination are persons with chronic cardiovascular- and pulmonary-disorders, renal dysfunction, diabetes mellitus, persons with furunculosis and their close contacts, immunologic compromised persons, children and teenagers in the age of 6 months to 18 years who use long-term-aspirin therapy, institutionalized mentally retarded and healthy persons older than 65 years of age. The total vaccination-population includes 3.8 million people. Since 1997, the vaccination-rate has stabilized at 75%, although the population vaccinated is still increasing. The lowest vaccination rate was found in high-risk children, aged 6 months to 18 years (55%), and the highest in adults aged ≥65 years with high-risk diseases.[20]

Costs of vaccine and immunisation programme

The total vaccination-costs have increased because of the annual increase in the number of vaccinations. The total vaccination-costs in 2003 were €34,629,817 for 2,885,369 vaccinations. The costs per vaccination were €12,00 (the restitution to general practitioners included).(S. vd Plas, personal communication CVZ)

5.2.3 Epidemiology of influenza in the Netherlands

During the ARI-EL study, a case control study on the incidence, aetiology, burden of disease and risk-factors of acute respiratory infections (ARI) conducted from October 2000 to October 2003, the estimated number of consultations for influenza-like illnesses (ILI) in general practices (incidence) was 12 per 10000 persons per year. During these years, the highest incidence was found in children aged 0-4 years (figure 5-2). In the past twenty years the mean incidence was 30 consultations per 10000 persons.[21] The incidence is probably underestimated since parts of the population will not consult their GP because of influenza.

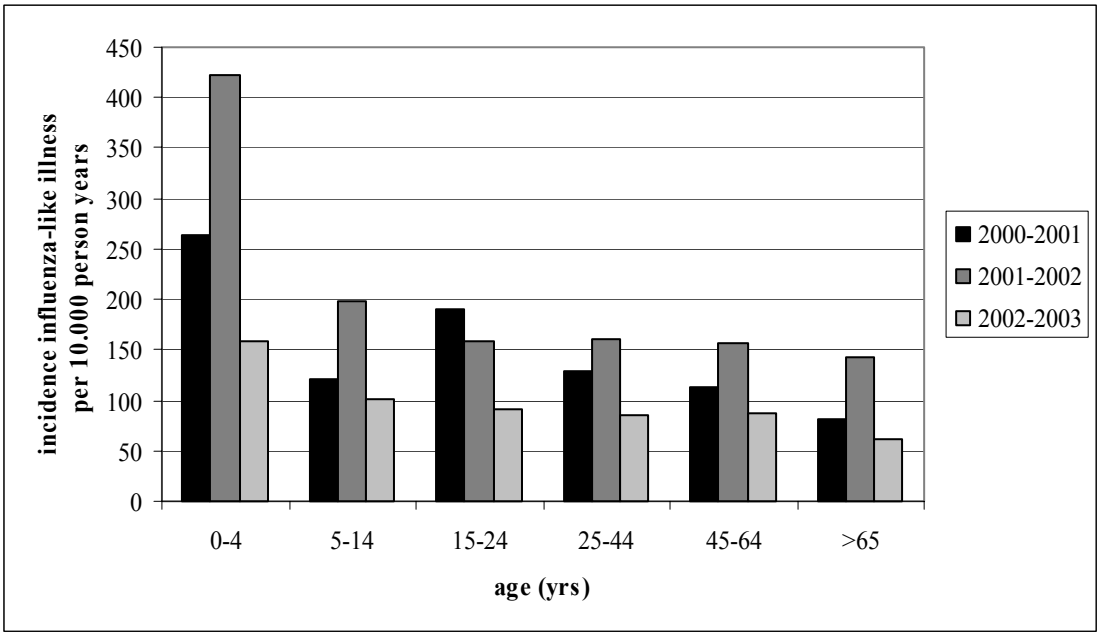

Figure 5-2: Incidence of influenza-like-illnesses per age group in the season 2000-2003.

Source: ARI-EL study.

5.2.4 Burden of influenza

Disability-adjusted life years (DALYs) lost due to influenza are estimated to be 13,934, of which 5,946 will be preventable by universal vaccination with a 60% effective vaccine (Appendix III).
In the Netherlands, it has been estimated that influenza accounts for 3,713 hospitalisation days per 100,000 and 744 hospitalisation days per 100,000 for high risk and low risk elderly, respectively. Additionally 2,000 excess deaths occur during influenza epidemics.[22,23] Unless there are complications, influenza virus infection does not result in long-term effects.

Care and costs

The most important types of resource use for influenza are general practice consultations and hospital days. In a Dutch study, it was estimated that on average 390,000 GP consultations take place per year, of which 118,500 in patients younger than 20 and 40,500 in patients over 65 years. The total costs for GP consultations amounts to €8 million.

For hospital admission, it was estimated that 1915 patients are admitted per year (including excess admissions for complications), of which 1500 patients are over 65 years.[24] The average length of stay for influenza varies by age: for patients under 20, the average is 5.4 days, for patients between 20 and 65, this is 6.4 days, and for patients over 65, the average is 15 days.[25]Assuming that these length-of-

stay estimates for influenza as primary diagnosis are also a valid proxy for the excess admissions for complications of influenza, the total number of admission days per year is estimated at 25200. The total costs for hospitalisation amount to €9 million per year.

Work loss and school absenteeism

At the micro-level, the ARI-EL case-control study, restrictions in daily activities due to airway complaints were reported for 114 ILI-cases (90%) and 213 other ARI-cases (78%). For 70% of these cases (ILI 65% and ARI 76%) these restrictions lasted one week at most, and for 95% (ILI 94% and ARI 96%) two weeks at most. Restrictions were evenly distributed over all age groups, though the duration was somewhat higher in the higher age groups. Bed rest was required for 107 ILI-cases (84%) and 163 ARI-cases (59%) for a median of respectively 5 and 3 days. Absence from school or work was reported for 92 ILI-cases (72%) and 154 ARI-cases (56%). The majority (69%) of these ILI-cases was absent for one week at most, as compared with 83% of the ARI-cases. For the concerning disease period, one contact to the GP was sufficient for more then 60% of both the ARI- and ILI-cases. [21]

At the macro-level, it has been estimated that yearly at least 1,4 million days of work are lost due to influenza, with an upper limit of 5.7 million days of work.[26] Based on an average working week of 30 hours [27], and an elasticity of 0.8 (indicating that 1 hour loss of work does not equal 1 hour loss of productivity), 1 day of work equals 5 hours of productivity loss.[28] At €34 per hour, the total costs of productivity loss due to influenza per year amount to €233-930 million.

5.2.5 Cost-effectiveness of influenza vaccination

The influenza vaccination in the Netherlands prevents on average 53% of all influenza related mortality and 48% of all influenza-associated hospitalisations. The effectiveness of vaccination was comparable in three adult risk groups, i.e. high risk adults aged 18-64 years, low risk elderly aged >65 years, high risk elderly >65 years. In these risk groups the incremental medical costs per life year saved were -€786 (range -2753 tot 2589), -€592 (range -1462 tot 852), and -€1427 (-2290 tot 548), respectively. Even allowing the uncertainty in these estimates, these ratios are very likely to be below the cost-effectiveness limit of €20.000. Possibly, vaccination in these risk groups is even cost-savingThe NPG is therefore cost-effective, and is even most likely cost saving for the adult groups who generally show a high burden of disease. In high-risk children (aged 6 months to18 years), the influenza vaccination prevented in a normal influenza season (1999/2000) on average 41% of the GP consultations. In the following mild flu season (2000/2001), vaccinating this risk group was not effective. In this high risk group, the medical costs per prevented GP consultation were €2,574 and with a probability of almost 98% above €1,500 per prevented consultation, which did not appear cost-effective. [20]

5.2.6 Alternative prevention and intervention measures for influenza

Antiviral drugs for influenza are an adjunct to influenza vaccine for controlling and preventing influenza in patients at risk or in case of a vaccine-mismatch for controlling influenza, in a broader population. Amantadine and Rimantadine can be used to prevent influenza A cases (not influenza B cases) while permitting subclinical infection and development of protective antibodies against influenza. The preventive efficacy of oral Amantadine compared to placebo in individuals aged 14-60 years is 61% (CI 95% 49-79%) and of oral Rimantadine: 64% (CI95% 41-78%). Disadvantages are central nervous system (CNS) (especially with Amantadine) and gastro-intestinal side effects and

drug-resistant viruses can appear in approximately one third of patients when either Amantadine or Rimantadine is used.[3,20] Oseltamivir and Zanamivir are active against influenza A and B. Zanamivir was registered in the Netherlands in May 2001 for therapeutic use (persons aged ≥12 years). In the European Union Oseltamivir has been registered in June 2001 for prophylactic (persons aged ≥13 years) and therapeutic use (persons aged ≥1 year). Compared to placebo these neuraminidase inhibitors were 74% (CI95% 50-87%) effective in preventing clinically defined influenza cases [29] Zanamivir is not recommended for patients with underlying airways disease because of deterioration of the respiratory function due to Zanamivir. Nausea and vomiting are side effects of both Zanamivir and Oseltamivir.[6] Development of viral resistance to Zanamivir and Oseltamivir has been identified, but does not appear to be frequent: 4% in children and 0.4% in adults. [30] In a recent study in Japan among children, 18% resistance was found.[31,32] Although transmission of neuraminidase inhibitor resistant virus in humans has not been reported, a recent study indicated that certain types of resistant strains can be transmitted in the ferret model for influenza.[33]

5.2.7 Considerations regarding uptake of influenza vaccine in the NIP

Elderly

The NPG could be extended by lowering the age-limit for the vaccination of healthy adults from 65 to 50 years of age, which would double the target group. In that case, the NPG will still be cost-effective. The incremental cost-effectiveness ratio was estimated at €1600 per life year saved, with again almost 100% certainty that this ratio will be below the limit of €20,000.[20] The CDC recommends the vaccination of persons aged 50-64 years, as this group has an increased prevalence of persons with high-risk conditions.[34] Persons without high-risk conditions in this group benefit from the vaccination due to decreased influenza rates, decreased work absenteeism and decreased need for medical visits and medication.[5,35,36]

Health care workers and household contacts of persons in high-risk groups

The CDC also recommends vaccination of persons who can transmit influenza to those at risk, like health care workers and household contacts of persons in high-risk groups. Vaccination of health care workers is associated with decreased deaths among nursing home patients.[37,38]Unfortunately, low vaccination rates among health care workers in the Netherlands (5-8%) and in other countries (around 40%) have been reported.[39-41]The NVVA (Netherlands association for nursing home physicians) recommends vaccination of health care workers in nursing homes against influenza.[39]

Children

Like in most other countries healthy young children are not a target group within the NPG.[42] Community studies pointed out however those school-aged children have highest rate of influenza infection, ranging between 15% (pre-school children) and 42% (school-aged children).[43] When the effects of influenza viruses and the respiratory syncytial viruses on hospitalisation rates are separated, otherwise healthy children <2 years and possibly children aged 2-4 years are at increased risk for influenza-related hospitalisation compared with older healthy children (<2 years:144-187 hospitalisations/100,000; 2-4 years: 0-25 hospitalisations /100,000; >4 years: 8-12 hospitalisations /100,000 persons without high-risk conditions).[44]Influenza-associated hospitalisation rates of children aged 6 months to <3 years were comparable with or higher than rates among children aged 3-14 years with high risk conditions (6 months to <3 years: 496/100,000 without high-risk conditions; <3-14 years: 92-320/100,000 with high-risk conditions).[45,46] Moreover, young children seem to be at a

higher risk of hospitalisation for influenza than are healthy 50-64 years old adults, for whom routine immunisation has been recommended.[43]

Among healthy children, the protective efficacy of trivalent inactivated influenza vaccine against culture proven influenza ranges from 30-95%, the highest value being reached when the vaccine-strains match the predominant circulating strains.[47,48] Furthermore, inactivated influenza vaccine has been reported to decrease the incidence of acute otitis media with one-third in children attending day-care centers.[49,50] The efficacy of two doses cold-adapted influenza vaccine against culture confirmed influenza was 96%, while the overall decrease in all episodes of otitis media among vaccine recipients during the influenza season was 8.7% and the decrease in all episodes of febrile otitis media was 30.1%.[48,51]

Vaccination of healthy children may also have a protective effect due to vaccine-induced herd immunity. In Canada, the vaccination of 85% of schoolchildren within one community led to a two-third lower incidence of influenza-like illness among adults compared to a community in which schoolchildren were not vaccinated. [52] In Japan, during the decades of the influenza immunisation programme for school aged children, community mortality due to pneumonia and influenza decreased by 10,000 to 12,000 per year and all cause mortality declined by 37,000 to 40,000 per year. [32] Finally, an Italian study reported that family members of influenza-vaccinated healthy children experienced significantly fewer respiratory tract infections, needed significantly fewer medical visits and missed significantly fewer working days than family members of unvaccinated children.[53]

Finally, a third aim could be fulfilled when implementing an influenza immunisation programme for healthy children: increasing our preparedness for a possible pandemic. In a normal epidemic, the highest attack rates are observed in the age group of 0-19 years, according to registration of influenza-like illnesses.[24] Although we cannot foresee how the age-specific attack rates during a pandemic will evolve, a well-organised immunisation programme for this mobile age group could be of use when the pandemic arrives.

For the universal immunisation programme, regular vaccines could be used. A disadvantage of these vaccines is that these need to be administered annually. It should be explored if annual influenza vaccination for children could be included in the general NIP for children. This programme has the capacity to follow birth cohorts in the first life years and at some points later in life, but the annual vaccination of children against influenza would lead to a major expansion of the programme. In the far future, influenza vaccines establishing heterosubtypic immunity may be available. By means of these vaccines a cytotoxic T-cell response and antibody response will be induced (in contrast to the present vaccines which only induce antibody response), which enables cross-protection to drift variants and to influenza virus strains of various subtypes.[54,55] Consequently annual influenza vaccination could potentially be replaced by a vaccination scheme with larger intervals.

Several published reports have assessed the economic implications of influenza vaccination in healthy children. Whether a universal programme leads to net cost or net savings depends on factors like attack rate, the rate of GP visits, hospitalisations and deaths and the costs of the vaccination itself. In addition, indirect costs like caregivers' working time lost when children need to be immunized play an important part.[56,57] It has been suggested that a universal influenza immunisation of young children may generate savings from a societal perspective if the vaccine is administered in a group-based setting or in a setting with flexible hours and if the total costs of immunisation are less than $30.- per child immunized. [43,53] Studies are needed to explore the cost-effectiveness of such a universal programme in the Netherlands.

Next to the cost-effectiveness of influenza vaccination of healthy children, we should also determine if this expansion of the NIP is feasible regarding the increased number of vaccines that will be needed. Ninety-five percent of the influenza vaccines delivered worldwide is manufactured by nine

countries. Moreover, for critical products the vaccine supply chain often relies on only one or two manufacturers. This makes influenza vaccine production vulnerable and shortages could occur. [58] An exploration of the possibilities of consistent influenza vaccine delivery, before the NIP is expanded would therefore be useful.

5.2.8 International perspectives of influenza vaccination

Worldwide, few countries included influenza vaccination of healthy children in their immunisation program. Since March 2003, the influenza vaccine coverage under the Vaccines For Children programme (VFC) in the USA was expanded to include all VFC eligible children aged 6-23 months and all VFC eligible children aged 2-18 years who are household contacts of children aged 0-23 months. In addition, the Russian immunisation programme included the vaccination of schoolchildren, while in 2000 the Canadian province of Ontario recommended the vaccination above 6 months of age.[42]

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5.3 Hepatitis A

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5.3.1 Introduction

Hepatitis A virus (HAV) is one of the viral causes of hepatitis. Most infections at young age are self-limiting and asymptomatic. In adults, however the infection is more serious with symptoms like jaundice, fever, malaise, lack of appetite, anorexia, dark urine, nausea and abdominal complaints. Complications of disease are prolonged cholestatic hepatitis with serious itching and relapsing hepatitis, occurring in about 10-15% of cases. [1,2] In developed countries there are certain risk groups for HAV, like homosexual men, injecting drug users and migrants from endemic countries.[3-7]

Infectiveness and transmission

The majority of HAV infections is transmitted faecal-orally. The virus enters through the oral cavity into the intestinal tract. Subsequently, multiplication takes place in the liver. Via the bile ducts, the virus is shed into the lumen of the intestinal tract and leaves the body with faeces. The average incubation period is 28 days (range: 2-7 weeks) and period of infectiveness starts 3 to 10 days before symptoms occur and ends 8 days after start of symptoms. Symptoms of hepatitis are mostly caused by immunologic mechanisms like deposits of immunocomplexes and decreased serum complement. HAV infection is more serious in patients with chronic active hepatitis B, hepatitis C or HIV infection. Chronic HAV infections have never been reported.[1]

Antigenic variation

HAV, a 7.5 kb single stranded RNA virus, is the prototype of the genus Hepatovirus and belongs to the family of Picornaviridae. All HAV variants belong to a single serotype, against which the HAV vaccine protects. Sequencing of the putative VP1/2A junction of the virus genome is used to differentiate HAV into seven genotypes, which differ in at least 15% of nucleotides. Genotypes I, II, III and VII have been detected in humans, the others are only found in old-world Monkeys. Matches in the VP1/2a nucleotide sequence can be used for contact tracing.[8]

5.3.2 Vaccines against hepatitis A

Availability

Different formaldehyde-inactivated HAV vaccines exist: Havrix (Glaxo SmithKline), Avaxim (Pasteur Mérieux MSD), and Epaxal (Berna Biotech Ltd).[2] A combination vaccine for hepatitis A and B is also available: Twinrix (combination of Havrix and Engerix).[8] The different commercially available vaccines are all adjuvated with aluminium hydroxide and all contain phenoxyethanol as preservative. (Havrix, VaqtA, Avaxim). The exception is Epaxal that has a narrower indication and contains liposome (reconstituted influenza virosomes) as adjuvant and no preservative.

In the Netherlands, Havrix (including Twinrix) and Avaxim are registered. The vaccine is given in two doses; the second dose is administered after 6-12 months. With Twinrix a third dose is given after one year.[1] The effect of Avaxim in children is not well examined, so Avaxim is not recommended for children.[1,9] In general, HAV vaccination is not administered to children below 12 months of age.[9] The costs per dose of Avaxim and Havrix are €30.61. One dose of Havrix Junior (for ages 1-15) costs €20.41 and one dose of Twinrix costs €33.39.[10]

Effectivity

In a study on seroprotection (100mlU/ml anti-HAV) following vaccination with Havrix, after two months all participants had antibodies against HAV. However, the geometric mean titres were 3-5 times lower than after natural infection.[11] In clinical studies for immunogenicity in 656 children aged 12 months to 15 years (inclusive), seroconversion rates, 2 weeks following vaccination, range from 95.4% to 99.1% depending on the study. One hundred percent of those tested at 24 and 28 weeks post-vaccination had protective antibody levels.[12, 13] In children with chronic hepatitis C, chronic hepatitis B and healthy children, 100% seroprotection was found after two injections with Havrix.[14] In addition, detectable levels of anti-HAV antibodies are not an absolute requirement for protective immunity, as underlying immune memory provides protection beyond the duration of anti-HAV antibodies.[15,16] Consequently, the International Consensus group on hepatitis A virus immunity concluded that there is no evidence to support to HAV booster vaccination after a full primary vaccination course in healthy individuals. [17] However, they consider further investigation necessary before deciding if boosters can be omitted in special patient-groups, such as individuals with chronic liver disease, HIV or clotting-factor disorders. The inactivated HAV vaccine provides protection for at least 10 years (after the second dose).[1]

Current indications for HAV vaccine in the Netherlands

Indications for HAV vaccine are based on pre-exposition prophylaxis, risk factors and post-exposition prophylaxis. Pre-exposition prophylaxis is given in case of travelling to high endemic countries and in case of occupational risk. Risk factors are persons with chronic hepatitis. Post-exposition prophylaxis is given in case of an explosion of hepatitis A in a (closed) community. HAV vaccine is only effective if it is given 8 days after the first day of clinical disease of the index-patient. Otherwise, immunoglobulines (passive immunisation) are given. If a choice is to be made for active or passive immunisation, the role of transmission of prion proteins for Creutzfeld Jacob Disease (CJD) by immunoglobulines is taken into account. In elderly people, the impact of CJD is less than among children. Therefore, children are mostly given HAV vaccine, even because the course of disease is not very serious among children.[1]

Adverse events following HAV vaccine

The local reactions of the HepA vaccines are usually mild and of limited duration.[18] About 20% of children experience some local reaction (redness, swelling and or tenderness) and up to 60% of adults, depending on used case definitions. Other systemic events are fever, fatigue, diarrhea and vomiting, occurring in less than 5%, age dependent. Headache is reported in 16% of adults and in less than 10% of children.

More severe local or systemic adverse reactions are rare and age dependent like collapse, febrile convulsion etceteras. Up until now, no severe adverse events have been definitively linked to the HepA vaccine; rates appeared to be not above the background incidence rates.

There are no severe contraindicating anaphylactic reactions reported since the introduction of hepA vaccine on the market. There are virtually no contra-indications for the use of HepA vaccine. The vaccine may be given to infants. The schedule is two doses except for Twinrix or Ambirix, combined HepA-HepB vaccine, for which three doses should be given. HepA vaccine administered simultaneously with other (childhood) vaccinations does not seem to increase severity and rates of adverse events. No negative effects on immunogenicity of other vaccines have become apparent.

5.3.3 Epidemiology of hepatitis A

To obtain insight into the epidemiology of hepatitis A in the Netherlands the following information was used: analysis of compulsory reports of the Inspection of Public Health (IGZ), use of a population-based cross-sectional serum bank, a study of HAV antibodies in high risk groups such as children from Turkey or Morocco in the larger cities in the Netherlands and studies of outbreaks.[4-6,19-24]

In the nineties of the previous century, the incidence was 5-7/100,000 person years in the Netherlands (see figure 5-3).[24,25]

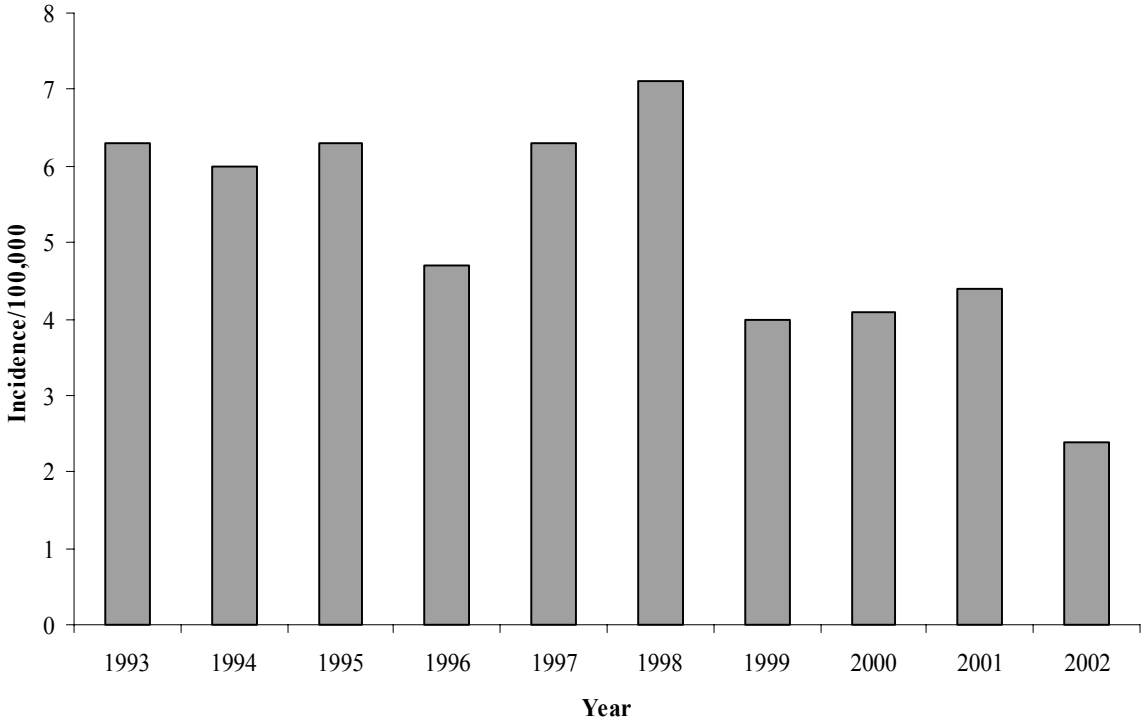

Figure 5-3: Incidence per 100,000 inhabitants of hepatitis A in the Netherlands[24]

Annually, 600-1200 cases were found of which 60% was younger than 20 years. However, since 1999 the incidence has decreased to 2.4/100,000 person years in 2002.[24] The number of cases in 2002-2003 was about 400 per year. The decrease in the incidence was mainly limited to endemic infections, while the number of infections acquired in Turkey and Morocco, the two most common foreign countries of infection, hardly changed. Consequently, since 1999, 39% to 51% of notified cases has been infected abroad.[24] Because of the decreasing incidence, the force of infection in the community has declined as well, leading to an increase in the mean age of infection. In the study of van der Eerden et al., an increase in mean age of infection was seen. For women mean age increased from 16.5 in 1993 to 23.0 in 2002, for men it increased from 16.3 to 25.4.[24] Because infections at higher age are more severe, this tendency poses a threat to public health. Of reported epidemics in one region in the Netherlands, 80% started at schools.[1] Of the 165 HAV clusters notified nationally since 1999 with information on location of infection, for 73% school was reported as the site of infection. Risk groups are children of immigrants, mainly Turkish and Moroccan children, young school children, children and workers on crèches, men having sex with men, travellers to endemic countries,

household contacts of cases, staff and inhabitants of institutions for mentally retarded individuals, sewage workers, individuals with chronic liver disease and immunocompromised individuals, including those with blood-clotting disorders and HIV.[4-7,19,21-23] Outbreaks in the Netherlands occur mainly in schools, within households and among homosexual men. Although internationally intravenous drug users are a risk group, infections in this group are hardly notified in our country.
In a Netherlands nation-wide sample, the prevalence of anti-HAV antibodies was determined. Seroprevalence was less than 10% in individuals under 35 years. It increased from 25% at 35 years to 85% at 79 years. Seroprevalence was higher among Turkish (91%) and Moroccan (96%) individuals. Low or middle- economic status was associated with a higher prevalence.[3]

5.3.4 Current burden of hepatitis A

According to the Central Bureau of Statistics from 1996-2003, 1 to 3 persons died of acute hepatitis A annually.[26] In general, the resource use in case of hepatitis A is limited. In most cases, a GP visit and blood tests will suffice. The average number of reported cases per year in 2000-2002 was 584, of which 287 in children younger than 15 years. On the one hand, it is reasonable to assume underreporting of cases, on the other hand, some of the cases, especially in children, will be asymptomatic. Assuming that these two effects cancel each other out, we estimate 584 GP visits at €20 per visit with blood tests of approximately €20 in each case.[27] This leads to estimate costs of approximately €23,500 per year.
For some patients, hospitalisation is required. Based on the Hospital Registry, we find that in 2000-2003, 206 patients were admitted for 1515 days for hepatitis A, with an additional 87 admissions and 822 days for unknown type of hepatitis. Using a price per in-hospital day of €359, the estimated costs for hospitalisation will be between €544,000 and €840,000 per year. Thus, the total direct medical costs associated with hepatitis A amount to approximately €567,500 to €863,500 per year. However, the costs of dealing with an outbreak should also be considered. An exploratory study in the Netherlands about the costs of hepatitis A vaccination suggested that there are approximately 15 outbreaks (2 or more related cases) per year. The costs of these outbreaks were estimated at (converted to 2004 prices) approximately €5000. These costs include the costs of 'contact tracing' and vaccination of people who have been in contact with the index patient. This would lead to an estimate of €75,000 per year for dealing with outbreaks.
It should be noted that the total number of outbreaks between 2000 and 2003 is much higher with 214 outbreaks.[24,27] The discrepancy may be caused by two factors. First, the definition of outbreaks in the latter study indicates that these were defined later, based on the registration database, and maybe not all of them lead to containment actions. Second, in the exploratory study, maybe only outbreaks that started among children were included. Thus, it appears as if the estimated €75,000 is a conservative estimate of the total yearly costs.
Several estimates of days work loss can be found in the literature. For instance, in a study in the USA by Jacobs et al., a total of 19 days was assumed. This study also assumed a duration of symptoms of 43 days. Another publication suggested that people who become ill lose an average of 27 days of work in the USA.[2,28] For the Netherlands, for the period 1991-1993 data from a national registry are available. In this period on average 50822 days of work per year were lost due to hepatitis. However, this number also includes patients with hepatitis B, and it is unclear which part is attributable to hepatitis A. A conservative estimate might be that 25% of days work lost is attributable to hepatitis A, which is 12,700 days. However, if we use the number of cases 2000-2002 of patients 15 years and older, 297, and multiply this by 19 days, we arrive at 5,650 days work lost. Using a value of €163 per day work lost we find that costs due to work loss will be between €5.5 million and €24 million.[27]

The total disability-adjusted life years (DALY) associated with hepatitis A annually was small and was estimated at 77, of which 70 could be prevented with a vaccine efficacy of 90%. The DALYs were almost exclusively caused by the small number of deaths (Appendix III).

5.3.5 Cost-effectiveness of hepatitis A vaccination

An exploratory study in the Netherlands in 2000 found that cumulated over six years, the costs of vaccinating Turkish and Moroccan children were lower than the current direct and indirect costs for HAV cases, in case of a vaccine price of €27. - (including second dose) and a vaccine coverage of 75%, assuming that 50% of workdays lost due to hepatitis could be attributed to hepatitis A. However, there were many uncertainties in this study.[29] Another study in this population used data from Amsterdam to estimate the costs and effects of hepatitis A vaccination. Based on a vaccine price of €16 per dose, they estimated that the total costs per adult HAV infection averted would be €13,500 compared to no vaccination at all, and €11,100 compared to the current situation of limited vaccination. These results are most sensitive to changes in the vaccine price.[30]
In Rotterdam, a study on cost-effectiveness of screening on HAV antibodies before vaccination in people either born before 1950 or having lived in an endemic country for more than 10 years or having had jaundice, showed that the screening policy was cost-saving for this population.[31]

5.3.6 Alternative options for prevention of hepatitis A

Contact tracing and immunisation (passive or active) is indicated for contacts of hepatitis A cases in the household, in schools, day-care centres, and institutions for mentally handicapped.[1] Additionally, infected children and workers (especially those working in health care, food industry or catering) should be kept away from nurseries, schools and work.[1].
Furthermore, hygiene practices are important in transmission of HAV. In general, it is important to wash hands with soap after visiting the toilet. In addition, travellers to endemic countries should abandon uncooked water, fruit juices and unwashed fruit and food.
Safe sex is important for prevention of infection, especially in oral-anal sex.[1]

5.3.7 Considerations regarding uptake of hepatitis A vaccine in NIP

Considering the still decreasing incidence, the small number of DALYs, the occurrence of the infections mostly in high-risk groups and the low cost-effectiveness, we think it is not profitable to include HAV vaccine in the NIP within the next five years. After that period, it should be re-evaluated taking into account more up-to-date information on the mean age at time of infection (currently around 25 years) and immunity in the adult population. This can be done in a new seroprevalence study, which was proved to be a good tool, indicate which populations are susceptible to infection.[32,33]
When children are vaccinated, it is primarily to protect other people from infection, as children themselves hardly ever experience illness. Vaccinating only the children of migrants could be considered, although we think it would not be cost-effective, because the vaccine is by far not as cheap as described in the small cost-effectiveness study.[30] To reduce costs it would be effective to screen first on antibodies against HAV, as the costs of the tests seem to be outweighed by the number of prevented vaccinations.[31] Nevertheless, it is considered important (and maybe is cost-effective?) to give better and more advice to parents of young migrant children by special pre-holiday outreach programmes, and to convince them to vaccinate their children at their own costs before travelling to their home country. Again, the ethical question remains, because few of these children will develop illness following infection. However, Richardus et al. argue that general vaccination of Turkish and

Moroccan children is recommended since many remain unprotected against HAV into adulthood with continuous risk of exposure in their home country. Alternatively, vaccination could be offered to teachers and parents of Netherlands children attending the same schools and day-care centres as the Turkish and Moroccan children. A drawback of this policy would be that in practice in large and middle-large cities almost all households with children would be vaccinated.
HAV vaccine could eventually be combined with HBV vaccine. The target groups for HAV vaccine and HBV vaccine almost the same. If it is combined (like Twinrix), it can be effective in MSM and Turkish and Moroccan children. A study on cost-effectiveness of combining HAV and HBV vaccination in these risk groups should be carried out.
In the Netherlands, travellers to HAV-endemic countries are already advised to take a HAV vaccination. In Amsterdam, a study was performed to find out the impact of travel advice.[34] Of Turkish and Moroccan Amsterdam people, 70% did not get any advice. More than half of the Turkish and Moroccan parents did not vaccinate their children before travelling to their country of origin (55% and 58% respectively). It is important to find out how advice can more effectively reach Turkish and Moroccan parents. Vaccination might be given in the infant welfare clinics as an alternative to reach these risk groups.[34] The study of van Steenbergen et al. recommended vaccination of all children of Turkish and Moroccan parents. This can be done in combination with hepatitis B vaccination.[35]
Vaccination is currently also advised, combined for hepatitis A and B, for men having sex with men. In the first half of 2004, a sudden increase in hepatitis A cases among homosexual men was noticed. In the national vaccination campaign for HBV co-ordinated by the MHS Netherlands, men who have sex with men are actively offered Twinrix, the combination vaccine, as an alternative (with some costs for the men themselves) to the free hepatitis B vaccine. From 1 November 2002 to 30 April 2004, 36% of homosexual men and 19% of bisexual men accepted this offer.[36]

5.3.8 International perspectives

WHO recommends vaccination of high-risk groups in HAV low endemic countries. The decision to include hepatitis A vaccine in routine childhood immunisation programmes should be made in the context of the full range of immunisation interventions available. This includes hepatitis B, Hib, rubella and yellow fever, and, in the near future, pneumococcal vaccines, all of which are likely to have a more profound public health impact.[37]
There have been some large outbreaks of hepatitis A. One in Italy with 886 cases and one in Egypt with 219 cases.[38] In the Netherlands, the low number of notifications (<3%) associated with contaminated food are found in travel-related cases and in cases who eat food brought to them from a foreign trip.[39,40] This indicates vaccination for people travelling to those countries.

References of hepatitis A

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5.4 Rotavirus

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5.4.1 Introduction

Group A rotavirus is the most common cause of severe gastro-enteritis in young children. It causes fever, diarrhoea and vomiting and, because of the risk of dehydration, can sometimes be fatal, especially in developing countries. In developing countries, the course is more severe than in industrialised countries. Each year, rotavirus causes approximately 111 million episodes of gastroenteritis requiring only home care (industrialised countries 7 million), 25 million outpatient clinic visits (industrialised countries 1.8 million), 2 million hospitalisations (industrialised countries 223,000) and 352,000-592,000 deaths (industrialised countries 63,000-106,000) in children aged under five years.[1]

Rotavirus replicates in mature villous epithelial cells of the upper small intestines. There it causes several physiologic and morphologic changes: a decreased capacity to absorb sodium, glucose and water and there are decreased levels of intestinal lactase, alkaline phosphatase, and sucrase.[2] In addition, an infection-associated enterotoxin is thought to play a role in development of diarrhoea. The disease begins with a sudden start of watery diarrhoea and vomiting. This can last 3-8 days. Fever and abdominal pain are common as well. [3] Mostly the disease is mild, but 1 in 75 children will develop severe dehydration which can result in death.[2]

Infectiveness and transmission

Transmission route is mainly faecal-oral. Other routes are via aerosols and other body fluids. Transmission can also occur via contaminated water or food.[3] Moreover, nosocomial infections have been reported.[4] The incubation period is approximately 2 days.[3] In the Netherlands risk factors that were identified for rotavirus-gastroenteritis were contact with a person with gastroenteritis outside the household and poor kitchen hygiene.[5]

Antigenic variation

Rotaviruses have a wheel-like appearance in electron microscopy.[3] Belonging to the Reoviridae family, rotavirus is characterised by 11 segments of double-stranded RNA enclosed in a triple-shelled protein capsid. The two outer proteins VP4 and VP7 define serotypes of rotavirus. These two outer proteins induce neutralising antibodies and designate the G (VP7) and P (VP4) viral serotypes. Genotyping (PCR-based) methods to determine P and G genotypes have shown that the most common combinations in human worldwide are P[8]G1, P[4]G2, P[8]G3 and P[8]G4.[6] In Europe more than 90% of Group A rotavirus strains that have been typed are of serotypes G1-4.[7]

5.4.2 Vaccines against rotavirus

Availability

Different candidate-vaccines are available for rotavirus. The first vaccines to be evaluated were a bovine strain virus (RIT4237), attenuated in calves by passage (200x) in bovine cells, another bovine vaccine strain (WC3) also attenuated but by much fewer passages (12x), and the third animal-origin rotavirus was a rhesus rotavirus vaccine (RRV) adapted to cell culture. These three vaccines showed inconsistent capacity to protect against disease, so they are not considered a potential vaccine

candidate anymore.[2] In China one animal-origin vaccine is licensed, that is Lanzhou Lamb Rotavirus Vaccine (LLR). Further studies on this vaccine are planned.[2] Animal-origin strains were reassorted with human-origin strains. Only one such a vaccine (Rotashield, Wyeth-Lederle, a reassortant of RRV with a human strain) has been registered in the USA, but its use was discontinued after about 1.5 million administrations because of an unusually high number of cases of intussusception (see further). Rotashield is a simian-human four-valent reassortant rotavirus. The vaccine is administered orally in three doses; immunisations are separated by at least 3 weeks.[2,3,8] One dose of the withdrawn Rotashield costs $38. A full course thus was $114.

Vaccines under study in phase III trials now are a WC-3 bovine reassortant rotavirus vaccine and the RIX 4414 vaccine. The last one is a live attenuated human strain (purified 89-12). This vaccine was very recently licensed in Mexico under the name Rotarix. Cost of Rotarix not known yet. It is given in a two-dose schedule. The two vaccines are concentrated on types G1-G4 and P1A. [2 9-11]

Effectivity

More than 90% of Rotashield-vaccinated children developed an immune response. Seven efficacy trials were done. Efficacy was greater against severe disease than against mild disease. Efficacy ranged from 48% to 68% against any rotavirus disease and from 64% to 91% against severe disease.[2,12] After clinical success of a quadrivalent vaccine, the pentavalent WC-3 bovine reassortant rotavirus vaccine is now under study.[13] Preliminary results are promising. Among 1,946 infants the vaccine conferred immunity against 59 to 77 percent of rotavirus infections.[14]

RIX 4414 is a purified vaccine of strain 89-12. The 89-12 strain gave an immune response of 94% of the vaccinees. Both vaccines are now studied in large placebo-controlled trials, including some in developing countries.[2] A recent study on RIX4414 (Rotarix) gave promising results with 61-91% of vaccinated infants developing IgA antibodies.

Rotavirus candidate- vaccines target the four types of human strains named above. However, uncommon genotypes or serotypes have been increasingly found in recent years, such as P[6]G9, P[8]G9 and P[9]G6. Especially serotype G9 seems to be emerging worldwide.[15-18 19] An outbreak with a G9 variant virus occurred in our country in a neonatal medium care unit in December 1999. [20 21] However, to what extent these 'emerging' types are circulating is unknown, as routine typing of rotavirus strains is not implemented.

Adverse events

The first licensed Rotavirus-vaccine was Rotashield (RRV Simian-Human reassortant rotavirus).[22] In the pre-licensure trials, this orally administered vaccine had a favourable safety profile in infants, with fever as the most frequent adverse event.[23] In 15% of the infants there was low-grade fever 3-5 days after the first dose (38-39^{o}C) and 1-2% had fever of 39^{o}C and over 3% of the infants had diarrhoea and abdominal cramps. Other events included anorexia, fussiness and listlessness. These incidence rates were consistently higher than the frequencies in the placebo recipients ($P<0.01$). After the second dose, fever was less prominent and slightly more frequent than in the recipients of placebo ($P<0.05$). After the third dose, adverse events following vaccine and placebo did not differ. A remarkable adverse event in the prelicensure trials was intussusception, but their was no statistically significant difference in vaccine recipients and controls, 5 of 11,000 vaccinated and one of 4500 non-vaccinated children developed intussusception. Intensified passive surveillance followed licensure.[22,24] Approximately one year after registration of Rotashield in August 1998, 15 children with intussusception after administration of Rotashield were reported to the Vaccine Adverse Event Reporting System of the Centers for Disease Control.[25,26] The Advisory Committee on Immunisation Practices recommended that the administration of rotavirus vaccine should be suspended, pending the

evaluation of a possible causal relationship. Subsequently, a retrospective cohort and a case-control study demonstrated that RRV-TV (=Rotashield) was associated with an increased risk of intussusception, mainly 3 to 7 days post-vaccination.[27] The RR was 37 (P<0.001) for dose 1 and 3.8 (P=0.05) for dose 2.[28] In contrast, analysing electronic databases in the USA revealed that in children aged <1 year, the number of hospital admissions for intussusception was 4% lower in the vaccination period in direct comparison with the pre-vaccination period. In children of 45-210 days old, there was an increase of 1%.[29]

The vaccine was taken off the market although still registered, because of the unfavourable risk balance in the USA. There where the burden of Rotavirus-disease is much greater this vaccine might still be beneficial overall.[22]

In a recent study, Rotarix was well tolerated and there was no increase in solicited symptoms as compared with placebo.[30] Of the newer vaccines, the safety profile is not yet known.

5.4.3 Epidemiology of rotavirus

All children are exposed to rotavirus and acquire antibodies by 3 to 5 years of age.[2]

Methods that are used in the Netherlands to get insight into epidemiology of rotavirus are: case-control studies with gastroenteritis cases at GPs, information from virological registrations and study of hospital admissions for gastroenteritis and laboratory surveys.[8,31-33]

In the Netherlands, 4% of gastro-enteritis cases in the community were caused by rotavirus.[33] Extrapolation of these data leads to an annual estimate of 192,000 infections, of which 66,000 among children between 0 and 4 years old. The registration of virological data showed no clear change in rotavirus incidence in last years (see figure 5-4).

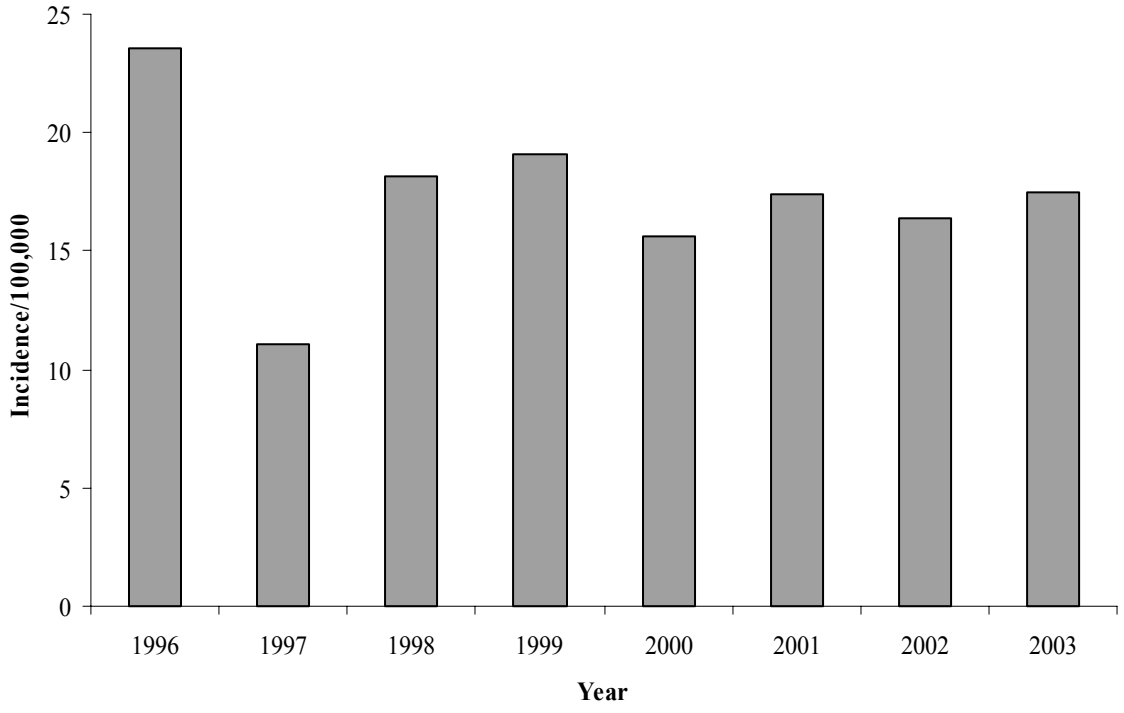

Figure 5-4: Incidence of rotavirus per 100,000 inhabitants. (source: Infectious Diseases Bulletin 15, 2004).

Among gastro-enteritis cases visiting general practices, 5.3% was caused by rotavirus.[32] Rotavirus was clearly more common among young children consulting their general practitioner: in children of age ≤1 and 1-4 years of age rotavirus was the cause in 21.2% and 15.2%.[8,32] There was a peak of cases in the winter and early spring. The proportion of hospitalisations for gastro-enteritis attributable to rotavirus ranged from 32% to 58% (about 1600 to 3300 per year), depending on whether it was a high- or low-endemic season.[31] The corresponding estimated annual incidence of hospitalisations for rotavirus among children aged under five was 90 to 270/100,000. In the USA, 20 to 40 persons die of rotavirus each year.[2]

5.4.4 Current burden of rotavirus

To estimate the number of hospital admissions for rotavirus, hospital discharge data were obtained from the National Disease Registry (NDR) for the period 1996-1998. Besides, in 1998, paediatricians reported hospitalisations with rotavirus in the Dutch Paediatric Surveillance Unit (DPSU). In children aged <5 years, admissions for RV infections were 0.9 per 1000 (DPSU) and 2.7 per 1000 (NDR) in 1998. The NDR annual estimate varied in the studied period between 1.6 and 3.4 per 1000 (1.9-4.1 if nosocomial rotavirus infections were included). [31] This amounts to a total number of hospitalisations of between 1500 and 3500 per year, where variation may be explained by both method of data collection and the fact that there is a large variation between years. The average length of stay in the hospital was 4 days.[12] Thus, at a cost per in-hospital day of € 359, the total costs for hospitalisation will vary between €2.2 and 5.0 million per year. The number of GP consultations in 1999 was 11,700.[8] By combining information from various studies, the total number of consultations will range between 7,000 and 15,000 per year, which, at a cost of €20 per visit, amounts to €140,000 to 300,000.[8,12,33,34] Other types of resources include laboratory tests and medication (mainly oral rehydration solution), but firm data about these costs are not available. Assuming only a fraction of patients visiting a GP will require a laboratory test (10%) or medication (50%), and based on estimated costs of €20 per laboratory test and €5 for the medications, the total costs amount to at most €68,000 per year. Adding all the costs, we find that the total medical costs for rotavirus will be between €2.4 and 5.6 million per year.

The number of work days that parents lose once their child has a rotavirus infection is 2.0 days for paid work and 2.8 days for unpaid work.[12] Based on an average working week of 30 hours, and an elasticity of 0.8 (indicating that 1 hour loss of work does not equal 1 hour loss of productivity), 1 day of work equals 5 hours of productivity loss. [35,36]At €34 per hour, the total costs of productivity loss due to rotavirus are €340. Based on 66,000 cases per year, the total costs due to work loss are €22.4 million per year.[33]

Assuming the same number of hours for a day unpaid work lost, at €8 per hour, the costs due to unpaid work lost are €112 per case, totalling €7.4 million per year.

The total disability-adjusted life years (DALY) associated with rotavirus each year was estimated at 1122, of which 673 to 1010 could be prevented with a vaccine efficacy of 60-90% (Appendix III).

5.4.5 Cost-effectiveness of rotavirus vaccination

An economic evaluation of the costs of vaccination in the Netherlands, based on the data from all studies combined, showed that introduction of a vaccine with the efficacy of the RRV-TV/Rotashield vaccine would be cost-saving if the costs of a complete vaccination (all required doses) are less than €12 to €27 (depending on the exclusion or inclusion of the productivity loss of unpaid work). When

the costs are assumed the $114 that the Rotashield vaccine cost, the cost-effectiveness ratio is estimated at about €27.000 per avoided hospitalisation. Possible extra costs for implementation of the vaccine in the NIP are not taken into account. If the vaccination schedule does not fit the current schedule, extra cost calculations are needed.

5.4.6 Alternative options for prevention

Personal hygiene is important in transmission of rotavirus to prevent secondary spread.[5,37]
Especially in households with children attending primary schools and day-care centres, this is important, as these places often form the sites from which the infections are introduced into a family, and can cause illness in adults.[5]

5.4.7 Considerations regarding feasibility of including rotavirus vaccine in NIP

Now there is no potential vaccine for inclusion in the NIP. So far, vaccines have not been proved effective enough and some have serious adverse events. Studies on efficacy and adverse events following newly developed vaccines should be awaited before considering inclusion of a rotavirus vaccine. Given the cost-benefit analysis, the vaccine price must be lowered sufficiently. The
RIX 4414 and the bovine (Strain WC3)-Human Reassortant Rotavirus vaccine are now studied in phase III trials. These trials consist of placebo-controlled trials with around 60,000 persons. The researchers expect to provide sufficient data in five years. Therefore, in the next five years a rotavirus vaccine shall not be included in the NIP. It should also be taken in consideration that the currently developed vaccines might not protect against the newly 'emerging' strains of rotavirus.

5.4.8 International perspectives

Rotashield is still registered in the USA, but not used. In China, an animal strain (Lanzhou, Lamb Rotavirus Vaccine) is used. This vaccine must be studied further for implementation in other countries.
In the developing world, Rotashield might be effective enough to use as prevention for rotavirus. The benefits of the vaccine will probably outweigh the cases of rotavirus disease. Many studies are carried out now to find out the effectiveness and safety of Rotarix.[10,38] However, in Mexico Rotarix is now licensed.

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5.5 Varicella Zoster Virus (VZV)

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5.5.1 Introduction

Varicella Zoster Virus (VZV, also known as Human Herpes Virus-3) is an alpha herpes virus, and the causative agent of chickenpox and shingles. VZV occurs worldwide, and infection and replication is restricted to primates. Although chickenpox is generally regarded as a benign disease, complications such as bacterial super infections (cutaneous infections, bronchitis, and otitis media) and acute neurological disorders are often reported. Varicella is a disease of childhood and in temperate climates up to 90% of the children is infected before the age of 10. During chickenpox, VZV establishes a latent infection in sensory nerve ganglia; shingles results when a latent virus reactivates and returns from the ganglion to infect the skin. Most often reactivation of VZV occurs with aging, following disease or various therapies such as steroid administration, cancer chemotherapy and irradiation. The incidence of zoster in a population begins to increase sharply at about 50 years of age to ~5/1000 annually (which is twice the incidence found in people in the age of 40-50), and a further increase is found by further aging.

Pathogenicity

Varicella: The incubation period of varicella ranges from 10 to 23 days, with an average of 14 days. Varicella is usually a self-limited disease characterised by fever and a generalised pruritic rash that lasts about 5 days. The rash is characteristically more concentrated on the trunk and head than on the extremities. Most children with varicella develop between 250 and 500 skin lesions. Residual scarring is exceptional, but depigmented areas may result and be persistent. Adults are more likely to develop more severe infections than children, presumably due to a lower cell-mediated immunity, which is generally lower in adults. The most frequent complication of varicella is super infection of the skin, lungs or bones. Severe morbidity and even mortality involves group A streptococcal super infection. For children with reduced cell-mediated immunity responds, such as caused by malignancy, acquired deficits (including aids), or by high doses corticosteroids, varicella may be severe and even fatal. Vaccination (with the only available, live Oka-VZV vaccine strain) and antiviral treatment is used to prevent varicella complication in these children.

Zoster: Zoster usually begins as a localised skin eruption involving one to three dermatome segments. The skin lesions resemble those of varicella, but are more often associated (or preceded) with pain instead of itching. Healing of the rash takes 2 to 6 weeks, depending on the immune states of the host. Following the healing of the rash, 25 to 50% of persons older than 50 years who develop zoster will have protracted pain known as post herpetic neuralgia, which may persist for month or years. Depending on which nerve is involved, zoster can cause a wide variety of complications such as dendritic keratitis, oral lesions, motor nerve defects, bladder dysfunction, partial paralysis of an extremity or even encephalitis.

Congenital varicella syndrome: If a woman develops varicella (or occasionally zoster) in the first of second trimester of the pregnancy, it is estimated that there is a 2% risk that her baby will be affected by the congenital varicella syndrome. This syndrome is often found to include abnormalities of extremities and mental retardation. [1]

Infectiveness and transmission route

VZV is a respiratory infection. It is highly contagious, both by aerosols of infected persons and direct contact from lesions of varicella and shingles. In temperate climates, the mean age of infection is lower than in (sub)tropical climates. This is probably due to the instability of the (enveloped) virus at higher temperatures and UV-inactivation.

VZV-seroprevalence data from the Netherlands Pienter-study (1995) shows that prevalence is >97% in 6-10 years old children (Unpublished results RIVM, De Melker, 2004). The seroprevalence is somewhat higher than in other countries. In Germany the seroprevalence amounted to 94% in children of 10 and 11 years a Swiss study showed an overall VZV-seroprevalence of ~90% in the adult people in Europe and somwhat higher prevalence rates for the northern European countries was reported.[2,3]

In the USA, before implementation of the general childhood varicella immunisation programme in 1995, there was a trend toward a decrease in the age of onset of varicella, thought to be related to the increased use of day-care facilities for young children.[4]

Antigenic variation

Only one serotype is known for VZV, in which three 3 different genotypes can be distinguished, with a different geographic distribution.[5] The Oka-vaccine will induce protection against all wild-type strains of VZV. Several methods (i.e. RFLP and PCR) have been developed to distinguish between wild-type and Oka-vaccine virus.

5.5.2 Vaccines against VZV

Availability

The Oka-vaccine, developed in Japan (Biken Institute, Japan, 1974) is the only vaccine currently available for VZV, and is licensed to several large vaccine companies (e.g. Merck (available as Provarivax, registered in the Netherlands), and GSK (available as Varilrix, not registered in the Netherlands)). This Oka-vaccine is a live vaccine derived form a wild-type virus, which has been attenuated by serial passages in guinea pig cell culture to become temperature sensitive. The Oka-vaccine strain is propagated on the human MRC5 cell-line. Not only is the virulence of the Oka-vaccine attenuated, but also its transmissibility. In a household setting, it is reported to be 4 to 5 times less transmissible in comparison to wild-type virus.[6]

The Oka varicella vaccine is currently administered as a single vaccine. However, recently, the live vaccines against Measles, Mumps and Rubella (MMR) in combination with the Varicella (i.e. MMRV) have been tested for effectiveness in clinical studies.[7,8] Such 4-fold combination vaccine appears to yield comparable protection (i.e. seroconversion rates and antibody levels) for Mumps and Rubella, the reaction against the Measles vaccine component (i.e. antibodies levels, and adverse effects) increased somewhat, while the reaction against varicella component was somewhat decreased. By adjustment of the amount of different live vaccine viruses, an equally effective combination vaccine MMRV seems to be possible. GSK has filed its MMRV vaccine (i.e Priorix-Tetra) for a European Mutual Recognition license in Germany, and approval is expected early in 2005. To reduce the frequency of breakthrough infections of varicella, this vaccine is advised to be given in a 2-dosis schedule in the second year of live (i.e at 12-14 month, and a second dose 6-8 weeks later). This schedule is equal to the current MMR schedule of Germany, Austria and the Czech Republic. Germany is one of the few European countries, which already has included universal VZV vaccination in its NIP. Merck is currently licensing a similar 4-fold MMRV (i.e. ProQuad) vaccine in Europe, and approval for this vaccine is expected for 2006.

The 4-fold MMRV combination vaccine will reduce the cost of administration substantially in comparison with a single VZV-vaccination. Furthermore, a combination vaccine would ensure a high vaccination rate (i.e. comparable with the MMR rates currently obtained). The replacement of the current MMR, which is administered according to the Dutch NIP at the age 14-month and 9-years of age to all Dutch children, by the MMRV vaccine, should be considered when it becomes available.

Effectiveness

The live varicella vaccine (Oka-strain) appears to be less effective after single dose vaccination then other live vaccine strains such as measles and mumps. Clinical studies from the USA show that the calculated vaccine efficacy ranges form 71 – 100%. Frequently wild-type chickenpox infections are reported among vaccinated children. [9] A ten-year follow-up study of VZV vaccination in the USA, showed a protective efficacy of 94.4% for a single dose vaccination, and this increases to 98.3% when an additional vaccination was given.[7] Independent factors associated with infection of VZV despite Oka-vaccination are:

- Vaccinated before 15 month of age.
- Asthma.
- Vaccination against varicella soon after the MMR vaccine (< 28 days).
- Vaccination >3 years before a VZV infection[10].

Recently it was shown that effectiveness of the varicella vaccination already declines significantly after 1 year.[8] Furthermore, it was shown that the age dependent difference (vaccination before or after 15 month of age) was only minor (P = 0.17), and that this difference was only due to a reduced overall protection in the first year after vaccination, but not in the years thereafter. Although breakthrough is relatively frequently reported, the clinical signs associated with a breakthrough wild-type infection are clearly reduced in comparison with varicella infection in unvaccinated children (e.g. a reduced number of lesions and smaller lesions).

The duration of induced protection for any vaccine is an important factor. For VZV this is even more important, as infection of VZV later in life is more serious, and associated with higher hospitalisation rates and has more side effects. Long-term data on waning VZV immunity of large cohorts of people who were vaccinated as child is not available. Some reports show that immunity does not wane in small groups of adults (21-year follow-up period after vaccination),[11] or children (20-year follow-up period after vaccination).[12] However, because it is expected that the recipients will have been exposed to circulating wild-type VZV, this data has to be interpreted with caution.

Furthermore, concerns over the effect of mass childhood varicella vaccination on the incidence of zoster in the adult population have been raised. The trigger for VZV reactivation is thought to depend on (age-related) decline in cellular immunity. Contact with wild-type VZV infected children is thought to boost the immunity of the adults. Replacement of wild-type VZV with the less transmissible Oka-vaccine VZV will diminish exposure of the adult and elderly.[12a] Despite this prediction, no such effect on zoster is reported in any age group in the USA after introduction in 1995 of universal childhood vaccination. A reason for this discrepancy could be that a subclinical reactivation of VZV may boost the immunity on its own. Longer-term data on zoster incidence following universal VZV vaccination is needed, however, since the increase in zoster is predicted to occur over 60 years.[12b] It is important that, in case universal VZV vaccination is considered in the Netherlands, adequate surveillance for zoster is established and maintained.

It has been shown that the Oka vaccine is able to boost cell-mediated immunity in elderly.[13-15] A large clinical trial is currently being performed in the USA to assess the efficacy Oka-vaccination on reduction of shingles by vaccination of elderly. If shingles in elderly will start to rise at a certain

period after introduction of universal childhood VZV-vaccination, the implementation of elderly VZV-vaccination is a potential control method.
On the long-term, the absence of latent wild-type VZV infection due to effective childhood Oka-VZV vaccination is expected to reduce the incidence of shingles in elderly. Data from immunocompromised children, which develop shingles much earlier in live, indicate that the varicella vaccination significantly lowers the incidence of shingles[16-19]. In addition, data of healthy children indicate that the incidence of shingles is reduced in children who received vaccination in comparison with those who were naturally infected.[20,21]

Adverse events
Adverse events tend to be mild and transient.[22] Immediate local reactions occur in 15-20%, more than in the control groups. Fever was reported in up to 14% of cases in the 7-21 days post vaccination period. Rashes with vesicles occurred in the same period in up to 4%, usually with also some lesions at the site of injection.[23] Sometimes high fever or extensive skin lesions occur
Data from the passive adverse event reporting system (VAERS) form the USA shows that serious adverse events due to Oka-VZV vaccination are low (2.9/100.000) and a casual relation with the Oka-vaccination was often speculative.[24-26] The Oka-vaccine has been used over 20 years in immunocompromised children, for which a wild-type varicella infection is often life threatening. Serious adverse events in this highly vulnerable group of children are extremely rare. Preliminary data of GSK indicate that adverse events following the 4-fold combination MMRV-vaccine are comparable with the MMR, without a significant increase in rate or severity.
Contra-indications for Varicella vaccine are severe immunodeficiencies and pregnancy. Severe anaphylactic reactions, if they occur at all, appear to be very rare.

Costs of vaccine and immunisation programme
In most of the studies included in this overview, the price of a shingle-shot VZV vaccine dose was \$30-\$40.[27] The costs of an immunisation programme will depend on the form. When the vaccine is administered at the same moment that other vaccines are administered, costs per case will be around €5. However, if vaccination is limited to certain groups, and vaccination takes places either at the GGD or at GPs, the costs per case will be around €9 or €20, respectively. When vaccination is limited to those who are sero-negative, the costs of serological tests need to be included. However, it is possible that with a more limited vaccination, the total costs will still be lower than for a universal vaccination.

5.5.3 Epidemiology of Varicella and Zoster in the Netherlands
In population-based seroprevalence study (1995-1996), seroprevalence of varicella zoster amounted to 95.6% (95%CI 94.9-96.3%) in persons aged 0-79 years.

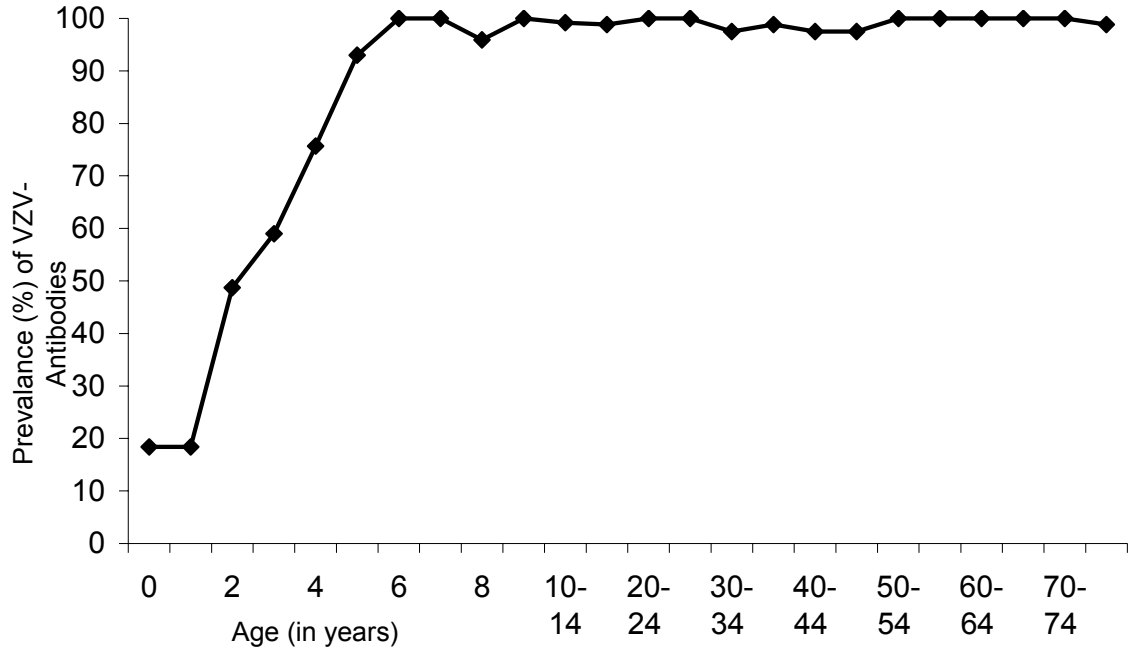

Figure 5-5: Age-specific prevalence of VZV antibodies in the general population (Pienter-project 1995-1996)

Very crude estimates of infection using this population-based seroprevalence for varicella zoster are: 30,000 per 100,000 for 1-year-olds, 10,000 per 100,000 for 2-year-olds, 16,000 per 100,000 for 3-year-olds and 18.000 per 100,000 for 4-year-olds.
Incidence of varicella as calculated from GP and hospital admission data decreases with age, while incidence of herpes zoster increases with age (Unpublished results RIVM, de Melker, 2004).
Risk factors for herpes zoster are age, sex, ethnicity, genetic susceptibility, exogenous boosting of immunity from varicella contacts, underlying cell-mediated immune disorders, mechanical trauma, psychological stress and immunotoxin exposure.[28] According to the CBS, in 2002 26 persons died of herpes (1999:25, 2000:14 and 2001:13). Only four 4 persons died of varicella in 2002 (1999:4, 2000:1 and 2001:3). In contrast to mortality, morbidity is quite high.

5.5.4 Current burden of disease

Varicella.
Disability-adjusted life years (DALYs) lost due to chickenpox are estimated to be 1158, of which 952 will be preventable with a 90% effective vaccine against severe varicella (Appendix III). The average annual incidence of GP visits due to chickenpox is estimated to be 221 per 100,000 (2000-2002). It was highest for 0-4-year-olds (3,102 per 100,000). This translates into a total of 35,360 cases that visit a GP, which, based on a cost per visit of €20, leads to total annual costs of €700,000.[29] The average annual incidence of hospital admissions due to chickenpox amounted to 1.3 per 100,000 (1994-2001) using main diagnosis. Based on the VTV-registration from 2000-2003, the total number of in-hospital days was 1,458. Thus, at a cost of €359 per day, the total costs for hospitalisation are €500,000 per year, leading to an overall estimate of annual medical costs of €1.2 million. Since in general in this report only main diagnosis was used for hospital admissions (side diagnosis less reliable), this could be considered as an underestimation (incidence main and side diagnosis 2.3 per 100,000).

Zoster.
Disability-adjusted life years (DALYs) lost due to zoster are estimated to be 605 (Appendix III). The annual incidence of herpes zoster based on General Practitioners consultations amounted to 325 per 100,000 (1998-2001). This translates into a total of 52,000 cases that visit a GP, which, based on a cost per visit of €20, leads to total annual costs of €1 million. Additionally, each year 1,100 patients undergo treatment in hospital (VTV 2000-2003). The costs for each patient are assumed to consist of two consultations with specialist (€126), an epidural injection (€114) and the costs of a day-admission (€229). Thus, the total costs for day-treatment is €516,000 per year.
The total number of hospital admissions per year is about 390, with an average length-of-stay of 10.5 days. Combined with costs per day of €359, and assuming that these patients also receive an epidural injection (or similar treatment); the total costs for hospitalisation are estimated at €1.5 million.
The overall costs associated with Zoster are thus estimated at €3.0 million per year.
Since in general in this report only main diagnosis for hospital admissions was used (side diagnosis less reliable), this could be considered as an underestimation (incidence main and side diagnosis 6.8 per 100,000).

Work loss and school absenteeism
An overview of a large number of economic evaluations of varicella vaccination showed that it is assumed that parents lose work for 0.59-2.7 days when their child has varicella. For infected adults, the number of workdays lost ranges from 14 to 23 days.[27]

5.5.5 Cost-effectiveness of VZV vaccination
Many cost-effectiveness studies addressing varicella vaccination have been published. An overview is presented in Thiry et al.[27] In most of the studies included in this overview, the price of a vaccine dose was $30-$40. When indirect costs were included, vaccination of infants was cost saving in most cases. However, these results are sensitive to changes in vaccine price and value/amount of work time lost. When only direct medical costs are considered vaccination is deemed cost-effective in most studies, although no savings occur. Studies in Belgium and Germany indicate that vaccination of teenagers with uncertain or negative history (possibly combined with a blood test) may be more cost-effective than universal infant vaccination.[30,31]
Note that most studies do not take a possible effect of varicella vaccination on the incidence of herpes zoster into account. In most studies, the current evidence is deemed inconclusive to show whether varicella vaccination is beneficial to the prevention of zoster.

5.5.6 Alternative prevention and intervention measures
Severe chickenpox is treated with acyclovir, a well-known inhibitor of VZV (and other alphaherpesvirus) DNA-polymerase. For treatment of shingles, the antivirals Valacyclovir and Famcyclovir are also indicated.

5.5.7 Considerations regarding uptake of VZV vaccination in the NIP
Several factors that have a negative effect on the cost-effectiveness of universal childhood varicella vaccination are present in the Netherlands in comparison with other western countries:

- The mean age of seroconversion is relatively low in the Netherlands. As severity of the varicella vaccination is increasing with the age, this means that health-related costs in the Netherlands are relatively low.
- Both hospitalisation and general practitioners visits are relatively low.
- Indirect costs, which are considerably in case of chickenpox infection, are usually not taken into account for evaluation of the cost-effectiveness of a treatment in the Netherlands.

Thus, cost-effectiveness studies from other western countries will be less favourable when translated to the situation in the Netherlands.

However, when a 4-fold combination vaccine (Measles, Mumps Rubella, and Varicella, MMRV) can be used, the cost-saving (or cost-effectiveness) of varicella vaccination might become more favourable, as the cost of administration will be considerably lower. In the universal Oka-VZV childhood immunisation programme of the USA (a single shot at 12-18 month of age) it is shown that the efficacy is only moderate (~70-90%).[8,24] Such a relative low efficacy (in comparison with our other NIP vaccines) will hamper the public acceptance. A 2-dosis MMRV schedule (i.e. 2-shots in the second year of life) induces a much better immunity against VZV. Such a vaccination schedule is equal to the current MMR vaccination schedule of, for example, Germany. In the NIP, however, the second MMR vaccination is given at 9-years of live. The long-term consequences of an earlier second MMR(V)-dose (i.e. at 2 instead of 9 years) are unclear now.

It is desirable that a cost-effectiveness study will be performed for the Dutch situation, once the 4-fold combination vaccines are registered for use. Furthermore, the consequences of a second MMR(V) vaccination at 2 instead of 9 years need to be evaluated.

5.5.8 International perspectives of VZV vaccination

Universal Oka-VZV vaccination (single component, single dose) is part of the NIP of the USA since 1995, and of at least two European counties (i.e. Finland, and Germany). When the 4-fold MMRV vaccines will have a European license it is anticipated that more European countries will introduce universal childhood Oka-VZV vaccination. The UK, however, wishes to delay introduction of universal VZV vaccination [12a] and has adopted a strategy of selective vaccination of (seronegative) health care workers. Furthermore, it is expected that a second dose of Oka-VZV will be added in those countries that currently have a single-dose schedule.

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5.6 Meningococcal disease group B

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5.6.1 Introduction

Meningococcal disease is caused by the Gram-negative bacterium *Neisseria meningitidis*. Based on the antigenic properties of the capsular polysaccharide several serogroups of *N. meningitidis* can be distinguished. The predominance of particular serogroups seems to depend amongst others on geographic location and composition of the population. Meningococci are found as commensal organisms in the throat of 5% to 20% of children and adolescents. Carriage is lower in adults. In sub-Saharan Africa group A meningococci are responsible for endemic disease, but this serogroup has nearly completely disappeared from Europe and the USA. In the Netherlands and in most other countries in Europe meningococcal meningitis is mainly caused by serogroup B and C. Before 1999 serogroup B predominated in the Netherlands, but after that an alarming rise in the incidence of serogroup C was seen.[1] This has led to the introduction of the polysaccharide conjugate vaccine in Dutch NIP in 2002.

Pathogenicity

There is no animal or environmental reservoir for meningococci. In some cases, the meningococcus can become pathogenic and cause invasive disease. The most important clinical presentations of meningococcal disease are meningitis and severe sepsis and despite availability of proper treatment, overall mortality still is 10% tot 15%. Population studies have shown that most invasive disease is caused by a limited number of subtypes, referred to as hypervirulent clones.[2] In contrast, some carriage lineages exist that never are associated with disease.[3] It is unknown what causes the meningococci to go from carrier state into disease, but it is likely that properties of both bacterium and host are involved. Once the bacteria enter the bloodstream it is important that patients rapidly clear the bacteria from their system. However, an impaired clearance and immune system such as the lack of a spleen and complement deficiencies may lead to severe disease. In addition, patients with a genetic make up resulting in increased intravascular fibrin deposition are at high risk in developing severe and fatal disease.[4]

Infectiveness and transmission route

N. meningitidis is transmitted by aerosol or direct contact with respiratory secretions of patients or healthy human carriers. Unlike the other agents that cause bacterial meningitis meningococci can cause epidemic disease and this is particularly true for serogroups W135 and A. The situation in New Zealand, where an epidemic with a particular hypervirulent Men B strain has killed 220 individuals since 1991, shows this is also true for Men B.

Antigenic variation

Meningococci exchange DNA by horizontal transfer at a high frequency. As a result, the genomes of this species are highly diverse in composition, which is reflected in the large number of sequence types identified by MLST. As mentioned before in a previous chapter the genes encoding for the capsular polysaccharide may be exchanged between serogroups and may for instance lead to a Men B strain with the characteristics of a hypervirulent Men C strain.[5] Studies have already shown that many

variants of the major candidate for the Men B vaccine, the PorA, exist and this could potentially result in the rapid emergence of escape variants once a PorA based vaccine is introduced.[6,7]

5.6.2 Vaccines against Men B

Availability

There are commercially available meningococcal polysaccharide vaccines for protection against serogroups A, C, Y and W135. In contrast to the capsular polysaccharide of the other serogroups, group B polysaccharide is poorly immunogenic, even when conjugated to a protein carrier. A possible explanation lies in the fact that Men B polysaccharide has significant similarity with antigens of the human central nervous system.[8] This has hampered the development of a Men B specific vaccine. For prevention of meningococcal B disease, the focus is on PorA containing outer membrane vesicle vaccines. Invasive Men B disease is caused by strains with many different PorA types. However, there are geographic differences and during epidemics, particular PorA types may dominate. Currently, a limited number of PorA types are associated with the majority of cases of invasive Men B and these PorA types are the focus in vaccine development.

Chiron has completed phase II clinical trials and now sells a MeNZB vaccine that protects against the New Zealand Men B strain (B:4:P1.7-2,4). The vaccine is composed of the outer membrane vesicles (OMV) derived from the B:4:P1.7-2,4 strain and is manufactured similarly to the Norwegian Men Bvac, which used a different strain (B:15:P1.7,15). The use of this vaccine has recently been approved by the New Zealand government and a campaign to immunize more than a million children and adolescents between 6 months and 20 years in age has started in August 2004.

The Cuban Finlay Institute produces the vaccine marketed as VA-MENGOC-BC, which is licensed in the USA. This vaccine contains OMV made from the Cuban strain Cu385 (B:4:P1.15) and the vesicles are complexed to Men C polysaccharide. In a partnership with the Finlay institute GlaxoSmithKline is developing a vaccine without the Men C polysaccharide based on the Cuban OMV.

No other Men B vaccines are available yet. However, several vaccine companies are now trying to develop generic Men B vaccines using currently available genome sequence data to select appropriate vaccine candidates. Most of these vaccines are still being tested in preclinical analysis or phase I clinical trials. The Netherlands Vaccine Institute (NVI) in the Netherlands is developing a vesicle vaccine against Men B in which six or nine PorA types are incorporated. The NVI considers such a multivalent Men B vaccine combined with a multivalent pneumococcal conjugate vaccine to be a likely candidate for introduction in the NIP.

Effectiveness

Based on serological responses in phase II clinical trials the MeNZB vaccine is expected to protect against meningococcal disease caused by the New Zealand strain only. There have not yet been prospective efficacy trials and correlates for protection have not been definitively established. However, the manufacturer reports that a vaccination schedule of three doses MeNZB given with an interval of 6 weeks demonstrated that in 75% of the children, and in 91% of the adults, a 4-fold rise in serum bactericidal antibody titres developed. This is similar to the results obtained with the Men Bvac, which closely resembles the MeNZB.[9]

The only Men B vaccines tested in large efficacy trials are the monovalent OMV vaccines carrying the PorA antigen.[10-12] The efficacy of the OMV vaccine has proven to be variable and often low, particularly in infants. The NVI is developing vaccines that incorporate 6 to 9 different PorA subtypes

in the OMV covering more than 75% of all subtypes in the Netherlands. These vaccines seem to be safe and immunogenic, but will require further evaluation in clinical trials.[13-15]

Adverse events

The Men B-vaccines under development are all slightly different in composition and content of non active ingredients like adjuvants or preservatives.[16]

The information on safety of these vaccines is limited since no Men B vaccine has been used extensively over a long period. Recently, a monovalent Cuban vesicle vaccine has been used in South America. Similarly, a monovalent vesicle vaccine has been licensed and used in New Zealand for management of the local epidemic (Chiron). The vaccines are generally well tolerated. Regarding serious events, information is lacking.[17-19]

5.6.3 Epidemiology of Men B in the Netherlands

Meningococcal disease occurs worldwide as an endemic infection.[20,21] The incidence of meningococcal disease during the last 30 years varied from 1 to 3 per 100,000/year in most industrialized countries and 10 to 25 per 100,000 in some third-world countries.

The NRBM collects meningococcal strains from blood and/or CSF isolates, skin biopsies and other clinical material of patients with meningococcal disease. Clinical microbiological laboratories throughout the country send these materials on a voluntary basis to the NRBM. Based on this laboratory surveillance the mean incidence of Men B disease amounted 2.9 per 100,000/year in 1993-2003. Traditionally Men B was the most common serogroup (80-90% of all isolates), followed by Men C (10-15%). However, in 2000-2002, an emergence of Men C occurred and the fraction of Men B decreased to 59% in 2001. The incidence also declined in these years, to 1.8/100,000 in 2003 (figure 5-6).

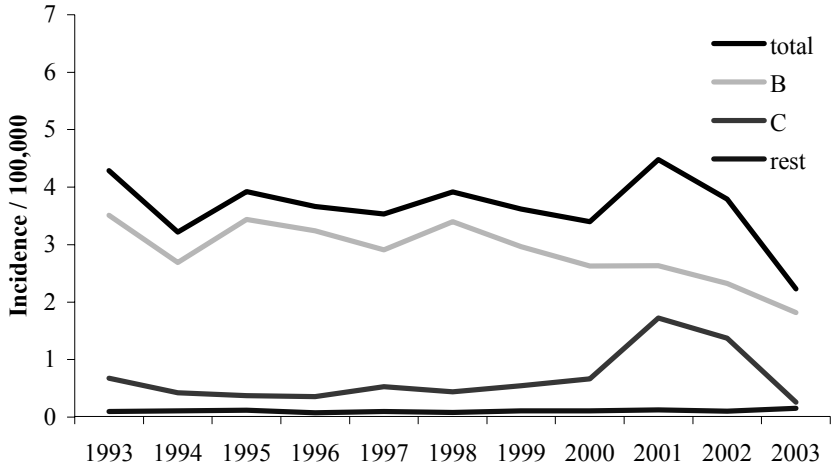

Figure 5-6: Incidence of meningococcal disease by serogroup, 1993-2003. Source: NRBM

The mean incidence in 1993-2003 (figure 5-7) was highest for 0-year-olds (36/100,000) and decreased with age, with another small peak among adolescents aged 15-18 years (8/100,000).

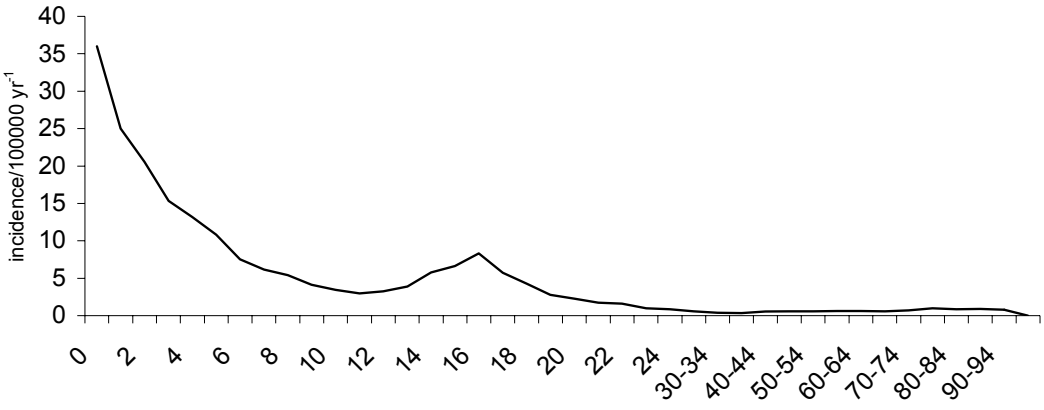

Figure 5-7: Mean incidence 1993-2003 of meningococcal B-disease by age. Source: NRBM

In 2003, 348 patients with meningococcal disease were notified and for 280 patients an intensified surveillance questionnaire was completed. The data from the questionnaire showed that 6% of the 215 Men B cases developed septicaemia without meningitis, 18% developed both and 45% only meningitis. In 2003 13 of the 348 (3.7%) notified patients died due to Men B disease in the Netherlands. According to a recent report, 5% of survivors of invasive Men B or Men C diseases in the Netherlands have physical complaints as scars and loss of limb and 4% suffer from neurological disorders.[22] The case fatality rate, frequency of septicaemia and sequelae in Dutch patients are similar as those reported in international literature.[23-26]

5.6.4 Burden of meningococcal B disease

Disability-adjusted life years (DALYs) lost due to meningococcal B disease are estimated to be 1907, of which 996 will be preventable (Appendix III).

Data on hospitalisation in the Netherlands (VTV data) show that the average number of in-hospital days for meningococcal meningitis and sepsis in 2003 was about 9 and 14 days, respectively. This number differs by age, for patients from 0 to 4 years old the average length-of-stay is about 7 days, for patients over 65 years, this is 15 days for meningitis and 30 days for sepsis. Data from the NRBM was used to estimate the proportion of Men B cases (84%) among all meningococcal hospitalisations in 2003.

Besides the costs of in-hospital days, meningococcal meningitis and sepsis are associated with minor direct medical costs such as GP visits, follow-up visits with specialist, diagnostic procedures etc. A detailed account of resource use is provided by Bos et al., and these estimates have been combined with recent unit costs.[27,28] In total, the direct medical costs for meningococcal meningitis and sepsis amount to €2.0 million for 2003, of which 44% is related to patients between 0-4 years, 10% to patients between 5-9 years, and 10% to patients over 65 years.

Besides these direct medical costs, the costs for long-term care for neurological sequelae, scars and amputation should be included. In their paper, Bos et al. presented cost estimates for these types of care, which have been adjusted by the price index.[27] The costs for scars and amputations are estimated at €15,000 and €14,000 per year, respectively. The costs for long-term care for neurological sequelae amount to between €3 - 4.3 million, depending on assumptions made about long-term care for elderly patients. Note that all above calculations have been based on 2003 numbers only, as there has been a

sharp drop in number of cases, both registered and hospitalised. If however the average number of cases over 2000-2003 is used, the above estimates increase by about 40%.

Work loss and school absenteeism

Little information is available about work loss and school absenteeism due to meningococcal B disease. On average, each year 97 cases of meningitis and septicaemia requiring hospitalisation occur in children between 5 and 20 years. In these cases, at least about 1 month of school will be missed. In adults between 20 and 65 years, 65 cases of meningitis and septicaemia occur. Here, at least 1 month of work will be lost.

In addition, parents of children with meningococcal disease will also miss work due to visits to GP and specialist, and for hospital visits. In the study by Bos et al., it was assumed that a total of three days of work are missed when a child has meningitis or septicaemia.[28]

5.6.5 Cost-effectiveness of meningococcal B vaccination

An economic evaluation of meningococcal B vaccination in infants in the Netherlands estimated that, assuming a vaccine price of €10 per dose, the cost-effectiveness is €15,720 per QALY gained or €21,420 per life-year gained. In that study, a total number of cases per year of 306 is assumed. However, in 2003 only 138 Men B cases occurred in children between 0 and 4 years. This influences the number of cases that can be prevented, and thus the costs that may be avoided and QALYs that may be gained. After adjusting the estimates for this, we arrive at an estimated cost-effectiveness of €31,000 per QALY gained or €42,000 per life-year gained.[28] If we assume that the report-rate is actually 100%, thus assuming only 138 cases occur, the ratios increase to €42,500 per QALY gained and €58,000 per life-year gained. These ratios can be seen as the upper-limit for the cost-effectiveness.

5.6.6 Alternative prevention and intervention measures for Men B disease

In most parts of the world, meningococci are still highly susceptible to penicillin, which is usually the drug of choice for treatment, although a single dose of oily chloramphenicol may be the preferred treatment in areas with limited health facilities. Other drugs, such as Rifampicin, are required to eradicate nasopharyngeal colonization. In recent years, the occurrence of meningococcal isolates with reduced sensitivity to penicillin has been reported mainly from Spain.

5.6.7 Considerations with regard to uptake of Men B vaccination in the NIP

It is clear that in the Netherlands meningococcal disease in children is mainly caused by serogroup B meningococci.[1] This is particularly true now that Men C invasive disease has virtually disappeared due to the introduction of the Men C conjugate vaccine in 2002. The high mortality and morbidity associated with meningococcal disease suggest that inclusion of Men B vaccination in the NIP is advised. A cost-effectiveness study has shown that vaccination against Men B would be cost-effective.[22] These calculations were based on the number of Men B cases that occurred in the period before 2000. However, in recent years the number of cases of invasive Men B disease has dropped considerably. This will lead to less favourable estimates of cost-effectiveness as indicated above.

The multivalent PorA-based Men B vaccine is still in the developmental/trial stage. It will take at least five more years before we can expect to see a commercially available Men B vaccine. As with other new vaccines acceptance of this new vaccine will be hindered by the fact that it will require an additional injection. Therefore, combination of the Men B vaccine with Men C and pneumococcal conjugate vaccine may be required for its acceptance.
Because there are many different PorA types that cause invasive Men B disease changes in the vaccine may be required to keep pace with the changes in the distribution of the PorA types. Although the NVI vaccine is designed to introduce such changes rapidly, prolonged registration procedures may hamper the licensing of variant vaccines. In addition, the use of a PorA based vaccine may result in the selection of PorA-deficient meningococci. A recent study in the Netherlands has showed that PorA-deficient variants do occur and that they may retain full virulence and may cause outbreaks of meningococcal disease.[1] For these reasons development and introduction of a serogroup independent meningococcal vaccine based on non-polymorphic antigens may be required.

5.6.8 International perspectives of Men B vaccination

Concurrent with the introduction of the Men C vaccine in the Netherlands in 2002 the number of Men B cases has dropped considerably. In 2004, the number of Men B cases was almost half of the number of cases seen in 2000. The reasons for this decrease in Men B incidence are unclear and it may reflect normal fluctuations in the incidence. However, a similar decrease has also been observed in other countries. In Belgium, the National Meningococcal Reference Centre reports 66 Men B cases in 2003 compared to approximately 125 cases in 2000. The data from the Health Protection Agency suggest only a 20% reduction of Men B cases in England and Wales. Also in Ireland, a 15% decrease in Men B disease was noticed in 2003 compared with 2001.
Within Europe the incidence of culture-confirmed cases of meningococcal disease varies widely, from 0.3 to 4.7 per 100,000 in 2002 (http://www.ndsc.ie). Serogroup B is the most common serogroup in Europe, followed by serogroup C. Introduction of the Men C vaccine in the UK, Ireland, Spain, Belgium, Iceland, Netherlands and parts of Portugal has decreased both the overall incidence and incidence of Men C disease.
It is unclear what is causing the steep decline in Men B cases in the Netherlands and Belgium and whether this decline is temporarily as seen before. In this respect, the relative change in subtype distribution is important to follow-up. Belgium and the Netherlands started vaccination against Men C at approximately the same time. However, it seems unlikely that vaccination with the Men C polysaccharide would confer any cross protection against Men B. The reduction in Men B cases may have major consequences for the cost-effectiveness of the Men B vaccine.

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5.7 Respiratory syncytial virus

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5.7.1 Introduction

Respiratory syncytial virus (RSV) causes most cases of bronchiolitis in infants and children, and is therewith the most common cause of infant hospitalisation in the developed world. Reinfection with RSV is common, and is a major cause of morbidity and mortality in immunocompromised and elderly persons. RSV disease during infancy may increase the risk of childhood wheezing and asthma in later life and may cause persistent infections.[1-4] Children with underlying disorders (like congenital heart disease, bronchopulmonary dysplasia, or cystic fibrosis), children with a history of premature birth, and children younger than three months of age at the time of their first infection all have an increased risk for hospital requirement due to RSV infection, and would therefore in particular benefit from vaccination.

Pathogenicity

The majority of children infected with RSV manifest upper respiratory tract symptoms. A third of children also develops acute otitis media. Dyspnoea characterises lower respiratory tract involvement. In bronchiolitis wheeze may be present with a prolonged expiratory phase and crackles. Bronchiolitis may lead to acute respiratory failure with severe bronchospasm and hypoxia. Some infants with RSV bronchiolitis develop long-term recurrent episodes of wheeze and cough, resembling asthma. While the immune response in most infants is able to clear the virus, there are clearly disease-enhancing effects of the host's immune response to RSV. These are only partly understood.

Infectiveness and transmission route

RSV is a seasonal virus, with annual outbreaks occurring during the winter in temperate climates. Its high infectiveness is illustrated by the finding that by 18 months of age, nearly 90 % of all children have serological evidence of infection. By the age of 3 years, virtually all children have been infected. Re-infections with RSV occur regularly throughout life, which, after the second infection, are usually symptom-less or restricted to the upper respiratory tract. Elderly may experience severe RSV-associated disease again. Transmission occurs through respiratory tract secretions either by direct transmission, or by contaminated hands.

Antigenic variation

RSV exists as a single serotype, but has two antigenic subgroups, A and B. The subgroups show a three- to four-fold reciprocal difference in neutralization by specific antisera. The existence of antigenic subgroups may be a factor favouring reinfection and may therewith be relevant in vaccine efficacy. Antigenic dimorphism is most evident with monoclonal antibodies directed against the G glycoprotein. Using post-infection sera, it has been established that the two subgroups are 25% related antigenically overall, with the F proteins 50% related and the G proteins 1 – 7% related. At the genome level, subgroups A and B are 81% identical. In most, but not all, studies subgroup A strains are found more virulent. In addition, amino acid sequence divergence occurs between the subgroups, which can be as high as 20% in the G protein between particular strains. These may co-circulate during epidemics. Analysis of viral isolates obtained during successive years indicates that the G

protein slowly accumulates relatively minor antigenic differences over time. The effect on cross-protection in vivo is unclear.[5]

5.7.2 Vaccines against RSV

Availability

At present, there are no licensed vaccines available for the prevention of RSV disease. Formalin-inactivated aluminium-adjuvated RSV was the first RSV vaccine used as an experimental vaccine in US children in the 1960-s. This vaccine not only failed to protect against a subsequent natural infection, but also enhanced disease severity after a subsequent natural RSV infection. This event has hampered the progression of RSV vaccine development. Any future candidate vaccine should not induce enhanced disease upon a subsequent infection with RSV. This is very hard to demonstrate, because the mechanisms underlying vaccine-enhanced disease are not clear. In addition, any RSV candidate vaccine should not exacerbate asthma. Different types of vaccine candidates are currently being developed, some of which are being tested in humans.[6-8]

To prevent serious RSV disease in infants and young children, a candidate vaccine has to be administered at a very young age. Since the peak incidence of lower respiratory tract illness lies between 2 and 6 months of age, infants should be immune at this time. In order to mount a sufficiently robust immune response before they become infected, infants should preferably be vaccinated at birth or shortly thereafter. Unfortunately, immune responses of infants are weak due to immune-suppressive maternal antibodies.[9] This might be overcome by maternal immunisation, which evidently necessitates extensive testing of safety issues, including the development of the immune system with regard to Th1 and Th2 responses and associated disease.

Live attenuated vaccines seem to be the most promising vaccines, especially for use in very young children and infants. It has been shown that live vaccines can replicate in the presence of maternal antibodies and thus may induce an immune response. In addition, live attenuated vaccines may be administered intranasally, will induce both local and systemic immune responses, and can be administered multiple times. Conditions for a successful live vaccine are genetic stability and an appropriate balance between attenuation and immunogenicity.

Biologically derived live attenuated vaccines include host-range mutants, cold-passage (cp) mutants and temperature sensitive (ts) mutants. Clinical evaluation of cp and ts mutants learned that these vaccine candidates were either underattenuated or overattenuated, or reversed to wild-type RSV.

Genetically engineered live attenuated vaccines exploit rDNA technology that may help to develop a variant with an optimal balance between attenuation and immunogenicity. Virus with ts mutations and a deletion in the SH gene or NS2 gene are currently being evaluated in clinical trials. Genetically engineering vaccines has also allowed the construction of chimeric viruses containing RSV F and/or G surface glycoproteins. This type of vaccines is being tested in non-human primates.

Subunit vaccines are designed to induce high levels of neutralising antibodies and are normally safe in RSV-seropositive individuals. They appear less suitable for vaccination of very young RSV-seronegative children and infants, but may be used in primed individuals, like the elderly, RSV-seropositive high-risk children, or pregnant women. Subunit vaccines became available, when the F and G glycoproteins could be purified from RSV. These viral glycoproteins are the most immunogenic proteins of the RS virus and induce neutralising and protective antibodies. Several purified protein vaccines have been evaluated in clinical trials: three purified F protein (PFP) vaccines from Wyeth (PFP-1, PFP-2, and PFP-3), co purified F, G and matrix (M) proteins from Aventis Pasteur, and BBG2Na from Pierre Fabre. The latter is a peptide from the RSV G glycoprotein

conjugated to the albumin-binding domain of streptococcal protein G. In addition, a chimeric FG fusion protein was evaluated in clinical trials in adults.
The efficacy of PFP-1 was tested in RSV-seropositive children. Depending on the dose given, part of the children had increased neutralising antibody titres and vaccine recipients were protected against RSV infections for several months after infection. The second-generation purified F protein vaccine (PFP-2) has a greater purity than PFP-1. The efficacy of the PFP-2 vaccine was tested in children with cystic fibrosis and in children with bronchopulmonary dysplasia. The vaccine induced a 4-fold increase in neutralising antibody titres in approximately 50% of vaccine recipients. Although repeated vaccination did not increase the percentage of children with elevated neutralising antibody levels, it decreased the number of children that developed lower respiratory tract disease. Because of the promising results with PFP-2, a third generation purified F protein vaccine was tested in RSV-seropositive children with cystic fibrosis.[10] PFP-3 vaccination induced neutralising antibodies, and reduced the incidence of lower respiratory tract disease. However, differences in children with lower tract disease between the immunised and placebo group were not significant, because the study was underpowered.
A Phase I clinical study was conducted in pregnant women with the PFP-2 vaccine. Vaccination had no adverse effects on mother or child and did not provoke enhanced disease after a RSV episode. The PFP-2 vaccine induced a 4-fold increase in anti-F IgG antibody titres in most vaccinees. These antibody were very efficiently (>100%) transferred over the placenta to the foetus. Transplacental transfer of neutralising antibodies was also efficient.
The subunit vaccine BBG2Na has been tested in Phase I and Phase II clinical trials in healthy young adults. The vaccine induced a ≥2-fold increase in neutralising antibodies against RSV A, but not RSV B, in 33 to 71% of vaccinees. Recently efficacy trials in elderly persons have been completed, but data are not available yet.
BBG2Na seems to be a good candidate for maternal immunisation, since the immune response of neonatal mice against BBG2Na was not suppressed in the presence of maternal antibodies.
The co purified F, G and M proteins (purified from RSV A) were tested in healthy adults and elicited immune responses against both RSV A and RSV B. Studies in other populations are in progress.

Adverse events
The adverse events following experimental live attenuated RSV vaccines in infants were congested nose, feeding, and sleeping problems following the immunisation. Genetically attenuated vaccines are under development affecting cp and ts genes and deletion of non-essential genes. They are used in trial setting currently.
Inactivated vaccines (formaldehyde) were abandoned because of enhancing natural disease (compare inactivated measles vaccines) in infants and young children.[11] The first generation live vaccines tried were either overattenuated or underattenuated.[12] They were either not protective or caused severe disease by return to wild type virus.
Now new generation of inactivated sub-unit vaccines are being tried in clinical studies for those that probably had a first infection previously.[13] They are intended for use in the elderly, pregnant women and in older high-risk children. The first studies of aluminium phosphate subunit vaccines (purified F glycoproteins, purified F-G-M glycoproteins and conjugated G glycoprotein) have been tried in children >12 months, pregnant women en children with cystic fibrosis. Although well tolerated and not followed by enhanced natural disease the effect on lower respiratory infections was equal in vaccine and placebo recipients.[14] Vaccines containing fusion protein G with Streptococcal protein G in phase 2 trial was followed by purpuric disease and 3 times by type III hypersensitivity reactions. This will have to be followed up.[15]

5.7.3 Epidemiology of RSV in the Netherlands

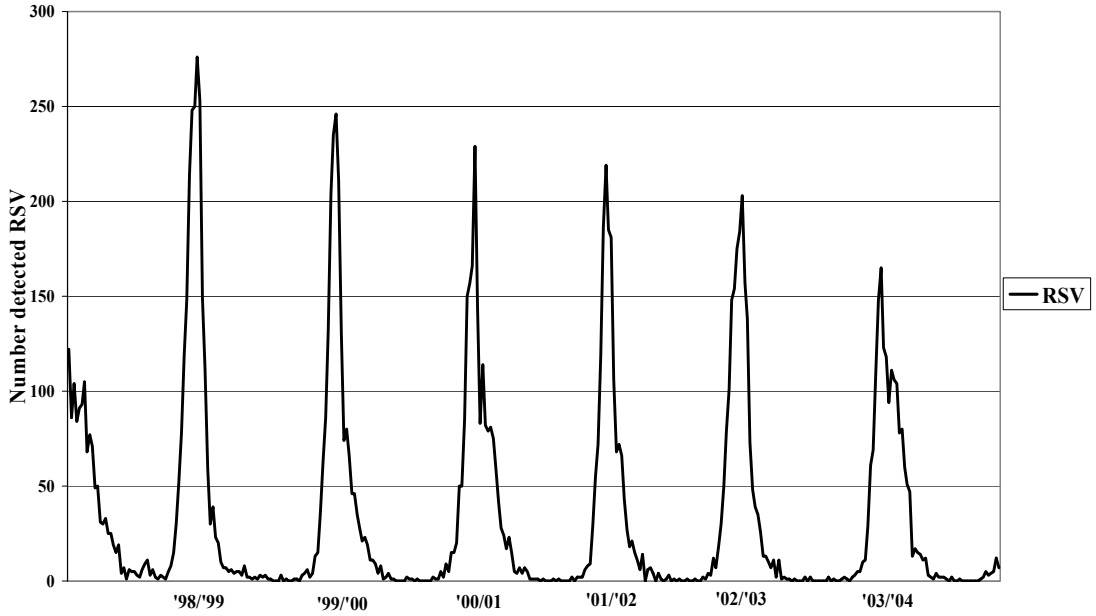

Figure 5-8: Number of RSV diagnoses by the Dutch working group of clinical virological laboratories in the winter seasons 1998/1999 to 2003/2004.

Annual outbreaks of RSV present consistently during the winter seasons. The Dutch working group of clinical virological laboratories showed in the past six seasons a downward trend in the number of RSV diagnoses (figure 5-8). Sentinel data pointed out that the incidence of RSV per 100,000 inhabitants in the period 1994-2003 was the highest in children aged 0-4 years. In the period 2000-2003, the average incidence within this age group was 181 per 100,000 per year, in contrast to the average incidence older children (age group 5-14 years) of 11 per 100,000 per year. In the Netherlands laboratory surveillance (ISIS) of the period 2001-2004 in which predominantly medical microbiology laboratories in the south of the Netherlands report their diagnostic test results, 83% of the RSV cases (defined according to surveillance diagnosis criteria) are children aged <1 years. Fifty-seven percent of all RSV cases are men.

5.7.4 Burden of RSV disease in the Netherlands

Care and costs

Though most cases of RSV infection are relatively mild, some of these cases, especially in infants, lead to hospitalisation. The two main reasons for hospitalisation are pneumonia and bronchiolitis. In the period 2000-2004, the average annual number of hospitalisations for pneumonia (caused by RSV) was 531, of which 450 were for patients ≤12 months, 76 for patients from 1 to 4 years and only 5 for patients 5 years or older. Not all cases of acute bronchiolitis that are hospitalised are caused by RSV. Assuming that 75% of the cases is caused by RSV, the average annual number of hospitalisations for bronchiolitis was 1723, of which 1529 were for patients ≤12 months, 168 for patients from 1 to

4 years and 26 for patients 5 years or older.
In a recent Dutch study, the total cost of hospitalisation for RSV was estimated at €3110 (costs 2000), which is €3421 after adjusting to 2004 costs.[16,17] Combining this with the total number of hospitalisations, this amounts to a total of €7.7 million per year, of which €6.8 million in patients ≤ 12 months. Note that this is a lower limit for the total health care costs for RSV, as it does not include patients who receive ambulatory care for RSV-related diseases. These costs might decrease when vaccination against RSV is implemented. Both RSV-high risk groups and RSV low risk groups show a relatively high burden of disease and for high-risk groups vaccination is cost-effective. For low risk groups cost-effectiveness of vaccination is still uncertain, however.
Disability-adjusted life years (DALYs) lost due to RSV are estimated to be 2200, of which 1540 will be preventable with a 70% effective vaccine (Appendix III).

Work loss and school absenteeism
A Dutch study among parents of hospitalized RSV-patients in three Netherlands hospitals showed that the median number of work days lost was 0.5 (range from 0 to 5) in the two weeks before the admission and 1.5 day (range 0 to 9) during the hospital stay.[18] However, this only concerns work days lost for infants who are hospitalized, and seems likely that work days will be lost for all infants who have a less severe form of RSV-infection.

5.7.5 Cost-effectiveness

A Dutch study about the cost-effectiveness of passive immunisation with Palivizumab against RSV in premature infants showed that the costs per hospitalisation prevented might vary between €17,500 and €888,600.[19] The lowest ratio is found in patients at the highest risk in December, while the highest ratio is found in patients at low risk in October. When treatment is limited to patients who are premature with bronchopulmonary dysplasia and to treatment only from November to January, the cost-effectiveness ratio amounts to €27,750 per hospitalisation prevented. Only when the price of Palivizumab reduces to one third of the current price do cost-savings occur. No detailed cost-effectiveness analysis of RSV vaccination has been made for the Netherlands. Now the Netherlands Vaccine Institute (NVI) conducts a study on the cost-effectiveness of RSV vaccination. The similarity of disease in moderate climates may justify the use of the cost-effectiveness analysis of the Institute of Medicine. This cost-effectiveness analyse was very favourable for an RSV vaccine.

5.7.6 Alternative options for prevention for RSV

As mentioned above, no licensed vaccine for the prevention of RSV infection or disease is available. Current treatments of RSV disease rest on supportive care and antiviral treatment or passive immunisation with Palivizumab. Supportive care mainly consists of fluid replacement, mechanical ventilation and oxygen support. Other treatments include bronchodilators, corticosteroids, exogenous surfactant, and heliox (a mixture of oxygen and helium). Children that are hospitalised with severe RSV disease may also be treated with the antiviral compound Ribavirin or RSV-IGIV.[20]
In addition to supportive care and antiviral treatment, Palivizumab can be given as prophylaxis. Palivizumab (Synagis) is a humanised monoclonal antibody (IgG) directed against the fusion protein of RSV. The American Food and Drug Administration approved it for the prevention of the development of severe RSV illness in children with an increased risk for hospitalisation in 1998.

5.7.7 Considerations regarding uptake of RSV vaccination in the NIP

Given the high burden of RSV associated disease, vaccination against RSV would be a major improvement of the NIP. This goal, however, will not be reached very soon, the major obstacle being the slow and difficult development of a RSV vaccine. An intranasal vaccine gives the advantage that no additional injections have to be administered. When candidate vaccines become available, they should be rigorously tested with regard to safety, especially with regard to the possibility of enhanced disease upon infection of vaccinated children, and with regard to the influence of vaccination on Th2-associated disease, such as asthma.

No detailed cost-effectiveness analysis of RSV vaccination has been made for the Netherlands. However, the similarity of disease in moderate climates may justify the use of the cost-effectiveness analysis of the Institute of Medicine. This cost-effectiveness analyse was very favourable for an RSV vaccine.[21] Specific attention should be paid to the possibility of maternal immunisation (in order to passively protect their newborns), and the possibility of vaccinating elderly against RSV depending on the burden of disease (cost-effectiveness ratio) in elderly. The significance of antigenic variation may be relevant.

5.7.8 International perspectives of RSV vaccination

Not applicable. Both the epidemiology and burden of disease appear roughly equal in moderate climates. Regional differences in hospitalisation policy may occur.

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5.8 Human Papilloma Virus

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5.8.1 Introduction

Human Papilloma viruses (HPV) are the most common sexually transmitted viral agents. Most of the HPV infections are transient. However, a persistent HPV infection might eventually lead to cervical cancer. About 20 different genotypes are able to cause cervical cancer, and the most prominent, so-called High-Risk genotypes are HPV-16 (~55% of cervical cancer cases) HPV-18 (~11%), HPV-45 (~4%) and HPV-31 (~3%). A large period (mean >20 years) is present between the start of the persistent infection and the development of cervical cancer.[1] A clear correlation is present between the severity of the cervical lesions (Cervical Intraepithelial Neoplasm, CIN) and HPV genotype. [2]

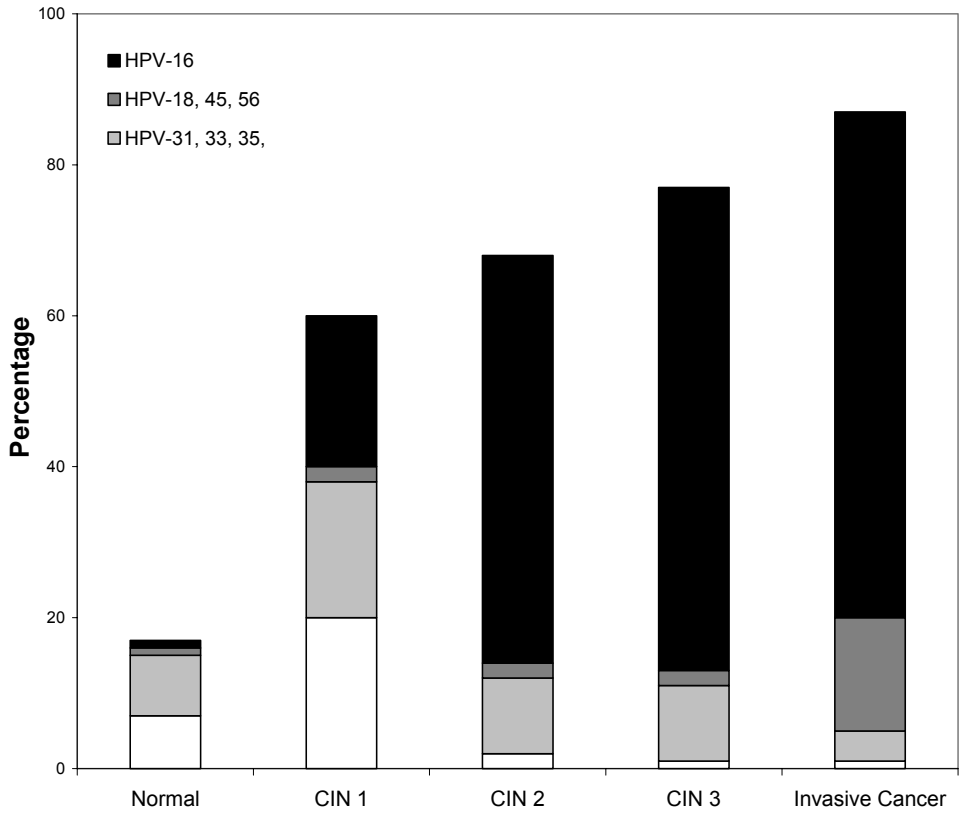

Figure 5-9: Percentage of different human papilloma viruses amongst the different cervical lesion[2]

Pathogenicity

Several animal species (and humans) are the host for the non-enveloped, single shelled papilloma viruses. These viruses normally establish sub-clinical infections, but might induce, depending on the genotype, (genital) warts or cervical cancer after (long-term) persistent infection. Risk groups are persons with multiple sexual contacts. Only ~1% of people infected with HPV-genotypes that are the

causative agents of genital warts, do indeed develop genital warts. A more serious course is found in immuno-compromised persons. Sometimes the so-called giant-condylomata or Burke-Löwenstein-tumours can arise. About 1/5 of people who develop genital warts will recover without treatment in three months and 90% will recover in 2 years.[1]

Infectiveness and transmission route
Depending on the tropism of the different papilloma viruses, the transmission routes are different. The genital HPV genotypes are mostly sexually transmitted.

Antigenic variation
There are large differences within the genus of HPV, which comprises about 90 different genotypes (largely corresponding to different serotypes). Up to 37 different genotypes are able to infect the human genitals, of which 18 different genotypes are associated with the development of cervical cancer. Antigenic variation seems to play no role, as the HPV genome, and hence the antigenic structure, is not reported to change during the long-periods (>20 year) of persistent infection, which precedes the development of cervical cancer.

5.8.2 Vaccines against HPV

Availability
Several major vaccine companies (i.e. GSK and Merck) are conducting phase 3 clinical trials with subunit vaccines based on heterologous expression of the major surface antigen L1. These recombinant L1 proteins are assembled into so-called Virus Like Particles (VLPs) which mimic the antigenic structure of infectious viral particles. Due to the major differences between the L1 sequences of the different genotypes of HPV, there is no cross-protection, and one person can be infected by multiple HPV strains at the same time. This complicates the development of broad-spectrum vaccines, as such vaccines have to contain the VLPs of multiple HPV genotypes.
The first results of a phase 2 clinical trial (n=1533) with a VLP-based HPV-16 vaccine have been published by Merck.[2] Currently Merck is recruiting 20.000 young women for a phase 3 clinical trial, which contains a combination of VLPs of four HPV-genotypes: HPV-16 and HPV-18 (most frequently found to induce cervical cancer) and HPV-6 and HPV-11 (most frequently found to induce genital warts).
GSK has recently published their results of a phase 2 (n=1113) clinical trial of its two-component (HPV-16, and –18; adjuvant is AS04) vaccine, which is also based upon L1 VLPs.[3] GSK has also initiated a 4-year phase 3 clinical trial (13,000 young women).

Effectiveness
The effectiveness of the subunit vaccines was determined in double blind, placebo controlled phase 2 clinical trials with a single component HPV-16 L1 subunit vaccine (Merck [2]) or a bivalent HPV-16/18 (GSK [3]) vaccine. Although transient infection with HPV-16(/18) still occurred in the treated group (vaccine efficacies = 78% (Merck) and 92% (GSK)), there was complete protection (vaccine efficacy = 100%) against persistent HPV-16(/18) infections.
Although the HPV-vaccines show complete protection against persistent infection of HPV-16(/18) in short-term studies (i.e. 17 month for the monovalent Merck vaccine, and 27 month for the bivalent GSK vaccine), no data on long-term protection is available yet. Recent data, presented at an ASM 2004 conference, indicates that the efficacy of the HPV-16 Merck vaccine indeed reduces over time, as persistent HPV-16 infections have now been found in 7 of 775 vaccinated women.

Adverse events

The results of the first phase 2 trials showed no difference in common adverse evens between vaccine recipients and placebo controls, with only 6.8 and 8.3% having no complaints whatsoever.[4-6]Adverse events were mild and transient.

In the phase 3 trial of the Merck vaccine, the rate of adverse events was similar in the vaccine recipients and the controls. The GSK vaccine had an excess of 6% in local reactions compared to the placebo recipients. This did not influence trial participation. No severe adverse events were encountered. However, the study population was too small for detection of more rare events.[7,8]

5.8.3 Epidemiology of HPV in the Netherlands

HPV is not monitored adequately in the Netherlands. Each year ~700 women are diagnosed with cervical cancer, with a 5-year fatality rate of ~30% (http://www.kwfkankerbestrijding.nl), and there are ~2000 hospitalisations for cervical cancer each year since 2000 (LMR-data). The age-standardised incidence rates decreased from 9.1 cases in 1989 to 7.4 cases in 2000 per 100,000 inhabitants. Age standardised mortality rates decreased from 3.3 in 1989 to 2.6 cases in 2000 per 100,000 inhabitants. Age-standardised incidence and mortality rates were highest among elderly women.[9] It is estimated that about ¾ of the population of the USA has been infected by at least one HPV genotype during their live time, while mean time after infection to development of cervical cancer is estimated to be 20 to

30 years.[10] In the Dutch STD-registration an absolute increase of 10% and 15% for HPV related genital warts was found in 2002 for men (546 cases; 496 in 2001; 25% of the affected men were homosexual) and women (396 cases; 345 in 2001).[11] Each year there are ~1200 hospitalisations due to genital warts.[12]

5.8.4 Burden of HPV related disease in the Netherlands

Care and costs

Cervix cancer leads to a broad range of health care resource use. It has been calculated that the total cost-of-illness for cervix cancer was €37.6 million in 1999.[13] The majority of these costs (€22.3 million) are for prevention, while €8.9 million is spent on hospitalisation, outpatient procedures and specialist care, and €5.3 million on pharmaceuticals. Disability-adjusted life years (DALYs) lost due to HPV are estimated to be 5930, of which 4150 will be preventable with a 70% effective vaccine (Appendix III).

For genital warts, one study has been published about the costs and pattern of treatment for external genital warts. This study was done in three dermatology clinics in 1998-1999, and a total cost of approximately €200 per episode was found.[14] It is to be expected that not all patients are referred to a dermatologist, so for some episodes the costs will be lower. However, a more expensive drug has become available for treatment (Imiquimod, approx. €100-150 per treatment), which may increase the cost per episode for some patients. Based on the cost per episode of €200, and the number of cases between 8000 and 14,000, the total costs for genital warts amount to €1.6 to 2.8 million.[7,14,15]

Work loss and school absenteeism

For cervix cancer, work loss may be substantial for some patients, especially for advanced disease. In an American study, it was reported that patients with lesions lost 1.6 days per year, whereas patients with cervical cancer lost 35.4 days per year.[16] Unfortunately, it is not clear from this publication

whether this number pertains to work days or days in general. For genital warts, it is reasonable to assume that work loss is limited to visits to the GP or specialist.

5.8.5 Cost-effectiveness of HPV vaccination

No data on vaccine-related costs are currently available. A USA-based study calculated the incremental cost-effectiveness to be $23,000 per QALY gained, using vaccine-related costs of $300 per 12-year-old girl, and vaccine effectivity at 75% against the high-risk genotypes. [9] Recently, Goldie et al. calculated the cost per QALY gained at $33,700 using total-vaccine related cost of $400 and a vaccine effectivity of 70% in 12-year-old girls against HPV-16 and -18 related cervical cancer.[17] However, it is anticipated that the introduction of vaccine programmes will have a large effect on the (costs of) the cervical cancer screening programme (less pre-stage of cancer that require follow-up diagnostics, and less frequent screening).[3] The financial impact of vaccination on the screening programme has not been taken into account in above quoted calculations. The cost related to screening programme are ~60% of the total burden of disease caused by cervical cancer (see also above).[12]

5.8.6 Alternative prevention and intervention measures of HPV

Screening programmes for cervical cancer are in place in most developed countries. Due to these screenings programmes a large reduction in progressed forms of cervical cancer has been achieved. A major drawback of the current screening programmes is the difficulty in recognising those pre-stage cervical cancers that will develop into progressed stages, as many pre-stage cervical cancers show spontaneous regression. Furthermore, the current screening programmes lack sensitivity, as it has been reported that about half of the cervical cancers in the USA are found among women who are participating in the screening programme.[18]

Genital HPVs are sexually transmitted, and transmission can most likely be prevented by the use of condoms.

5.8.7 Considerations regarding uptake of HPV vaccination in the NIP

Genital HPVs, capable of inducing cervical cancer, are generally found within the Dutch population. A large screening programme is in place to reduce the incidence of cervical cancer. This screening programme however has major drawbacks such as the high costs (~€22 million per year), and the low specificity and sensitivity. Furthermore, the screening programme has little impact on transmission, as it is secondary instead of a primary prevention program.

The recent reports of effective HPV vaccines, based upon L1 VLPs by major vaccine companies, are very encouraging, and it is anticipated that the HPV vaccines Merck (HPV-6, -11, -16, and -18) and GSK (HPV-16, and -18)) will receive a license in Europe in the USA in 2005/2006.

If the effectiveness of these vaccines indeed lasts for a long time, a HPV-16/18 vaccine will be a prime candidate for the incorporation into our NIP. The questions, which will have to be answered before a balanced decision about such an introduction can be taken, are: [19]

- What are the most prevalent carcinogenic HPV serotypes in the Dutch population?
- What are the incidence, prevalence and transmission of HPV-16 and 18 in the Netherlands?
- Will universal adolescent or only the female adolescent vaccination be the most (cost-) effective?
- What are the advantages and disadvantages of childhood vs. adolescent vaccination?
- How will a HPV vaccination affect (the costs off) our cervical cancer screening program?

A (cost-) effectiveness study specific for the Netherlands should preferably be made in the coming years. This will ensure that a decision on the introduction of HPV vaccines can be made quickly and on basis of sound data, once these vaccines have received a license.

5.8.8 International perspectives of HPV vaccination

Considering the promising results of large phase 2 HPV-trials, the potential introduction of HPV vaccination is a relevant issue in several developed countries and for the WHO. [18-22] In view of the large burden of disease (~6000 DALYs in the Netherlands) and the amount of DALYs which is estimated to be vaccine-preventable (~4000 DALYs), the introduction of effective, prophylactic HPV vaccines is highly desirable.

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5.9 Herpes simplex virus

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5.9.1 Introduction

Human herpes viruses are the causative agents of both oral/facial herpes (Herpes Simplex Virus-1; HSV-1) and genital herpes (Herpes Simplex Virus-2; HSV-2). Both HSV-1 and -2 infect the central nervous system, and establish latent infections in the dorsal root ganglia. Reactivation occurs following a variety of local or systemic stimuli. HSV-1 and -2 are found worldwide. HSV-2 is usually sexually transmitted. There is a direct correlation between number of sexual partners and acquisition of HSV-2.

Pathogenicity

Herpes Simplex Viruses causes oral-facial, genital, and cutaneous infections. Furthermore, it can be vertically transmitted and cause neonatal HSV infection (both HSV-1 and HSV-2). Neonatal herpes is very serious and often results in death or neurological damages. HSV-2 is in most parts of the world the leading case of neonatal herpes; however, in the Netherlands (and some other European countries) neonatal herpes is attributed largely to HSV-1 (i.e. ~73% of the cases).[1]

Infectiveness and transmission route

HSV-2 (genital herpes) is usually acquired through sexual contact. Seroprevalence data indicate that ~20% of the adolescent and adult people in developed countries are infected with HSV-2.

Antigenic variation

Herpes viruses establish latent infection by interfering with the cellular immune response. No relevant antigenic variation has been described for HSV-2.

5.9.2 Vaccines against HSV-2

Availability

Phase 3 clinical trials have been, and are being performed with prophylactic HSV-2 subunit vaccines containing either 2 glycoproteins (Chiron, glycoproteins B and D, adjuvant: 5% squalene oil-in-water emulsion MF59) or 1 glycoprotein (GSK, glycoprotein D subunit adjuvant: alum and 3-O-deacylated-monophosphoryl lipid A (MPL).[2,3] Results of these randomised, double-blind, placebo-controlled clinical trials show either no protection against the disease with the Chiron HSV-2 vaccine or partial protection (about 74%) in only a sub-population of the group receiving the GSK HSV-2 vaccine.[2,3] The sub-population that was partly protected by the GSK HSV-2 vaccine consisted of women that were seronegative for both HSV-1 and HSV-2 at base-line. The disappointing result of their phase 3 trail was the reason for Chiron to abandon its HSV-2 vaccine development program. GSK (in co-operation with National Institute of Health, USA) has started a new phase 3 trial with the gD vaccine (coined Simplirix) at the end of 2002, which aims to enrol about 7500 HSV-1 and HSV-2 negative women between ages of 18 and 30 years. Recent reports (April 2004) indicate that GSK has troubles in enrolling enough women for their phase 3 trial.

New vaccine developments

A live, disabled infectious single cycle (DISC) vaccine (DISC-PRO), that is based upon a glycoprotein H deletion mutant of HSV-2 (Xenova, UK, http://www.xenova.co.uk/dc_disk_pro.html) has been developed. This vaccine was found to be well tolerated and immunogenic in a phase 1 study (n=110). Despite the promising results, no phase 2 clinical trial has been initiated yet.

Effectiveness

Based upon data from the USA and UK it appears that at least 50% of the children are being infected with HSV-1. This fact will severely limit the use of the currently gD-HSV-2 GSK vaccine under investigation, as the phase 3 trial has shown that it is only (partly) effective in women who are seronegative for both HSV-1 and HSV-2. Thus only ~20% of the adolescent (i.e. 0.75 [vaccine efficacy] * 0.5 [women] * 0.6 [HSV-1 negative]) will probably be protected through universal vaccination. This vaccine will thus most likely be unsuitable for universal vaccination. Another point of concern is the duration of the protection by the gD-HSV-2 GSK vaccine. As the follow-up time in the completed phase 3 study was only 19 month, no long-term protection rates, or decline in protective immunity can be calculated or estimated yet.

Adverse events

Of the currently tested vaccines in phase 2/3 trials, the most frequent adverse reactions were local soreness and induration/swelling in the majority of vaccinees, affecting use of the arm and interfering with normal activities in 5% (slightly but significantly more than in the participant receiving placebo, (3%).[4] [5,6]For systemic adverse events, mild to moderate and transient, there was no significant difference between recipients of vaccine or placebo. The studies are too small to shed any light on the more rare adverse events. Since there are still problems to be solved concerning the effectiveness with subsequent changes in formulation, final judgment has to be postponed.

5.9.3 Epidemiology of HSV in the Netherlands

Cross-sectional serum bank surveys in the Netherlands report an age-standardised seroprevalence of 8% for HSV-2 and 60% for HSV-1. Seroprevalence increases with age (for HSV-2 up to age 35) and women were more likely to be HSV-2 positive.[7,8] The seroprevalence of HSV-1 among girls aged 0 to 11 years was 25% (0 years: 3%, 1-4 years 18%, 5-9 years 33% and 10-14 years 41%).

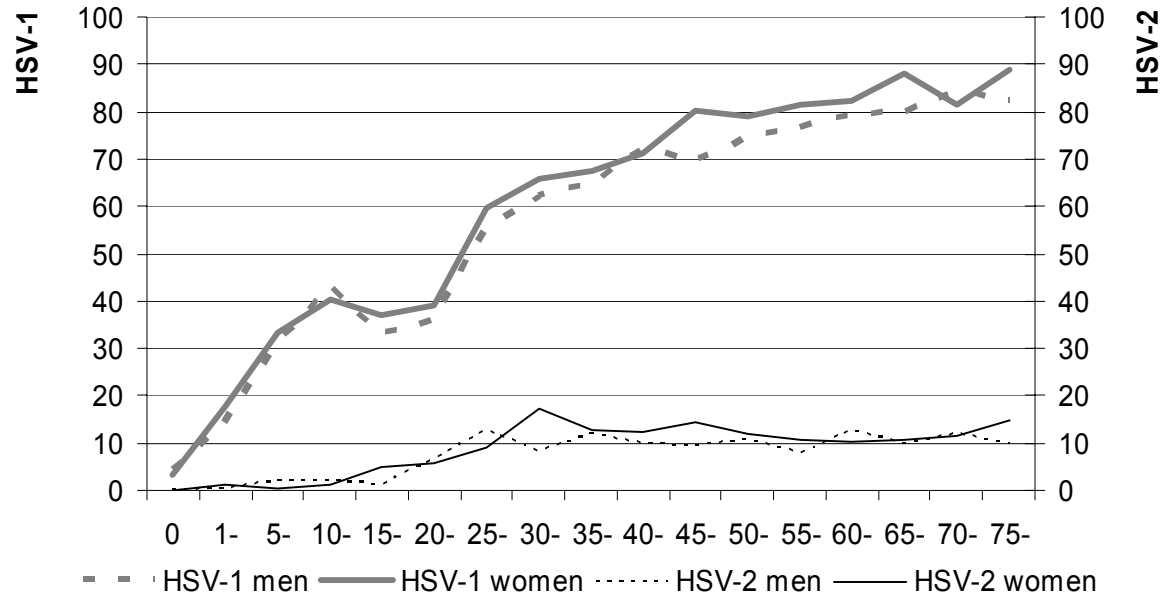

Figure 5-10: Age-specific prevalence of HSV-1 and HSV-2 antibodies in the general population (Pienter-project 1995-1996)

Seroprevalence data from pregnant women from 3 selected cities in the Netherlands (n=1507) show that ~20% are positive for HSV-2 and ~70% for HSV-1.[9] Among Sexually Transmitted Disease Clinic (STDC) attendees in Rotterdam seroprevalence of HSV-2 was 20% in 1998. An increase of ~40% of genital herpes diagnosis (n=606) was reported on basis of STD-clinic data for 2003 in comparison with 2000.[10]

5.9.4 Burden of HSV disease in the Netherlands

Disability-adjusted life years (DALYs) lost due to HSV-2 are estimated to be ~87, of which ~61 will be preventable with a 70% effective vaccine (Appendix III).

Mortality from HSV-2 is quite low in the Netherlands (11 in 2000, 5 in 2001, and 8 in 2003 according to CBS data [http://statline.cbs.nl]), but morbidity is high. USA-Based studies show that ~30% of HSV-2 infected peopled have clear herpes symptoms and ~60% have unrecognised herpes-like symptoms.[11,12] Due to the establishment of latent infection, repeated manifestation of clinical symptoms and subsequent psychological problems can arise.[13]

Neonatal herpes incidence differs from one case per 2500-8500 deliveries (USA) to one per ~65,000, while in the Netherlands (1992-1998) it is reported to be 1 per ~40,000 (i.e. ~5 cases annually).[1]

Care and costs

In the USA, direct medical costs were estimated at a maximum of $984 million for 3.1 million episodes in 1996. Indirect costs to the society accounted for further $214 million. An analysis of 1,565 cases in a claims database gave a minimum national estimate of $283 million direct medical costs.[14]

For the Netherlands, no such detailed studies are available. Thus, only a rough estimate can be made, based on various data sources. In the Netherlands, the average incidence of genital herpes in the GP practice is about 6500 cases per year.[15] Based on another study, it was estimated that the average incidence in GP and specialist practices is about 8700 cases.[15]

Thus, we estimate that 2,200 cases visit a specialist. At a cost of €20 per GP visit and €63 per specialist visit, this leads to an estimated cost of €260,000.[12] Patients are treated with either a topical cream (which is inexpensive) or an anti-viral drug, such as Acyclovir. If the latter is prescribed, the costs of one course of treatment are about €30 (including prescription charge). If patients have many recurrences, more than five per year, it is suggested that patients take the acyclovir for a longer period, at costs of €2 per day. Therefore, assuming that all patients receive the short course of Acyclovir, the costs of medication amount to €260,000 per year.
Some patients require hospitalisation for genital herpes. Between 2000 and 2003, the average number of in-hospital days is approximately 200.[16] At a cost of €359 per day, this amounts to €72,000.
Combining all cost estimates, we arrive at estimated costs of €592,000 (i.e. 3,700 EUR/100,000 per year) for the Netherlands on a yearly basis, which is considerably less than calculated for the USA situation (i.e. 97,000 USD/100,000 per year).

Work loss and school absenteeism
In a study about patients' perspective on the burden of recurrent genital herpes, patients with at least two symptomatic episodes of genital herpes in the previous year were asked about quality of life and workplace productivity.[13] The average number of recurrences in the 298 included patients was 6.0 in the last year, with 50% of the patients having had 2-4 recurrences. During a typical episode, about 3.2 days of work are effected by the herpes symptoms. Furthermore, on average, 0.4 workdays were missed in the preceding 3 months because of genital herpes symptoms.
However, it should be noted that this is a relatively small population of all patients with genital herpes. According to SOA clinics, of the total number of consultations for genital herpes, between 13% and 23% concerned recurrent patients.[15]

5.9.5 Cost-effectiveness

No cost-effectiveness studies have been published about HSV vaccination, except for the Institute of Medicine study.[17] On their website, a spreadsheet can be downloaded, in which some (rough) calculations are made about the cost-effectiveness of a hypothetical vaccine for HSV. When we limit their calculations to genital and neonatal herpes, the two types associated mostly with HSV-2, the cost-effectiveness ratio amounts to $35,250 per QALY gained. This estimate is based on vaccination of about 50% of all 12-year olds, and a vaccine efficacy of 75%.
For the Dutch situation, it seems reasonable to expect that the cost-effectiveness ratio is higher, i.e. less favourable, as health care costs are higher in the US.

5.9.6 Alternative prevention and intervention measures for HSV

HSV-2 is a sexual transmitted disease, and transmission can be most likely be prevented by the use of condoms. An HSV-2 infection is often (< 50%) not recognised. Active HSV infections are best treated with the antiviral acyclovir, but this will not prevent the establishment of a latent infection with unpredictable reactivation.

5.9.7 Considerations regarding uptake of HSV-2 vaccine in the NIP

There is only one vaccine (the sub-unit gD-HSV-2 vaccine of GSK) which is currently tested in a phase 3 clinical trial. This vaccine has shown only limited potential in a previous phase 3 clinical trial, as it was only partially protective in women who were negative for both HSV-1 and HSV-2 at the start of vaccination. Due to the high infection rate of HSV-1 (>50% in pre-adolescent) and HSV-2 (up

to 20%) in sexually active women, it is unlikely that the current gD-HSV-2 vaccine will be suitable for universal vaccination.
It is anticipated that it will take >10 years before an HSV-2 vaccine will be available for introduction into our NIP.

5.9.8 International perspectives of HSV-2 vaccination

HSV-1 as a cause of genital herpes is increasing world-wide, and for the UK it is estimated that half of the primary cases of genital herpes are now caused by HSV-1.[18,19] The relative importance of HSV-1 in genital herpes in the Netherlands is also found in neonatal herpes, as ~3/4 of the cases are caused by HSV-1.[1]

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5.10 Tuberculosis

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5.10.1 Introduction

Tuberculosis (TB) is caused by bacteria from the *Mycobacterium TB*-complex. The name is derived from the typical 'tuberculae' (Latin for nodes), which are found in the affected tissues and indicate a granulomatous inflammatory reaction. In the Western world, TB has declined since living conditions were improved. Other reasons for this decline are decontamination of livestock, good organized TB control programmes and adequate treatment. In developing countries, TB is still on the rise and causes most deaths among adults compared to other infectious diseases. Reasons for this increase are the ongoing growth of the population and the global HIV epidemic. Human tuberculosis has been labelled a global emergency by the World health Organization, with an estimated 8.7 million new cases and 1.7 million deaths from TB each year.[1]

Transmission and infectiveness

Transmission of tubercle bacteria occurs via aerosols and dust. After inhalation, they are engulfed by the macrophages in the lung alveoli, followed by transportation to the regional lymph nodes. Antigen presentation results in T-cell mediated immune response

Pathogenicity

About 10-15% of infected persons develop active TB in life. 80% Takes place in the first two years. Symptoms are fatigue, apathy, weight loss, sub febrile temperature and night sweats. In case of lung TB there is a productive cough and eventually haemoptoe. Severe course results in miliary TB or meningitis. Incubation period varies from some weeks to lifelong.[1]

Antigenic variation

There is strain variation in susceptibility for antibiotics. Resistant strains have developed because of inadequate treatment courses. In the Netherlands, there are about 10 patients yearly with multiresistant TB until 2002. In 2003 there were 17 patients with multiresistant tuberculosis, which could indicate an increase.[2] These are mostly cases from abroad. Multiresistant TB is defined as resistance against at least Izoniazid and Rifampicin. Multiresistant TB is often accompanied with longer duration in hospital and treatment, increased mortality (14%) and more surgical operations. By monitoring of multiresistant transmission and taking prevention measures, many costs can be saved.[3] One type that is found more and more in the Netherlands is the Beijing-genotype. This type is associated with multiresistance. In March 2004, it was the first time that secondary cases of multiresistant TB were found. 6 People were infected by a patient from Eastern Europe and this outbreak was associated with high costs.[3]

5.10.2 Vaccines against Tuberculosis

Availability

Two French investigators developed the Bacille Calmette-Guérin (BCG) -vaccine, which is licensed since the first half of the 20th century. BCG is a live attenuated bovine strain. It is inexpensive to

produce and administration is simple. WHO advises BCG vaccination for all neonates in countries with a high incidence of TB. In countries with low incidence BCG vaccination is limited to high-risk populations.[4] In the different countries varying strains of BCG are used, strain variation is caused by continued cultivation.[1] The Netherlands and the USA are the only countries that never recommended routine vaccination with BCG.[4] In the Netherlands, travellers to high endemic countries for more than 3 months and children of parents from high endemic countries with indication for frequent travelling to their country of origin are advised to get BCG vaccine.
New vaccines are in development like plasmid DNA vector-based vaccines, recombinant and mutant BCG vaccines, subunit vaccines and attenuated *M. tuberculosis* vaccines. A clinical trial with a new TB vaccine (MVA85A) is planned in the UK. In calves a booster with MVA85A vaccine gave better efficacy than BCG vaccine alone.[4,5] Clinical trials with a novel modified BCG vaccine expressing a major secreted protein from *M. tuberculosis* (rBCG30) have started in the USA and South Africa.

Effectivity
Mean duration of protection is 10 to 15 years.[6] There have been many studies on the effect of BCG vaccine with many inconsistencies in results. The most important point in BCG vaccination is that it does protect against the severe forms like miliary TB and meningitis, but efficacy against TB-infection itself is unknown. Efficacy ranges from 0%-80%. These differences can probably attributed to different incidences of TB, different kind of vaccines and different kind of measurement-tools used in these studies. The studies with a high efficacy (75% or more) were done in northern geographic areas with low prevalence and the methodology and statistical precision of these trials have been judged superior to the other trials with lower efficacy. [4,7]

Adverse events
The adverse events following BCG vaccine are usually mild and transient.[8] Local reactions are common, depending on age, technique, skill and preparation. 95% of vaccinees develop an ulcer, which will leave a scar, more prominent in adults and older children than in infants. Adults suffer from muscle ache in 75% of cases and have regional lymphadenopathy in 2%. Ulceration of superlative lymphadenitis is reported in less than 1%. Disseminated BCG-itis is a rare complication in immunocompetent vaccinees, with frequent vaccination and faulty procedures as risk factors. Silent non-fatal dissemination does also occur, but the rate is not known; granulomas in unrelated death cases have been found. In rare cases, spread of the mycobacterium to other body sites or to other persons is documented, but it is very unusual of the BCG particles to become airborne.
A disadvantage of BCG vaccination is that the diagnostic value of tuberculin testing disappears.

5.10.3 Epidemiology of Tuberculosis in the Netherlands

TB is a disease that must be reported to the Inspection of Health in the Netherlands. So, cases of TB in the Netherlands are registered there.[3] About 1400 new TB patients are registered annually. In 2000, 63% had a non-Dutch nationality.[1,9] Incidence rate among non-Dutch persons was 136/100,000 and among Dutch persons it was 4.3/100,000 persons. 30 Percent of new active cases is being registered in four big cities (Amsterdam, Rotterdam, The Hague and Utrecht). The number of new TB patients decreased in 2002 with 8% (from 1436 to 1368).[3] However, in the big cities the number of newly registered TB patients levelled of or even increased. In Amsterdam in 2003 195 patients were registered of which 3 died of TB.[9] If patients are not treated, half of them will die in two years.[10] TB in the Netherlands is mostly found among high risk groups.[11] Risk groups are asylum seekers, other migrants from countries with a high prevalence of TB, detainees, family members, caretakers,

partners and other contacts of infective patients, older patients, drug users, illegally, sailors and homeless people.

5.10.4 Burden of TB disease

The total number of cases per year is about 1400. Hospitalisation is required for 625 patients per year (2000-2004), with an average length of stay of 23 days. In addition, 115 patients are admitted for day-treatment.
Disability-adjusted life years (DALYs) lost due to tuberculosis are estimated to be 1342, of which 537-1073 will be preventable with a 40-80% effective vaccine (Appendix III).

Care and costs
An RIVM study about the cost-of-illness of TB shows that the annual costs amount to €35 million. These costs include the costs of diagnostics and treatment (€13 million), prevention and surveillance (€21 million) and diagnostics and treatment for people suspected to have been infected by the index patient (€0.7 million).[12]

5.10.5 Cost-effectiveness of Tuberculosis vaccination

In a study in Japan where TB incidence is low too, universal prevention with vaccination gave higher costs than treatment of all TB cases. The costs of treatment in a 2-year old child with TB were estimated at $10500, while the cost of preventing one case of TB was estimated at $ 35950 to
$ 175862, for a vaccine efficacy of 80% and 40%, respectively. This result was heavily dependent on the duration of protection.[13]

5.10.6 Alternative options for prevention of tuberculosis

If asylum seekers or immigrants enter the Netherlands, they are screened for TB with an X-ray or with a tuberculin test. If there is a TB patient, the Municipal Health Service (MHS) starts contact tracing in the first ring of contacts of the patient. After that, the second ring is investigated and so on. Contacts get prophylaxis, so they will not develop TB. The patient itself is kept away from work, school and kindergarten. The patients are taught how to cough in a hygienic way. For contact tracing, the tuberculin test is used. However, patients born before 1945 and vaccinated patients will almost all have a positive reaction. There is a new TB test on the market. This test can also be used in vaccinated persons and persons who ever had TB. TB can be found in an early stadium, which is important for starting therapy.[14] Treatment consists of four antibiotics: Izoniazid (INH), Streptomycin, pyrazinamid and ethambutol for 2 months. After that, Izoniazid and ethambutol are taken for four more months. In the Netherlands, patients who get medication for TB are observed while taking their medicines by social nurses. This strategy is called Directly Observed Treatment (DOT). Patients have to come to the MHS or TB clinic (Dekkerswald or Beatrixoord) to take their medicines. In this way, the nurse can monitor if all medications are taken and when the patient does not show up, she can start action to find the patient. The major goal of DOT is completion of treatment, which is needed to cure the patient and to prevent development of resistance.[1,11]

5.10.7 Considerations regarding uptake of TB vaccination in the NIP

The current BCG vaccine is considered not to be valuable for the NIP for the following reasons. There are only 1400 cases yearly in the Netherlands. There is a good treatment procedure in the Netherlands even for asylum seekers. However, treatment course must be taken care of, because of the long duration and some side effects. If the treatment course is not fully completed, there is a risk for development of resistance. Social nurses apply Directly Observed Treatment in the Netherlands. This medication regime gives a low mortality of TB in the Netherlands. In addition, there are many prevention methods like contact tracing with radiology and tuberculin tests. Asylum seekers and immigrants are screened at the time they come in the Netherlands.

A significant part of the cases is illegal and has no insurance. It is impossible to vaccinate those people, because they caught the disease in their country of origin before coming to the Netherlands.

The effect of BCG is not known for preventing TB itself. Miliary TB and meningitis are prevented, but the effect on the disease itself is unknown. Because of the low overall prevalence, with concentrated epidemics only in high-risk groups, and the unknown effect of the vaccine, it is too early to say whether the vaccine should be incorporated in the NIP. It must be taken into consideration that more people from Eastern Europe will come to the Netherlands now that many Eastern European countries have become part of the European Union. In those countries, TB prevalence and incidence are very high, especially of multiresistant TB. Therefore, in the near future possible implementation of vaccination against TB might have to be re-evaluated because the incidence of TB can increase. In addition, if novel more efficacious vaccines would become available the feasibility of vaccination should be reconsidered.

5.10.8 International perspectives

More and more countries are trying to implement DOT. This treatment regime has 82% success in TB cases. The only problem in this treatment is the finding of cases. Programmes are set up to find TB cases. The development and execution of good contact tracing programmes gets high priority.[3] WHO has recommended a single dose of BCG for all newborns in developing countries with a high prevalence rate of infectious tuberculosis. The UK adopted this strategy. The optimal vaccine strain of BCG, the dosing schedule, the route of administration, and the age of the recipient have not been established firmly. Many countries that saw a decline in TB cases have discontinued or want to discontinue BCG vaccination. The HIV epidemic has a great influence on TB. The effect of BCG vaccination in HIV infected children is unknown. Epidemiology and autopsy studies will be particularly useful in establishing the role of mass BCG vaccination in developing countries.[4]

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Appendix I. Overview changes NIP since 2000

Table 1: National Immunisation Programme 1st July 2001 – 31st August 2002 (change: P_a added at 4 years of age, for all children born on or after 1.1.1998).

Age	Injection 1	Injection 2
2 months	DTP_w-IPV-1	Hib-1
3 months	DTP_w-IPV-2	Hib-2
4 months	DTP_w-IPV-3	Hib-3
11 months	DTP_w-IPV-4	Hib-4
14 months	MMR-1	
4 years	DT-IPV-5	**P_a**
9 years	DT-IPV-6	MMR-2

Table 2: National Immunisation Programme 1st September 2002 – 28th February 2003 (change: Men C added at 14 months of age, for all children born on or after 1.6.2001. For details about the catch-up campaign see paragraph 2.1)

Age	Injection 1	Injection 2
2 months	DTP_w-IPV-1	Hib-1
3 months	DTP_w-IPV-2	Hib-2
4 months	DTP_w-IPV-3	Hib-3
11 months	DTP_w-IPV-4	Hib-4
14 months	MMR-1	**Men C**
4 years	DT-IPV-5	P_a
9 years	DT-IPV-6	MMR-2

Table 3: National Immunisation Programme 1st March 2003 – 31st December 2004 (change: Hib given combined with DTP_w-IPV, and HB added for infants in specified risk groups born from 1.1.2003 onwards).

Age	Injection 1	Injection 2
2 months	**DTP_w-IPV-1 / Hib-1**	**HB-1***
3 months	**DTP_w-IPV-2 / Hib-2**	
4 months	**DTP_w-IPV-3 / Hib-3**	**HB-2***
11 months	**DTP_w-IPV-4 / Hib-4**	**HB-3***
14 months	MMR-1	Men C
4 years	DT-IPV-5	P_a
9 years	DT-IPV-6	MMR-2

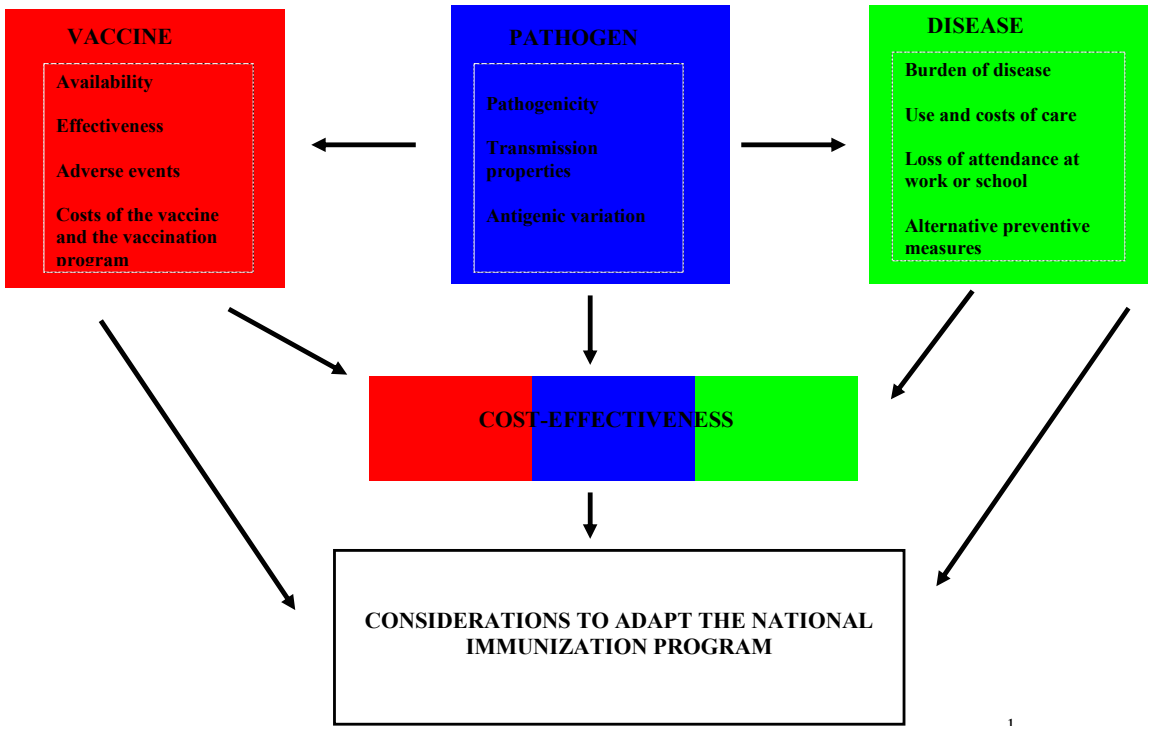
*Only specific groups

Table 4: National Immunisation Programme 1st January 2005 onwards (change: P_w replaced by P_a at 2,3,4 and 11 months of age).

Age	Injection 1	Injection 2
2 months	DTP_a-IPV / Hib - 1	HB-1*
3 months	DTP_a-IPV / Hib - 2	
4 months	DTP_a-IPV / Hib - 3	HB-2*
11 months	DTP_a-IPV / Hib - 4	HB-3*
14 months	MMR-1	Men C
4 years	DT-IPV-5	P_a
9 years	DT-IPV-6	MMR-2

*Only specific groups

Appendix II. Diagram for systematic approach composition National Immunisation Programme



Appendix III. DALYs

The tables below present the burden of disease expressed in disability-adjusted life years (DALYs). DALYs are the sum of life-years lost and disease year-equivalents. Disease year equivalents are calculated by multiplying the number of years diseased with a weight for severity of disease, as judged by an expert panel. These estimates are mainly based on a previous RIVM report (Van der Zeijst et al., 2001, 'Towards a Dutch national vaccination programme for the 21st century'. RIVM-report No. 000001001) about the future of the Dutch immunisation programme. In that report, details are given about the assumptions and data-sources underlying the DALY-estimates. In this report, we present these numbers, with adjustments for situations where either better estimates of disease incidence have been obtained, or where the incidence has changed in the last few years. See the relevant chapters for more details on these estimates. For HPV and RSV, incidence and mortality estimates are still valid, so these have not been changed.

Pneumococcal disease 0-4 years	**Total burden of disease (DALY)**	**Preventable burden of disease (DALY)**
Life-years lost meningitis + sepsis, age 0-4 years Number of deaths: 20*; life expectancy 75 years; efficacy vaccine 40%	1517	600
Life-years lost pneumonia, Age 0-4 years Number of deaths: 7*; life expectancy 75 years; efficacy vaccine 47%	559	261
Disease year-equivalent acute meningitis, Age 0-4 years Incidence: 119*; Weight 0.1 (year-equivalent); efficacy vaccine 40%	12	5
Disease year-equivalent Acute pneumonia, age 0-4 years Incidence: 149*; Weight 0.1 (year-equivalent); efficacy vaccine 47%	214	85
Disease year-equivalent Meningitis sequelae, Incidence: 14*; Duration 75 year; Weight 0.2; efficacy vaccine 47%	15	7
Total (excluding otitis media)	2317	958
Disease year-equivalent Otitis media 1-4 years Incidence: 200,000; Weight 0.1 (year-equivalent); efficacy vaccine 27%	1000	270
Disease year-equivalent Hearing loss after otitis media Incidence: 5; Duration 75 year; Weight 0.12; efficacy vaccine 45%	100	45
Total including otitis media	3417	1273

*Numbers have changed from previous report

Invasive pneumococcal disease 65+ years	**Total burden of disease (DALY)**	**Preventable burden of disease (DALY)**
Life-years lost **Number of deaths: 160; life expectancy 10 years; efficacy vaccine 64%**	1600	1024
Disease year-equivalent **Incidence: 4000; Weight 0.1 (year-equivalent); efficacy vaccine 64%**	400	256
Total	2000	1280

Influenza*	**Total burden of disease (DALY)**	**Preventable burden of disease (DALY)**
Life-years lost **Number of deaths: 369** **Efficacy vaccine 60%**	3134	376§
Disease year-equivalent **Incidence: 1,075,100** **Efficacy vaccine 60%**	10800	5570†
Total	13934	5946

*Information based on "National Compass Public Health 2000" – www.rivm.nl

§ Almost all deaths occur in people over 65 years. In this group, the percentage of vaccinated people was 81% in 1998. Thus, only in the remaining 19% can additional life-years be gained.

† Based on 10% of cases 65+ and 90% 65-; 81% currently vaccinated in patients of 65+, and 6.6% in patients 0-64 years

Hepatitis A	**Total burden of disease (DALY)**	**Preventable burden of disease (DALY)**
Life-years lost **Number of deaths: 2*; life expectancy 36 years; efficacy vaccine 90%**	72	65
Disease year-equivalent **Incidence: 600*; Duration 0.04 years; Weight 0.21; efficacy vaccine 90%**	5	5
Total	77	70

*Numbers have changed from previous report

Rotavirus	**Total burden of disease (DALY)**	**Preventable burden of disease (DALY)**
Life-years lost	0	0
Disease year-equivalent **Incidence 0-4 years: 66,000*; Weight 0.017 (year-equivalent); efficacy vaccine 60-90%**	1122	673-1010
Total	1122	673-1010

* Numbers have changed from previous report

Varicella zoster virus	**Total burden of disease (DALY)**	**Preventable burden of disease (DALY)**
Varicella **Life-years lost** **Number of deaths: 3.5; life expectancy 45 years; efficacy vaccine against severe varicella 90%**	158	142
Disease year-equivalent **Incidence: 200,000; Weight 0.005 (year-equivalent); efficacy vaccine against severe varicella 90%**	1000	810
Zoster **Life-years lost** **Number of deaths: 17; life expectancy 5 years; efficacy childhood vaccine unknown**	85	-
Disease year-equivalent **Incidence: 52,000*; Weight 0.01 (year-equivalent); efficacy childhood vaccine unknown**	520	-
Total	1763	952

*Number has changed from previous report

Meningococcal disease B	**Total burden of disease (DALY)**	**Preventable burden of disease (DALY)**
Life-years lost, age 0-12 months Number of deaths: 8.3*; life expectancy 75 years; efficacy vaccine 31%	623	194
Life-years lost, Age 1-4 years Number of deaths: 16*; life expectancy 72 years; efficacy vaccine 64%	1130	723
Disease year-equivalent acute disease, age 0-12 months Incidence: 63*; Weight 0.1 (year-equivalent); efficacy vaccine 31%	6	3
Disease year-equivalent Acute disease, age 1-4 years Incidence: 118*; Weight 0.1 (year-equivalent); efficacy vaccine 64%	12	8
Disease year-equivalent sequelae, Incidence: 9*; Duration 75 year; Weight 0.2; efficacy vaccine 50%	136	68
Total	1907	996

* Numbers have changed from previous report

RS-virus	**Total burden of disease (DALY)**	**Preventable burden of disease (DALY)**
Life-years lost Number of deaths: 4; life expectancy 50 years; efficacy vaccine 70%	200	140
Disease year-equivalent Incidence: 200,000; Weight 0.01 (year-equivalent); efficacy vaccine 70%	2000	1400
Total	2200	1540

Human papilloma virus Cervical cancer	**Total burden of disease (DALY)**	**Preventable burden of disease (DALY)**
Life-years lost Number of deaths: 234; life expectancy based on patient-specific data; efficacy vaccine 70%	4600	3220
Disease year-equivalent Incidence: 700; Duration 1 year; Weight 1.9; efficacy vaccine 70%	1330	930
Total	5930	4150

Herpes simplex type 2	**Total burden of disease (DALY)**	**Preventable burden of disease (DALY)**
Life-years lost	0	0
Disease year-equivalent Incidence: 8700*; Weight 0.01 (year-equivalent); efficacy vaccine 70%	87	61
Total	87	61

* Numbers have changed from previous report

Tuberculosis*	**Total burden of disease (DALY)**	**Preventable burden of disease (DALY)**
Life-years lost Number of deaths: 91; efficacy vaccine 40-80%	1152	460-922
Disease year-equivalent Incidence: 830; Duration 1 year; Weight 0.23; efficacy vaccine 40-80%	190	76-152
Total	1342	537-1073

*Information based on "National Compass of Public Health 2000" – www.rivm.nl