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The effects of vaccination, the incidence of the target diseases

S van den Hof, MAE Conyn-van Spaendonck,
HE de Melker, ELPE Geubbels, AWM Suijkerbuijk,
E Talsma, AD Plantinga, HC Rümke

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RIVM National Institute of Public Health and the Environment
PO Box 1, 3720 BA Bilthoven, the Netherlands tel +31 30 2749111, fax +31 30 27422971

Mailing list

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145	Réseau National de Santé Publique Hospital National Saint- Maurice, Saint-Maurice, Dr.S.Baron
146	Centre International de l'Enfance et de la Famille, Paris, Dr.N.Guérin
147	Instituto Superiore di Sanita, Communicable Disease Unit, Laboratory of Epidemiology & Biostatistics, Rome, Dr.S.Salmaso
148	Instituto Nacional de Saudé, Lisboa, Dr.T.Paixao

149 Swedish Institute for Infectious Disease Control, Stockholm, Dr.J.Giesecke
150 Swedish Institute for Infectious Disease Control, Stockholm, Dr.P.Olin
151 Communicable Disease Surveillance Centre, London, Dr.E.Miller
152 Communicable Disease Surveillance Centre, London, Dr.K.Osborne
153 Communicable Disease Surveillance Centre, London, Mr.Nigel Gay
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Abbreviations

AFP	Acute Slappe Verlamming / Acute Flaccid Paralysis
CBS	Centraal Bureau voor de Statistiek / Central Bureau of Statistics
CIE	Centrum voor Infectieziekten Epidemiologie / Department for Infectious Diseases Epidemiology
CMRN	Continue Morbiditeits Registratie Nijmegen / Continuous Morbidity Registration Nijmegen
CRS	Congenitaal Rubella Syndroom / Congenital Rubella Syndrome
CSF	Cerebrospinaal vocht / Cerebrospinal fluid
GGD	Gemeentelijke of Gemeenschappelijke GezondheidsDienst / Public Health Service
IGZ	Inspectie GezondheidsZorg / Inspectorate of Health
ISIS	Infectieziekten Surveillance Informatie Systeem / Infectious Diseases Surveillance Information System
LMR	Landelijke Medische Registratie / National Medical Registration
LNR	Landelijke Neonatologie Registratie / National Neonatological Registry
LSI	Laboratorium Surveillance Infectieziekten / Laboratory Surveillance Infectious Diseases
LVR	Landelijke Verloskunde Registratie / National Obstetrical Registry
MML	Medisch-Microbiologische Laboratoria / Medical Microbiological Laboratoria
NIVEL	Nederlands Instituut voor Onderzoek van de Gezondheidszorg / Dutch Institute for Research on Health Care
NSCK	Nederlands Surveillance-Centrum Kindergeneeskunde / Netherlands Paediatric Surveillance Centre
PCR	Polymerase Ketting Reactie / Polymerase Chain Reaction
PEA	Provinciale EntAdministratie / Provincial Vaccination Administration
RBM	Referentielaboratorium Bacteriële Meningitis / Netherlands Reference Laboratory Bacterial Meningitis
RIVM	Rijksinstituut voor Volksgezondheid en Milieu / National Institute of Public Health and the Environment
RVP	RijksVaccinatieProgramma / National Vaccination Programme
SAS	Statistical Analysis Computer Program
SES	Sociaal Economische Staat / Social Economic Status
SIG	Stichting Informatiecentrum Gezondheidszorg / Foundation Information Centre for Health Care
SOP	Standard Operating Procedure
SSPE	Subacute Sclerosing PanEncephalitis
TNO	Nederlandse Organisatie voor Toegepast-Natuurwetenschappelijk Onderzoek / Netherlands Organisation for Applied Scientific Research

Contents

Samenvatting

Door verbetering van sociaal-economische omstandigheden en de daarmee samenhangende hygiëne, en de invoering van het Rijksvaccinatieprogramma (RVP), komen de doelziekten uit het RVP tegenwoordig weinig meer voor. Inzicht in het vóórkomen van de ziekten blijft nodig om zo tijdig mogelijke secundaire effecten van het vaccinatieprogramma te herkennen. De vaccinatiegraad is erg hoog in Nederland maar er zijn grote geografische verschillen binnen het land. De vaccinatiegraad is laag in gemeenten waar groepen die vaccinatie om religieuze redenen afwijzen, zijn geclusterd. De groepsimmuniteit zou kunnen worden doorbroken in sociaal en geografisch geclusterde niet-gevaccineerde groepen. Dit wordt geïllustreerd door de laatste polio-epidemie in 1992-1993, waar alleen personen getroffen werden die op grond van hun religieuze overtuiging tegen vaccinatie zijn. Verder komen in deze gemeenten met een lage vaccinatiegraad, maar ook in gemeenten met een hoge vaccinatiegraad, nog steeds epidemische verheffingen van mazelen en kinkhoest voor.

In dit rapport wordt het vóórkomen van de doelziekten uit het RVP (mazelen, bof, rode hond, difterie, tetanus, kinkhoest, poliomyelitis en invasieve *Haemophilus influenzae* type b (Hib) infecties), van hun complicaties en van invasieve meningokokken- en pneumokokken-infecties, waartegen op dit moment vaccins worden ontwikkeld, beschreven op basis van data verkregen uit diverse surveillance-systemen.

Sterfte wordt geregistreerd door het Centraal Bureau voor Statistiek (CBS) en ziekte in verschillende registraties. Alle doelziekten van het RVP behalve invasieve Hib-infecties zijn aangifteplichtig, als ook invasieve meningokokken-infecties. Andere landelijke instituten waarin ziekten worden geregistreerd zijn de Landelijke Medische Registratie (LMR) van de Stichting Informatiecentrum Gezondheidszorg (SIG), waar ziekenhuisopnames worden geregistreerd, het Nederlands Signalerings-Centrum Kindergeneeskunde (NSCK), waar een aantal (zeldzame) aandoeningen bij kinderen worden geregistreerd, en de Katholieke Universiteit Nijmegen waar subacute scleroserende panencephalitis (SSPE) wordt geregistreerd. Regionale registratie wordt uitgevoerd door de European Registration of Congenital Anomalies (EUROCAT), waar aangeboren afwijkingen worden geregistreerd en de Continue MorbiditeitsRegistratie Nijmegen (CMRN), waar redenen voor huisartsbezoeken worden vastgelegd. Door het Nederlands Instituut voor Onderzoek naar de Gezondheidszorg (NIVEL) is een huisartsenpeilstation opgezet dat ongeveer één procent van de Nederlandse bevolking beslaat. Landelijke laboratoriumsurveillance wordt uitgevoerd door het Nederlands Referentie-laboratorium Bacteriële Meningitis (RBM), waar elk bacteriologisch laboratorium isolaten heen kan sturen voor typering, door het RIVM dat bijna exclusief voor Nederland serologische testen voor kinkhoest uitvoert en door de klinisch-virologische laboratoria.

Op basis van de resultaten geven wij aanbevelingen voor de surveillance van de doelziekten van het huidige RVP en van invasieve meningokokken- en pneumokokken-infecties. Naast voortzetting van de surveillance wordt aanbevolen additioneel onderzoek te doen bij epidemische verheffingen en epidemieën om zodoende meer inzicht te krijgen in de circulatie en eventuele antigene varianten van de ziekteverwekkers en in kenmerken van de personen die erdoor getroffen worden.

Summary

As a result of improved socio-economic conditions with improved hygiene, and the introduction of the National Vaccination Programme (RVP), the incidence of the RVP target diseases is low nowadays. Insight into the occurrence of the diseases remains necessary in order to be able to signal possible secondary effects at an early stage. The vaccination coverage is very high in the Netherlands, but considerable geographic differences exist within the country. The vaccination coverage is low in municipalities where groups that reject vaccination on religious ground, are clustered. Herd immunity can be broken in socially and geographically clustered groups of unvaccinated people. This is illustrated by the poliomyelitis outbreak that occurred in 1992-1993, where only persons opposed to vaccination on religious grounds were affected. Furthermore, outbreaks of measles and pertussis still occur in some municipalities, no matter whether vaccination coverage is low or high.

In this report, we describe the occurrence of the RVP target diseases (measles, mumps, rubella, diphtheria, tetanus, pertussis, poliomyelitis and invasive *Haemophilus influenzae* type b (Hib)), their complications, and invasive meningococcal and pneumococcal infections. We draw information from the data from various surveillance systems, for our description. Mortality is registered by the Central Bureau of Statistics (CBS), and morbidity in various registrations. All RVP target diseases, except Hib disease, are notifiable, as is meningococcal disease. Other national institutes with disease-registration systems are the National Medical Registration (LMR) of the Foundation Information Centre for Health Care (SIG), which registers hospital admissions, the Netherlands Paediatric Surveillance Centre (NSCK), which registers rare diseases in children, and the University of Nijmegen which registers subacute sclerosing panencephalitis (SSPE). Regional registration is carried out by the European Registration of Congenital Anomalies (EUROCAT) and the Continuous Morbidity Registration Nijmegen (CMRN) in which reasons for consulting the general practitioner are registered. The Dutch Institute for Research on Health Care (NIVEL) is a general practitioners' sentinel that covers approximately one percent of the Dutch population. National laboratory surveillance is carried out by the Netherlands Reference Laboratory Bacterial Meningitis (RBM) (where laboratories can send isolates from normally sterile sites for typing), by the RIVM (that does serological tests for pertussis diagnosis almost exclusively for the whole country), and by virological laboratories (that report data on positive findings to the RIVM).

On the basis of the findings, recommendations are made for the surveillance of the RVP target diseases and of invasive meningococcal and pneumococcal infections. Besides continuation of the current surveillance, additional research in case of outbreaks and epidemics is recommended, in order to obtain more insight into the circulation and possible antigenic variants of the pathogens and into characteristics of those who are infected.

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1. General introduction

The Dutch National Vaccination Programme (Dutch acronym: RVP) was started in 1952, offering vaccination against diphtheria, tetanus and poliomyelitis (DT-IPV-vaccine) to all children living in the Netherlands with catch-up campaigns for children born in 1945-1951. Nowadays the National Vaccination Programme includes vaccination against diphtheria, pertussis, tetanus, poliomyelitis (DTP-IPV-vaccine), measles, mumps, rubella (MMR-vaccine) and *Haemophilus influenzae* type b infections (Hib-vaccine). Inclusion of hepatitis B vaccination in the RVP is now discussed. The vaccination scheme of the National Vaccination Programme as of 1 July 1993 is shown in table 1.

Table 1 Vaccination scheme of the National Vaccination Programme since 1 July 1993

Age	Vaccinations
3 months	DTP-IPV-1 + Hib-1
4 months	DTP-IPV-2 + Hib-2
5 months	DTP-IPV-3 + Hib-3
11 months	DTP-IPV-4 + Hib-4
14 months	MMR-1
4 years	DT-IPV-5
9 years	DT-IPV-6 + MMR-2

The vaccination coverage is very high in the Netherlands. This is a result of the elaborate registration by the Provincial Vaccination Administrations (Dutch acronym: PEA). All municipalities automatically send data on newborns and mutations of all children up to the age of 13 to the PEAs. The PEAs send notices for vaccination to all registered children and, if necessary, they send reminders. Parents who do not want their children to be vaccinated, are requested to return the notice with the reason for refusal. The PEAs keep administration on the vaccine status of all children and on reasons for not vaccinating.
The PEAs also register the vaccination coverage in the Netherlands. Per municipality data on all children from the population register are compared with the data in the registration of the PEA. For DTP-IPV-vaccination reliable information is available for all birth cohorts born since 1962, for DT-IPV-V since 1971, for DT-IPV-VI since 1970, for rubella since 1977. For MMR-vaccination information is available since this vaccination was introduced in the National Vaccination Programme in 1987. No data on Hib vaccination coverage are reported so far officially since the coverage is registered at the end of the third calendar year of life and the report for 1997 is not yet published (1).
The Inspectorate of Health (IGZ) reports on annual figures on vaccination coverage in the Netherlands. A mean of 97% of the children has received at least three DTP-IPV vaccinations at the end of their third calendar year of life and a mean of 94% of the children has received

the first MMR vaccination at that same time (1). The first full birth cohort that was offered Hib vaccination within the framework of the RVP, was the birth cohort of 1994. The preliminary figure of the Hib vaccination coverage per 1 January 1997 is 95.5%. In figure 1, 2 and 3 the vaccination coverage for the first three DTP-IPV doses, the first three Hib doses and the first MMR dose per municipality on 1 January 1997 is shown.

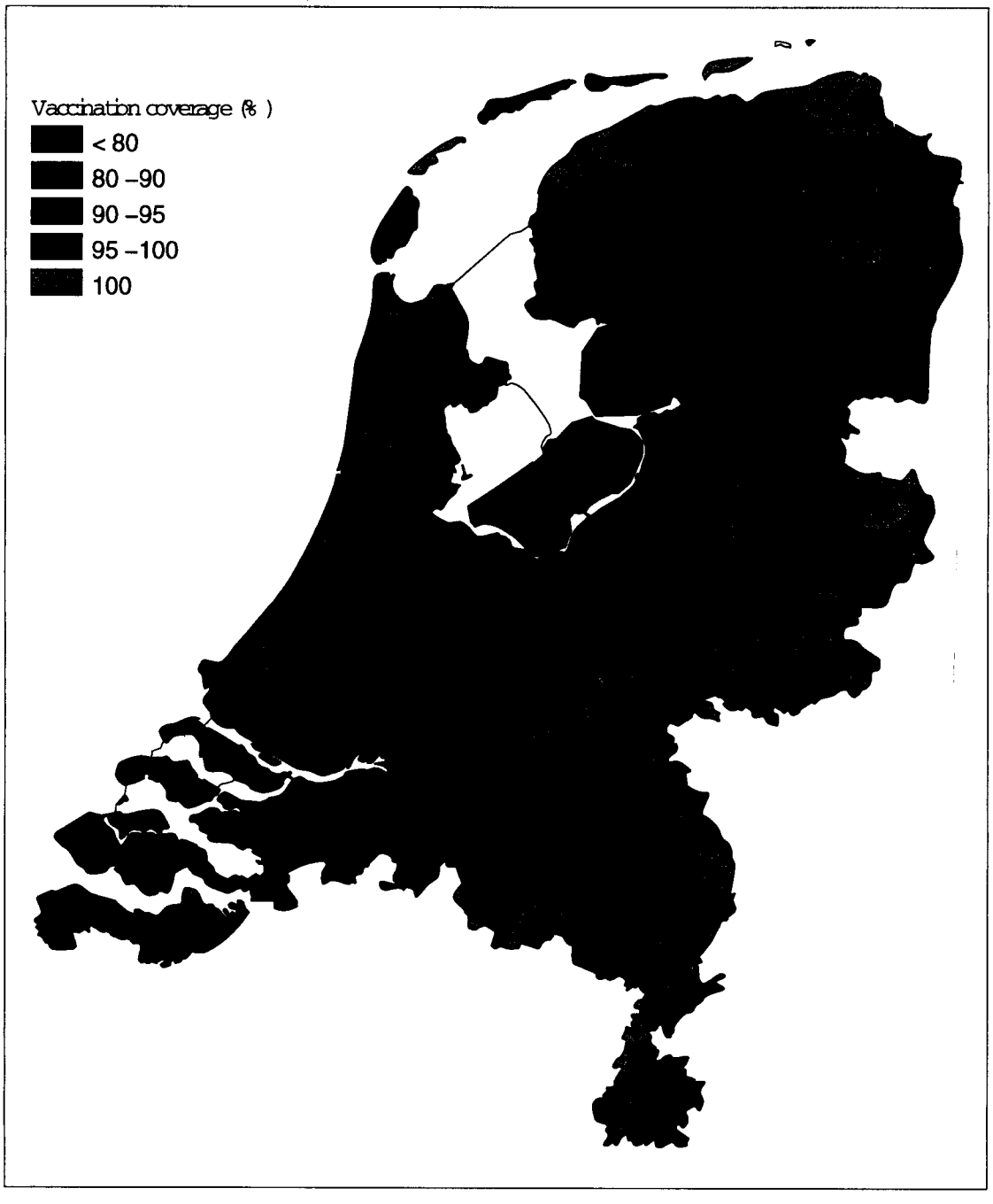

figure 1 Vaccination coverage for the first three DTP-IPV vaccinations per municipality, for the birth cohort 1994, per 1 January 1997 (source: IGZ)

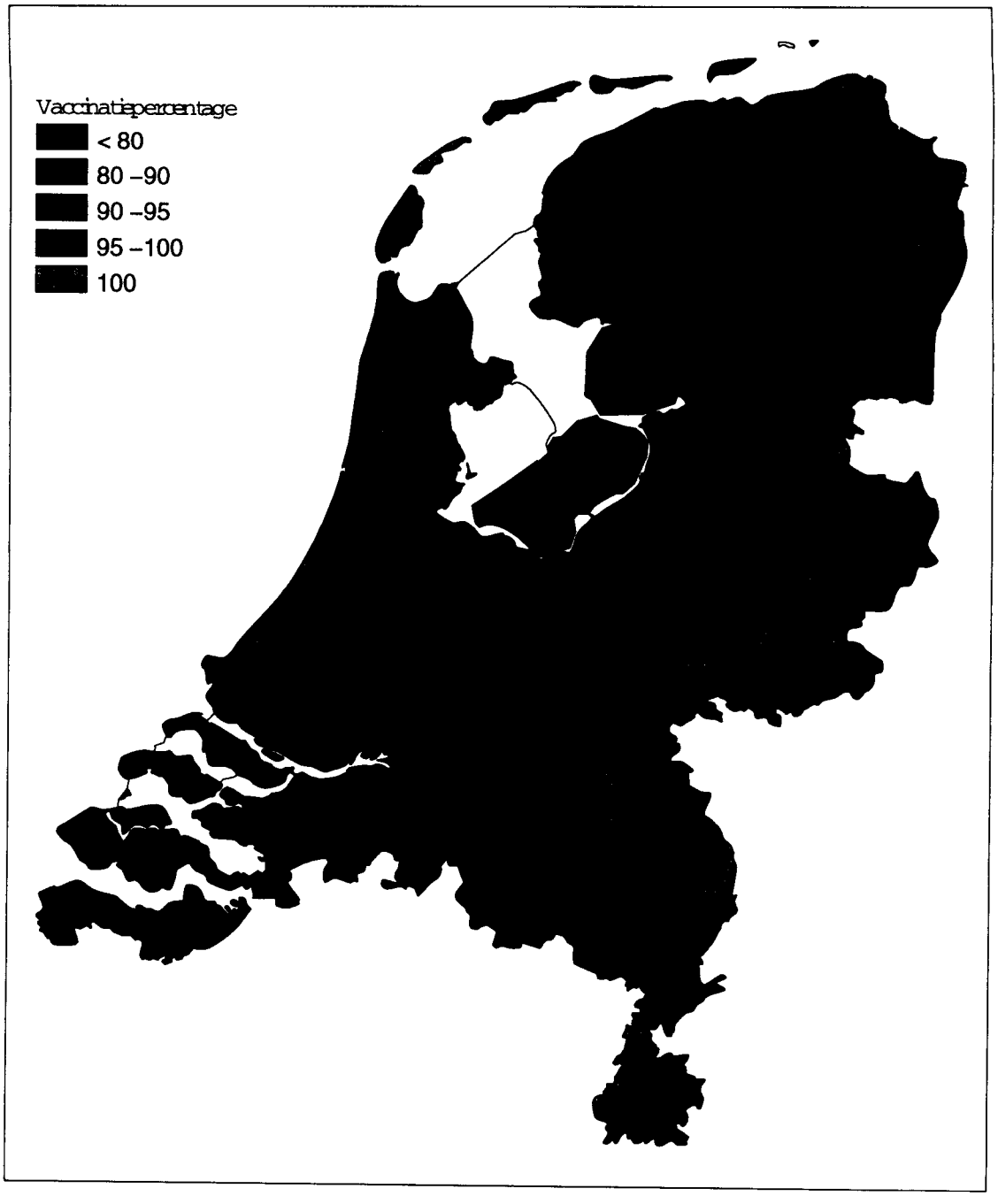

figure 2 Vaccination coverage for the first three Hib vaccinations per municipality, for the birth cohort 1994, per 1 January 1997 (source: IGZ)

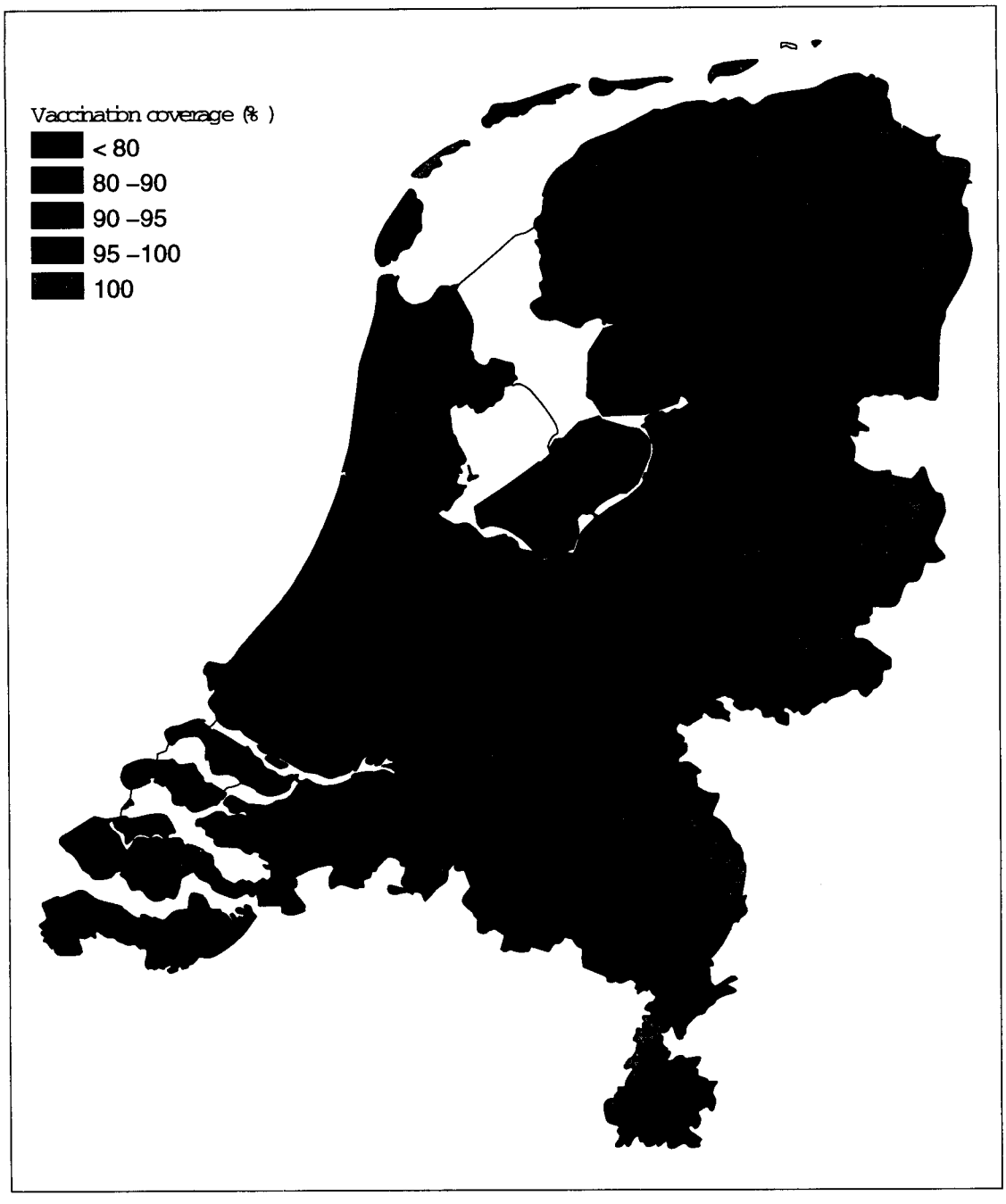

figure 3 Vaccination coverage for the first MMR vaccination per municipality, for the birth cohort 1994, per 1 January 1997 (source: IGZ)

Since the vaccination coverage has been very high in the Netherlands ever since the start of the RVP, the incidence of the target diseases and its complications has decreased drastically right after the introduction of the vaccine. Outbreaks of measles and pertussis still occur in the Netherlands and an increase of diphtheria is also seen as a possibility (2, 3, 4).
The example par excellence of successful disease control by means of vaccination is smallpox vaccination. Just before smallpox was eradicated world-wide, vaccination was stopped in the Netherlands in 1976. Poliomyelitis and measles are the next diseases on the agenda of the World Health Organisation for world-wide eradication.
The incidence of most target diseases of the National Vaccination Programme is low nowadays, but continuous alertness remains necessary to evaluate whether the aimed objectives are achieved and to trace possible secondary consequences of mass vaccination (5).
Even though the overall vaccination coverage is very high, there are geographical differences throughout the country. Especially municipalities where groups that refuse vaccination on religious grounds mainly have their residence, show a lower vaccination coverage (see figure 1 and figure 2). These municipalities are situated in a geographic band over the country that stretches from the Southwest to the mideast. Since the government has chosen not to make vaccination a mandatory requirement, the vaccination coverage will never be 100%.
Herd immunity can be broken if unvaccinated groups are socio-demographically clustered, because the density of susceptibles, persons that are not protected by either vaccination or natural infection, will grow. Epidemics may occur in these groups. This is illustrated by the last polio epidemic in the Netherlands which was purely restricted to groups who refuse vaccination for religious reasons and live in communities with a low vaccination coverage (6).
Since the circulation of pathogens will decrease as an effect of mass vaccination, the force of infection, i.e. the rate of acquisition of infection by a susceptible person, decreases also (7). As a result the mean age of infection increases, meaning that for some diseases the chance of clinical manifestations and complications increases. This stresses the importance of measuring the age-specific incidence through which possible risk groups can be identified (5).
The decrease in circulation of pathogens may also result in a lack of boosting opportunities for the immune system. Thus persons may not be protected lifelong anymore. Also, most adults nowadays are immunised through vaccination instead of having acquired protection by natural infection and subsequent immunisation. It is possible that their antibody titres are lower, resulting in a shorter duration of maternal immunity in their children. This could mean that the National Vaccination Programme should be adjusted and vaccination should be started at a lower age. On the other hand, the force of infection has to be taken into consideration; if this is very low, it is not necessary to advance the starting age.
If the incidence of a certain disease is very low because of a high vaccination coverage, the limited number of cases will rather frequently represent vaccine failures. All parents should be aware of the fact that nót vaccinating is more dangerous than vaccinating, despite a (small) chance of adverse events following vaccination.
Another consequence of a high vaccination coverage is that after a while physicians may not recognise a target disease anymore since they will not encounter many cases.
Another important factor that may influence the incidence of certain infectious diseases

-besides vaccination- is the increased mobility of the population both within and outside the Netherlands. This is an important risk factor for reintroducing pathogens into the Netherlands from distant endemic areas.

For all reasons mentioned above surveillance of the effects of the National Vaccination Programme is still necessary. This surveillance has four key elements (5):

- disease surveillance
- immunosurveillance studies
- microbiological surveillance
- surveillance of adverse events following vaccination

The last three elements are incorporated in the PIENTER-project (immunosurveillance study of an age-stratified sample of the general Dutch population in 1995-1996), in ISIS (Infectious diseases Surveillance Information System, automated registration system of laboratory data and notifications) and in the (passive) surveillance of adverse events by the RIVM (Laboratory for Clinical Vaccine Research).

This report refers to the disease surveillance and describes trends in time in morbidity and mortality of the target diseases (and its complications) until and including 1996 in order to evaluate the National Vaccination Programme: measles, mumps, rubella, diphtheria, pertussis, tetanus, poliomyelitis and *Haemophilus influenzae* type b (Hib). In addition, the trends in morbidity and mortality of the two other major causes of meningitis besides Hib, *Neisseria meningitidis* (meningococcus) and *Streptococcus pneumoniae* (pneumococcus), are described.

2. General methods

Three different kinds of data are used: mortality data, morbidity data and laboratory data. These data and the data sources are described in this chapter.

2.1 Mortality data

2.1.1 Central Bureau of Statistics

The Central Bureau of Statistics (CBS) registers mortality data from death certificates on a statutory basis. In the registration is stated whether it concerned a natural death, a non-natural death or a still-born child. In case of natural death the physician should report the following data:

1. a. Illness or disease which has directly led to the death (secondary diagnosis)
   b. Illness or disease which has led to the cause of death as in a. (primary diagnosis)
2. Additional diseases and specifics, still present at the moment of death, which have contributed to the death.

The CBS codes causes of death according to the International Classification of Diseases (ICD). This classification is adjusted every ten years or so, which has to be taken into account when following mortality trends. Data from 1996 were not published yet at the time this report was written.

2.2 Morbidity data

2.2.1 Notifications

Physicians are obliged by law to report infectious diseases to the Public Health Services, who pass it through to the Medical Inspectorate of Health (Dutch acronym: IGZ). There are three categories of obligatory reporting diseases:

A. diseases in this category have to be reported nominally within 24 hours of suspicion of the disease and direct intervention measures have to be taken by the physician.
B. diseases in this category have to be reported nominally within a week of setting the diagnosis (by physician) and intervention measures have to be taken by the physician.
C. diseases in this category have to be reported non-nominal within a week of setting the diagnosis for statistical purpose.

There is a serious underreporting and delay in reporting which differs per disease (8).

Diseases relevant for the evaluation of the RVP that are in this registration are poliomyelitis (category A), diphtheria, tetanus, pertussis, measles, rubella, meningococcosis (category B) and mumps (category C).
Notification data from 1988 onwards are available from the Registration Infectious Diseases database (RIF database) and before then from "paper". Notification data are shown according to date of notification. The vaccine status of the notified cases is available since 1993.

2.2.2 Hospital admissions

The National Medical Registration (Dutch acronym: LMR) collects acquittal diagnoses of all patients that are admitted to a Dutch hospital (with the exception of admissions to two short-stay categorical hospitals). This means that out-patients' diagnoses are not registered. The diseases are coded as main or as side diagnosis according the International Classification of Diseases Ninth revision, Clinical Modification (ICD-9-CM) coding. The registration has existed since 1963 and is managed by the Foundation Information Centre for Health Care (Dutch acronym: SIG). The coverage of this registration is about 99%. All diseases from the RVP are registered by main as well as side diagnosis. Data from 1980 onwards will be given. The use of main diagnosis is common practice for calculating the incidence and morbidity of a disease (9). We also show the number of hospital admissions with a specific disease as side diagnosis in order to get a more complete picture.

2.2.3 Sentinel network of General Practitioners

There are two important sentinels of general practitioners.
The continuous morbidity registration sentinels of the Dutch Institute for Research on Health Care (NIVEL) consists of 45 sentinel centres throughout the Netherlands, covering approximately 1% of the Dutch population. Registered is the reason for contact of patient-physician per consultation (main and side diagnosis) for an alternating selection of diseases on a weekly basis. Measles was included in the registration in 1975-1979 and 1990. Mumps was registered only in 1990. Since these diseases were monitored only for one year or long ago, this registration is not suited for the observation of trends in morbidity of the target diseases of the RVP. We will use the data to compare incidences with those found by other sources.
The Continuous Morbidity Registration Nijmegen (CMRN) is a regional general practitioners' sentinel. Since 1971 it has consisted of four general practitioners' practices in the central-Eastern part of the Netherlands with a total of approximately 12,000 patients. This registration is managed by the general practitioner's research institute of the Catholic University of Nijmegen which collects data on all consultations of the general practitioners (10).

2.2.4 Netherlands Paediatric Surveillance Centre

The Netherlands Paediatric Surveillance Centre (NSCK) was set up by the Dutch Association for Paediatrics and is managed by TNO Prevention and Health. This registration started fall

1992. Hospital-based paediatricians report all cases of certain (alternating) rare diseases on a monthly basis. Over 90% of the clinical paediatricians take part in this registration (11). Researchers, who are mostly extern, are informed on reports and can send questionnaires to the physician for additional information.
At this moment, relevant diseases for the RVP that are registered are: pertussis (since 1997), *Haemophilus influenzae* type b (October 1993-1997), CRS (only 1996) and acute flaccid paralysis (AFP, since October 1991). AFP is a collective noun for diseases with acute flaccid paralysis as main clinical picture, e.g. poliomyelitis and Guillain Barré Syndrome. AFP is registered in relation to poliomyelitis; by performing a faeces culture, poliomyelitis should be excluded as the cause of the paralysis.

2.2.5 EUROCAT

Two EUROCAT (European Registration Of Congenital Anomalies) centres report on the incidence of children or foetuses with congenital anomalies in the Netherlands of which the mother lived in the EUROCAT region at the time of birth. At the start in 1981 there was one station that covered the most part of Groningen and this expanded to whole Groningen and a part of Drenthe in 1985. This station has covered the North of the Netherlands (the provinces Groningen, Friesland and Drenthe) since 1989. The other station has covered the Southwest of the country (the province Zeeland, a part of the provinces Zuid-Holland and Noord-Brabant) since 1990. Together the two stations cover approximately 25% of all new-borns in the Netherlands.

2.2.6 SSPE-registration

The SSPE-registration has registered subacute sclerosing panencephalitis (SSPE), a lethal late complication of measles since 1976. This nation-wide registration is managed by the SSPE working group in Nijmegen (contact person: dr. J. Galama, Catholic University of Nijmegen). The aim of the registration was to evaluate the effect of the measles vaccination, which was introduced in 1976, on the incidence of SSPE and to investigate the pathogenesis of this disease. Although the registration still exists, the coverage is considered to have been incomplete since 1990, because of the very low incidence of SSPE and the resulting unfamiliarity of physicians with the registration; it is a passive registration.

2.3 Laboratory data

Laboratory diagnostics are very important in infectious diseases; about 75% of all infectious diseases can only be diagnosed by laboratory tests (12). This is why laboratory data are important for information on trends in the incidence of infectious diseases. However, for self-limiting vaccine preventable diseases, often no laboratory confirmation is sought. Another disadvantage of laboratory data sources is that mostly only limited information on patients is registered.

2.3.1 Laboratory Surveillance Infectious diseases

The RIVM and the 16 regional laboratories of public health carry out laboratory surveillance of infectious diseases on a project basis. The project is called Laboratory Surveillance Infectious Diseases (LSI project). First isolates of certain pathogens are weekly reported to the RIVM on a voluntary basis. Pathogens included that are relevant for the evaluation of the National Vaccination Programme are *Haemophilus influenzae* type b and *Bordetella pertussis*.

2.3.2 National pertussis surveillance

Serological tests for diagnosis of pertussis in the Netherlands are almost exclusively performed by the Laboratory for Infectious Diseases Diagnostics and Screening (LIS) at the RIVM. Furthermore all isolates of Bordetella sent in by the regional laboratories of public health are serotyped at the RIVM. National pertussis surveillance is carried out on the basis of these data and notifications.

2.3.3 Netherlands Reference Laboratory Bacterial Meningitis

The Netherlands Reference Laboratory Bacterial Meningitis (RBM) of the RIVM is located at the University of Amsterdam. All bacteriological laboratories in the Netherlands voluntarily send isolated bacterial strains of meningitis and sepsis patients to the RBM for (free of charge) identification of strains and serotyping. Since 1995, strains of other manifestations of invasive bacterial disease can be sent in too.

2.3.4 Virological laboratories

Virological laboratories send data to the RIVM on a monthly and voluntary basis. Not all virological laboratories in the Netherlands participate and not all participating laboratories send in data every month. Positive findings are integrated in annual reports. It is important to realise that the presence of virus does not automatically implicate disease. Data on measles, mumps, rubella and poliomyelitis have been available since 1981 (13).

In the following chapters, where the trends in incidence of the target diseases are described, it is explained in greater detail and per disease which data are abstracted from which data sources. Incidences will be given by year and in addition by age and sex. Data are tabulated in appendix I.

3. Measles

3.1 Introduction

Measles (morbilli, rubeola) is an acute viral disease with very high infectivity; it is transmitted via droplet infection. The clinical manifestation of measles includes fever, red maculopapular exanthema with cough and conjunctivitis. The exanthema is not always easily distinguishable from other exanthema such as rubella exanthema.
Complications as bacterial superinfections and pneumonia can arise as a result from an infection with the measles virus (14). A serious complication is encephalitis which presents itself right after a measles infection in about 1:1000 cases (15). In very exceptional cases subacute sclerosing panencephalitis (SSPE), a progressive fatal neurological disorder, can arise several years after a (primary) measles infection (16).
Since 1976 measles vaccination has been part of the RVP: at first as a plain live attenuated measles vaccine offered to toddlers of fourteen months, since 1987 as a component of the MMR-vaccine, given at the age of fourteen months and nine years. 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.

3.2 Methods

Data on mortality due to measles are registered at the Central Bureau of Statistics and will be described from 1901-1995.
Information on the incidence of measles in the period 1976-1996 was obtained from statutory notifications; measles is a category B notifiable disease. From 1983 onwards, a case definition is used (see appendix II for case definition). Data from the National Medical Registration (LMR) of the SIG that registers clinical diagnoses of hospital admissions (ICD-9-code 055 and further subdivisions) in the period 1980-1996 are shown.
Data on general practitioner's practice visits for measles from the Continuous Morbidity Registration Nijmegen in the period 1967-1996 and from the NIVEL sentinel in the period 1975-1979 and 1990 are given.
Positive findings on measles from virological laboratories in 1981-1996 are shown.
The incidence of SSPE from 1976 onwards was monitored by means of data from the SSPE-registration in Nijmegen.

3.3 Results

3.3.1 Mortality

CBS

Death caused by measles affected mostly children under four years of age. Mortality decreased from over 2500 in the beginning of the century to a level of 1 to 14 just before vaccination was started in 1976. A few years later, maximal two persons per year died of measles. The last cases of death due to measles was registered in 1988.

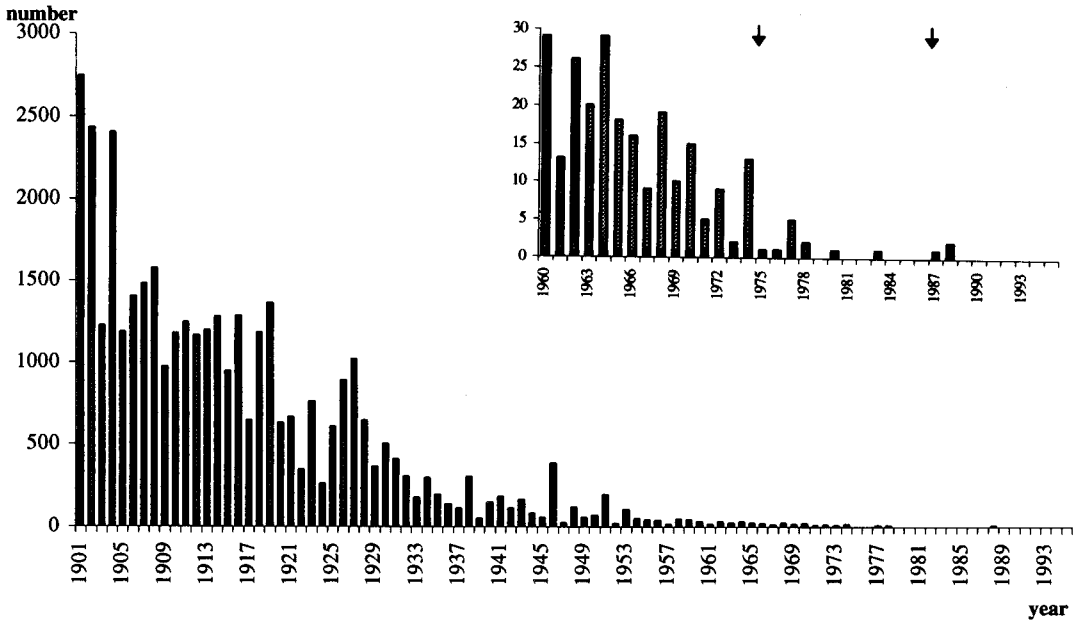

figure 4 Mortality of measles in the period 1901-1995 (source: CBS)

(see Appendix I, table 1)

3.3.2 Morbidity

Notifications

Since vaccination was introduced in 1976 the number of notifications has decreased drastically. Figure 4 shows that both after implementation of the one-dose and two-dose strategy, notification peaks were seen every three to five years (1983, 1988, 1992-1993). The mean age of the notified cases increased after vaccination was introduced; the percentage of cases under five years of age decreased rapidly from almost 60% in 1976 to around 30% in the 1980s and 1990s; the percentage of notified cases under 10 years of age decreased from approximately 95% to approximately 70%. No effect on gender was seen. Vaccination status of the notified cases was available from 1993 onwards and 92%, 90%, 91% and 49% of them

respectively were not vaccinated in 1993-1996. Most of them were not vaccinated for religious and other ideological reasons.

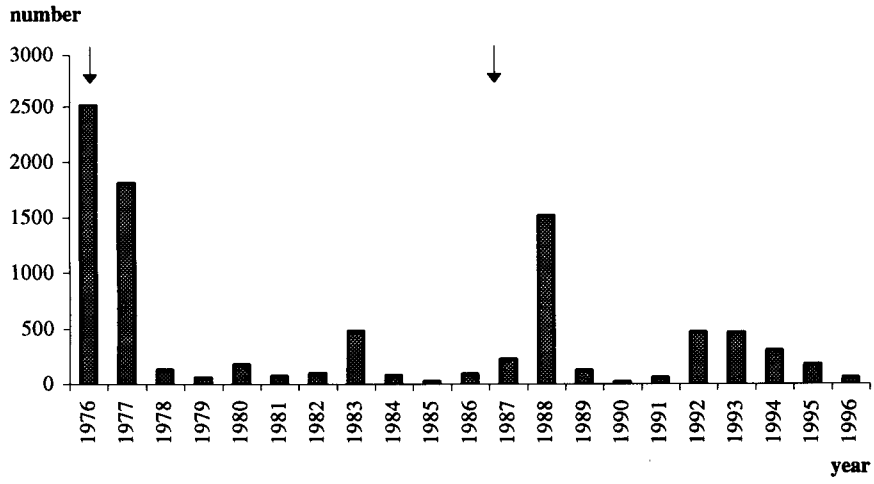

figure 5 Number of notifications of measles in the period 1976-1996 (source: IGZ) (see Appendix I, table 2)

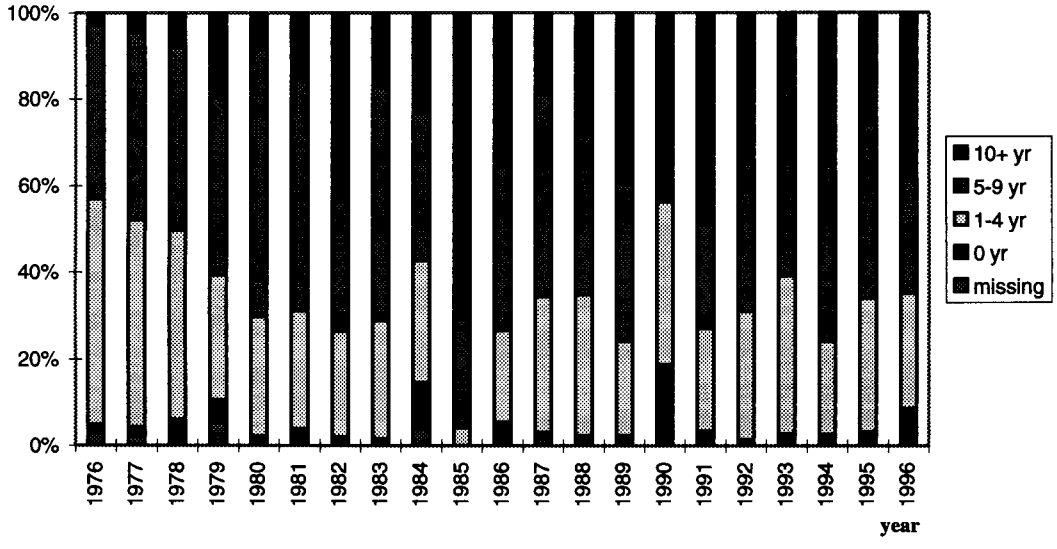

figure 6 Age distribution of measles in the period 1976-1996 by age (source: IGZ) (see Appendix I, table 2)

Hospital admissions

The number of hospital admissions for measles shows the same epidemiological pattern as the notification data with high numbers of hospital admissions in the years 1980, 1983, 1988 and 1992-1993. The mean age gradually increased since 1980 and no effect of gender was seen. Over half of the patients hospitalised for measles (63%) were admitted for measles without a complication being registered. In case of a registered complication this mostly was pneumonitis (45%).

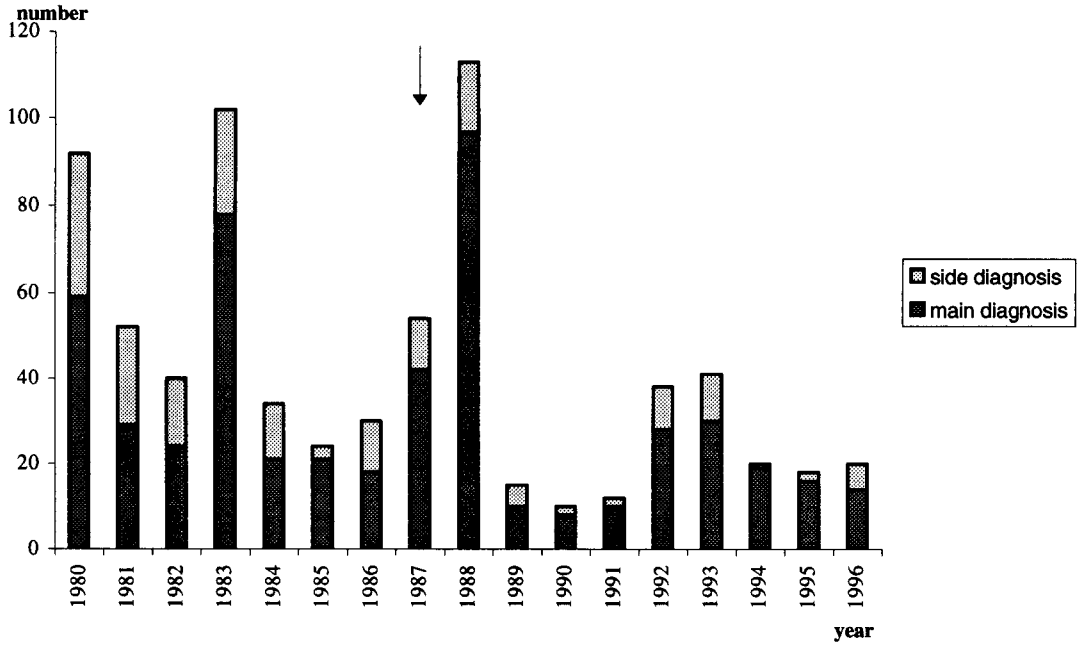

figure 7 Number of hospital admissions for measles in 1980-1996 (source: LMR) (see Appendix I, table 3)

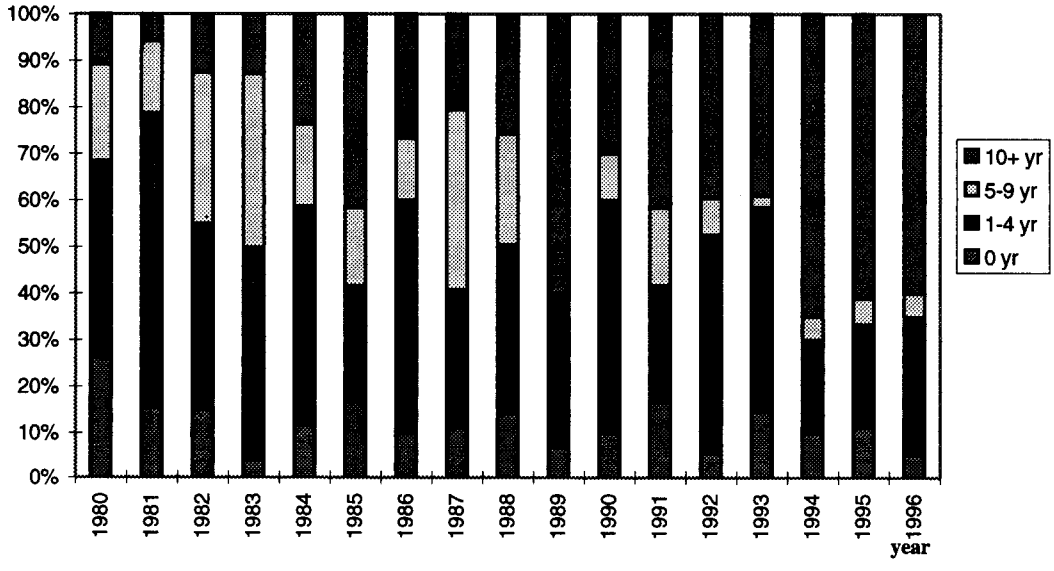

figure 8 Age distribution of hospital admissions for measles in 1980-1996 (source: LMR)
(see Appendix I, table 3)

Sentinel centres

The CMRN-registration shows that the incidence of measles has decreased since vaccination for measles was implemented in 1976. The last case was registered in 1992. Extrapolation of the figures amounted to an expected national number of over 200,000 in 1974 and almost 108,000 cases of measles in 1976, the year mass vaccination was introduced.

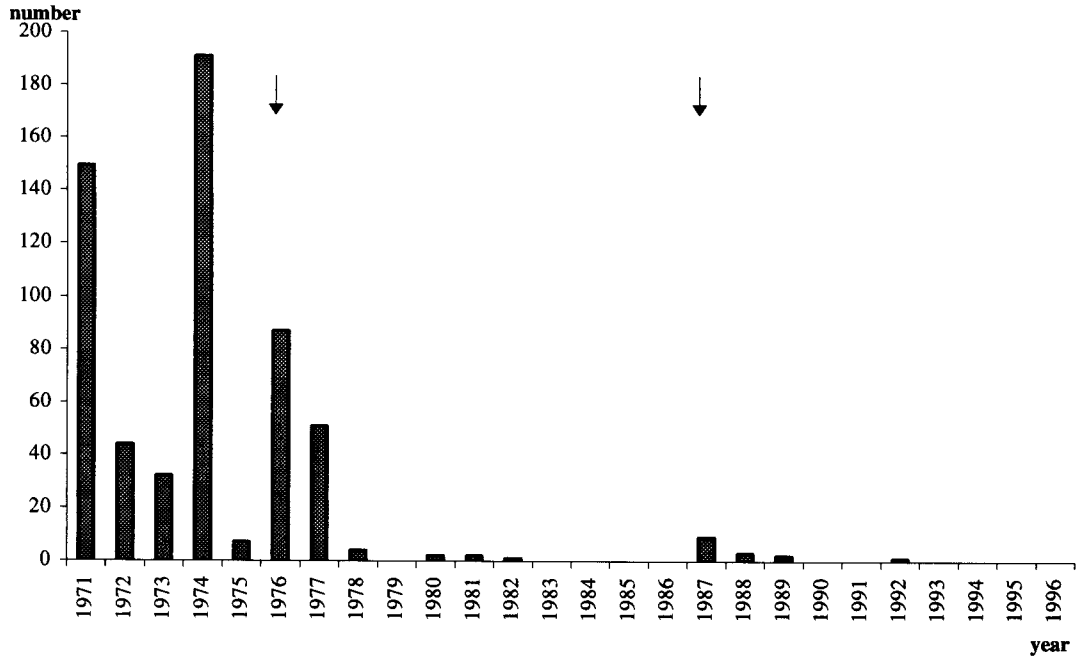

figure 9 Number of registered cases of measles in 1971-1996 (source: CMRN)

(see Appendix I, table 4)

Extrapolation of the number of measles patients found in the NIVEL sentinel centres in 1975-1979 amounted to respectively ± 11,000, ± 87,000, ± 66,000, ± 5,400 and ± 4,500 cases in the Netherlands. About two-third of the cases were not vaccinated (17).

In 1990 just one patient with measles was seen in the NIVEL sentinel centres. This patient was not vaccinated because of young age and developed no complications (18).

Virological laboratories

In 1983, 1988 and 1993 higher levels of positive findings of measles were seen in the virological laboratories. No decreasing trend is seen in the average number of positive findings over the years.

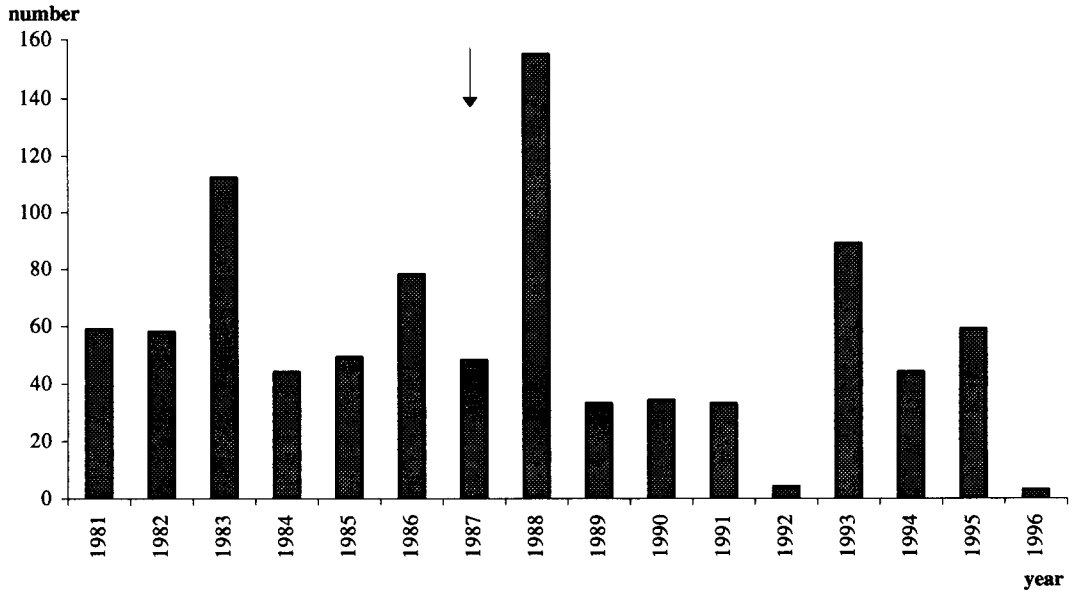

figure 10 Number of positive serology or virus isolation for measles in 1981-1996 (source: clinical virological laboratories and RIVM)

(see Appendix I, table 5)

SSPE-registration

Since 1976 cases of SSPE have been registered at the SSPE-registration Nederland. In the first four years of the registration a mean of 13 cases per year were notified. The last registered cases date from 1991 and 1992; in both years one case was registered. These both were unvaccinated individuals. Boys were affected three times more than girls, and the median age was 10 years (range 2-23 years). Only three patients were vaccinated; two at an age that measles could already have been contracted before. The other one got vaccinated at the age of four and had a measles-like rash one week hereafter. Possibly this case is vaccine-related. (19, 20).

3.4 Discussion

Mortality

As a result of improving living conditions mortality due to measles has been decreasing steadily since the beginning of the century and mortality was already low before vaccination was introduced in 1976. Afterwards mortality figures declined even faster; the last death due to measles was seen in 1988.

Effects of vaccination

The number of notifications and hospital admissions clearly decreased after 1976. This was an epidemic year so the number would have decreased in 1977 anyway (17), but thereafter morbidity figures remained low in comparison with the pre-vaccination era. Epidemic peaks were still seen after measles vaccination was introduced. Before vaccination, every two year an epidemic occurred but after 1976 these epidemic peaks were seen every 4-6 years (2). This is a result of high vaccination coverage; in the pre-vaccination era almost all susceptibles were infected (mostly young children) and acquired immunity. As a result of mass vaccination the pathogen can not spread as widely as before, the pool of susceptibles only slowly grows and interepidemic periods become longer.

No further changes of the incidence was observed when the second dose of measles vaccine was introduced in 1987. But possible future outbreaks due to an increase of susceptibles not immunised by the first dosis (primary failure) or not vaccinated may have been prevented. The majority of the children who received the second dose at the age of nine years, will have been vaccinated at fourteen months also, and have acquired immunity as a result. Therefore, the proportion of immunes will probably not have grown considerably.

Another observed effect of vaccination is the increase in age as a result of decreased force of infection. Measles is not a childhood disease anymore as it used to be in the pre-vaccination era. In industrial countries complications of measles infections are more often seen at higher age, but both the absolute number and the percentage of complications in hospital admissions due to measles has not increased.

The number of SSPE-cases also declined after the introduction of mass vaccination. The unawareness of (young) physicians with the SSPE registration in the last years has to be taken into account, but the registration is considered reliable up to 1990. Only in one SSPE patient the disease was possibly vaccine-related; this supports the view that vaccination against measles strongly protects against SSPE, which was also found by others (16, 19).

There are groups in the Netherlands that refuse vaccination on religious grounds and since these groups are often clustered in certain areas, herd immunity may not be sufficient in these areas and explosions are possible. Outbreaks have also been seen in areas with high vaccination coverage for measles (21, 22, 23). This could be due to reinfection of vaccinated persons, which is more likely to occur than in persons with naturally acquired immunity.

In the measles epidemic in 1987-1988 90% of the cases was not vaccinated; 64% for religious reasons, 16% for anthroposophic reasons and 10% for unknown reasons (22). From 1993-1995 at least 90% of the notified cases were not vaccinated, but this percentage was 49% in 1996. This last figure could be due to the low number of notifications in 1996 but should carefully be monitored in the years to come.

The chance of acquiring natural immunity through infection for unvaccinated individuals has become small. Women born in the vaccination era but themselves not vaccinated are approaching the child-bearing age. Most of their babies will not be protected by maternal antibodies and are at risk of being infected, especially at times of outbreaks.

Global measles eradication is technically feasible with available vaccines by 2010 according to the WHO, with the proviso that vaccination strategies that rely on administration of a single dose of vaccine are a routine one-dose vaccination strategy does not. A two-dose strategy should be adopted by all countries that do not already have done so (24). Surveillance of measles is important to detect virus circulation in the population and to assess the effectiveness of the vaccination strategy. According to the WHO, initially notification should be based on clinical suspicion rather than rigid case definitions, as used in the Netherlands since 1983; then (clusters of) cases can be recognised in time, so that adequate (case) investigations can be performed. However, case definitions should be applied in further outbreak investigations. All isolated cases of measles and at least one case from each chain of transmission should be confirmed by laboratory tests.

Comparison of sources

In the pre-vaccination era the incidence of measles infection in epidemic years is estimated to approach the number of newborns, due to the high infectivity of the measles virus. The estimated number of patients was 87,000 in 1976 according to the NIVEL and almost 108,000 according to the CMRN, while the number of births was close to 200,000. One has to bear in mind that a certain percentage of infections will be subclinical and not all parents take their children to a physician for measles.

Even though the data from notifications, the sentinel centres and hospital admissions show the same trend in time, only a very small part of the number of estimated cases according to the NIVEL (2-3% in 1975-1979) and an even smaller percentage of the estimated cases according to the CMRN are notified. Because of this considerable underreporting, measles outbreaks should be treated as opportunities to reinforce surveillance, study the transmission of measles in a highly vaccinated population with attention for possible subclinical reinfection, and identify appropriate measures to prevent future outbreaks. Furthermore data on hospital admissions will give insight in the severity of the disease and should be used to monitor the effects of a further shift in age distribution.

4. Mumps

4.1 Introduction

Mumps is a rather innocent acute viral childhood infection with aerogenic transmission. Parotitis (parotid swelling) is the most important clinical manifestation of mumps and can be both bilateral and unilateral. Infections with mumps virus are subclinical in about 30% or they only affect the upper respiratory tract. Meningitis is a complication of mumps which is the major reason for vaccination and occurs in 0.4% to 1% of the cases. Other complications are encephalitis, oophoritis, pancreatitis and orchitis, but these very rarely occur. The last complication mentioned is feared for the possibility of subsequent sterility, but this only seldom occurs since the infection is mostly unilateral. The prognosis for these complications most often is good (25, 26).
Since 1987 mumps vaccination is introduced in the National Programme (RVP); the live-attenuated mumps vaccine is included in the MMR combination vaccine offered to children at the age of fourteen months and nine years.

4.2 Methods

Data on mortality due to mumps from the Central Bureau of Statistics are presented for the period 1950-1995.
Notification data from the Inspectorate of Health are described for the period 1976-1996; mumps is a category C-notifiable disease.
Hospital admission diagnoses (ICD-codes 072 and further subdivisions) from the National Medical Registration in the period 1980-1996 are shown.
The incidence in the Continuous Morbidity Registration Nijmegen in 1967-1996 is presented.
Positive findings on mumps from the virological laboratories are given.

4.3 Results

4.3.1 Mortality

CBS
Mortality of mumps in the last decades has decreased according to the CBS, while vaccination probably has sped up the process. The last case of death due to mumps was registered in 1988, one year after introduction of mass vaccination. Death caused by mumps affected most often older persons over fifty years of age and to a lesser extent children under ten years of age according to the CBS; since 1950 34 deceased persons over fifty and 24 deceased children under ten were registered. This age distribution seems odd since mumps is, and especially so before mass vaccination was introduced, a typical childhood disease.

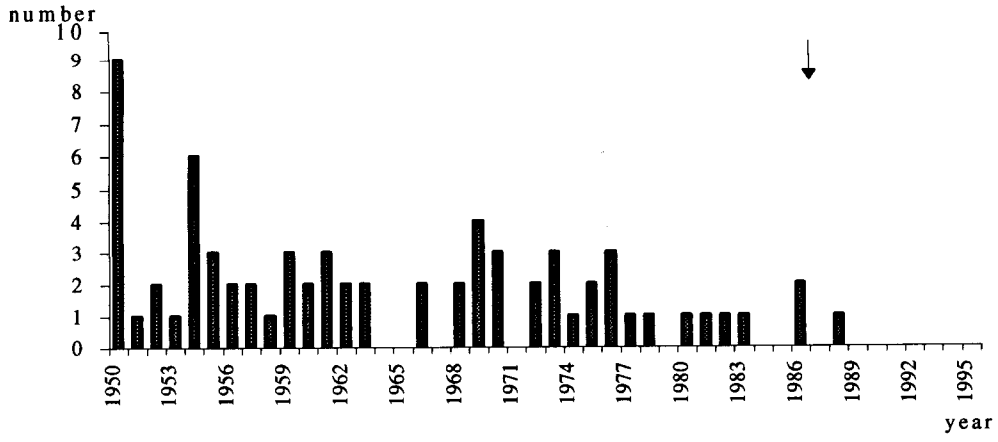

figure 11 Mortality of mumps in the period 1950-1995 (source: CBS)

(see Appendix I, table 6)

4.3.2 Morbidity

Notifications

Since 1976 mumps has to be notified obligatory: the number of notifications decreased from nearly 1200 and 1600 in 1976 and 1977 to approximately 400 in 1986 and 1987. The number of notifications for children under 1 year of age in the vaccination era is nearly zero; most cases do occur in childhood. The proportion of notified cases over 50 years of age increased after vaccination was introduced; it was below 1% before mass vaccination was introduced and 4% in the period 1987-1996 and seems to be increasing. Over the years almost constantly 55% of the cases were male. No data are available on complications and vaccine status of the notified cases.

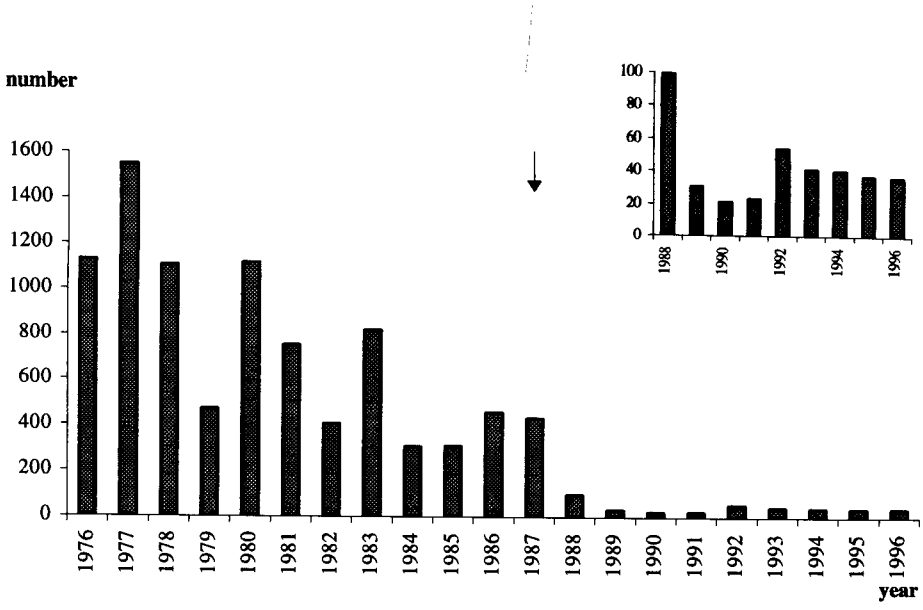

figure 12 Number of notifications of mumps in 1976-1996 (source: IGZ) (see Appendix I, table 7)

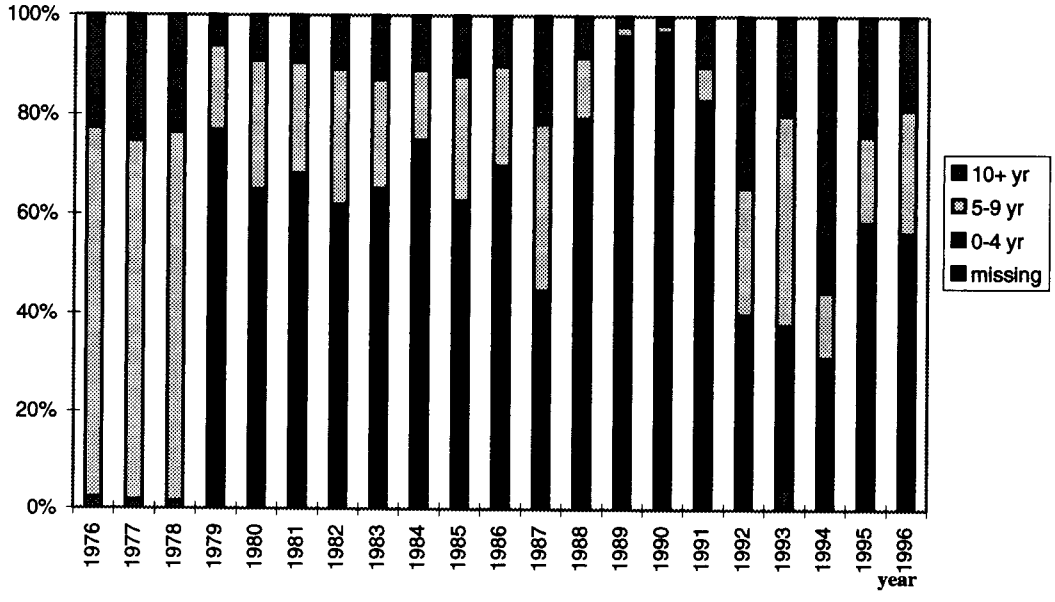

figure 13 Age distribution of notifications of mumps in 1976-1996 (source: IGZ) (see Appendix I, table 7)

Hospital admissions

The number of hospital admissions for mumps has decreased drastically after the implementation of vaccination in 1987. In the pre-vaccination era up to 800 patients were admitted in epidemic years while this number varied from 300-400 in in-between years. The

number of hospital admissions due to mumps decreased dramatically after 1987 to a few or no cases per year. These last years after 1987 relatively more older persons were admitted than before. The percentage of hospitalised patients over 19 years of age doubled from 9% in 1980-1987 to 18% in the period 1988-1996. No patients over fifty years of age were registered after 1992. Up to 1987 71% of the hospitalised patients were male, after 1987 no effect of gender was seen but this could be the result of low numbers. Before vaccination was introduced and in the year thereafter, most admitted patients were hospitalised for mumps with complications (67%); after 1988 this percentage decreased and mumps without complications registered has become the most common cause for hospitalisation of mumps patients. Meningitis was the most common complication (65%) before vaccination was introduced, afterwards no specific distribution was seen anymore.

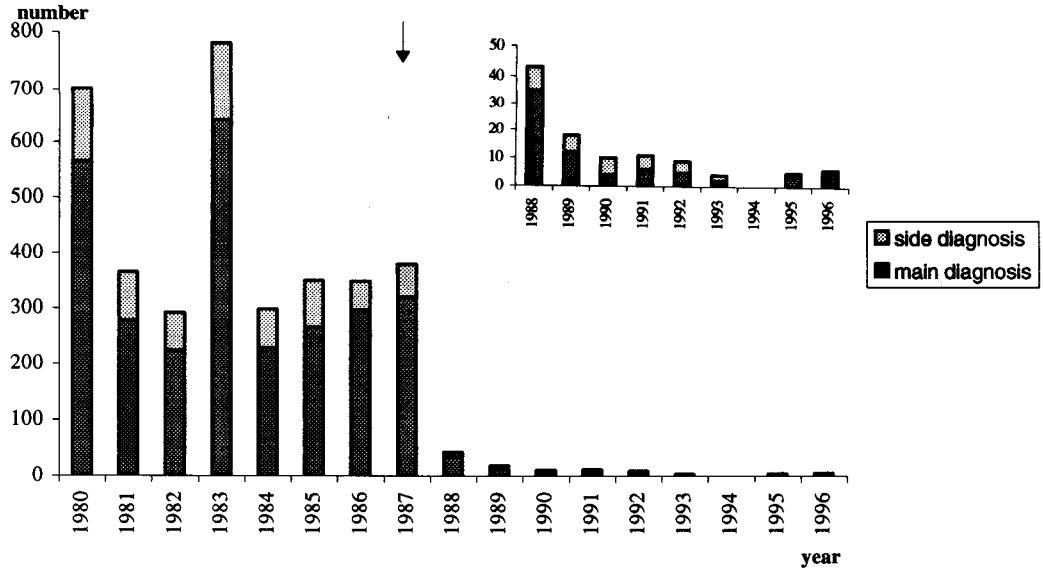

figure 14 Number of hospital admissions for mumps in 1980-1996(source: LMR) (see Appendix I, table 8)

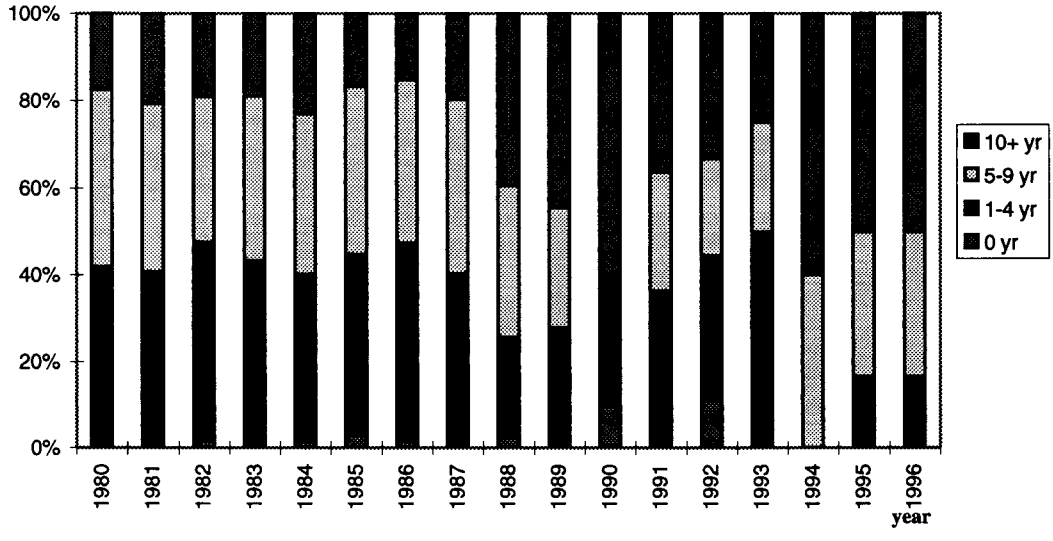

figure 15 Age distribution of hospital admissions for mumps in 1980-1996 (source: LMR)
(see Appendix I, table 8)

Sentinel centres

From the data in the CMRN-registration it can be seen that the incidence has been decreasing since vaccination for mumps was implemented in 1987 and that only sporadic cases occur nowadays.

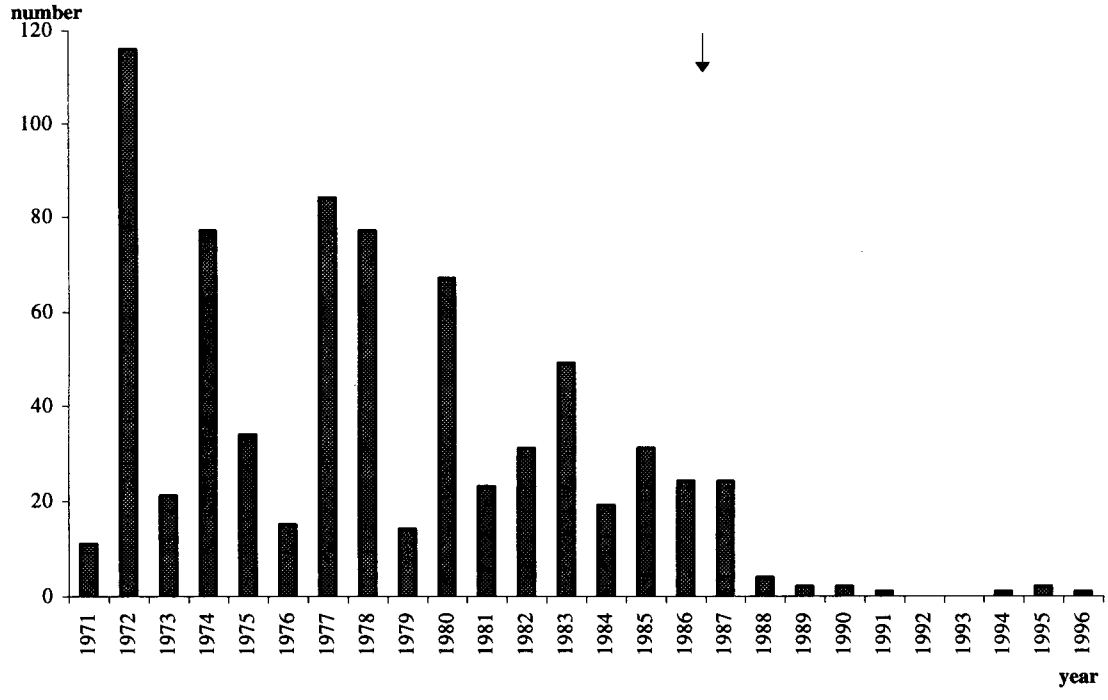

figure 16 Number of registered cases of mumps in 1971-1996 (source: CMRN) (see Appendix I, table 9)

In the NIVEL Sentinel centres in 1990 six patients with mumps were seen. No laboratory confirmation was done. Four out of the six patients were not vaccinated.

Virological laboratories

The number of positive virological findings decreased drastically after 1987, the year vaccination was introduced, from a mean of 262 in 1981-1987 to an average of 16 in 1989-1996.

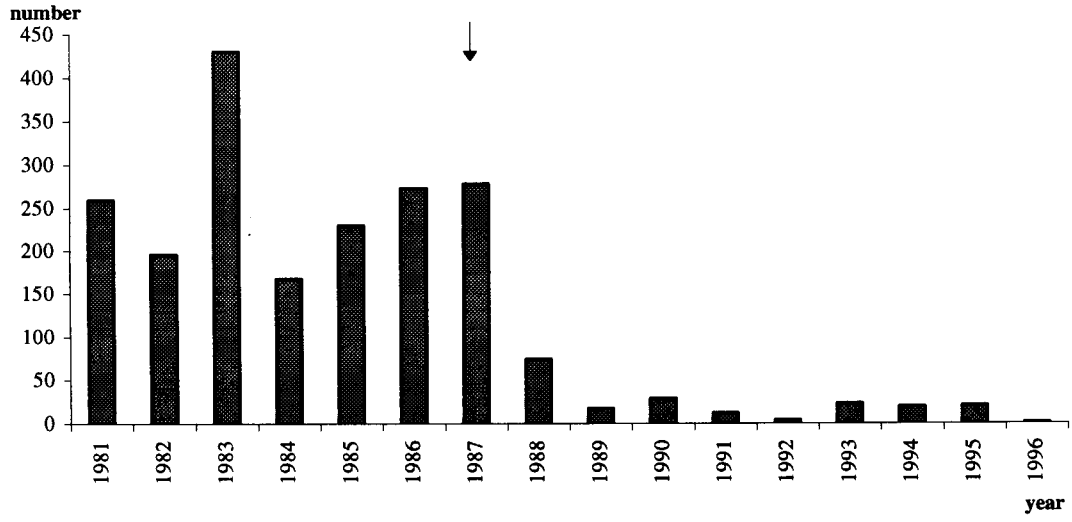

figure 17 Number of positive serology or virus isolation for mumps in 1981-1996 (source: clinical virological laboratories and RIVM)

(see Appendix I, table 10)

4.4 Discussion

Mortality

Mortality due to mumps was never high and only one death due to mumps was seen after mass vaccination was introduced. No explanation was found for the high proportion of deaths (34 out of 70 in 1950-1996) of patients over fifty years of age.

Effects of vaccination

The notifications, hospital admissions, sentinels and virological laboratories all show a decrease in mumps incidence after the introduction of mass vaccination in 1987 to a stable low level.

After vaccination had started an increase in age of mumps cases was seen, due to a decreased force of infection, in all registrations but despite this, relatively less complications were registered in the hospital admissions. In 1993 it was already shown that the number of hospital admissions for mumps -with and without complications- had declined drastically after the introduction of mumps vaccination in 1987 (27). This means a hugh reduction in hospital costs, while the extra costs for adding mumps vaccination to the RVP were minimal: at first

because of the implementation of the vaccine in the MMR cocktail vaccine, and secondly because of the simultaneous administration of the second dose of this vaccine with the DTP-IPV vaccine (27). The increase in age could cause an increase in the number of mumps patients with orchitis, since this complication only occurs in adult men (25). This effect was not seen in the hospital registration; no patient was registered with orchitis due to mumps after 1993. The observed increase in the proportion of mumps patients over fifty years of age in the notification data should be monitored in the future.
In case of an epidemic or cluster of cases, the chance of falsely diagnosing mumps on clinical grounds is small, but in isolated cases this chance is substantial since other viruses, like enteroviruses and influenza viruses, have become a more frequent cause of parotitis than the mumps virus in the vaccine era (28). Laboratory confirmation should therefore be encouraged.

Comparison of sources
The surveillance of hospital admissions due to mumps reflect the incidence of mumps infections and give a good insight in the severity of complications of mumps disease. For the evaluation of the effect of vaccination, it would be useful to register information about previous vaccinations of cases.

5. Rubella

5.1 Introduction

Rubella is a mild viral childhood infection. The clinical manifestation of rubella includes fever, red eyes and maculopapular exanthema, spreading downward from the face. The exanthema is absent in over half of the infected persons and is difficult to distinguish from other exanthema such as measles exanthema. Rubella is spread via droplets. For children the illness is harmless, but in adults it occasionally causes arthritis and arthralgia. Serious complications can arise after primary infection of a pregnant woman in the first 16 weeks of the pregnancy. Congenital anomalies as mental retardation, cataract, deafness and cardiac abnormalities or miscarriage can arise as a result of the infection of the foetus in utero (Congenital Rubella Syndrome (CRS)) (29).
To prevent CRS rubella vaccination was given to girls at the age of 11 years since 1974. This way virus circulation would persist and girls would either obtain natural or vaccine-induced immunity before they became sexually mature. In 1987 the strategy was changed from selective to general rubella vaccination with the aim to eliminate virus circulation. The vaccine was included in a cocktail with mumps and measles vaccine; this MMR-vaccine is now offered to girls and boys at the age of fourteen months and nine years.

5.2 Methods

Data on mortality due to rubella from the CBS in 1950-1995 are presented.
Information on the incidence of rubella from the Medical Inspectorate of Health in the period 1952-1995 are described; rubella is a category B notifiable disease. CRS has to be notified also, but is not distinguished from acquired rubella infections.
Data on hospital admissions due to rubella (ICD-codes 056 and further subdivisions, and 647.5) and Congenital Rubella Syndrome (ICD-code 771.0) in the period 1980-1996 were obtained from the National Medical Registration.
Figures on the incidence of rubella seen at general practioner's practices of the Continuous Morbidity Registration Nijmegen in the period 1971-1996 are shown.
Positive findings of rubella by virological laboratories are given for 1981-1996.
Data on the incidence of Congenital Rubella Syndrome in 1981-1996 was also obtained from the two EUROCAT centres (North Netherlands and South West Netherlands) and from the Netherlands Paediatric Surveillance Centre, which actively carried out surveillance on CRS in 1996.

5.3 Results

5.3.1 Mortality

CBS

Death caused by rubella affected only young people under ten years of age since 1950, with the exception of one patient deceased in 1973 who was an adolescent. The last case of death due to rubella was registered in 1985.

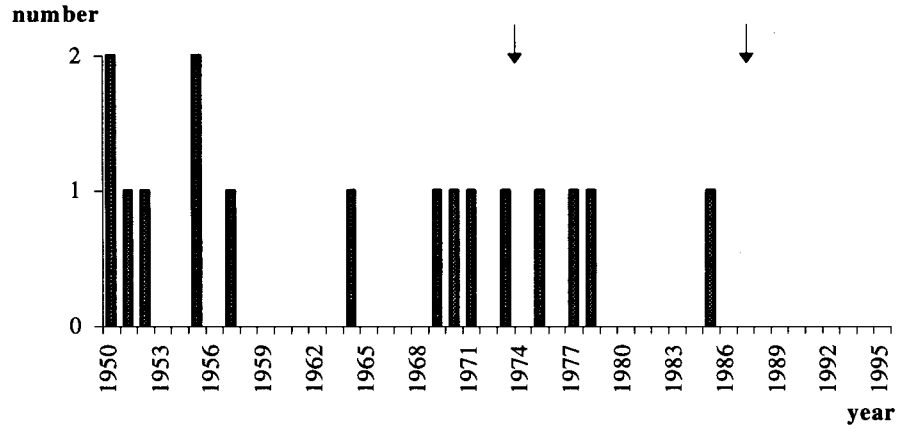

figure 18 Mortality of rubella in the period 1950-1995 (source: CBS)

(see Appendix I, table 11)

5.3.2 Morbidity

Notifications

After vaccination of 11-year old girls with rubella vaccine started in 1974 an epidemic cycle of two to four years was still seen, but in the 1980s the number of notifications clearly dropped, even before mass vaccination for boys and girls was started. In 1992 only nine cases were notified but this number increased in the following years to 39 in 1996. This increase is due to an increase in notified cases over ten years of age.

Before 1974 more girls than boys (47%) were notified, then in the period 1975-1987 gradually more boys were notified (mean 50%), and from 1988 onwards the percentages fluctuated enormously because of low numbers, but the mean percentage of notified boys was 55%.

The percentage of the notified cases that was not vaccinated increased from 38% in 1993 to 92% in 1996. It has to be mentioned though that in 1993 and 1994 the percentage with an unknown vaccine status was high; 12% and 21% respectively against 0% and 3% in 1995 and 1996.

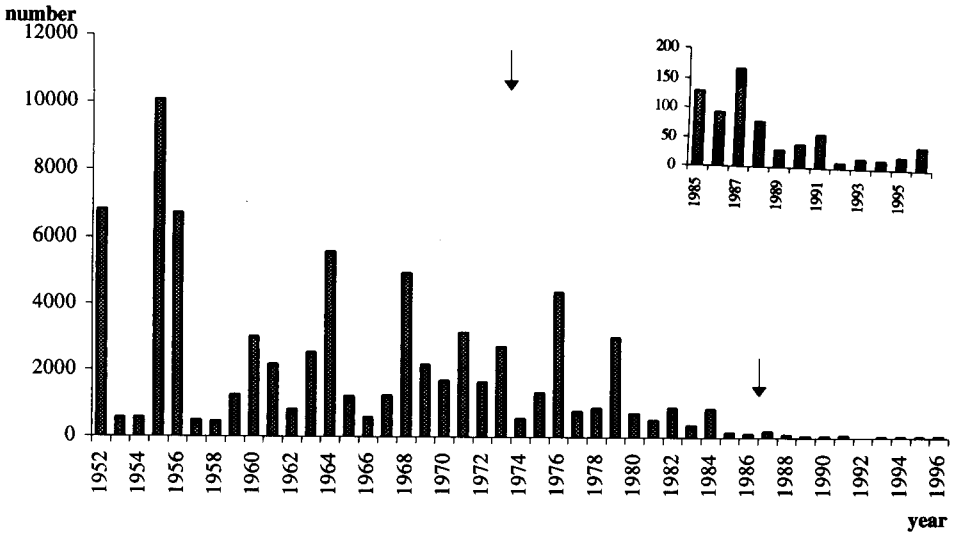

figure 19 Number of notifications for rubella and CRS in 1952-1996 (source: IGZ)
(see Appendix I, table 12)

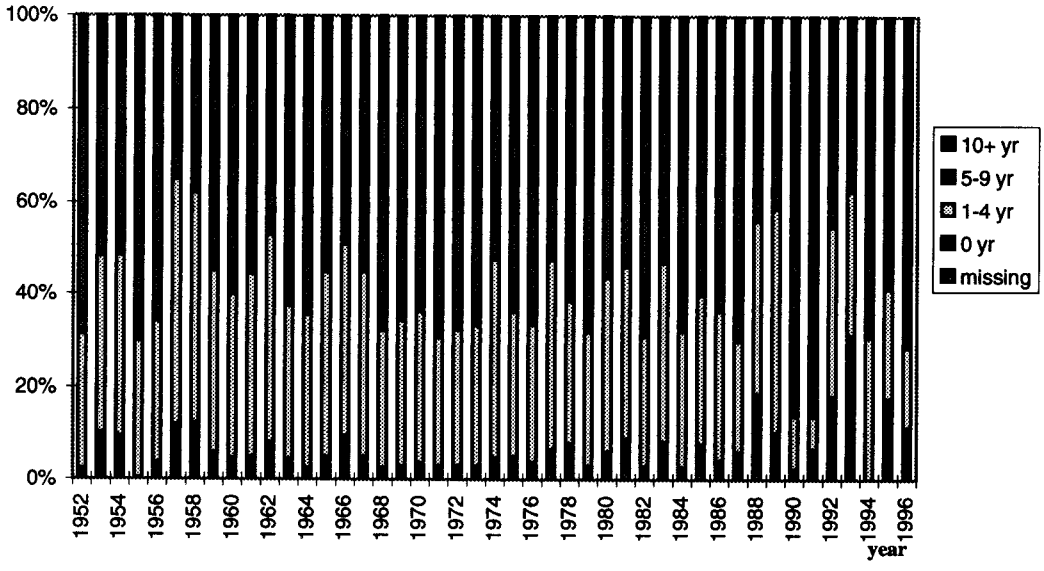

figure 20 Age distribution of notifications of rubella and CRS in the period 1952-1996 (source: IGZ)
(see Appendix I, table 12)

Hospital admissions

The number of hospital admissions for rubella which can be interpreted as acquired infection (ICD code 056 and further subdivisions), has also decreased drastically since 1987. Until vaccination against rubella was implemented the age distribution was rather constant with a

mean of 75% of the cases being under the age of ten years. In the period 1988-1996 the proportion of patients under nine years decreased to a mean of 47%. Before 1987 no gender effect was seen (49% males) and due to low numbers the percentage males admitted fluctuated enormously from 0% to 71% after 1987 but still no specific influence of gender was seen. Most hospitalised cases were admitted with rubella without complications (84%).

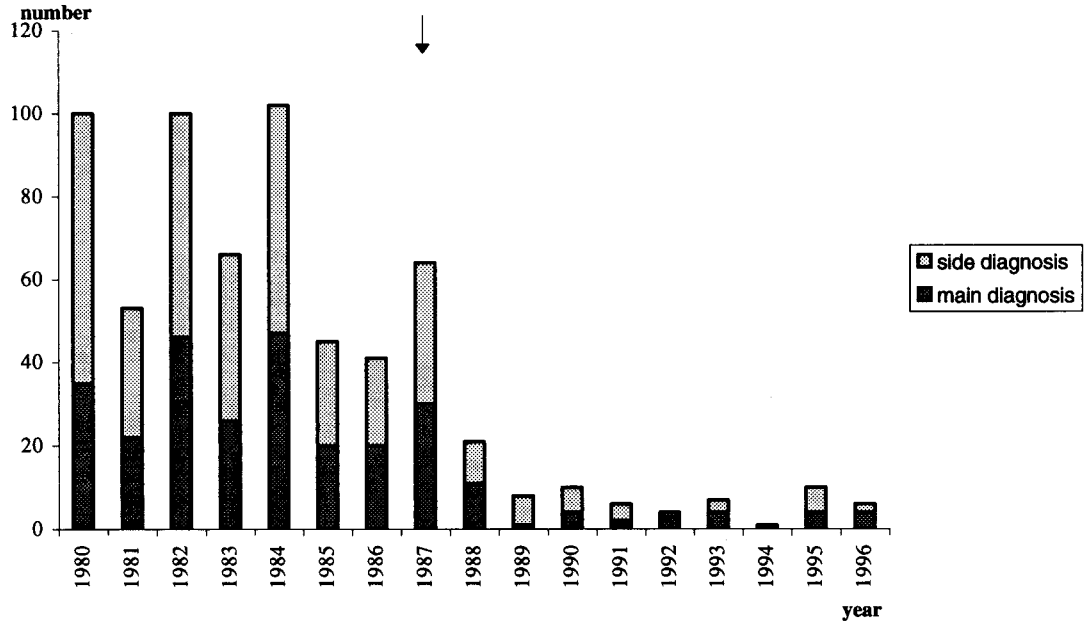

figure 21 Number of hospital admissions for acquired rubella (source: LMR) (see Appendix I, table 13)

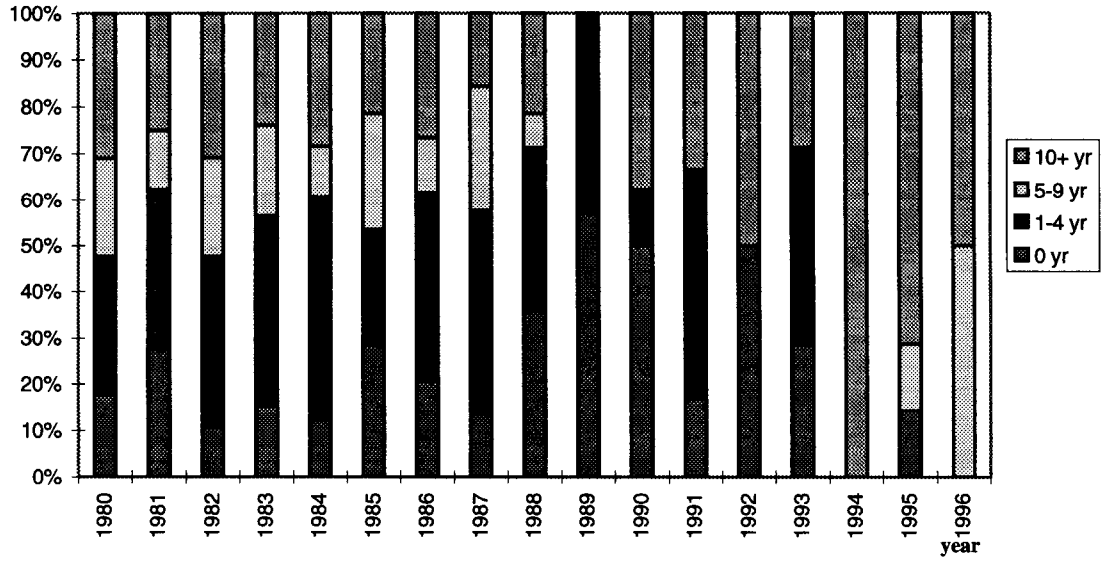

figure 22 Age distribution of hospital admissions for acquired rubella (source: LMR) (see Appendix I, table 13)

Sentinel centres

The CMRN-registration shows that after the introduction of selective vaccination epidemic peaks still occurred (23rd). The proportion of female cases of rubella also stayed at the same level of around 50% after the implementation of vaccination of girls at 11 years of age. The cases were mostly young individuals who had not been vaccinated (yet). It is clearly shown that immediately after the introduction of immunisation of both men and women at the age of 14 months and nine years, less cases of rubella were registered. The last patient was registered in 1990.

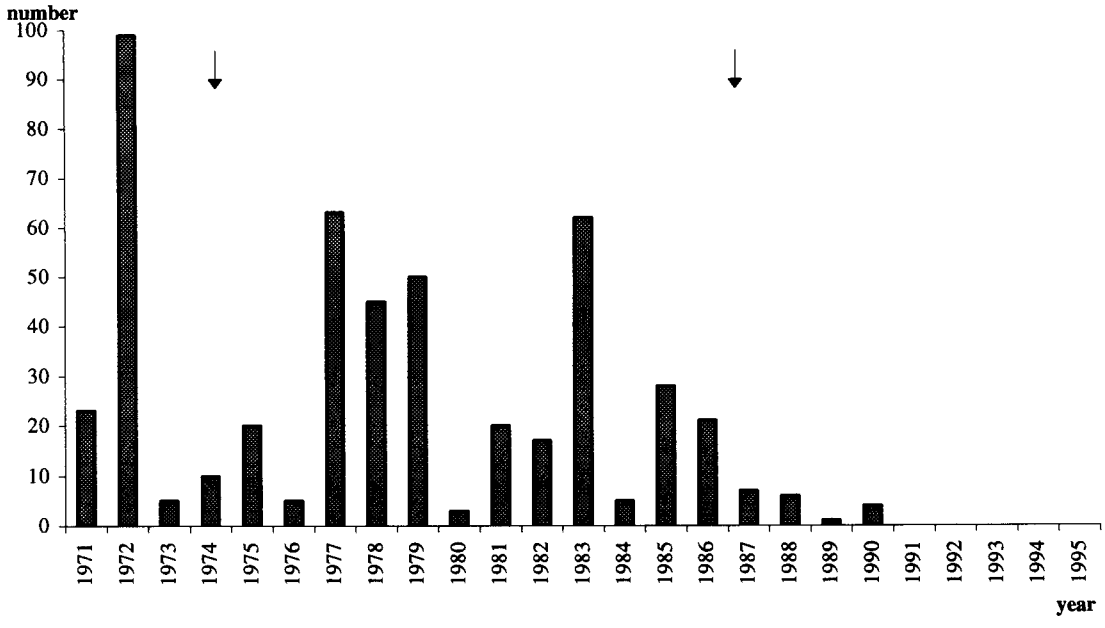

figure 23 Number of registered cases of rubella (source: CMRN)

(see Appendix I, table 16)

In the NIVEL sentinel centres rubella and rubella-like illnesses were reported in 1971. This was an epidemic year and an extrapolation of 20.5 cases per 10.000 inhabitants would imply that ± 26,000 cases of rubella and rubella-like illnesses occurred in this year.

Virological laboratories

The number of positive findings decreased right after the vaccination strategy changed from selective to mass vaccination in 1987.

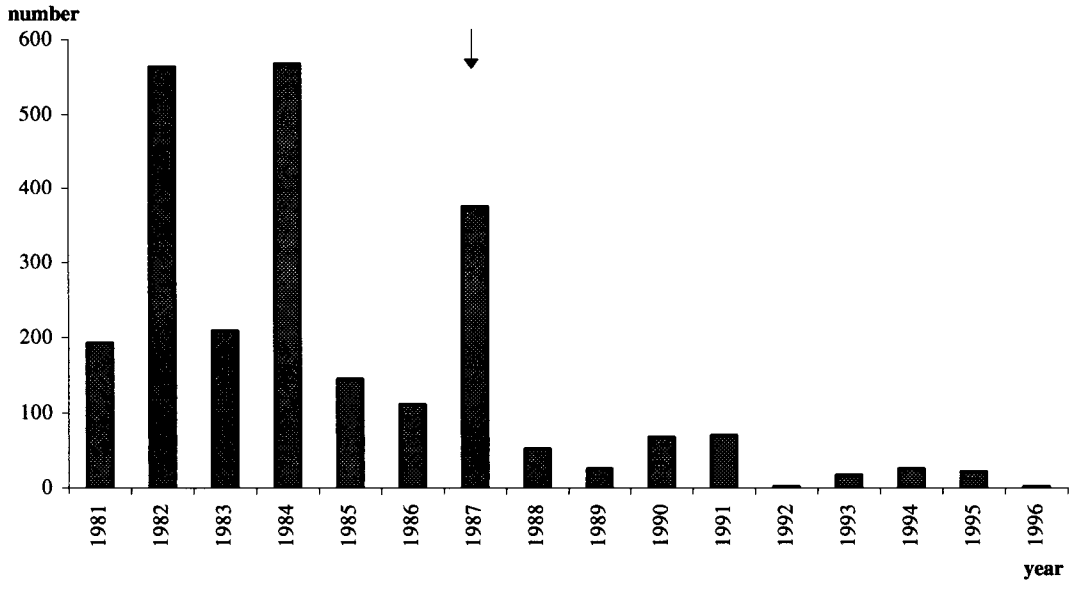

figure 24 Number of positive serology or virus isolation for rubella in 1981-1996 (source: clinical virological laboratories and RIVM)

(see Appendix I, table 17)

Hospital admissions for CRS

A downward trend in hospital admissions for congenital rubella syndrome (ICD-code 771.0) was seen already before 1987 and the number of hospital admissions then stayed at the level of approximately 10 admissions per year until 1994. It is only in the last two years that the number of cases seems to decrease further to five and two respectively (25th). Most patients were admitted with CRS as side diagnosis (65%). Furthermore the cases are mostly under the age of one year. The percentage and absolute number of patients over 10 years of age in the 1990s however is higher than in the pre-vaccination period.

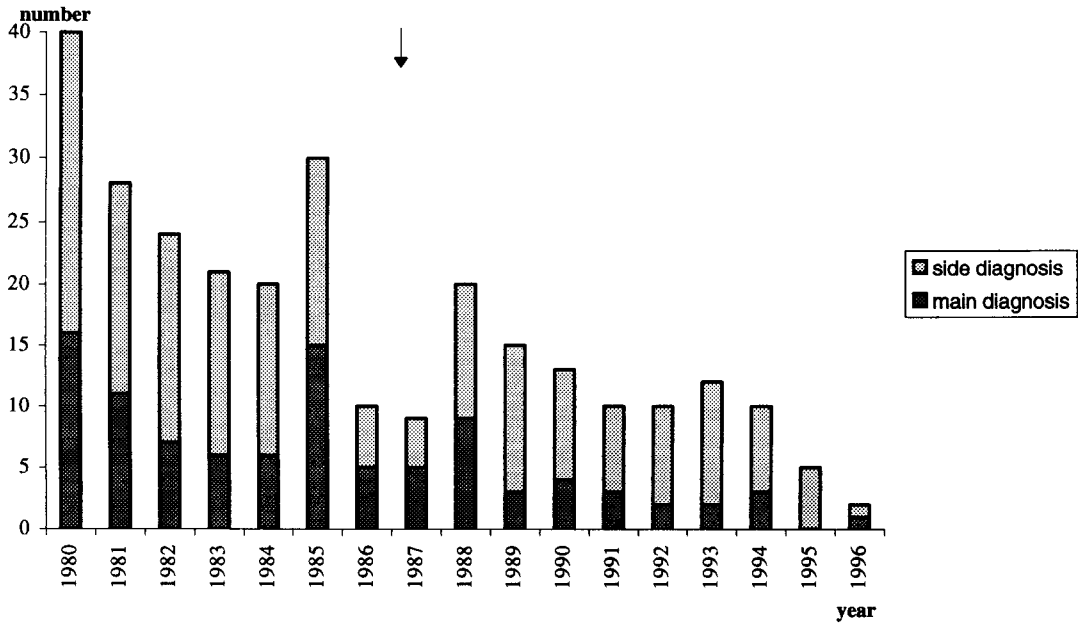

figure 25 Number of hospital admissions for CRS in 1980-1996 (source: LMR)

(see Appendix I, table 14)

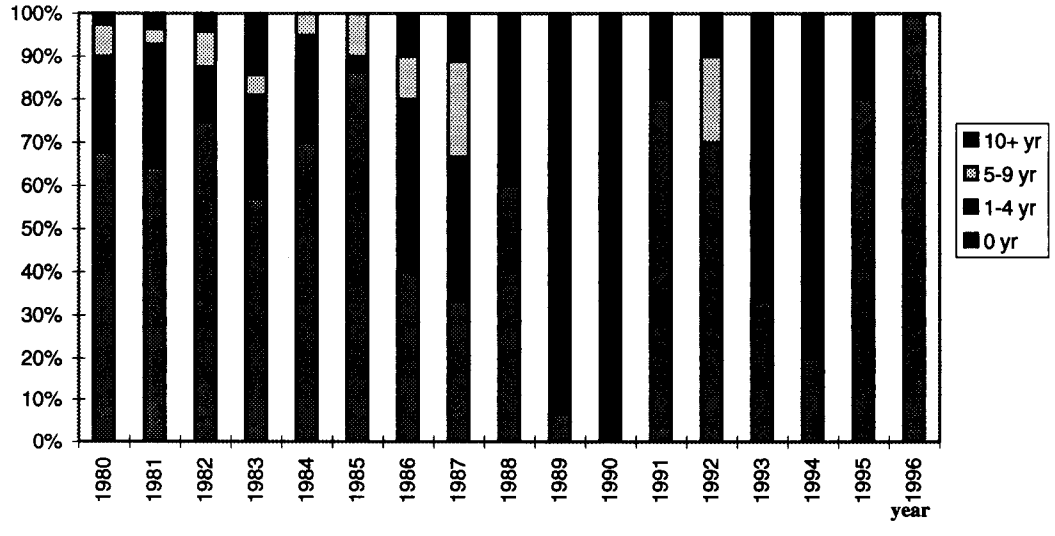

figure 26 Age distribution of hospital admissions for CRS in 1980-1996 (source: LMR)

(see Appendix I, table 14)

Hospital admissions for pregnant women with rubella infection

The ICD-code 647.5 is used in case of a pregnant woman with a rubella infection, this being a complication during pregnancy, at delivery or after delivery period. This code can be used to follow the trend of the incidence of non-immunised women in childbearing age. After introduction of vaccination the number of infected childbearing women decreased but in the 1990s still some cases are hospitalised every year (27th).

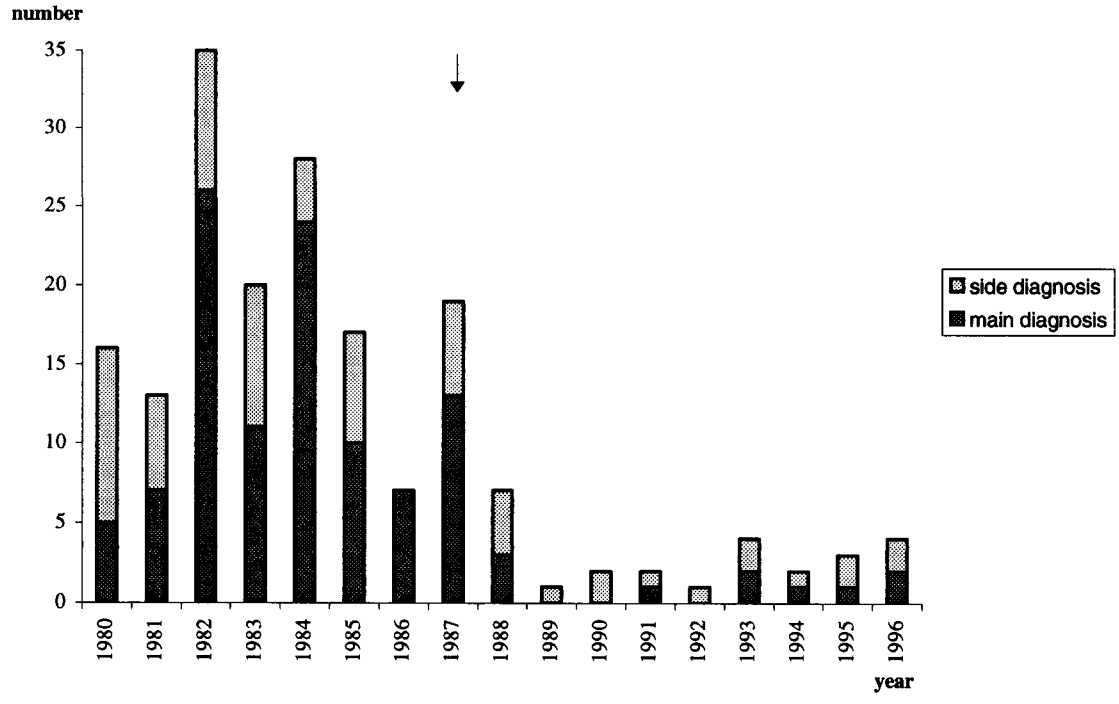

figure 27 Number of hospital admissions for pregnant women with rubella infection, this being a complication during pregnancy, at delivery or after delivery period in 1980-1996 (source: LMR)

(see Appendix I, table 15)

EUROCAT

EUROCAT (a registration of congenital disorders) in the North- and Southwest of the Netherlands has registered three confirmed cases of CRS from 1981 to 1996, the last case in 1993.

NSCK

No case of CRS was reported during one year of surveillance through the NSCK in while two cases were admitted to a hospital according to the LMR. These could also have been prevalent cases though.

5.4 Discussion

Mortality

Mortality has always been very low (0-2 deaths per year) since 1950; the last death due to rubella was seen in 1985, before then in 1978.

Effects of vaccination

No influence of the selective vaccination strategy that was implemented in 1974, was seen on the epidemic cycle and the number of notifications that had gradually been declining already before then. After mass vaccination was introduced in 1987 the number of notifications decreased even faster than before. This decrease after 1987 was also seen in the number of hospital admissions and in the figures of the CMRN and virological laboratories.

The mean age has increased due to a decrease in the force of infection but no increase was seen in the percentage of hospitalised cases with complications, which has always been low anyway, or in the number of CRS cases. An explanation for the increasing age of hospitalised CRS patients is probably that patients nowadays are admitted several times for treatment as a result of improved treatment possibilities.

The gender ratio for rubella without a link to pregnancy was very variable after vaccination was started and no specific pattern was seen, neither in notifications or hospital admissions. In Sweden, where also first selective and then mass vaccination was introduced, a dramatic shift in gender distribution was found. In 1974 (the year vaccination was started) men constituted 13% of the diagnosed cases while this was figure was 54% in 1987, five years after general vaccination was implemented (30). These years were both epidemical years for rubella in Sweden. This shift has to be considered with caution though. It could also be an effect of shifted attention from purely female patients to male and female patients because of the introduction of vaccination.

In 1993-1995 a mean of 29% of the notified cases were vaccinated and this proportion was 5% in 1996. This could indicate that vaccinated people can be reinfected, although viraemia is probably rare (31). This is an indication that reinfected vaccinated persons can contribute to the spread of the virus without being clinically infected. In literature is was shown that reinfection is more likely to occur in those with vaccine-induced immunity than in those with naturally acquired immunity (32).

Right after mass vaccination was started in 1987 a decrease of the number of childbearing women infected with rubella admitted in hospitals was seen. This is the result of a decrease in spread of the virus in the country. After all, most of these women were not vaccinated since selective vaccination was started in 1974. The chance of acquiring natural immunity through infection for unvaccinated individuals has become small. Women born in the vaccination era but who were not vaccinated themselves (e.g. for religious reasons) are approaching the child-bearing age. They are at risk of acquiring a rubella infection during pregnancy and their foetuses at risk of developing CRS, the preventable disease which was the main reason why vaccination against rubella was introduced. No increase in hospital admissions for pregnant women with a rubella infection or for CRS patients was seen until now, but can be expected

on theoretical grounds in the near future. This has already been observed in unvaccinated communities in the USA (33). Furthermore, no rubella vaccination has been offered to the birth cohorts before 1963. Although these women of 35 years and older could have been vaccinated at their own expenses, there is a potential risk of CRS with the increasing maternal age in the Netherlands. Immunosurveillance studies are started to monitor the lack of immunity in the population at childbearing ages.

Comparison of sources

Congenital rubella syndrome is a notifiable disease but can not be distinguished from notifications for rubella. Since there are much less cases of CRS than of rubella, no significant overestimation of rubella will occur, when considering all notifications as rubella. However, the notification data can not be used as monitor for CRS.

Only 1-5% of estimated number of cases found in NIVEL in 1971 were notified to the IGZ (0.59 ipv 20.5 cases per 10,000 inhabitants) and an even smaller percentage of the estimated number of cases according to the CMRN in the period 1972-1990, when the last case was seen in that sentinel. The NIVEL physicians registered rubella ánd rubella-like diseases. It is probable that in the NIVEL study exanthema of unknown cause were also registered as rubella-like disease. This is supported by the fact that there was a great coherence with age and gender ratio in the reported cases of exanthema of unknown cause in 1970 (34). In a study 50% of the cases diagnosed clinically as acute rubella infection were actually caused by the rubella virus (31). Also, it is unknown how reliable extrapolation of the figures from the NIVEL and CMRN centres is, but it is not expected to be unreliable enough to explain the difference; thus it can be concluded that there is a considerable underreporting.

The LMR seems to be a good indicator for the incidence of severe disease due to acquired rubella infection, the added value of notification data is the availability of information on vaccination status. Notification of CRS should be separated from notification of rubella.

The LMR gives an overestimation of the incidence of CRS patients, since prevalent cases can not be distinguished from new patients. So unless data can be acquired on an individual level, this registration does not give good insight in the incidence of CRS. The EUROCAT centres only found three cases in 16 years. This seems an unlikely low number even though not the whole North and Southwest of the country was covered since then; this was only since 1989 and 1990 respectively. The manager of the Northern EUROCAT told us however that she knows more cases of CRS exist in the area, even though they were not reported to the EUROCAT registration. Therefore this source does not seem sensitive enough for surveillance of CRS in the future. Since no data on notifications for CRS are available, not one registration can provide us with reliable information on the occurrence of new CRS patients.

Two national perinatal registers, the National Obstetrical Registry (Dutch acronym LVR) and the National Neonatological Registry (Dutch acronym LNR), were combined and turned out to be mostly complementary with respect to the registration of congenital anomalies. For sixteen important diagnoses the overlay of the combined database with EUROCAT in the Northern region was studied; 35% of these congenital anomalies were registered in both

systems, 43% in EUROCAT only, and 22% in the combined national database only (35). The advantage of the combined system over EUROCAT is the national coverage. The LVR and LNR suffered from underreporting, but new software is developed and in use now, through which the accuracy is expected to improve importantly. Furthermore an unique mother-child identification number will probably be introduced at the end of 1998, which will improve the accuracy of the data and through which prevalent cases can be easily identified from incident cases. In the future this combined database of congenital anomalies can become an important additional source for the monitoring of CRS.

6. Diphtheria

6.1 Introduction

Diphtheria is caused by toxigenic strains of *Corynebacterium diphtheriae*. The transmission route is aerogenic. The organism itself is not invasive, but it is capable of producing the potent exotoxin that can cause renal damage, myocarditis, circulation problems, polyneuritis and paralyses (palate and eye muscles). The infection is most often subclinical, but fast fatal outcomes also occur, especially in very young children and older persons. Asymptomatic respiratory carriage is important for the spread of the bacteria and immunisation reduces an individual's change of being a carrier (36).

In the pharyngeal form of diphtheria a tough pseudomembrane can be seen in the throat as a reaction on the adherence and penetration of *C. diphtheriae*. Apart from general features of infection, like fever and drowsiness, the breathing problems are characteristic. Diphtheria can also manifest itself as an infection of the skin (impetigo-like lesions), navel or wounds but these are less often seen in temperate zones. Humans are the only known reservoir for *C. diphtheriae*.

Natural infection does not always provide immunity and -natural or vaccine induced- immunity does give protection against invasive systemic disease, but not against local colonisation and infection.

Before the advent of routine vaccination, diphtheria was a common cause of morbidity and mortality. In temperate zones, more than 1 in 20 inhabitants suffered from clinical diphtheria during their lifetime and 5-10% of these died of the disease (37).

In the Netherlands before and after the Second World War vaccination against diphtheria, with a toxoid, was applied on a limited scale. In 1952 mass vaccination was introduced and nowadays children aged three, four, five and eleven months are vaccinated (DTP-IPV vaccine) and booster vaccinations for children aged four and nine years (DT-IPV) are offered.

6.2 Methods

The mortality registered by the CBS for the period 1950-1995 is described.

The incidence of diphtheria as derived from notifications for the period 1940-1996 are given; diphtheria is a category B notifiable disease.

6.3 Results

6.3.1 Mortality

CBS

Mortality due to diphtheria decreased from ±600 in 1947 to 230 in 1948 and steadily further down to 149 in 1953. Then the yearly mortality figure decreased drastically to one in 1962 and in the period 1963-1995 four deaths due to diphtheria have been registered.

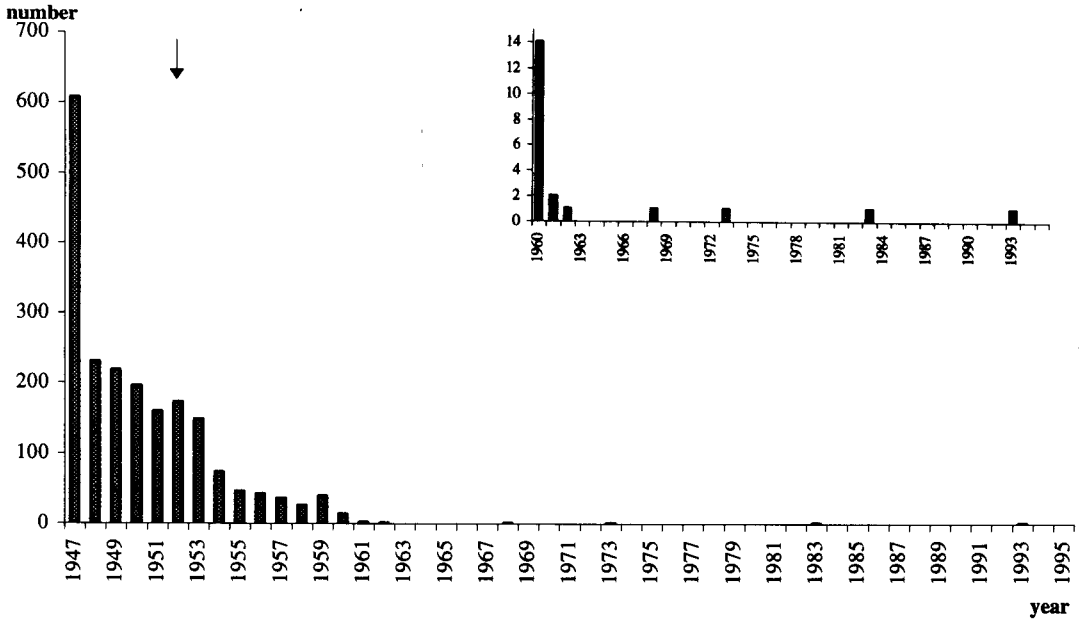

figure 28 Number of mortality cases due to diphtheria from 1950-1995 (source: CBS) (see Appendix I, table 18)

6.4 Morbidity

Notifications

In the Netherlands the last epidemic occurred during the Second World War. In the period 1942-1947 224,000 cases of diphtheria were notified. The number of notifications decreased from 2985 in 1950 to 15 cases in 1962. In the period 1963-1969 12 cases were notified and in the 1970s 8 notifications were registered. In the period 1980-1996 6 cases were notified. Most patients notified in the last two decades were adults. The diphtheria patient notified in 1991 suffered was a non cutaneous indigenous case; the patient notified in 1995 suffered from skin diphtheria. He had probably been infected in Africa and he was inadequately vaccinated for ideological reasons.

In the period 1980-1996 two patients with diphtheria-like symptoms, in whom bacteriological investigations could not confirm the diagnosis, have been observed (45).

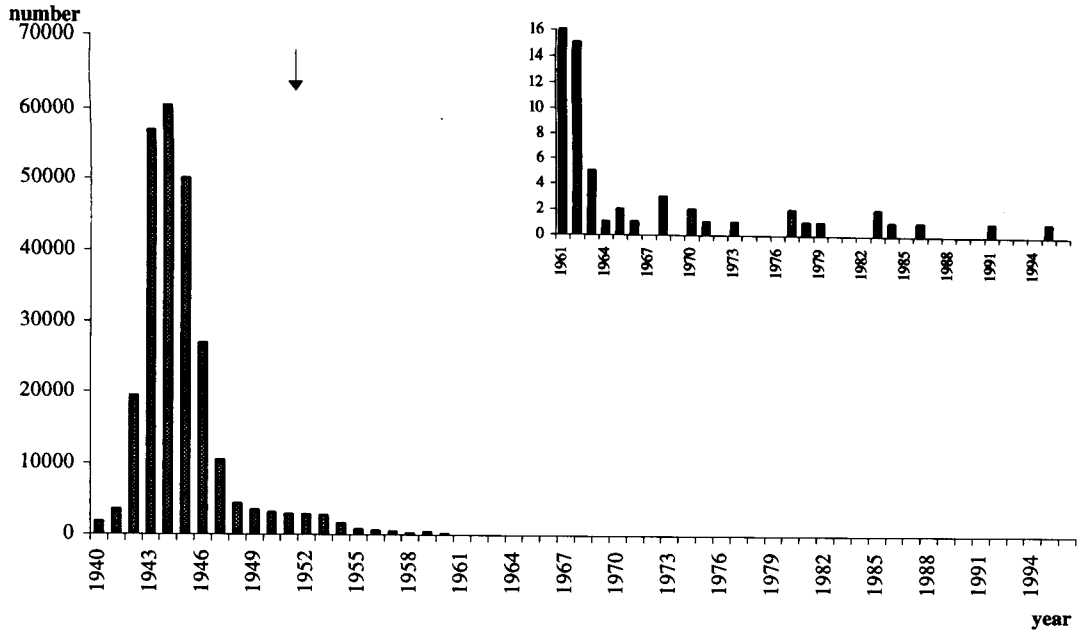

figure 29 Number of notifications of diphtheria from 1947-1996 (source: IGZ)

(see Appendix I, table 19)

6.5 Discussion

Mortality

The epidemic seen in the Netherlands in the 1940s was also seen in other European countries like Denmark, Switzerland and Sweden. In 1945 approximately one million cases were seen in Europe and 50,000 persons died of diphtheria that year leading to an estimated fatality rate of 5% (38, 39). Following the introduction of routine vaccination with diphtheria toxoid in 1952 with catch-up campaigns for persons born in 1945 or later, diphtheria mortality showed a fast decline but rates already began to fall before the implementation of mass vaccination for diphtheria.

Effects of vaccination

The mass vaccination led to the virtual elimination of diphtheria over the last three decades in the Netherlands.

Since the mid-1980s there has been a striking resurgence of diphtheria in several countries of Eastern Europe. For 1993, WHO received reports of 15,211 diphtheria cases in Russia and 2,987 cases in Ukraine (39). In the newly independent states of the former USSR, particularly in Russia and Ukraine in 1994 47.000 people contracted the disease. More than 2500 people have died in the period 1990-1994 (40). The epidemic is now under control as a result of collaborate actions of various world-wide organisations, which included mass vaccination (41). The main reason for the epidemic in Russia and Ukraine were: decreasing vaccination

coverage among infants and children, waning immunity to diphtheria in adults, movements of the population during the last few years, and an irregular supply of vaccines (39). The epidemic has spread to other European countries, but only in small numbers (39). In 1993 the first cases were imported from the newly independent states of the former USSR by travellers to other European countries (40). In the Netherlands only sporadic import cases of diphtheria were notified in the last decades, and only one since the beginning of the epidemic in the former USSR. This patient probably imported the bacteria from Africa though. In Finland, with its frequent contacts with the newly independent states, four import cases were registered in 1993, following thirty years of zero reporting, but no secondary cases were observed (39).

A Rumanian study showed that the diphtheria bacterium is less likely to be toxigenic in immunised individuals than in non-immunised persons. In Rumania 86% of surveillance isolates gathered before an improved vaccination programme was introduced in the late 1960s, was toxigenic and this percentage dropped to 7% thereafter. This low prevalence of carrier state might be the result of the fact that toxin production confers no advantage for the bacterium in an immunised individual (36, 42). Therefore toxigenic strains are less likely to colonise vaccinated individuals, thus enhancing herd immunity.
The experience of the last years in the Netherlands and other Western countries indicate that herd immunity as a result of both naturally acquired and vaccine-induced immunity is probably sufficient: only sporadic cases of import occurred and fortunately this has not led to further spread of diphtheria.
Although herd immunity seems (still) sufficient, the reduced circulation of *C. diphtheriae* has led to gaps in the level of anti-toxic antibodies in older age groups (43). As unvaccinated persons have no or reduced opportunity to acquire immunity, they remain susceptible. For vaccinated persons, immunity starts to wane after some years and opportunities for natural boosting are less common than in the pre-vaccination era. A serological survey of the Dutch population showed that in 1980 and 1985 a little less than half of the persons born before 1950 had antibody titres adequate for protection (≥0.1 IU/ml) while this percentage was over 80% in younger age groups (birth cohorts 1951-1976). A part will have diphtheria antibody titres between 0.01 and 0.1 IU/ml though, which is considered as possibly adequate and which could explain why spread of diphtheria did not occur in the last decades. Some of these persons may have 'memory immunity', their antibody titre has dropped, but when in contact with the causative micro-organism or after (re)vaccination a strong antibody response will occur as a result of immunological memory obtained during former contact with the micro-organism (44). In a study on vaccination status and the consequences of revaccination in a small group, 54 out of 59 persons with an antibody titre below 0,1 IU/ml showed a booster reaction indicating memory immunity (44). The Dutch Health Council has advised to conduct an investigation of the feasibility of an increase in the vaccination coverage in the cohorts born before 1950 (45).
As the antibody titres wane with age, booster vaccination every 15 years is recommended in the Netherlands for persons who travel to endemic areas. Periodic revaccination every ten years has been proposed for persons at increased risk of acquiring diphtheria (46).

The risk for diphtheria spread after import is probably higher in groups that refuse vaccination. The members of these mainly religious groups form 'pockets' with low vaccination coverage in geographical defined areas. In these pockets the effective herd immunity may be to low. Since the introduction of vaccination for poliomyelitis this has led to some epidemics of poliomyelitis, nearly exclusively among these groups. The risk for an epidemic of diphtheria after introduction of toxigenic *C. diphtheria* in these pockets is unknown.
The European region of the World Health Organisation has set the goal for elimination of the disease diphtheria by the year 2000. Elimination of the toxogenic bacterium is not considered possible in the near future since vaccination aims at the exotoxin, so carriage of the bacterium can not be prevented completely (47). The epidemic in the former USSR seems to fade and so will the chance of import of the bacterium, but elimination of the disease before the turn of the millenium seems not feasible.

Comparison of sources
The mortality and morbidity figures show the same trend in time. The notifications by law for diphtheria seem to be a reliable surveillance source: due to the seriousness of the illness, notifications probably give information on nearly all diphtheria patients in the Netherlands.
In 1993 the CBS reported one death due to diphtheria while no cases were notified. It is not clear whether this is due to misclassification in the CBS data or underreporting to the IGZ.

7. Tetanus

7.1 Introduction

Tetanus is an acute, spastic illness caused by tetanospasmin, the neurotoxin produced by *Clostridium tetani. C. tetani* is a gram-positive sporeforming bacterial pathogen whose natural habitat is soil, dust, the intestines of various animals (especially horses and cows) and the human skin.

The clinical picture of tetanus is one of the most dramatic in medicine and diagnosis can be made clinically. Most cases of tetanus are associated with a traumatic injury, often a penetrating wound contaminated with a dirty object or soil (48).

Tetanus may be either localised or generalised. Localised tetanus results in painful spasms of the muscles adjoining the wound site and may precede generalised tetanus. In generalised tetanus trismus (or 'lockjaw') is the presenting symptom in about half the cases. Headache, restlessness and irritability are early symptoms, often followed by stiffness, difficulty in chewing, dysphagia and neck muscle spasm. The so-called sardonic smile of tetanus ('risus sardonicus') results from intractable spasm of facial and buccal muscles; furthermore the patient may adopt an arched posture, the so-called opisthotonos, in which only the back of the head and the heels touch ground. Laryngeal and respiratory muscle spasm can lead to airway obstruction.

Neonatal tetanus (tetanus neonatorum), the infantile form of generalised tetanus, typically manifests within 3-12 days after birth as progressive difficulty in feeding (i.e. sucking and swallowing), with associated hunger and crying. Paralysis or diminished movement, stiffness to the touch, and spasms, with or without opisthotonos, characterise the disease.

Natural infection with tetanus does not provide immunity but vaccination does. Since 1952 tetanus vaccination is implemented in the National Vaccination Programme in the Netherlands, with a catch-up campaign for persons born in 1945 or later. Nowadays active vaccination begins in early infancy with combined diphtheria, tetanus, pertussis and polio (DTP-IPV) vaccine at three, four, five and eleven months of age, with a booster (DT-IPV) at four and nine years of age.

Tetanus prevention measures following trauma in unvaccinated/non-protected persons, consists of passively providing antitoxic antibody (human tetanus immunoglobulin), and of simultaneously inducing active immunity by starting active vaccination.

7.2 Methods

Mortality figures from the CBS in the period 1947-1995 are given.
Notifications to the Medical Inspectorate of Health in the period 1952 - 1996 were analysed; tetanus is a category B notifiable disease.
The third source consulted is the National Medical Registration (LMR) of the SIG for hospital admissions for (neonatal) tetanus (ICD code 037 for tetanus and 771.3 for neonatal tetanus) in the period 1980-1996.

7.3 Results

7.3.1 Mortality

CBS
Mortality of tetanus declined from around fifty right after World War II to 25-30 right before mass vaccination was introduced and gradually decreased even further in the vaccine era. Nowadays only sporadic deaths due to tetanus occur.

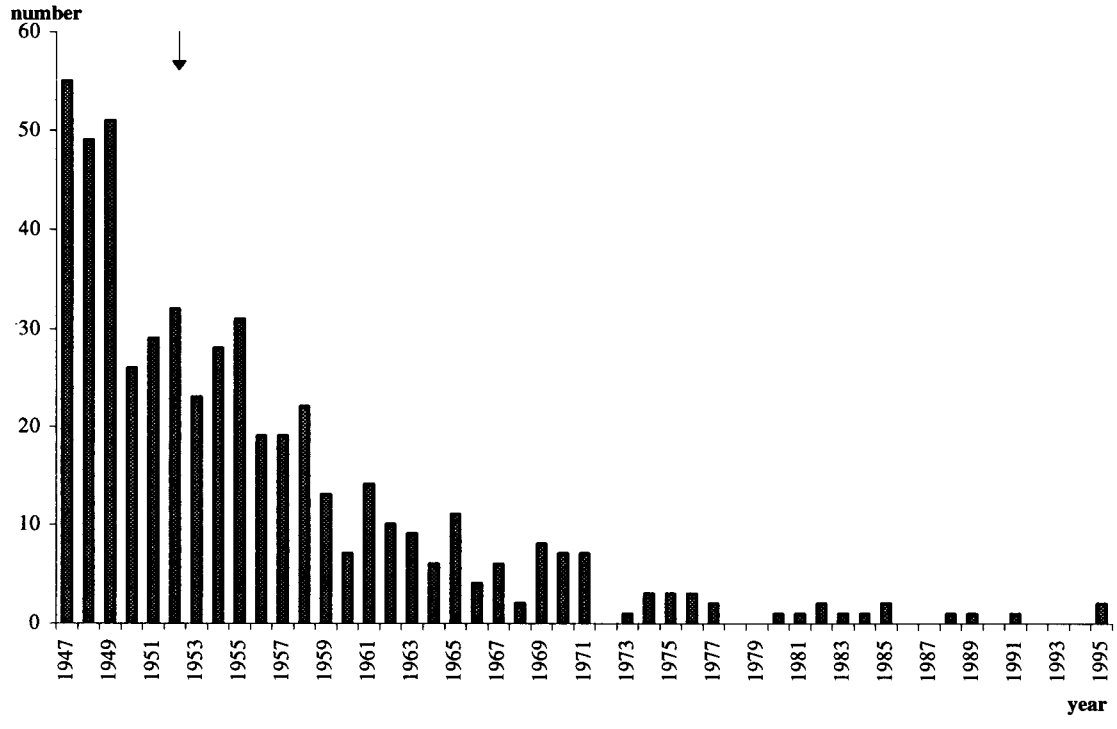

figure 30 mortality of tetanus in the period 1947-1995 (source: CBS)
(see Appendix I, table 20)

7.3.2
Morbidity

Notifications
Notification data have been available since 1952 and the first decennium after vaccination was introduced, no decline was seen in the number of tetanus cases. Then the number of cases gradually dropped and this decennium a mean of two cases per year was notified. Of the eight cases notified since 1993, seven were not vaccinated; they were all born before 1945. Of one patient the vaccination status was unknown. Most people got ill as a result of an injury. The number of cases were approximately similar for men and women.

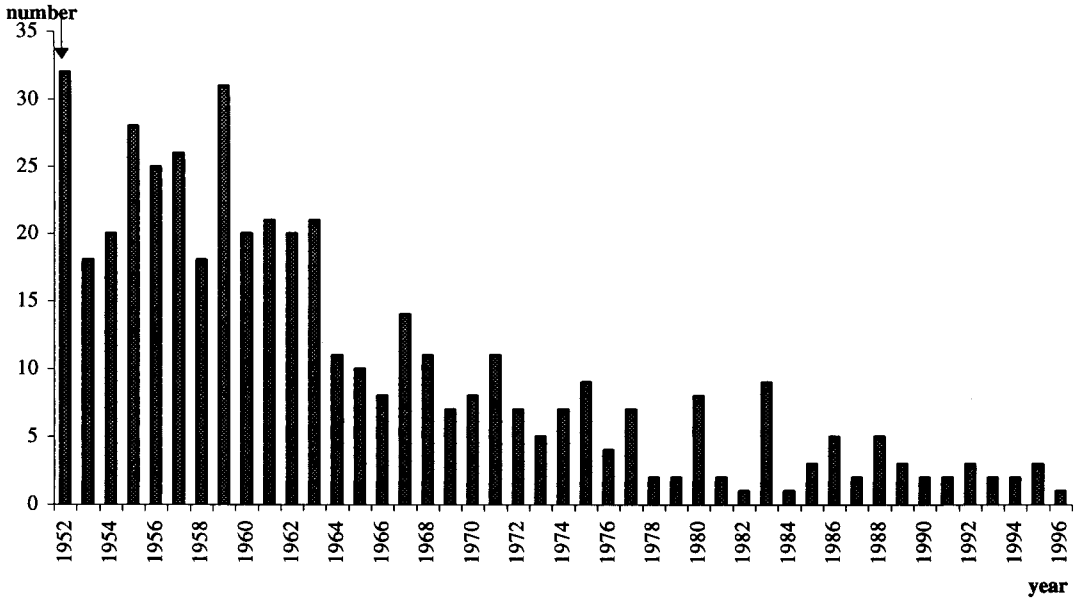

figure 31 Number of notifications of tetanus in the period 1952-1996 (source: IGZ)

(see Appendix I, table 21)

Hospital admissions
The number of hospital admissions for tetanus and neonatal tetanus are not shown since we doubted the validity of the figures. This will be explained in greater detail in the next section.

7.4 Discussion

Mortality
Only sporadic deaths due to tetanus were seen in the last decennium, and they all occurred among unvaccinated individuals.

Effects of vaccination

The introduction of vaccination with tetanus toxoid in the Netherlands started in 1952, but at that time people could choose the combined DP-vaccine or the combined DTP-vaccine. The DP-vaccine was abolished in 1959 (49). After the more systematic vaccination with the combined DT(P)-IPV-vaccine the number of notifications declined, especially in younger segments of the population. In the Netherlands where tetanus vaccination is operational now for several decades, covering the population up to about fifty years old, tetanus has become a rare disease, occurring mainly in elderly persons.

In a study conducted by the NIVEL and RIVM in 1980 and 1985 it was shown that at least 90% of individuals born after 1950 had adequate immunity against tetanus, while this percentage decreased to less than 10% in persons born before 1916 (43). Alertness is therefore needed for the older people who are not immune for tetanus and are injured. On the other hand doctors have to be careful not to hyperimmunise the patients, because arthrus-like reactions may occur. In a study where 10 persons with inadequate antibody titres for tetanus (<0,1 IU/ml) were revaccinated, 9 of them acquired immunity after one vaccination and the other one after two doses (44).

In literature we find that men are better protected than women, probably due to additional vaccinations given during military service or professional activities (43, 50, 51). This was not reflected in the notification data, which can be explained by the fact that a considerable part of the persons born before 1945 has never been vaccinated and thus is not immunised.

Sources of information

In this report the hospital admissions for (neonatal) tetanus are not presented; the information was collected, but the number of cases was far too high to be realistic, knowing the epidemiological situation in the Netherlands. For example the National Medical Registration registered 25 hospital admissions for neonatal tetanus in 1994, while in industrialised countries the decline in neonatal tetanus morbidity started well before tetanus toxoid was widely available, because of improved obstetrical techniques and improvements in hygiene (52). The high number of hospital admissions for neonatal tetanus provided by the LMR of the SIG is probably due to a wrong code, misclassification with the medical diagnosis 'tetani' or an error in writing. To verify our disbelief we asked the opinion of some experts. They too thought this number of hospital admissions due to neonatal tetanus was too unlikely to be true.

Tetanus occurs world-wide and is endemic in most developing countries, but its incidence varies considerably. The most common form, neonatal (umbilical) tetanus (caused by unhygienic cutting of the umbilical cord or application of potentially infectious substances to the umbilical stump), kills at least 500,000 infants each year because the mother is not vaccinated. World-wide an estimated 15,000-30,000 unimmunised women die each year from maternal tetanus, which results from post-partum, post-abortal or post-surgical wound infection with *C. tetani*(52). Furthermore (neonatal) tetanus is such a dramatic disease that at least a part of these 'cases' would have been reported to the Medical Inspectorate of Health, but no neonatal cases have been notified since 1984.

The number of hospital admissions for tetanus is higher than all notifications of tetanus in that period, possibly also caused by the above mentioned registration or writing errors since it is not to be expected that patients will be hospitalised several times. The notifications by law are known to be biased by underreporting, although we expect that patients with tetanus, a severe and rare disease, would all be reported.
In the future notifications to the Medical Inspectorate of Health seem to be sufficient for the surveillance of tetanus. The notification system has the advantage of the availability of supplementary information on vaccination history and personal circumstances. The validity of hospital data registered by the National Medical Registration does not seem sufficient and improvement is necessary in the ICD-coding of acquittal diagnoses, either on the side of the hospital or at the SIG.

8. Pertussis

8.1 Introduction

Pertussis (whooping cough, 'cough of hundred days') is a highly contagious and severe infection of the respiratory tract, caused by the obligatory human bacterial pathogens *Bordetella pertussis* or (more rarely) *Bordetella parapertussis*. The disease is characterised by long-lasting paroxysmal cough, accompanied by whoops, cyanosis, apnoe and vomiting and sometimes (modest) fever. In very young infants (0-5 months) pertussis may run a complicated course with secondary pneumonia, convulsions and encephalopathy and has a case-fatality rate of approximately 1%. In older persons the fatality rate is 0.1% to 0.2% (53).
Nation-wide vaccination against pertussis was introduced in 1952 at the start of the National Vaccination Programme with the DT-IPV-vaccine. Nowadays children are vaccinated against pertussis at the age of three, four, five and eleven months (DTP-IPV-vaccine). Immunity induced by the pertussis vaccine starts to wane after three years, after which period the once vaccinated individual may contract natural infection again, albeit with less severe and often atypical and unrecognised symptoms. The currently available pertussis vaccine, consisting of killed whole cells of *Bordetella pertussis*, can not be applied safely as a booster beyond childhood, because of increasing risk of side-effects. Acellular pertussis vaccines have been developed, which consist of a limited number of non-toxic and relevant antigens of bacterium such as pertussis-toxoid. These acellular vaccines offer the opportunity for a booster vaccination beyond childhood (54). Introduction of acellular vaccine in the National Vaccination Programme is considered. For assessment of (changes in) vaccine efficacy the incidence of pertussis should be monitored carefully.
Pertussis has been a notifiable disease since 1976. During the 1980s the number of notifications increased dramatically. The cause of this increase is thought to be partly due to increasing application of serology for pertussis diagnosis and its too liberal interpretation (55). Therefore a restrictive case definition that included criteria for laboratory diagnosis was introduced in 1988 (see Appendix II).

8.2 Methods

Deaths due to pertussis registered in the period 1905-1996 at the CBS are described.
Since 1976 notification of pertussis (category B notifiable disease) is obligatory by law, but no case definition was used. Due to the introduction of the case definition in 1988 the notification data before and after 1988 are not directly comparable.
Since 1989 all 16 Public Health Laboratories report the number of isolates of Bordetella on a weekly basis to the RIVM and positive serology data from 1989-1996 are shown. Data on the hospital admissions for pertussis (ICD-codes 033 and further subdivisions) from the National Medical Registration (LMR) of the SIG in the period 1980-1996 are given.

8.3 Results

8.3.1 Mortality

CBS

In 32nd the mortality due to pertussis from 1905 onwards are given. The mortality declined from 1226 cases in 1905 to 626 cases in 1930, 145 cases in 1950, 30 cases in 1955 to 6 cases over the period 1964 till 1995.

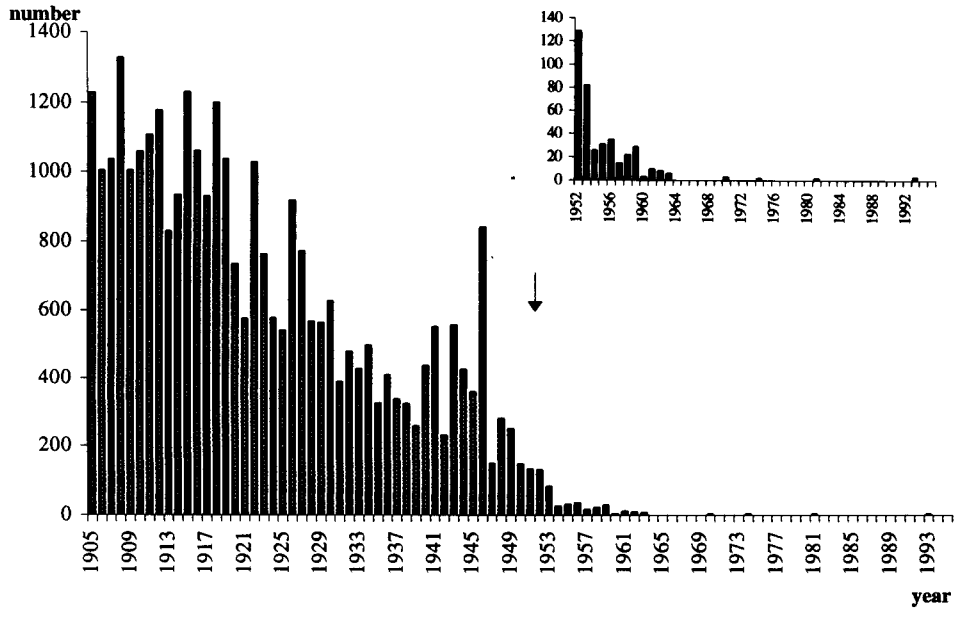

figure 32 Mortality due to pertussis in the period 1905-1995 (source: CBS) (see Appendix I, table 22)

8.3.2 Morbidity

Notifications

Until the 1980s, the incidence of pertussis seemed to be very low, since only incidentally cases were reported. Then the number of notifications increased from 50 in 1981 to 2709 in 1987 but as mentioned before, no criteria for notifications were used. The year the restrictive case definition with inclusion of criteria for laboratory diagnosis was introduced, the number of notified pertussis cases dropped immediately from 2709 in 1987 to 112 in 1988. In 1989-1990 and 1993-1994 a higher incidence was seen than in the surrounding years. Then in 1996 a very high number of pertussis cases was notified.

In 34th the proportional age distribution of notifications in the period 1976-1996 is shown. Due to the low absolute numbers before 1980 the age distribution is not very reliable. The percentage of children under the age of one decreased from 50% in 1981 to 4% in 1987, then increased to 15% in 1988 (when a case definition was introduced) and remained relatively

stable until 1993 around 22%. Then the proportion decreased again to 7% in 1996. The percentage of notified cases over nine years of age increased from 2% in 1981 to 43% in 1987 and then remained relatively stable with fluctuations between 15% and 27%.
More female patients (55%) were notified than males in 1988-1996.
The proportion adequately vaccinated notified cases increased from 56% in 1993 to 70% in 1994, 77% in 1995, and 85% in 1996. The reasons for not being vaccinated were mostly being too young or too old or of religious/ideological origin.

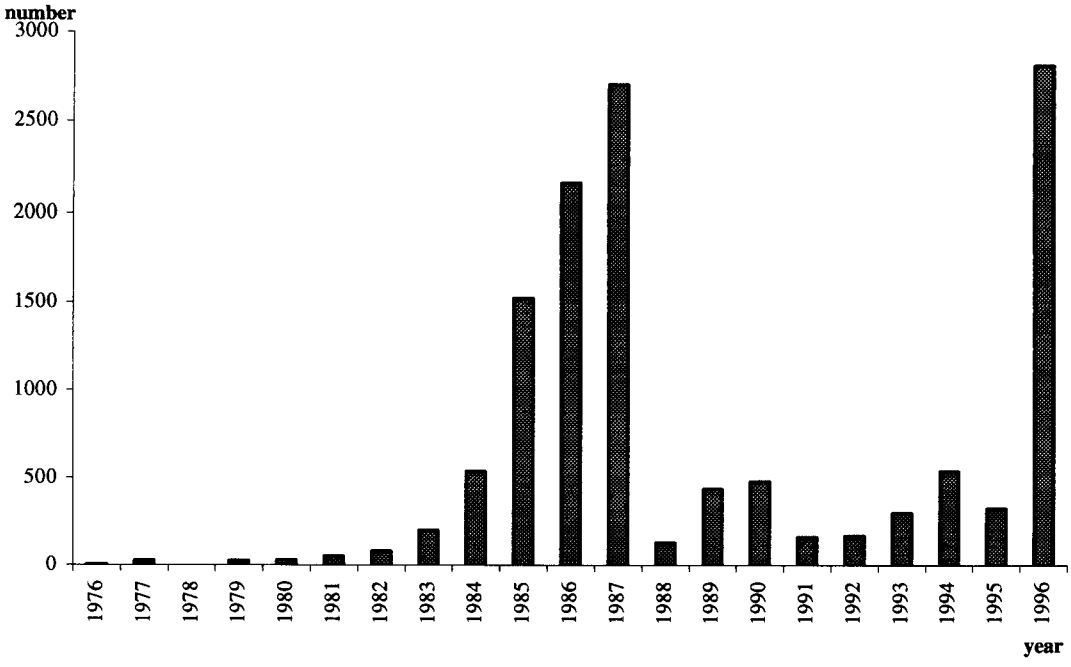

figure 33 Number of notifications for pertussis in the period 1976-1996 (source: IGZ)

(see Appendix I, table 23)

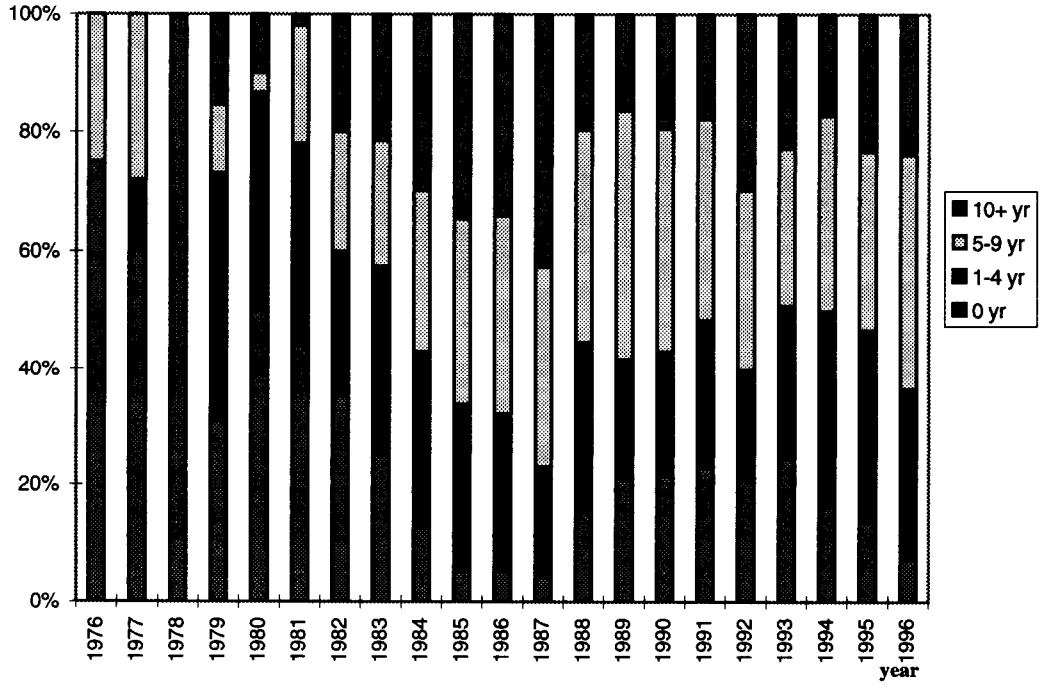

figure 34 Age distribution of notifications for pertussis in 1876-1996 (source: IGZ)

(see Appendix I, table 23)

Hospital admissions

The number of hospital admissions for pertussis increased from 73 in 1980 to 542 in 1987 and then similar peaks as in the notification data were observed. Mostly infants under one year of age were hospitalised; this proportion decreased from 75% in 1980 to 52% in 1986, then increased again to 74% in 1990 and varied between 58% and 77% in 1991-1996. More females (54%) were admitted in hospitals than males in the period 1980-1996.

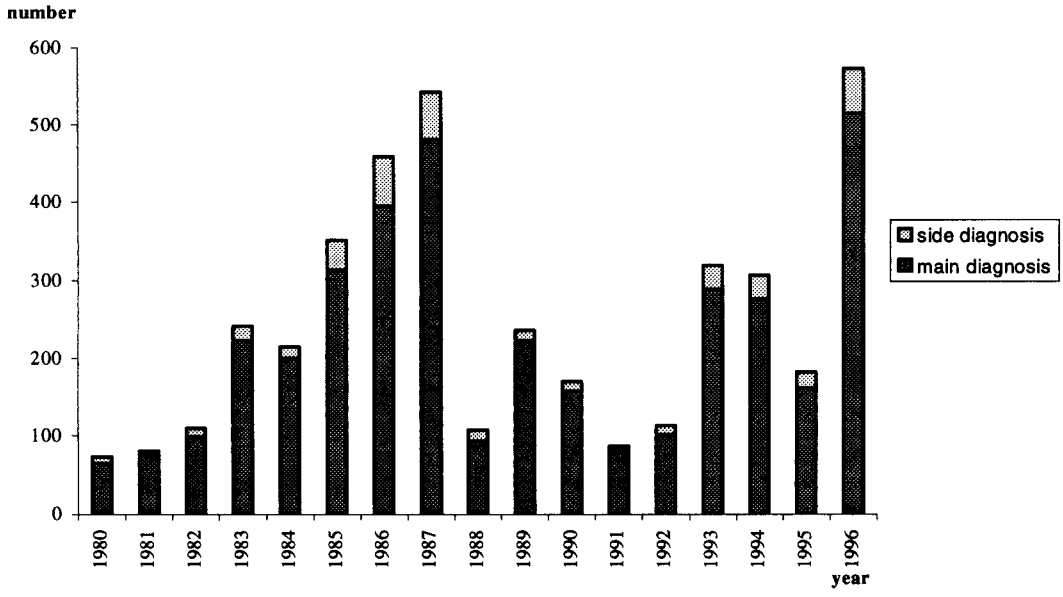

figure 35 Number of hospital admissions for pertussis in the period 1980-1996 (source: LMR) (see Appendix I, table 24)

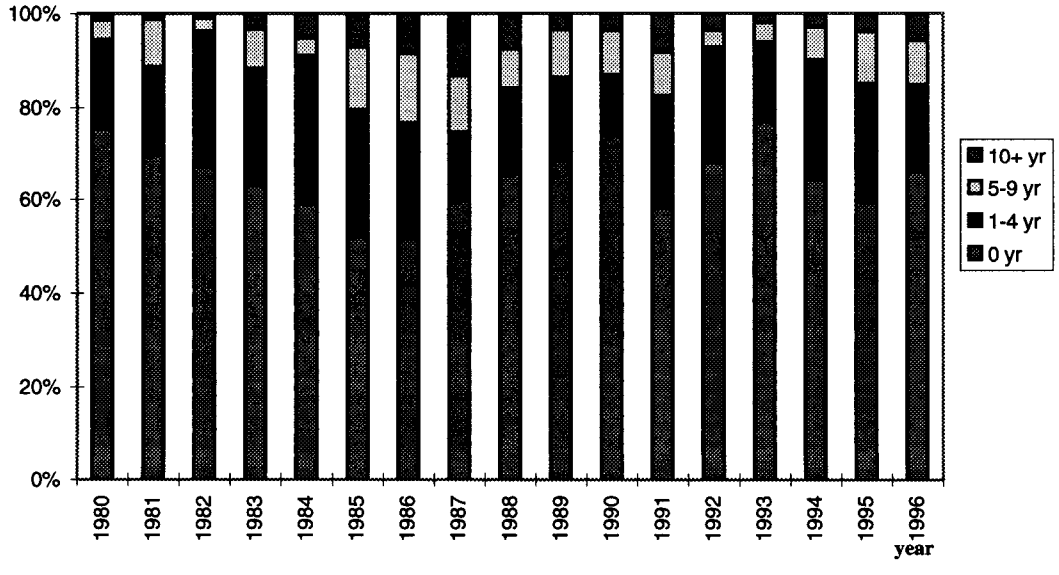

figure 36 Age distribution of hospital admissions for pertussis in 1980-1996 (source: LMR) (see Appendix I, table 24)

Serological results

The positive serological data show the same cycle as the notifications and hospital admissions, namely peaks in 1989 (n=2110), 1993-1994 (n=1971 and 2365 respectively) and a very high peak in 1996 (n=9739). In all years, the incidence in children under one year of age was highest, especially the incidence in children under six months of age. The incidence in 5-9 year-olds was two-fold higher than the incidence in 1-4 year-olds in 1989 and this ratio shifted throughout the years; in 1991-1992 the incidence was about equal and in 1993-1995 the incidence in 1-4 year-olds was higher. Then in 1996 the incidence was higher in the 5-9 year-olds (56).

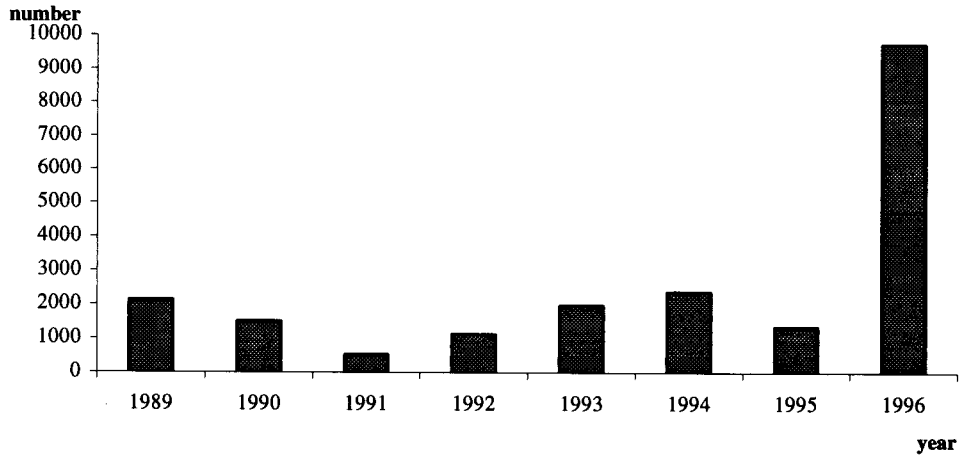

figure 37 Number of positive serological results (two-point and/or one-point serology) for *Bordetella (para)pertussis* in the period 1989-1996 (source: RIVM/LIS) (see Appendix I, table 25)

8.4 Discussion

Mortality

In the 20th century the yearly mortality rate for pertussis declined from over 1000 registered deaths in the beginning of the century to zero or one registered death in current years. However, the mortality rate did already decrease before the introduction of vaccination, most probably as a result of improved hygiene and antimicrobial therapy. After the introduction of vaccination the mortality declined further.

Effects of vaccination

Pertussis was not a notifiable disease until 1976 so the effect of the introduction of vaccination can not be observed in the notification data. In literature however, we do find that after the introduction of vaccination in 1952 the incidence of pertussis decreased. Nevertheless, although over 95% of children at the age of 3, 4, 5 and 11 months is vaccinated against pertussis, pertussis remains endemic with epidemic peaks in the Netherlands (6). Pertussis is not only affects children but also adults, which is shown by the morbidity data presented above.

Insight into the incidence of pertussis from 1976 to 1988 derived from notification data is complicated by the availability of serological tests and the change in case definition for notifications in 1988 (57, 58). In 1981 and 1984 IgA-immunoassays and IgG-immunoassays became available respectively (59, 60). Serology is now the most used diagnostic test in the Netherlands. Before 1988, high titrs in one serum sample, and after 1987, only a significant increase of the titre in paired sera were considered to confirm the clinical diagnosis of pertussis. In the period 1989-1995, when a case definition was used, the epidemic pattern was consistent with a classical pattern of epidemic peaks every three to five years (in 1989 and 1993-1994). Then a sudden and unexpected increase was seen in 1996. The same pattern was seen in hospital admissions and in the serological data, except that the notification data showed a slight delay in time. This is due to the fact that the median delay between first day of illness and notification date was 63 days in 1988-1996 and since peak incidences are seen in fall and winter, some of the cases could be notified after the turn of the year.

The incidence in 1996 was higher than in 1987 in all three registrations. Cases were seen all over the country; no geographic clustering was observed, even not in regions with low vaccination coverage or in a region near Germany where vaccination coverage for pertussis is very low (3). A higher awareness, changes in diagnostic practice or a lower vaccination coverage could not explain the epidemic. There are indications that changes occurred in the circulating strains of the bacterium, resulting in a possible mismatch between vaccine and circulating *Bordetella* strains (3). First, a high proportion of vaccinated individuals was seen among the notifications. Second, the vaccine efficacy estimated with the screening method, based on notification data for 1-4 years-olds amounted 91% in 1993, 70% in 1994, 72% in 1995 and 27% in 1996 and was even 7% for 5-9 year-olds in 1996 (56). However, estimation of vaccine efficacy from surveillance data should be interpreted with caution since bias can not be ruled out totally.

The proportion of hospital admissions to notifications amounted 0.6 overall and 1.9 for children under 1 year of age. This emphasises the seriousness of the illness for young infants. The proportion remained constant over the years indicating that the virulence of the circulating strains did not change.
Both in the notification data and the hospital acquittal diagnoses more female patients were seen: 55% and 54% respectively.
Data from other countries in Europe indicate that the pertussis epidemic is restricted to our country, but in the United States and Canada a resurgence has been noted since the late 1980s. No single factor has been found to explain this resurgence (61, 62).
In 1997 active surveillance of hospitalised pertussis cases was started through paediatricians within the NSCK, allowing for additional data collection on severity of disease. Moreover, in October 1997-January 1998 notifications were followed by data collection through a questionnaire in a comparable way. These studies will provide more insight into the vaccine efficacy in relation to severity of disease.

Comparison of sources
The increased incidence of *Bordetella pertussis* infections emphasises the necessity of continuous surveillance. Information from different data sources (notifications by law, serodiagnosis and hospital admissions) has to be relied on, with cautious interpretation of these data regarding inevitable biases (56). A important advantage of notifications data is the information on vaccination status. These data can be used to monitor the vaccine efficacy. Notifications by law are probably severely biased by underreporting though. This is illustrated by the fact that in some years the number of hospital admissions exceeded the number of notifications.
An advantage of data on serodiagnosis is that it can give a indication on the completeness of notifications. However, confirmation of pertussis is not always based on serodiagnosis, but also on positive culture or PCR or an epidemiological link to a index case (58). If the serodiagnosis can be performed by more laboratories in the future, this source will lose its value, unless it will appear possible to aggregate data from different laboratories at a national level, e.g. through ISIS.
Data on hospital admissions give a global insight into (changes in) seriousness of the illness (mainly in young infants). Protection of these young infants is the main reason for pertussis vaccination. Surveillance through the NSCK is more useful even if no complete coverage can be guaranteed, as it allows for additional collection of data on clinical presentation, diagnostic tests and vaccination status. As the mortality due to pertussis is very low and as some experts noted that a few deaths of pertussis were not registered at the Central Bureau of Statistics, this surveillance source is less important.

9. Poliomyelitis

9.1 Introduction

Poliomyelitis anterior acuta ('polio') is a serious disease caused by the poliovirus, an enterovirus that replicates in the gastrointestinal tract. Serologically three types can be distinguished: type 1, 2, and 3. In 90-95% of those infected the infection is subclinical; 4-8% experience mild symptoms, like a headache, fever, sore throat or gastrointestinal problems; in only a very small proportion (0.1 to 1%), the virus invades the nervous system, thus causing paralysis and/or sometimes meningitis (63). No cross immunity exists between the three types of polio virus; infection with one type of polio virus does not provide immunity against the other two types.

As from 1957 vaccination against polio is offered to all children at the age of three, four, five and eleven months (DTP-IPV) and a booster vaccination at the age of four and nine years (DT-IPV). A catch-up campaign was conducted for those born in or after 1945.

The vaccine used in the National Vaccination Programme is the Inactivated Polio Vaccine (IPV- or Salk-vaccine), which is administered intramuscular. Most other 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 under epidemic conditions, when wild poliovirus is circulating, because it rapidly infects the gastrointestinal tract, thus blocking the spread of the wild virus.

In 1988 the 41st World Health Assembly launched the initiative to eradicate poliomyelitis by the year 2000 (64). If this formidable enterprise succeeds, it will be the solution for the specific situation in the Netherlands. To prevent epidemics like those seen in the past few decades, the absence of import of wild poliovirus is essential, since outbreaks of polio after import of wild virus can continue to occur, as long as clustering of unvaccinated people in the Netherlands exists.

Continued surveillance is needed in order to demonstrate progress towards eradication. Recently it has been proposed to base the surveillance on (65):

- clinical surveillance consisting of mandatory notification of suspected patients and of reporting of patients with acute flaccid paralysis (AFP, a syndrome with numerous possible causes besides infection with polio virus, like Guillain Barré syndrome, a tumour or an other infection) born in 1957 and thereafter. An expert committee has to be established for final classification of cases.
- virological surveillance comprising (a) diagnostic investigation of suspected polio patients and AFP patients, (b) analysis of a selection of enterovirus strains isolated in Dutch virus diagnostic laboratories, and (c) environmental surveillance
- serological surveillance to determine the level of protection to poliomyelitis in the general population and specific risk groups
- Collection of information on vaccination coverage.

Improvement of epidemiological and virological investigation of AFP cases, enterovirus surveillance, and environmental surveillance and the establishment of a national expert committee for classification of cases is considered necessary.

9.2 Methods

Mortality figures from the CBS in the period 1905-1995 are given.
Notifications for poliomyelitis (category A notifiable disease) has been obligatory by law from 1924 onwards and is shown for the period 1924-1996.
Hospital admissions for acute poliomyelitis registered in the National Medical Registration from 1980-1996 were used. The diagnosis codes used in this latter source are ICD-9-CM code 045 and further subdivisions.
The Netherlands Paediatric Surveillance Centre has provided information on cases of acute flaccid paralysis (AFP) seen in paediatric practice (children below the age of 15 years) since 1 October 1992.

9.3 Results

9.3.1 Mortality

CBS
An epidemic cycle was seen before vaccination was started in 1957. After 1964 only sporadically polio-related deaths were registered; the last death occurred during the 1992-1993 epidemic.

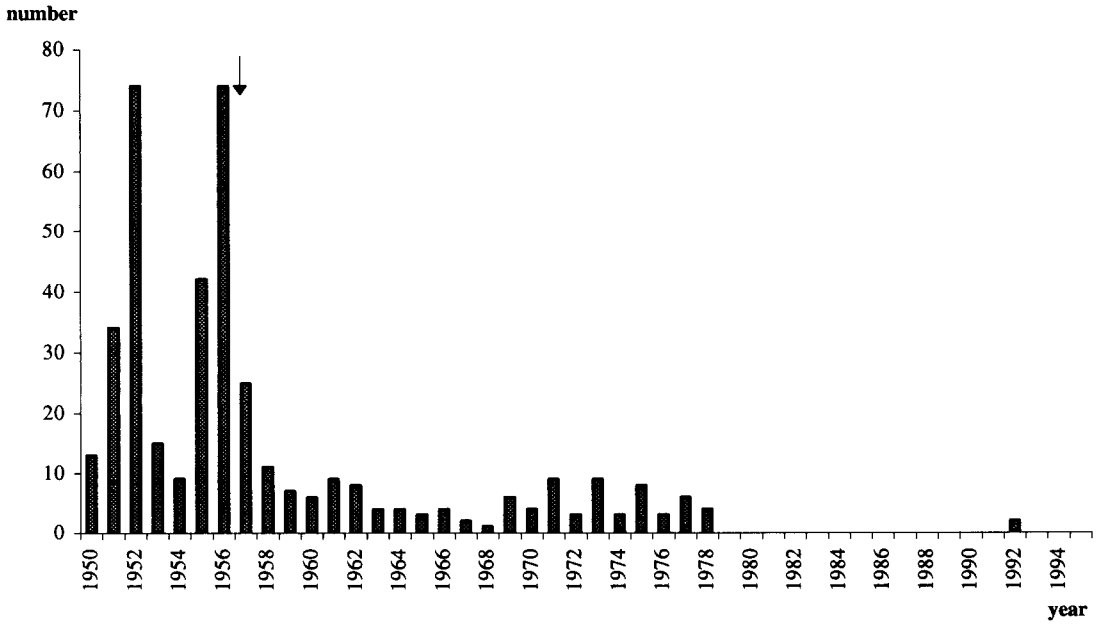

figure 38 Mortality of poliomyelitis in the period 1905-1995 (source: CBS)

(see Appendix I, table 26)

9.3.2 Morbidity

Notifications

In 39th the number of notifications of poliomyelitis from 1924 onwards is presented. Before vaccination was introduced in 1957, a peak incidence was seen every 4 to 5 years, with as many as 2206 notified cases in 1956. After the decline of the incidence that followed the introduction of vaccination, small local outbreaks (all caused by poliovirus type 1) occurred in the 1960s and early 1970s, the largest of which took place in the village of Staphorst in 1971 where 39 people were affected. In 1978 there was a large nation-wide outbreak of poliovirus type 1 infection, which affected 110 people in several provinces. Thereafter only three (imported) cases of poliomyelitis had been reported, until in 1992/1993 another nation-wide outbreak took place; this time poliovirus type 3 was the causing pathogen. A total of 71 cases was reported in a time course of about 6 months; two patients, a 61-year old man and a boy of 10 days old, died.

All cases in the local and nation-wide outbreaks after the introduction of vaccination were seen in non- or incompletely vaccinated persons, all of whom (except for one 61-year old man in the 1992/1993 outbreak) belonged to the orthodox reformed groups that reject vaccination for religious reasons. These religious groups mainly live in communities that are situated across the country in the geographic region that stretches from the Southwest to the mideast. It was in these communities that local outbreaks occurred during the 1960s and early 1970s. In 1978 and in 1992/1993 nation-wide outbreaks occurred which affected this whole area. No cases were reported among the far larger number of unvaccinated people who live scattered about the country; they seemed to be protected by herd-immunity (66,67).

The age of the patients in the 1992/1993 outbreak ranged from 10 days to 61 years, the median age was 18 years. This was much higher than in previous outbreaks; in 1956 the median age category was 1-4 years, in 1971 5-9 years and in 1978 10-14 years.

In all outbreaks described above more male than female patients were seen. The relative contribution of men ranged from 55% (in 1956) to 60% (in 1978).

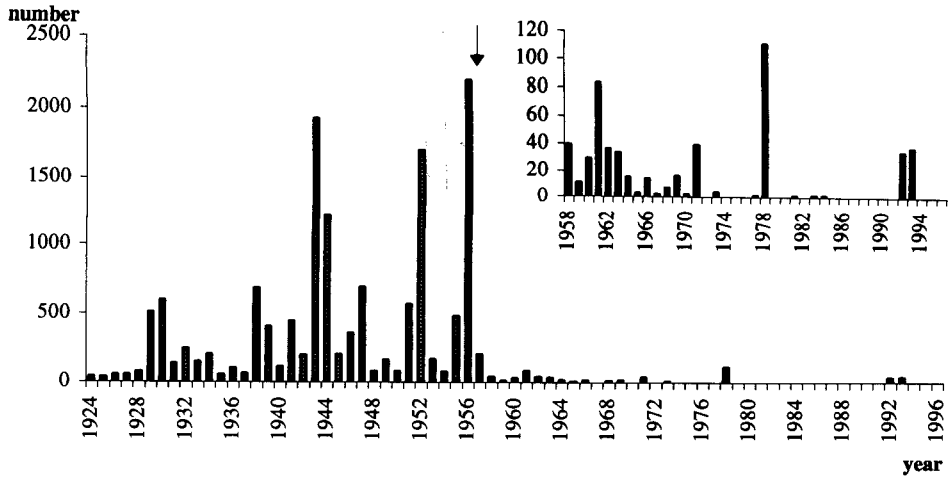

figure 39 Notifications of poliomyelitis in the period 1924-1996 (source: IGZ)
(see Appendix I, table 27)

Hospital admissions

40th shows the number of hospital admissions due to poliomyelitis (including side diagnoses) from 1980 up to and including 1996. During the epidemic years 1992 and 1993 a total of 70 cases was admitted, while 71 cases were notified. In other years the annual number of admissions ranged from zero to six cases. Patients were seen in all age ranges and more men (64%) were hospitalised than women.

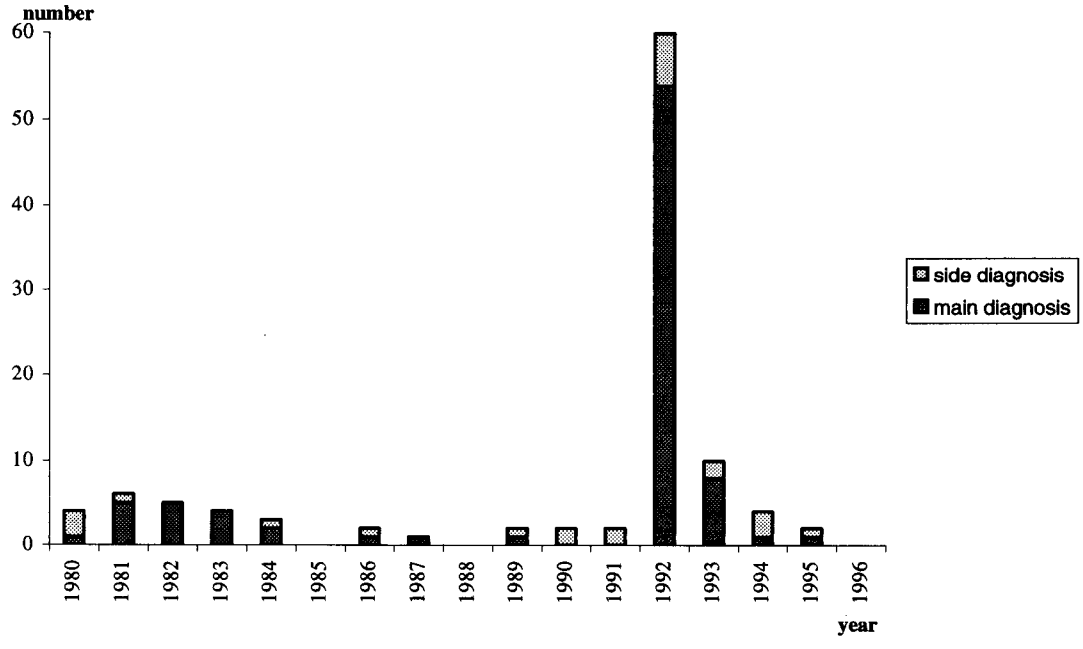

figure 40 Hospital admissions due to poliomyelitis in the period 1980-1996
(source: LMR)
(see Appendix I, table 28)

NSCK

In the 1992/1993 outbreak seven cases of acute flaccid paralysis (AFP) confirmed as poliomyelitis in persons younger than 15 years (out of eighteen paralytic cases that actually occurred in this age group) were reported by the Netherlands Paediatric Surveillance Centre (68). In 1994-1996 no cases of poliomyelitis were seen in the NSCK out of 59 AFP patients. About half of the AFP patients were diagnosed with Guillain Barré syndrome (GBS) (69).

Virological laboratories

The 1992-1993 outbreak of polio type 3 is also seen in the number of positive virological findings of wild polio virus. The positive findings outnumbered the notified cases and hospital admissions, which is plausible since contacts of patients could have been tested also and only a small percentage of infected persons develop the disease poliomyelitis.

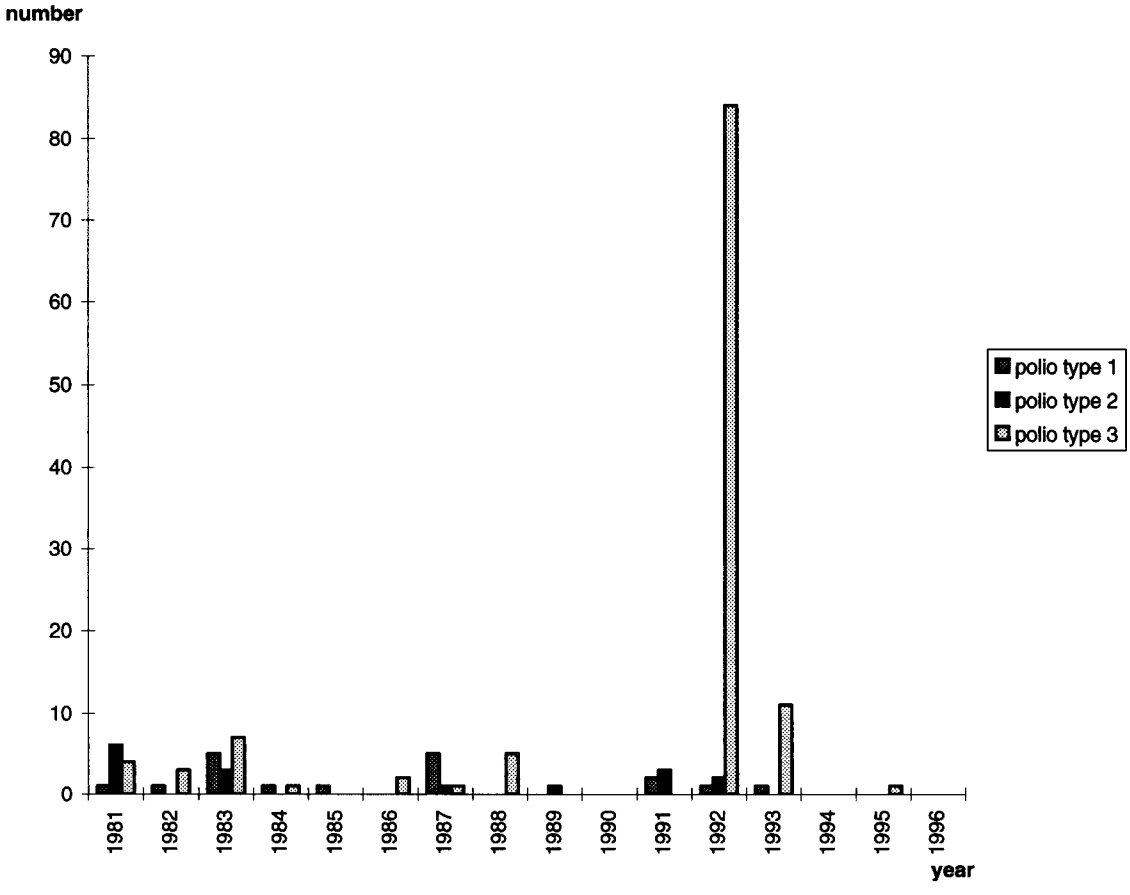

figure 41 Number of positive serology or isolation for poliovirus type 1, 2, and 3 (source: clinical virological laboratories and RIVM)

(see Appendix I, table 29)

9.4 Discussion

Mortality

Mortality of poliomyelitis has been decreasing gradually from the beginning of the century and in 1957, the year mass vaccination was started, the number of polio related deaths was at its lowest with 13 deaths. The effect of mass vaccination became clear a few year later; after 1964 only sporadically deaths were seen. Mortality figures reflect both death due to acute poliomyelitis and death due to late sequelae of poliomyelitis.

Effects of vaccination

In 1957, the year in which vaccination against poliomyelitis was introduced on a national scale, the incidence of poliomyelitis declined sharply. This also would have happened when vaccination had not been introduced in that year: as a result of the large number of people that must have been subclinically infected and thereby have become immune in the previous epidemic year 1956, the circulation of the wild virus must have been declining anyway. The vaccination schedule did prove to be effective however, as major nation-wide epidemics like those seen in the previous decades did not occur anymore in the 1960s and early 1970s. Only smaller outbreaks did occur in isolated communities during these years (67). In these communities a high percentage of the orthodox reformed inhabitants is not vaccinated for religious reasons. Considering the fact that these unvaccinated inhabitants live in socially and geographically clustered groups, they are not protected by herd immunity, whereas herd immunity does protect the far larger number of unvaccinated people that lives scattered all over the country. These communities were localised in the area where most orthodox reformed people live, but they did not spread throughout that whole area. In 1978 and 1992/1993 however, the outbreaks did spread, but only to other communities with a similar reformed denomination. This is probably due to the intensified contact between these communities, even if they are situated in different parts of the area (e.g. at schools or mission days) (70). In 1978 the epidemic (polio type 1) even spread from the Netherlands to Canadian communities of similar religious denomination; this resulted in 11 confirmed cases of poliomyelitis in several Canadian provinces and the viral strain then spread to an Amish population in the United States, causing a further ten paralytic cases in four states (71). During the 1992/1993 epidemic, a poliovirus surveillance was initiated in a Canadian community with presumed contact with affected communities in the Netherlands and inhabitants with similar religious background. The viral strain (polio type 3) responsible for the outbreak in our country was isolated, but no cases of paralytic poliomyelitis were observed, probably because of the lower paralysis rates associated with polio type 3 than with type 1 (72). As long as this clustering of unvaccinated people exists, outbreaks of poliomyelitis can continue to occur at any moment, unless introduction of the wild poliovirus into the Netherlands can be prevented. This seems to be achievable only by world-wide eradication of the virus.

When looking at the age distribution of the epidemics in 1956, 1971, 1978 and 1992/1993 there appears to be an age shift towards older age groups. This can be contributed to the fact that as virus circulation decreases over the years, the chances of being infected and thereby

immunised decrease as well. Therefore persons can remain susceptible for a longer period and contract the disease at an older age. Since the chances of getting paralytic poliomyelitis after infection by the virus increase by age, the relative contribution of older age groups to all cases will become higher. Also at an older age the symptoms are more severe, more often quadriplegy and bulbar paralysis are diagnosed (68).
In a study conducted by the NIVEL and RIVM it appeared that adults born in the pre-vaccination era were in general protected but that a considerable part of the persons born between 1930 and 1945 lacked neutralising antibodies (GMT ≤ 3) against the different polio viruses: 10%, 22% and 25% respectively for type 1, 2, and 3 (43). Another study demonstrated however that 92%, 89% and 83% of the persons with very low or no titres of antibodies showed rapid booster reactions for type 1, 2, and 3 respectively (an at least fourfold titre rise) and therefore were sufficiently immune (44).

Comparison of sources
Poliomyelitis is a very serious disease and is an important public health and political issue in the Netherlands. Therefore the assumption is justified that every case will be notified to the Medical Inspectorate of Health. Because of the seriousness of the disease, one would expect all cases of poliomyelitis to be admitted at a hospital. In the epidemic of 1992/1993, there appeared to be 70 hospital admissions (compare: 71 notified cases). It is not clear whether these are (almost) the same persons, because individual linking of records is not possible. In the non-epidemic years 1994 and 1980-1991 however a total of 35 cases of acute poliomyelitis have been diagnosed according to the National Medical Registration, whereas only three cases of (imported) poliomyelitis have been notified in these same years. It is not evident what causes this overestimation. It might partly be due to misclassification on the part of the doctors who set the diagnosis (e.g. misdiagnosis of hospital admissions for late sequelae of an acute poliomyelitis infection or even for post-poliomyelitis syndrome). Also, some patients may be hospitalised several times for poliomyelitis. And finally, typing errors when entering the diagnosis codes into the computer might have occurred. A few years ago the SIG implemented some interactive quality checks in the data-entry programme, which ought to prevent these mistakes in the future.
In the paediatric surveillance of acute flaccid paralysis a substantial underreporting existed. This might be contributed to the fact that many cases of AFP (including those with polio) are referred to a neurologist and therefore will not be reported by a paediatrician (68). Moreover it seemed that some paediatricians did not realise that cases with Guillain Barré Syndrome should be reported too. The strength of the paediatric surveillance should be that additional clinical and laboratory information can be collected for patients with AFP, for example about virological examination, serology of polio antibodies and vaccination history. But since these examinations are not performed on a standard basis and the present form of AFP surveillance operated rather slowly, often it is too late to ask for virological examination. Recently several measures have been taken to improve the AFP surveillance according to the WHO performance criteria.

Data on isolation of polioviruses (both wild virus and vaccine virus) in persons with and without health complaints are available from virological laboratories in the country. The positive finding may relate to polio cases, but also to infected persons who did not develop disease, such as contacts of patients and importations (e.g. asylum seekers, adoptive children). Therefore this system is not fit for specific epidemiological questions.
Considering the fact that no additional information can be obtained from the medical registry of the SIG which is not already known from the Medical Inspectorate of Health, for poliomyelitis it is not necessary to obtain the data provided by the National Medical Registration in the years to come. As the WHO has included adequate AFP surveillance as a criterion in the certification process as polio-free, the AFP surveillance will need to be continued and permanent attention should be payed to the performance of the system (65).

10. Introduction on invasive *Haemophilus influenzae* type b, meningococcal, and pneumococcal infections

Bacterial infections, like all infections, can be either non-invasive and invasive. Non-invasive infections are frequently seen, but usually they are not life-threatening in contrast to some invasive infections. Important non-invasive infections are upper respiratory infections, pneumonia, conjunctivitis, sinusitis and otitis media. The most prominent invasive infections are bacterial meningitis and sepsis. Before the introduction of vaccination against *Haemophilus influenzae type b* (Hib), three organisms accounted for 88% of the cases of bacterial meningitis, with or without sepsis, in the Netherlands (80): *Neisseria meningitidis* caused about 47% of the cases, *Streptococcus pneumoniae* 17% and *Haemophilus influenzae* 24%.

Meningitis is an infection of the meninges, that surround the brain and spinal cord. Sepsis is a clinical diagnosis caused by a blood-borne infection. Meningitis and sepsis share a common aetiology and pathogenesis. Several organisms such as viruses, bacteria, parasites and fungi can cause meningitis and sepsis, but bacterial meningitis with or without sepsis has the highest clinical importance in the Netherlands. Transmission of the pathogens occurs through droplets and they colonise a part of the population without causing disease, but sometimes they reach the bloodstream and may cause bacteraemia. If the pathogens reach the meninges through the bloodstream, meningitis may develop. In some cases the pathogen can reach the meninges by direct access through a surgical procedure, trauma, or serious ear infection.
The clinical picture of bacterial meningitis consists of fever, headache, meningismus and signs of cerebral dysfunction and in case of sepsis fever and shock is seen (73, 74). An infection of the respiratory tract, such as pneumonia, otitis media or sinusitis, often precedes the disease. If untreated, an invasive infection usually progresses to a fatal outcome. Frequent neurological complications of the disease are deafness, mental retardation, epilepsy and hydrocephalus (48).
The bacterial pathogens constantly colonise a part of the population; therefore adequate diagnosis should be based on isolation of the pathogen from a normally sterile site.
The proportional distribution of the meningitis causing pathogens differs enormously from country to country and varies with age. Before vaccination against Hib became available in the United States for instance, Hib was the predominant causative organism of meningitis (75). In the Netherlands the predominant bacteriae are *Neisseria meningitidis* (meningococcus), *Streptococcus pneumoniae* (pneumococcus), and *Haemophilus influenzae*, from the age of three months onward. *Streptococcus agalactiae*, *Escherichia coli* and *Listeria monocytogenes* mainly cause neonatal meningitis and after the age of 50 the pneumococcus is the predominant organism causing invasive infections (76).
At this moment only a vaccine against Hib infections is included in the RVP, but improved vaccines against meningococci group B and pneumococci are being developed and hopefully can be included in the RVP in the future. Therefore surveillance data on meningococcal and pneumococcal disease are described in this report also.

11. Invasive *Haemophilus influenzae* type b infections

11.1 Introduction

Haemophilus influenzae can cause asymptomatic nasopharyngeal colonisation, non-invasive respiratory infection, and occasionally invasive infection (77). *Haemophilus influenzae* can be divided into non-capsulated and capsulated strains. Non-encapsulated strains are mainly associated with respiratory infections. The capsular polysaccharide is the major virulence factor for *Haemophilus influenzae* (79). Six capsular types have been identified and are designated serotype a to f. Serotype b traditionally is the most important cause of invasive *Haemophilus influenzae* infections.
Invasive *Haemophilus influenzae* type b (Hib) infections are frequently accompanied by bacteraemia or even sepsis. The clinical manifestation of the infection is dependent on age: the highest incidence of meningitis was found in children of 6-12 months of age; epiglottis predominantly occurred at the age of 2-3 years before Hib vaccination was introduced (78). The case fatality rate of Hib meningitis is about 2%; in children who survive, neurological damage remains in about 9% of the cases in the Netherlands (79).
Hib vaccination was introduced in the National Vaccination Programme in 1993. All children born 1 April 1993 or later were offered vaccination against Hib. The tetanus toxoid conjugated polyribosylribitolphosphate (PRP) vaccine is administered simultaneously but in another limb with the DTP-IPV-vaccine at the age of three, four, five and eleven months.

11.2 Methods

Four sources of information were used: the Central Bureau of Statistics (CBS), the Netherlands Reference Laboratory for Bacterial Meningitis (RBM), the National Medical Registration (LMR) of the SIG and the Netherlands Paediatric Surveillance Centre (NSCK). Mortality figures on *Haemophilus influenzae* meningitis in the period 1991-1995 are given.
The RBM collects information on isolates of *Haemophilus influenzae* (from CSF and blood) of patients with meningitis and/or sepsis. Information has been available since 1975. Since 1994 strains isolated from a normally sterile site in case of other invasive *Haemophilus influenzae* infections can be sent to the RBM as well for further serotyping. A *Haemophilus* strain isolated from both cerebrospinal fluid (CSF) and blood is coded as an isolation from CSF in this report. Isolates from CSF are regarded as originating from patients with meningitis and isolates from blood as coming from patients with sepsis or bacteraemia (80).
From the National Medical Registration data on hospital admissions for meningitis (ICD-code 320.0) and sepsis (ICD-code 038.41) caused by *Haemophilus influenzae* were obtained. Data on *Haemophilus influenzae* meningitis are given for the period 1980-1996; for *Haemophilus influenzae* sepsis data have been available for the period 1991-1996.
The NSCK started Hib surveillance in October 1993. This surveillance system provides data on the following invasive Hib infections: meningitis, sepsis, epiglottitis, osteomyelitis and

arthritis. Since 1 January 1995 cellulitis has been included in the case definition as well and the case definition was extended to invasive *Haemophilus influenzae* infections, causing meningitis, sepsis, epiglottitis, arthritis, osteomyelitis and cellulitis, irrespective of serotype (81). The NSCK registers patients until the age of fifteen.

11.3 Results

11.3.1 Mortality

The absolute mortality due to *Haemophilus influenzae* meningitis according to the CBS in the Netherlands was 6 in 1991, 4 in 1992, 3 in 1993 and 1994, and 1 in 1995. The preliminary figure for 1996 is 0. Mortality for children under five was 5 in 1991, 2 in 1992, 3 in 1993 and 1994, and 0 in 1995.

11.3.2 Morbidity

NSCK

table 2 Results of serotyping of invasive infections by *Haemophilus influenzae* registered by the NSCK

serotyping	1994 number	(%)	1995 number	(%)	1996 number	(%)
serotyped	109	(84)	38	(93)	22	(92)
serotype*:						
serotype b	*106*	*(97)*	*37*	*(97)*	*18*	*(82)*
serotype f	*1*	*(1)*	*0*	*(0)*	*1*	*(5)*
not typeable	*2*	*(2)*	*1*	*(3)*	*3*	*(14)*
not serotyped	19	(15)	3	(7)	2	(8)
unknown	1	(1)	0	(0)	0	(0)
total	129		41		24	

* Case definition in 1994 only included *Haemophilus influenzae* type b infections

In 1994 129 patients with invasive infections were reported to the NSCK, including 106 type b infections. Although the case definition in 1994 only included Hib disease, also patients with serotype f and non-typeable *Haemophilus influenzae* disease were reported. In 1995 and 1996 41 and 24 patients respectively met the case definition (all invasive *Haemophilus influenzae* infections) (82).

In the first two years 97% of the serotyped strains were type b while 82% were so in 1996. Since the case definition officially did not include non-type b *Haemophilus influenzae* in 1994, this percentage of non-type b disease seen by paediatricians could have been higher in reality.

The distribution of clinical symptoms did not vary considerably over the three years; 39% (n=75) with meningits, 26% (n=51) of the reported patients were diagnosed with meningitis or meningitis with sepsis, 25% (n=47) with epiglottitis, 6% (n=12) with sepsis and 5% (9%) with other symptoms as arthritis, cellulitis and osteomyelitis (82).
The median age of meningitis patients was 21, 38 and 23 months in 1994, 1995 and 1996 respectively. The age-specific highest incidence shifted from one-year-olds in 1994 to two-year-olds in 1995 to four-year-olds in 1996.
In the period 1994-1996 seven vaccine failures were seen, of which two patients were known to have special predispositions (chromosomal abnormality and immunodeficiency).
The underreporting for Hib meningitis in the NSCK surveillance in comparison with the RBM surveillance amounted 32% over the years 1994-1996. Concern exists about the underreporting of invasive diseases other than meningitis, which will probably be even higher because the proportion of meningitis cases registered by the NSCK did not decrease with increasing coverage of the risk group by vaccination over the years 1994-1996 (82).

Hospital admissions
The number of hospital admissions for *Haemophilus influenzae* meningitis from 1980 onwards shows an increase in the late 1980s and a sharp decline from 1994 onwards to 34 patients in 1996. The percentage of meningitis patients under five years of age decreased from a mean of 94% in 1980-1993 to 70% in 1996. Fifty-three percent of the patients were males.
The number of hospital admissions for *Haemophilus influenzae* sepsis decreased from a mean of 76 patients in 1991-1994 to 51 and 53 patients in 1995 and 1996 respectively. The percentage of sepsis patients under five years of age decreased from a mean of 67% in 1991-1993 to 30% in 1996. Fifty-nine percent of the hospitalised patients were males in the period 1980-1996.

Epiglottitis is in at least 80% of the cases caused by Hib (77) and therefore a decline in the incidence of epiglottitis is expected as an effect of mass Hib vaccination. The number of hospitalised patients due to epiglottitis was on average 224 in 1991-1993 and decreased after introduction of Hib vaccination to 117 in 1996.
The percentage of hospitalised patients under five years of age declined from 63% in 1991-1993 to 29% in 1996. Sixty-five percent of the patients were males. The mortality of epiglottitis decreased already before the introduction of Hib vaccination and declined further to five deaths in 1995.

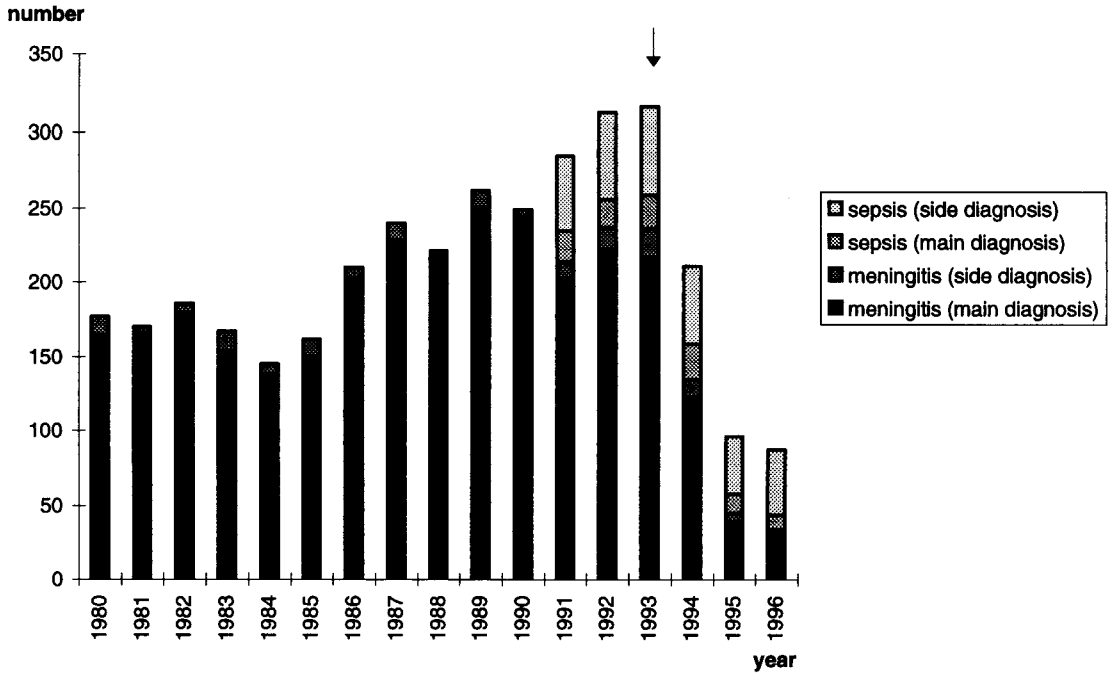

figure 42 Number of hospital admissions for *Haemophilus influenzae* meningitis in 1980-1996 and sepsis in 1991-1996 (source: LMR)

(see Appendix I, table 30)

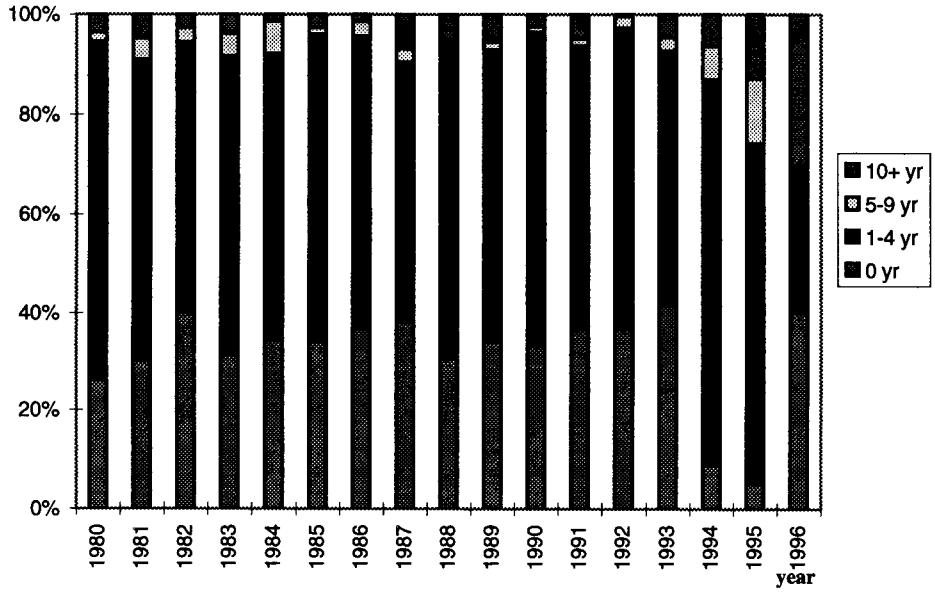

figure 43 Age distribution of hospital admissions for *Haemophilus influenzae* meningitis in 1980-1996 (source: LMR)

(see Appendix I, table 30)

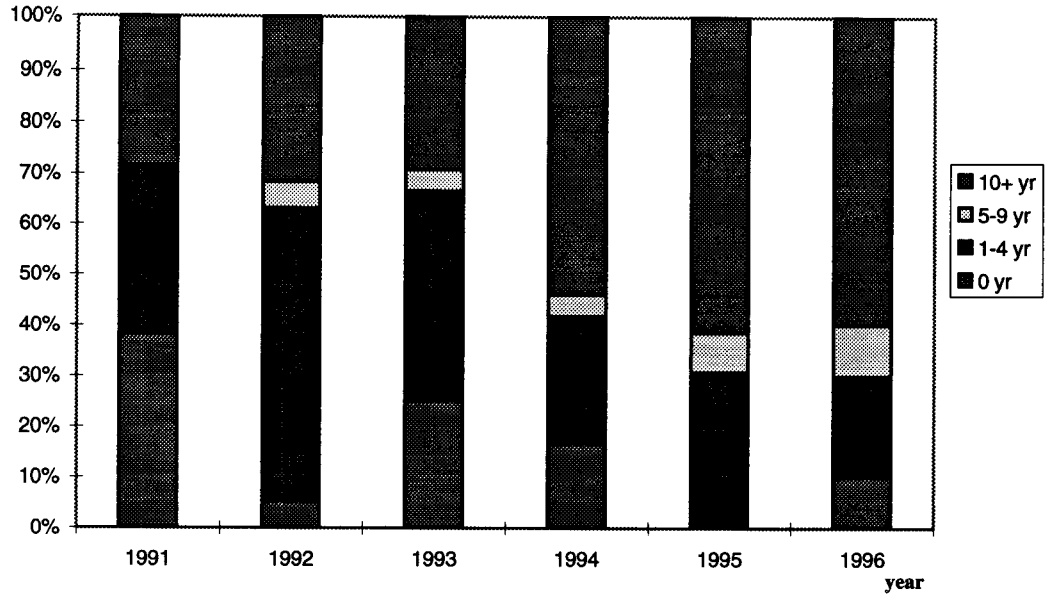

figure 44 Proportional age distribution of hospital admissions for *Haemophilus influenzae* sepsis in 1991-1996 (source: LMR)

(see Appendix I, table 30)

RBM

The total number of *Haemophilus influenzae* isolates from CSF and/or blood typed at the RBM increased from 72 in 1976 to 342 in 1989, with a temporary very slight decrease in 1982-1984, and varied around 300 from 1990 to 1993 and thereafter sharply decreased to 88 in 1996.

The proportion of *Haemophilus influenzae* serotype b decreased from 93% in the period up until 1993 to 34% in 1996. The absolute number of non-type b has been increasing from 1976 on and the rise sharpened in 1995 and 1996. This increase is the result of a rise in the number of non-typeable strains in blood isolates since the number of non-typeable strains in CSF isolates did not alter. These non-typeable strains were isolated more frequently than type b strains from patients older than ten years.

Before vaccination was introduced about 90% of the isolates were from 0-4 year-olds; this figure decreased to 38% in 1996 while the relative incidence in patients over 50 years of age increased from around 5% to 41% in the same period. In 1996 strains of 16 male and 10 female patients were sent in; this proportion varied from year to year but mostly more male patients were seen.

The proportion of beta-lactamase producing strains, indicating resistance to penicillins, appeared to stabilise at 10% after a slow increase during the period 1988-1995.

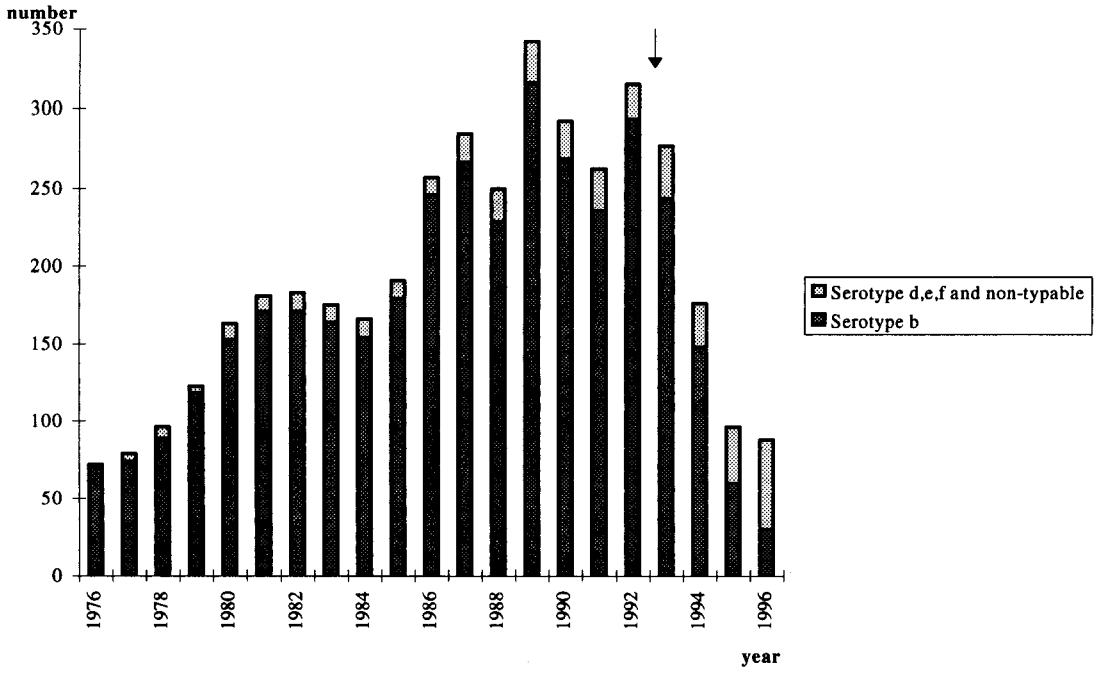

figure 45 Number of *Haemophilus influenzae* isolates serotyped at the RBM in 1976-1996 by serotype (source: RBM)

(see Appendix I, table 31)

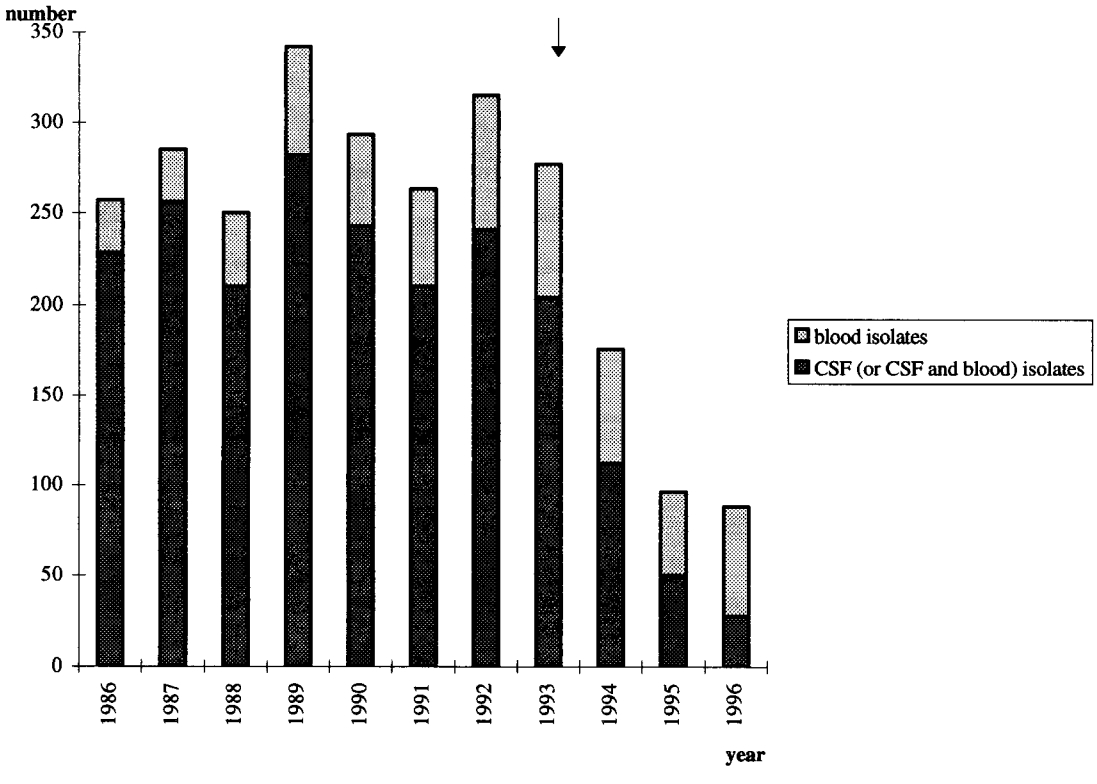

figure 46 Number of *Haemophilus influenzae* isolates typed at the RBM in 1986-1996 (source: RBM)
(see Appendix I, table 31)

11.4 Discussion

Effects of vaccination

Meningitis (with or without sepsis) is the foremost complication of the *Haemophilus influenzae* infections and was almost invariably caused by type b strains. The incidence of invasive Hib meningitis decreased quickly after vaccination was introduced according to the NSCK, LMR and RBM. The effect of Hib vaccination on sepsis and epiglottitis is considerably less striking. Sepsis is more often seen in older persons, who are not vaccinated, than in young children. Furthermore the contribution of Hib sepsis to bacterial sepsis is very small in contrast with the contribution of Hib meningitis to bacterial meningitis in the pre-vaccine era (80). Epiglottitis is often seen at the age of three to five year olds (83), and this group was for the most part born before Hib vaccination was included in the RVP.
The sharpened increase in the absolute number of non-type b strains from blood isolates according to the RBM is most likely due to an increased awareness after the introduction of the Hib vaccine (80). In case of epiglottitis adequate culturing does not frequently take place but instead diagnosis is made on clinical grounds. Therefore in epiglottitis patients the bacterial pathogen is not often specified. This could explain the low frequency of reported epiglottitis patients to the NSCK in comparison with the number of patients according to the LMR. Moreover these patients could have been diagnosed by other specialists other than paediatricians.

No catch-up campaign was conducted for older children in the Netherlands. As a result a shift in age distribution was seen. Before vaccination the highest incidence of Hib meningitis was found at 8-9 months of age (84). The age of highest incidence did shift up yearly with approximately one year of age, after vaccination was introduced, according to NSCK data. The number of hospital admissions in the zero age category dropped immediately when vaccination was introduced and the number of patients in the age category of 1-4-year-olds declined gradually as was to be expected. This was also seen in the RBM data.

In a recent study the occurrence of Hib meningitis in the Dutch population in the three years before and three years after the introduction of Hib vaccination in the National Vaccination Programme was compared, in order to determine the contribution of herd immunity to the decline of Hib meningitis. No effect of Hib vaccination was seen on disease among unvaccinated individuals. This is probably because no catch-up campaign was conducted for older children through which herd immunity could be created (85). The full effect of mass vaccination in the Netherlands will be seen in 1998 when most children under five years of age, where the age specific incidence was highest before vaccination, will be vaccinated.

The male:female ratio for invasive *Haemophilus influenzae*(b) infections varied slightly but a sex preference for boys was seen over the years. This did not change after the introduction of mass Hib vaccination. Various studies showed the same small effect of gender (79, 86).

Vaccine

No information is available on the long-term protection of these conjugated Hib vaccines (87). Further prospects for addition of other serotypes to the *Haemophilus influenzae* vaccine are limited, since the small proportion of remaining *Haemophilus influenzae* infections are caused by nontypeable (non-encapsulated) strains, which are not suitable for vaccine development analogue to conjugated Hib vaccines.

Comparison of sources

Now Hib vaccination is part of the National Vaccination Programme, adequate culturing and serotyping has become increasingly important. This is necessary for assessing vaccine failures and a possible increase of *Haemophilus influenzae* infections by serotypes other than type b, as a result of vaccination (88). Information on types can be acquired from the RBM and from the NSCK, who acquire this information indirectly from the RBM.

The paediatric surveillance only registered information on patients under fifteen years of age and the underreporting for meningitis in comparison with the RBM was 32% (82). The coverage of the RBM is also not complete but is expected to have remained constant over the years; over 80% of the isolated strains from meningitis patients are sent to the RBM by the clinical microbiological laboratories in the Netherlands (80, 89).

An important value of the NSCK is the clinical information gathered, which the RBM does not provide. With an isolation from CSF it can reasonably be assumed that the patient had meningitis but with an isolation from blood it is not clear what the clinical picture is without additional information: it is possible that a patient has a bacteraemia secondary to some type of organ localisation other than meningitis. Furthermore isolation from blood is not necessary for setting the clinical diagnosis sepsis or epiglottitis, indicating that the underreporting for these diseases could be higher than for meningitis.

The RBM historically registered only isolations from CSF and blood. Since December 1994 it is possible to serotype every isolate of *Haemophilus influenzae* from a patient with invasive *Haemophilus influenzae* disease. This is an improvement in the coverage of the surveillance of invasive *Haemophilus influenzae* infections.

Taken the underreporting of the NSCK surveillance system into account, and having weighted the added value of paediatric surveillance against the efforts and resources, the NSCK surveillance was stopped in 1998 and the RBM was requested to collect clinical information, especially information necessary for the surveillance of vaccine failures.

The LMR can also provide clinical information and furthermore valuable data on trends in incidence and age distribution but does not give information on vaccination status and distribution of serotypes.

A disadvantage of the LMR is that patients with meningitis or epiglottitis as main diagnosis and sepsis as side diagnosis will be registered twice in the LMR, thus overestimating the number of hospital admissions for invasive *Haemophilus influenzae* disease. This could be prevented by collecting data on hospital admissions due to invasive *Haemophilus influenzae* disease on an individual level.

In conclusion it is recommended to use data from the RBM and LMR for assessing trends in incidence of invasive *Haemophilus influenzae* disease in the future.

12. Invasive meningococcal infections

12.1 Introduction

Neisseria meningitidis (meningococcus) is the most frequent cause of meningitis in the Netherlands. The meningococcus can be subdivided into various serogroups on grounds of the capsule. In our country the predominant serogroup is B (80). Ten percent of the Dutch population is a pharyngeal carrier of a meningococcus (90). Most strains of the meningococcus are not invasive, but provide people with antibodies that give cross-immunity to pathogenic strains, which explains the relative low incidence of invasive meningococcal disease. The first months of life infants are protected by maternal immunity.
The case fatality rate of meningococcal disease is dependent on the clinical picture of invasive infection; the lethality varies from around 2% in case of meningitis to over 15% in case of sepsis without meningitis, which can be lethal within twelve hours (syndrome of Waterhouse-Fridrichsen) (90, 91, 92).
Serogroup B and C have distinct age distributions. Whalen et al. found a median age for group B of 1,9 years, 13 years for group C and 18 years for the other serogroups (96). An effective vaccine against meningococcus serogroup B, the most common cause of meningitis in the Netherlands, could not be made yet because the capsular polysaccharide is not or only slightly immunogenic and because a number of different sero- and subtypes should be included. Vaccines against meningococcus type A and C exist but are not immunogenic for children under two years of age (92, 93, 94,95, 96).

12.2 Methods

Four sources of information were used: the Central Bureau of Statistics (CBS) for mortality figures, the Inspectorate of Health (IGZ) for notification data, the National Medical Registration (LMR) of the SIG for hospital admissions and the Netherlands Reference Laboratory for Bacterial Meningitis (RBM) for the number and types of meningococcal strains.
Meningococcal meningitis and sepsis are category B-notifiable diseases. Notification data on meningococcal meningitis are shown for the period 1947-1996. Notification of meningococcal sepsis has been obligatory since 1976 (97). Meningococcal sepsis and meningococcal meningitis were recorded separately from this year onwards.
Data on hospital admissions for meningococcal meningitis (ICD-code 036.0) and meningococcal sepsis (ICD-codes 036.2 and 036.3) from the National Medical Registration were used.
The RBM has requested Medical Microbiology Laboratories to send in isolates of *Neisseria meningitidis* from blood and CSF since 1959. The RBM performs serogrouping, serotyping and subtyping on the isolates received. Data from 1985 onwards are shown. Whenever a meningococcal strain was isolated from both CSF and blood, it was coded as an isolation from

CSF in this report. Isolates from CSF are assumed to be originating from patients with meningitis and isolates from blood as coming from patients with sepsis or bacteraemia (80).

12.3 Results

12.3.1 Mortality

Mortality of meningococcal disease has increased since the second half of the 1980s and seems to have stabilised around on average 47 deaths per year in the 1990s.

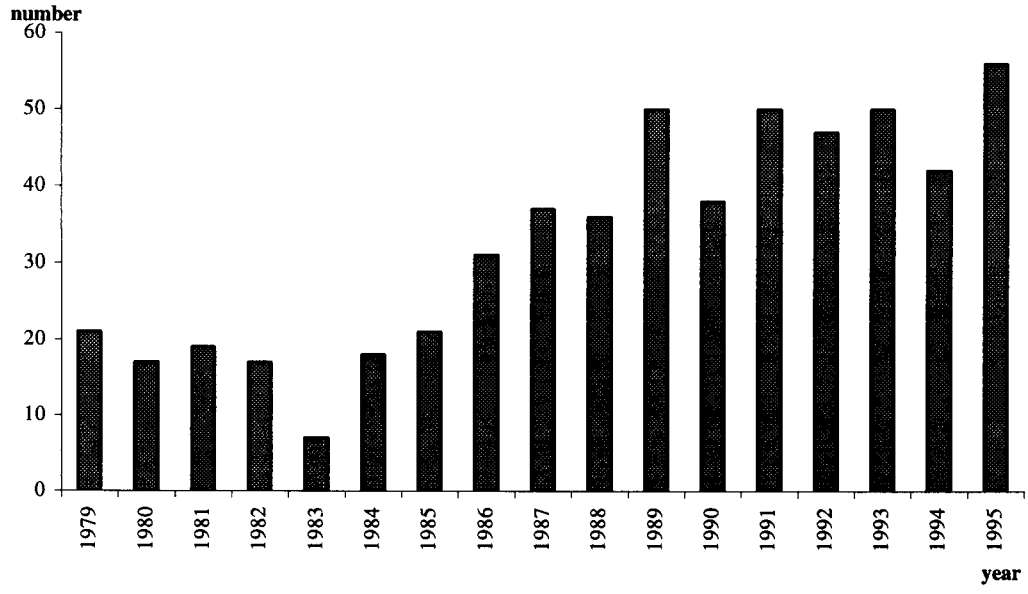

figure 47 Mortality of meningococcal disease in 1979-1995 (source: CBS)

(see Appendix I, table 32)

12.3.2 Morbidity

Notifications

The number of notifications of meningococcal meningitis showed a fluctuating pattern since the second world war. The number of notifications of meningococcal meningitis was 956 in 1947 and then dropped dramatically to a stable level of around 300 and declined even further from 1957 onwards to a level around 150. Then in 1966 an increase was suddenly seen to 516 notifications. The following years the number of notified cases decreased gradually to 100 in 1983 and thereafter increased again to almost 300 in the late 1980s and seems to have stabilised around 250 in the 1990s so far.

The number of notifications for meningococcus sepsis was very low in the late 1970s and early 1980s and increased to a mean of around 240 in the 1990s.

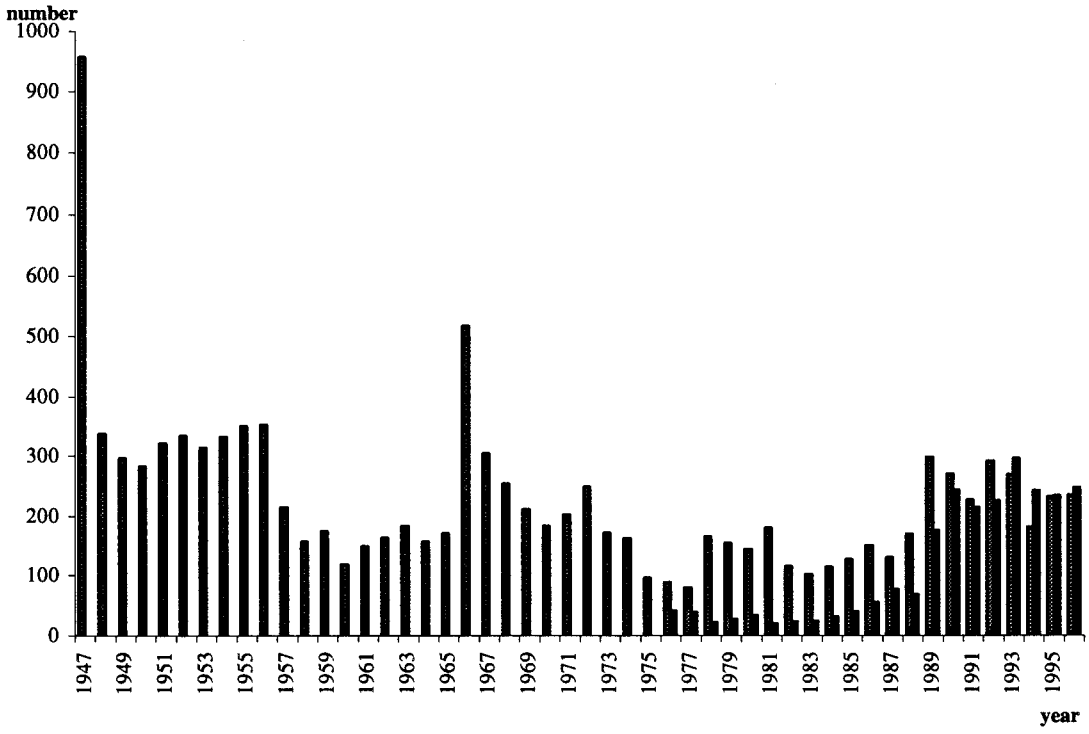

figure 48 Number of notifications of meningococcal meningitis in 1947-1996 and sepsis in 1976-1996 (source: IGZ)

(see Appendix I, table 33)

Hospital admissions

The number of hospital admissions for meningococcal meningitis and sepsis are shown in 49th. The number of meningitis patients was around 200 in the early 1980s and increased in the late 1980s to a stable level of around 500. The number of patients with sepsis increased gradually from 75 in 1980 to around 400 in the 1990s.

The age distribution of meningitis and sepsis patients did not differ and did also not significantly vary in time. A mean of 15% of the hospitalised patients for meningococcal infections was under 1 year of age and almost half of the patients (46%) was under five years of age. Over half of the patients were of the male sex (53%).

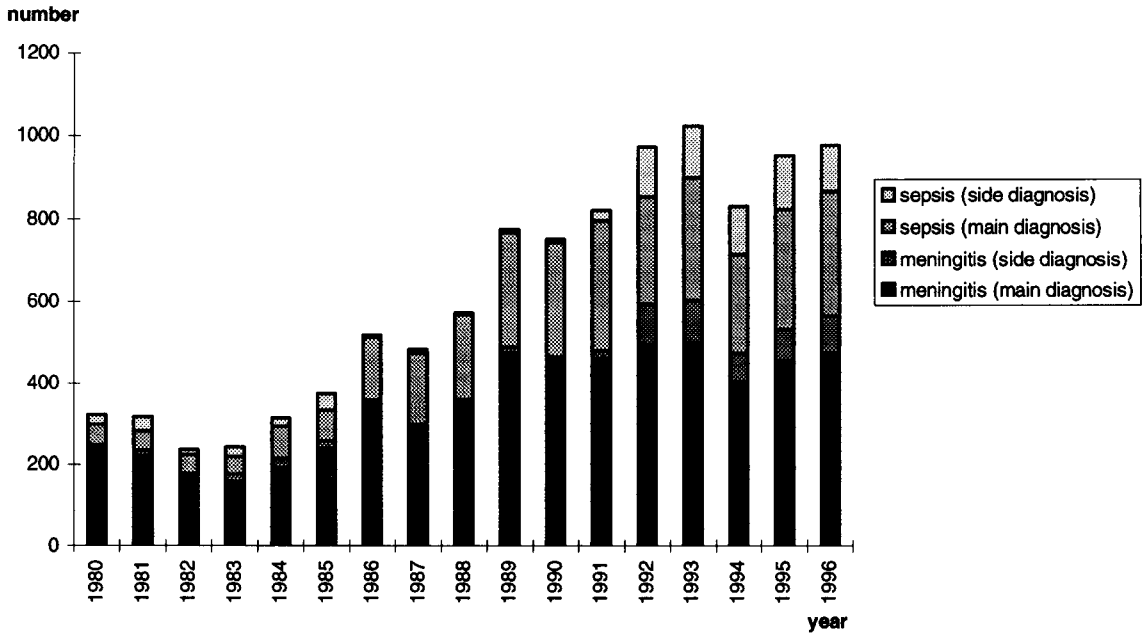

figure 49 Number of hospital admissions for meningococcal meningitis and sepsis in 1980-1996 (source: LMR)

(see Appendix I, table 34)

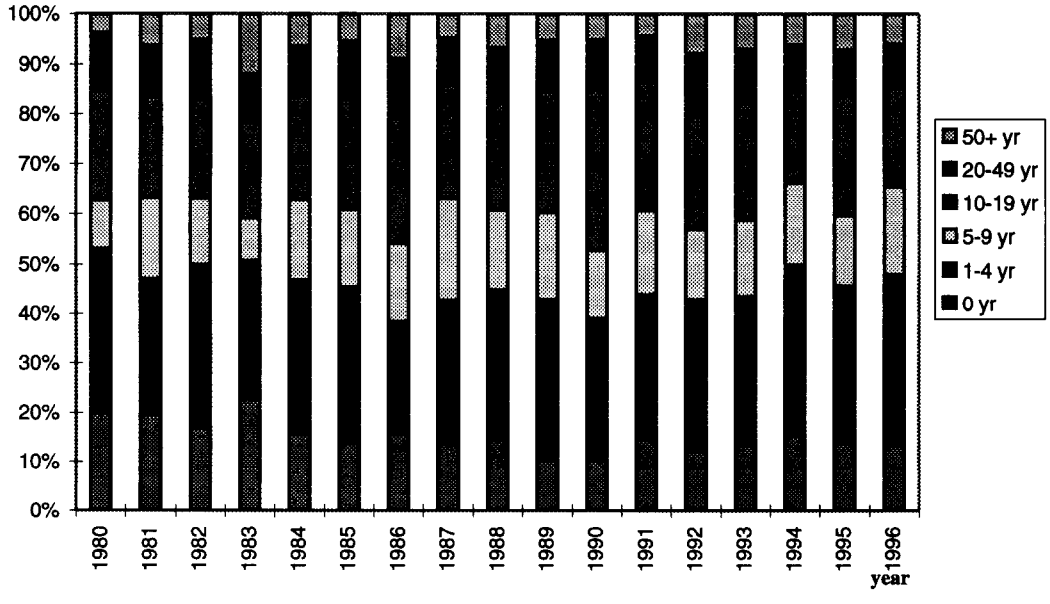

figure 50 Age distribution of hospital admissions for meningococcal meningitis and sepsis in 1980-1996 (source: LMR)

(see Appendix I, table 34)

RBM

The number of strains from CSF or CSF and blood typed by the RBM has increased from 223 in 1985 to 480 in 1993 and varied thereafter from 350 in 1994 to 445 in 1995 and 414 in 1996. The number of isolates from blood steadily increased from 31 in 1985 to 155 in 1996. The relative contribution of the number of isolates from blood only to isolates from CSF (or CSF and blood) thus increased; from 12% in 1985 to a mean of 27% in 1993-1996.

The age specific incidence was highest in patients under five years of age and a second, but much lower, peak was seen in 15-19 year-olds. The male to female ratio varied from 1.0 to 1.2 (80).

Serogroup B was always the predominant type meningococcus but the proportion increased steadily over the years from 47% in 1980 to 82% in 1993 to 89% in 1996. The increase in meningococcal disease was mainly caused by an increase in serogroup B isolations. A rise in the number of serogroup C isolations took place until 1991, although much weaker, and then decreased till 1993 and the number has remained stable since then. In 1980 serogroup A represented 30% of the isolates, but the contribution declined until in 1995 and 1996 no serogroup A meningococcus was encountered.

Antibiotic resistence has not posed a real problem in meningococcal disease yet in the Netherlands; in 1996 all strains were susceptible to choramphenicol and rifampicin and 1% of the meningococci isolated from CSF (or CSF and blood) and 2% of the isolated strains from blood had a decreased susceptibility to penicillin (80).

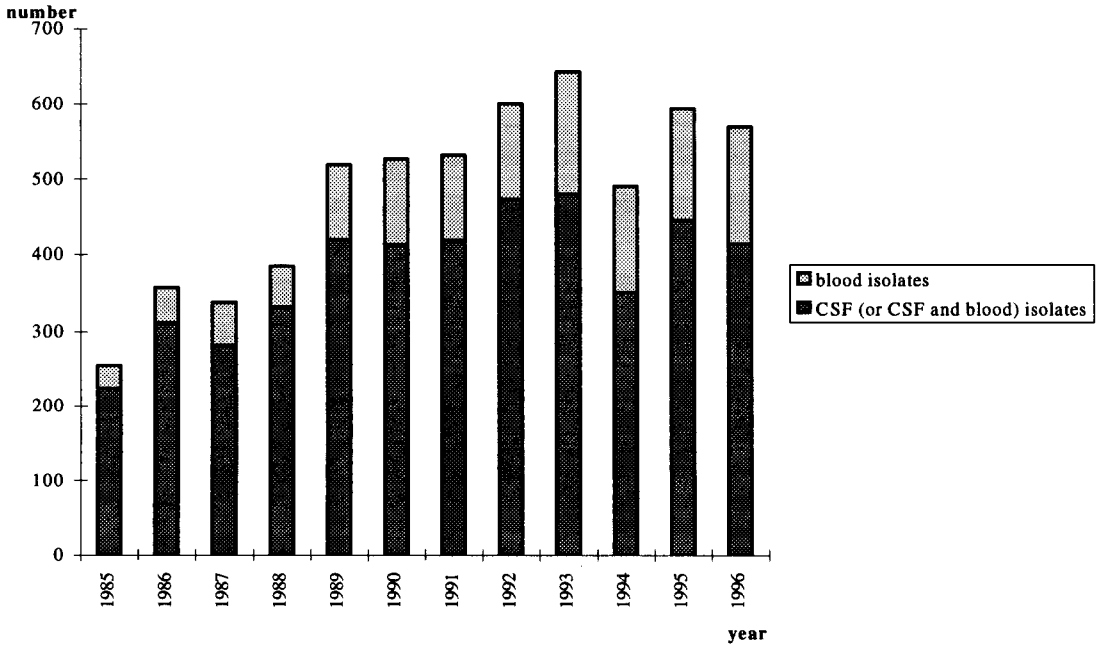

figure 51 Number of meningococcal isolates typed at the RBM in 1986-1996 (source: RBM)

(see Appendix I, table 35)

12.4 Discussion

Mortality

The absolute number of deaths due to meningococcal disease has increased until the 1990s but the estimated case fatality rate seems to have remained fairly constant over the years 1985-1995 when comparing mortality figures to hospital admissions for meningococcal meningitis and sepsis (7% for main diagnoses, 3% for main and side diagnoses) and typed meningococcal strains at the RBM (9%).

Incidence

The notifications, RBM and the LMR show the same trend in incidence of meningococcal meningitis and sepsis. After a decrease in the late 1970s and early 1980s there is a substantial increase from 1983 to the late 1980s, early 1990s. The absolute number of meningococcal meningitis and/or sepsis patients seems to have stabilised in the last few years but because of the decrease in Hib disease as a result of vaccination, the proportional contribution of meningococcal disease has grown. The rise in meningococcal disease is mainly caused by serogroup B. The cause of the increase in meningococcal type B disease in the 1980s is unknown.

The incidence of meningococcal meningitis is characterised by epidemic peaks every 10 to 25 years. The increase in incidence in the last century could partly be due to a low level of antibodies against components of the meningococcal cell wall in the population (98). It is to be expected that this antibody level will increase gradually and as a result the incidence will decline again.

The pattern of the age-specific incidence for meningococcal sepsis and meningitis is the same: it is highest in the zero age-category declining to a low level after the age of twenty. More males were seen with an invasive meningococcal disease in all three data sources.

The mean incidence of laboratory confirmed meningococcal disease in Europe rose with 50% from 1993 to 1996 (0.9 to 1.4/100,000) (99). Data from different countries are not very well comparable because of mostly unknown but varying coverage of the registration systems. In the Netherlands the laboratory confirmed incidence was 3/100,000. A third of the European cases were septicaemic and the overall case fatality rate was 8% (range 0%-30%). The case fatality rate was at its lowest in 5-9 year-olds and at its highest in infancy and with advancing adulthood. Infections with serogroups B and C predominated, accounting for 62% and 32% of cases respectively. The peak for serotype B disease was seen in children under five years of age, the peak for C in 1-4 and 15-19 year-olds. The incidence of meningococcal disease in Europe was higher in 1996 than in two preceding years and half of the cases were at least 45 years of age (99).

Types and vaccination

The proportional contribution of serogroups differs from country to country and may change in time. A vaccine, that has the quality to be used in the National Vaccination Programme, should include the most important subtypes of group B to be effective.

Since the age specific incidence is not as high in young children as it is for Hib, these meningococcal vaccines will not lead to a fast decrease in incidence as spectacular as seen in Hib infections, unless broad catch-up campaigns are organised offering vaccination to older children. The RIVM is developing a vaccine against meningococcal disease (100).

Continued monitoring of serogroups is necessary because the proportional contribution of the different serotypes and subtypes is changing in time. The relative contribution of the different subtypes and serogroups will probably change significantly after the introduction of a vaccine into the National Vaccination Programme.

Comparison of sources

The interest in meningitis has probably grown as a result of the introduction of a vaccine for *Haemophilus influenzae* type b. Surveillance of Hib infections has probably stimulated to send in isolates both from blood, CSF as from other normally sterile sites. The isolates submitted to the RBM are essential for the successful development of a meningococcal vaccine in the Netherlands; they provide data on the distribution of serogroups, serotypes and subtypes. The surveillance on the basis of isolates would be significantly improved if clinical information was systematically gathered, since pathogens isolated from blood do not necessarily implicate sepsis.

Invasive meningococcal disease will always lead to clinical treatment because of its severity and most patients are admitted only once, so the data from the LMR are considered most reliable.

The number of typed meningococcal strains from CSF (or CSF and blood) at the RBM is lower than the number of registered hospitalised patients with meningococcal meningitis (92% for main diagnoses, 85% for main and side diagnoses). The number of typed strains from blood isolates at the RBM data is substantially lower than the number of sepsis patients according to the LMR (42% and 33% respectively). One possible explanation is that the isolates in many cases are not sent to the RBM, thus causing underreporting in this surveillance system; but it is also possible that (meningococcal) sepsis is diagnosed on clinical grounds solely, without positive blood cultures with *Neisseria meningitidis*. Another explanation is overregistration in the LMR due to double counting.

The clear separation between meningococcal meningitis and sepsis is often rather artificial because an important part of the patients with meningococcal disease have both meningitis and sepsis simultaneously (99, 89). Which disease in a patient with both meningitis and sepsis will be registered as main diagnosis and which as side diagnosis will be dependent on the predominant clinical picture, but in either case the patient will be registered twice with meningococcal disease. This resulting overestimation of the occurrence of meningococcal

disease can be prevented if data could be used on an individual level. Another disadvantage of the LMR is that it does not provide data on serogroups.
The number of notifications for meningococcal meningitis and sepsis were substantially lower than the data recorded by the LMR and RBM. On the other hand the number of cases with meningococcal sepsis according to notifications in recent years is close to the number of patients with sepsis as main diagnosis according to the LMR. The number of blood isolates containing a meningococcal strain sent in to the RBM, was substantially lower. This could be due to the dramatic clinical picture of meningococcal sepsis, this being a great incentive for notification, while sepsis can be diagnosed clinically.
In conclusion not one single registration system should be used to measure the incidence of meningococcal disease, but data from the IGZ, LMR and RBM should be considered simultaneously.

13. Invasive pneumococcal infections

13.1 Introduction

Streptococcus pneumoniae (pneumococcus) is an alpha-haemolytic Gram-positive diplococcus. Pneumococcal pneumonia is the most common community-acquired pneumonia and the incidence is highest in older persons with underlying illness. Furthermore the pneumococcus is the most frequent cause of bacterial meningitis in adult patients and it is a common agent in otitis media (48).
Pneumococcal meningitis usually gives a rapidly progressive meningitis with symptoms of headache, neck pain and neck stiffness. Of the important types of bacterial meningitis, infection with *Streptococcus pneumoniae* has the highest case fatality rate of up to 19% (101). In the capsular polysaccharides of *Streptococcus pneumoniae* almost 100 antigenic differences have been identified. The anti-phagocytic polysaccharide capsule is the principal virulence determinant. Vaccination against the pneumococcus is currently not part of the National Vaccination Programme. It is offered to a selected risk group, such as patients who are immunodeficient or underwent splenectomy. An 23-valent vaccine is currently available which can be used from the age of two onwards.

13.2 Methods

Data obtained from the Netherlands Reference Laboratory for Bacterial Meningitis (RBM) and the National Medical Registration (LMR) of the SIG were used for the evaluation of the incidence of pneumococcal meningitis and sepsis.
Pneumococcal meningitis and sepsis (ICD-9-CM codes 320.1 and 038.2) registered in the LMR in the period 1980-1996 are shown.
The Medical Microbiology Laboratories have been asked to send in isolates of *Streptococcus pneumoniae* from blood and CSF to the RBM since 1975. The RBM performs serotyping on the isolates received. A strain isolated from both CSF and blood is coded as an isolate from CSF in their reports. Isolates from CSF are regarded as originating from patients with meningitis and isolates from blood as coming from patients with sepsis or bacteraemia (80).

13.3 Results

13.3.1 Morbidity

Hospital admissions
The number of hospital admissions for pneumococcal meningitis registered in the LMR seems to have increased somewhat in the 1990s. The number of hospitalisations for pneumococcal meningitis increased from 155 in 1980 to 276 in 1990, but the increase in registered patients with pneumococcal sepsis was even much more stronger. Both the number of pneumococcal

sepsis as main diagnosis and as side diagnosis increased; from around 50 for both in the early 1980s to 179 and 251 respectively in 1996. The increase in the last year was substantial. One has to bare in mind that part of the patients with meningitis as side diagnosis may have sepsis as main diagnosis and vice versa, thus enhancing overestimation of incidence. However, the observed incidence also increased when taking into consideration main diagnoses only.
The age distribution differed for meningitis and sepsis. The incidence of pneumococcal meningitis seemed higher than pneumococcal sepsis for infants under one year of age. For both an increase was seen in the mean age of the patients, but the age of the sepsis patients was higher, mainly due to an increase in the proportion of patients over 50 years of age: this proportion increased from around 25% to around 45% for meningitis in the period 1980-1996 and from approximately 50% to approximately 70% for pneumococcal sepsis.
For both meningitis and sepsis more male patients were seen (57%).

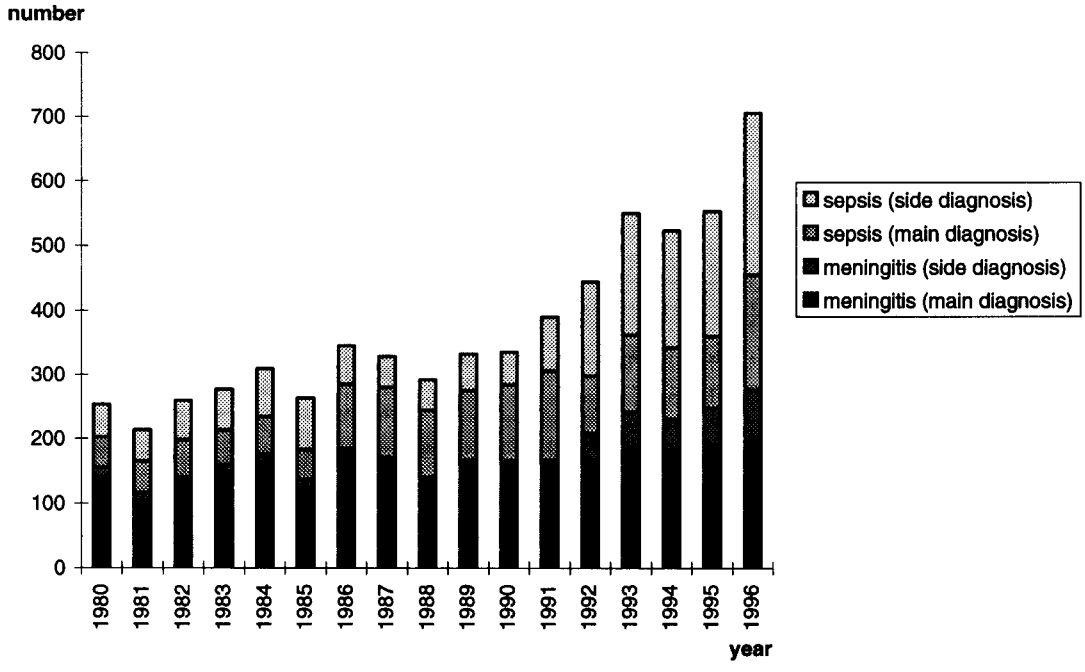

figure 52 Number of hospital admissions for pneumococcal meningitis and sepsis in the period 1980-1996 (source: LMR)
(see Appendix I, table 36)

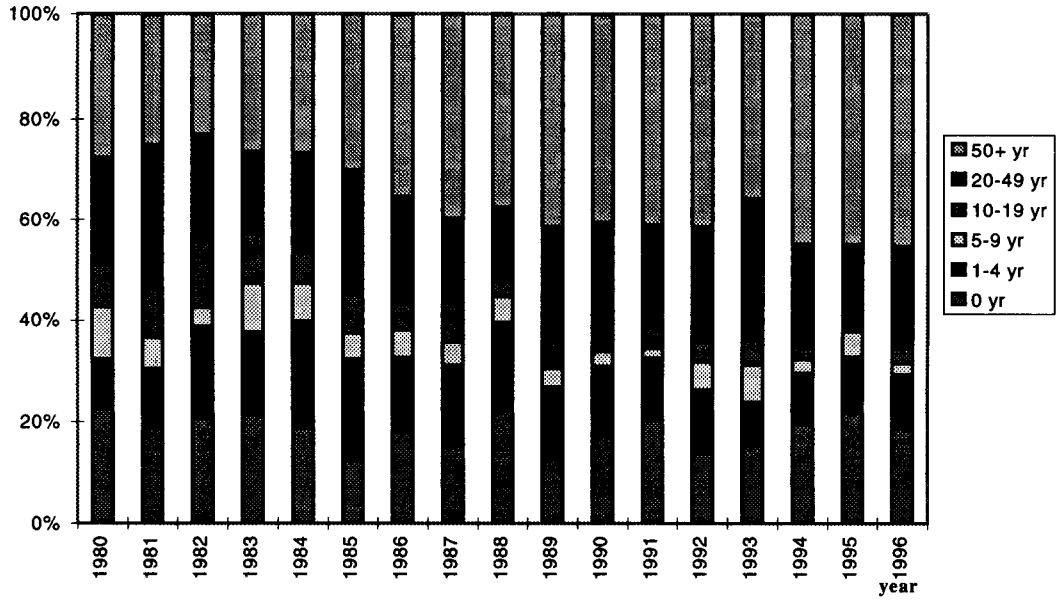

figure 53 Age distribution of hospital admissions for pneumococcal meningitis in 1980-1996 (source: LMR)

(see Appendix I, table 36)

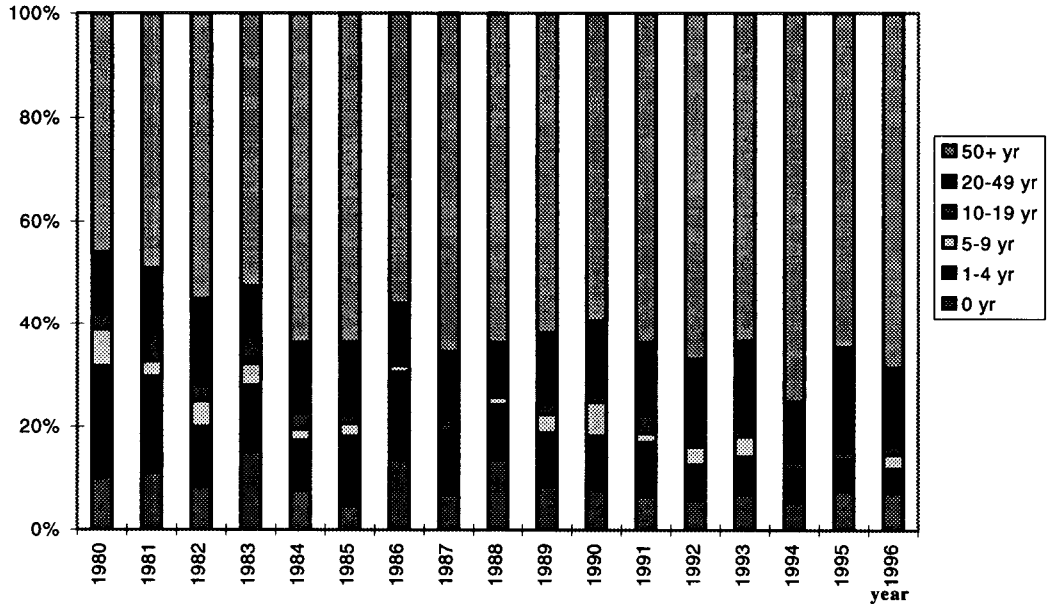

figure 54 Age distribution of hospital admissions for pneumococcal sepsis in 1980-1996 (source: LMR)

(see Appendix I, table 36)

RBM

The number of strains sent in to the RBM that were isolated from CSF (or CSF and blood) gradually increased from 73 in 1984 to 236 in 1996 and the isolates from blood rose from 74 to 726 in that same period. The increase in 1996 was higher than in the years before. The proportion of *S. pneumoniae* to the total of bacterial strains isolated from CSF also increased from 15% in 1990 to 25% in 1994 and 1995 to 29% in 1996 (80).

The increase in pneumococcal isolates seems to be mainly due to an increase for people older than 65 years of age. For isolates of CSF, the incidence was highest in infants under one year of age and older persons. For isolates from blood, only a high age-specific incidence for older persons was observed (80).

One out of the 962 strains sent in to the reference laboratory in 1996 was resistant to both penicillin and chloramphenicol, two were less susceptible to penicillin and resistant to chloramphenicol, one was resistant to chloramphenicol only and two were less susceptible to penicillin only (80).

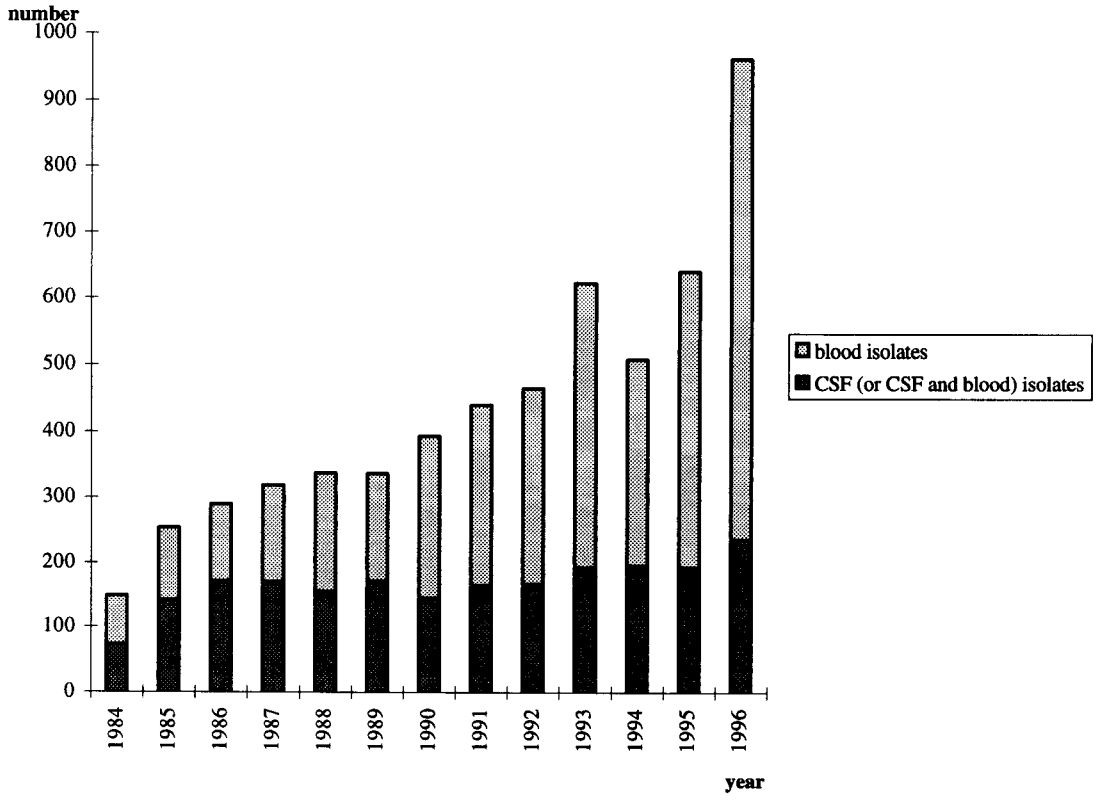

figure 55 Number of typed pneumococcal isolates at the RBM in 1984-1996 (source: RBM)

(see Appendix I, table 37)

13.4 Discussion

Incidence

The absolute number of pneumococcal meningitis has slightly grown in the period 1980-1996 according to the LMR and RBM. Pneumococcal sepsis showed a greater increase according to these two registrations; particularly the number of typed pneumococcal strains from blood increased strongly as did the number of hospitalised patients with sepsis as side diagnosis. This could implicate that other presentations of pneumococcal disease are more frequently accompanied by bacteraemia and/or sepsis.
The increase in proportional distribution of pneumococcal meningitis to bacterial meningitis is for the most part the result of a decline in incidence in *Haemophilus influenzae* meningitis as a result of Hib vaccination; the increase of pneumococcal sepsis does not seem to be caused by bias.
In the relative age distribution a shift to was seen to older age groups for both meningitis and sepsis, but for sepsis more pronounced although the median age of these patients was higher already. Severe pneumococcal infections are a threat for the aging population.
The proportion of male patients with pneumococcal meningitis was 58%. This is a common phenomenon seen in literature (102).

Types and vaccine

Continued surveillance remains of importance to detect changes in the relative contribution of the different pneumococcal types (73). The pneumococcal vaccine can contain only a limited number of types so choices have to be made about the formulation of the vaccine.
Most of the current pneumococcal vaccines are poorly immunogenic in infancy and older target groups. The ability of the immune system to provoke an antibody response to polysaccharides matures approximately at the age of two. The same technique that has been used for the development of Hib vaccines is applied now for pneumococcal vaccines. With this technique pneumococcal capsular polysaccharides are linked with carrier proteins as diphtheria and tetanus toxoid. The first results are promising, but further studies are necessary to evaluate the clinical value of these new vaccines. Information about the proportional contribution of the different types remains necessary with these conjugated vaccines. It is not possible to rely on information from other countries because the contribution to pneumococcal disease of the different types varies from country to country and in time.

Comparison of sources

If we compare the incidence of pneumococcal meningitis seen in the medical registration of the SIG and the RBM from 1985-1990, they are similar. Afterwards the numbers diverge. The number of meningitis patients according to the RBM is still close to the number of patients with meningitis as main diagnosis, but considerably lower than the number of patients with meningitis as main and side diagnosis. The number of sepsis patients increases according to the RBM and the LMR, but the rise is steeper in the RBM data. In the 1990s the number

according to the RBM exceeds the number according to the LMR, even if we consider main ánd side diagnosis. No solid explanation can be given.
Invasive pneumococcal disease will always lead to clinical treatment because of its severity and most patients are admitted only once, so the data from the LMR can be considered fairly reliable. An important disadvantage is that it does not provide data about type of pneumococcus and patients with both pneumococcal meningitis and sepsis can be registered twice. The resulting overestimation in pneumococcal disease could be prevented if data could be linked on an individual level.
The RBM does provide valuable data about pneumococcal types that can not be drawn from any other source. A disadvantage of the RBM is the lack of information on the clinical picture, especially in case of a strain from a blood isolate, which does not necessarily implicate sepsis. A positive culture of the cerebrospinal fluid is essential for the diagnoses pneumococcal meningitis so in case of a typed strain from CSF it is reasonable to assume meningitis.
In conclusion both the LMR and RBM provide valuable information on the incidence of pneumococcal meningitis with the RBM being of utmost importance for information on types of pneumococcus.
Looking forward to the availability of a pneumococcal vaccine for paediatric use, systems should be developed for the surveillance of other clinical presentations of pneumococcal infections, such as pneumonia and otitis media.

14. General discussion and conclusions

Comparison of sources
In order to determine whether the RVP is successful in sufficiently immunising the population and thus preventing disease, we looked at the morbidity and mortality of the target diseases. Morbidity and mortality are estimated on the basis of data from various surveillance sources. We will briefly discuss the registration systems from which we acquired data. As discussed in the chapters on the various diseases, the sources recommended for future surveillance differ for each disease. For a more detailed discussion on the value of the various sources, we refer to the chapters on the various diseases.

CBS Not much information is available on the accuracy of the mortality figures. It is not always obvious which pathogen is responsible for a given infectious disease, although the clinical diagnosis may be clear. In such a case, the physician's motivation to find the underlying cause of death may be low. This may lead to more than 50% misclassification of rare diseases (103). Since it is unlikely that misclassification varies significantly over time, this source probably does provide a valuable picture of the trends over time.

IGZ The data for serious and rare diseases such as poliomyelitis and tetanus seem to be very accurate. Underreporting is probably considerable for milder and more common diseases. The advantage of notification data is the availability of additional information about the probable source of infection and vaccination status, for example.
When considering notification data, changes in the notification system have to be taken into account. For example, the change in the case definition of pertussis in 1987 led to an immediate decline in the number of reported cases.
We calculated the administrative delay in notifications when the first day of illness was also reported. The delay between the date of definite notification and the first day of illness varied considerably per disease in the period 1988-1996; the median duration amounted to 21 days for meningococcosis, 29 days for rubella infection including CRS, 32 days for measles, 60 days for tetanus, 63 days for pertussis, 113 days for diphtheria and 392 days for poliomyelitis. The notification date for mumps, and thus the delay were not available. A long administrative delay between the onset and the definite notification of a case reflects mainly administrative problems; it does not always mean that the actual signal is not passed on immediately to those who should know. As an example, we refer to the poliomyelitis outbreak of 1992-1993, when even the national authorities were alerted immediately on the day of hospitalisation of the first case. Whether this would have happened for diseases such as measles, which are considered less serious such as measles, might be questioned. Nevertheless, at the local level of the GGD the information is available at an earlier stage, thus allowing for further (case and/or outbreak) investigations and control measures. Since the amount of underreporting and misclassification in the notification system probably does not vary much in time, it is appropriate for monitoring purposes.

LMR Since it is not possible to distinguish prevalent cases from incident cases in the LMR, overreporting might have occurred, for example in hospital admissions for CRS which may have led to several hospitalisations per year. For most severe diseases for which it can be assumed that hospitalisation will happen only once (e.g. diphtheria and tetanus), LMR figures are expected to be reliable. In contrast, we found that the system was very unreliable for tetanus, probably due to misclassification. For infectious diseases, most of which do not require hospital care, this registry gives information on the incidence of serious complications which is also very valuable. Estimates of the incidence derived from hospital admissions are in most cases based on main diagnoses. However, when a reliable, close to the truth incidence of a disease was known, we could show that the total of main diagnoses and side diagnoses resulted in a better estimate of the incidence. Comparing hospital admission data with the notifications of poliomyelitis during the 1992-1993 epidemic and comparing hospital admissions for bacterial meningitis with RBM figures made this possible.

Sentinels The sentinel registrations of the NIVEL and the CMRN are very helpful for the estimation of the occurrence of measles, mumps and rubella because of their great accuracy; incidences can be measured very precisely. Extrapolation is expected to give a fairly accurate picture of the incidence for the whole country, since regional differences are probably small in the Netherlands. However, one has to realise that not all parents take their children to a physician for measles, mumps or rubella, and that a certain percentage of infections will be subclinical. These two facts cause an underestimation of the incidence.

NSCK Although there are doubts on the sensitivity of the NSCK surveillance, the added value of the NSCK is an opportunity for additional data collection. In 1998, AFP en pertussis are the RVP diseases being monitored by the paediatric surveillance. The WHO requires quite intensive investigation of all cases of AFP, including virological tests of faecal samples, which appears difficult to incorporate into the paediatric surveillance scheme in practice.

EUROCAT This source does not seem sensitive enough for surveillance of CRS. In the future, a combined database for congenital anomalies, the LNR and LVR, will be able to provide important additional information on CRS.

SSPE registration This registry was very helpful for the surveillance of SSPE before 1990. It is considered unreliable thereafter because of the very low incidence of SSPE and the resulting unfamiliarity of physicians with this passive registration.

RBM The surveillance of meningitis and sepsis by the RBM has a long history and has proven its value with its high coverage. Nevertheless, the completeness of the surveillance of other invasive diseases as epiglottitis, cellulitis and arthritis for which isolates from a normally sterile site can be submitted for typing can still be improved. This extension of the services of the RBM since 1994 is probably not yet equally known in all laboratories. Attention should be paid to collecting complete information about the clinical picture and vaccination status. The

latter is particularly important for Hib and for meningococcal and pneumococcal disease, once vaccines have become available.

Virological laboratories Information on the coverage of registration and on the completeness of the data sent by virological laboratories to the RIVM on a monthly basis is not available. Improvement can be expected once the laboratories are included in ISIS. The data on the positive findings of the laboratories can be used for monitoring purposes, in addition to the notifications. A new law on infectious diseases is expected in the near future. The laboratories will be legally obliged to report positive findings of diseases for which notification is compulsory. This will greatly improve the notification system. However, for some self-limiting rash diseases, underestimation will continue as long as no laboratory confirmation is sought, at least for some of the cases. An enhanced surveillance with laboratory testing in a sentinel network should be considered.

Pertussis surveillance An advantage of additional pertussis surveillance on the basis of serodiagnostic data is that it can indicate the completeness of notification. It can also help to exclude the influence of increased awareness in case of a rise in notifications, as it was done during the 1996/1997 outbreak. A prerequisite, however, is that the serodiagnostic data must be available on a national level. Moreover, confirmation of pertussis is not always based on serodiagnosis, but can be bases on a positive culture or PCR or an epidemiological link to an index case (58). Changes in diagnostic practice, be they the introduction of new methods or the availability of testing in more laboratories, have a major influence on the surveillance based on the RIVM laboratory data. If the serodiagnosis of pertussis is performed by more laboratories in the near future, this source will lose its value, unless it is possible to aggregate data from various laboratories at a national level (e.g. through ISIS). Continuation of the intensified surveillance of pertussis based on several sources is necessary, on the one hand because no definite cause of the 1996-1997 outbreak has been found and a new increase could occur, and on the other hand because of the changes in the pertussis vaccination policy that are foreseen for the near future.

There are several surveillance systems based on the collection of data on disease occurrence, but they are not integrated and there is limited information on the precision of these systems. It is certain though, that almost every surveillance system is subject to underreporting, to misclassification and/or to delay in reporting.
Underreporting causes a surveillance system to present a rosy picture of the occurrence of diseases, while misclassification can result in either under- or overreporting. It is not possible to determine the actual degree of under- or overestimation of the true incidence with the current data. Since the degree of underreporting and misclassification probably does not vary much over time, the various sources, and particularly a combination of some systems, are appropriate for following morbidity and mortality trends over time.
Effects of vaccination

Morbidity had declined, and mortality even more so as a result of the improved socio-economic status in combination with improved hygiene and advances in medical care, even before mass vaccination for the target diseases was started in the Netherlands. After the introduction of vaccination, the incidence of most diseases declined even faster as a result of a decreased force of infection. Then the incidence of most diseases stayed at a low and more or less stable level. Exceptions are poliomyelitis and pertussis, epidemics of which occurred long after vaccination was implemented. During the 1992-1993 poliomyelitis epidemic, an upward shift in the age distribution due to the decrease in force of infection was observed. The possibly resulting increase in complications of measles due to a shift in age was not yet visible, when hospital admission was used as a criterion for complications. A lack of maternally derived antibodies can be expected in newborns of unvaccinated women. Being born in the vaccination era, they also may not have acquired natural immunity. The occurrence of polio in neonates during the poliomyelitis epidemic in 1992-1993 is evidence of this. The persistence of maternal antibodies due to a lower level of vaccine-induced, and not boosted, antibodies in the mother may not last as long as the persistence of naturally acquired antibodies. The immunoprevalence in newborns will be studied in the Pienter-project. Adjustments of the vaccination scheme might be recommended as a result.
In order to guarantee high acceptance of the RVP, it is of utmost importance to continue a watchful surveillance and to try to explain uneventful occurrences, especially now that the incidence of most RVP target diseases is low. The absolute number of cases caused by vaccine failure may be higher than the absolute number of cases in the group of unvaccinated persons, but the proportion of cases caused by vaccine failure to all cases is very low.

We now give the most important conclusions per disease.

Measles
Notwithstanding the fast decline in the occurrence of measles after the implementation of measles vaccination, epidemic peaks still seem to occur, albeit at a much lower level. However, there is a large degree of uncertainty about the estimates available. In the view of the WHO initiative to eliminate measles, which will probably be emphasized even more once poliomyelitis is eradicated, we should put more effort into getting better figures on the occurrence of measles.
Measles outbreaks should be treated as opportunities to study the transmission of measles in a highly vaccinated population. Attention should be paid to possible subclinical infections and appropriate measures for preventing future outbreaks should be determined. In this light, laboratory confirmation of the diagnosis is necessary. This will be more feasible once saliva tests become widely available, so that taking blood samples from children will no longer be necessary.
The mean age of those infected has increased as a result of a decrease in the force of infection. Unvaccinated women born in the vaccination era are approaching childbearing age. Surveillance remains necessary in order to identify a possible increase in the incidence of measles in newborns with unvaccinated mothers.

Mumps

After the introduction of mumps vaccination in 1987, its occurrence declined even more sharply than in the pre-vaccination era. Since 1992, the number of notified cases of mumps has been increasing, but this increase is not as clearly visible in the hospital registration, virological findings and the CMRN general practitioners sentinel. No explanation has been found for this. The mean age of mumps patients increased after the implementation of mass vaccination as a result of the decreased force of infection. A theoretically possible increase in orchitis as a complication of mumps infections in men due to the increase in age of the susceptible men should be monitored. Laboratory confirmation is important, since viruses other than mumps will now more frequently cause parotitis.

Rubella

Although selective vaccination for rubella was introduced in 1974, reports of its occurrence did not show a lower level, and epidemic peaks still occurred. After the implementation of mass vaccination in 1987, the occurrence declined quickly according to various sources. No more epidemic peaks were seen, and the proportion of infected adults increased.
The number of CRS patients seems to be at a low level, but an increase of CRS in newborns with unvaccinated women is theoretically possible. It is likely that these women have no natural immunity either because they were born in the vaccination era. This needs to be monitored closely.

Diphtheria

Mass vaccination has led to the virtual elimination of diphtheria over the last three decades in the Netherlands. The epidemic in the newly independent states of the former USSR, which started in 1993, has not led to imported cases of diphtheria in the Netherlands in the period 1993-1996. Spreading to other industrialised countries, even countries with frequent contacts with the newly independent states, has also been limited. This indicates that herd immunity as a result of both naturally acquired and vaccine-induced immunity is probably sufficient.
Although herd immunity (still) seems sufficient, the reduced circulation of *C. diphtheriae* has led to gaps in the level of anti-toxic antibodies in older age groups (104). As the antibody titres wane with age, booster vaccination every ten years is recommended in the Netherlands for persons who travel to endemic areas. Periodic revaccination every ten years has been proposed for persons at increased risk of acquiring diphtheria (105).The Dutch Health Council has advised an investigation of the feasibility of improving the immunoprevalence in the cohorts born before 1950 (106).

Tetanus

Tetanus antibodies can only be acquired through vaccination. Tetanus vaccination has been operational in the Netherlands for several decades, covering the population up to about fifty years old. Tetanus has become a rare disease, occurring mainly in elderly persons. Neonatal tetanus no longer occurs because of good hygiene and passive maternal immunity.
Immunity against tetanus is known to wane, leading to gaps in antibody levels in older age groups. Periodic revaccination of older persons should therefore be considered.

Pertussis

From 1989, when a case definition for notification was introduced, until 1995, the epidemic pattern was consistent with a classical pattern of epidemic peaks every 3 to 5 years (in 1989 and 1993-1994). Then a sudden and unexpected increase was seen in 1996. There are indications that changes occurred in the circulating strains of the bacterium, resulting in a possible mismatch between vaccine and circulating *Bordetella* strains (3).
In 1997, active surveillance of hospitalised pertussis patients was started by paediatricians within the NSCK. This allowed for additional data collection on the severity of disease. Moreover, from October 1997 to January 1998, notifications were followed by data collection by means of a questionnaire. These studies will provide more insight into the vaccine efficacy in relation to severity of disease.
The increased incidence of *Bordetella pertussis* infections and the foreseen changes in vaccination policy, emphasise the necessity of continuous surveillance.

Poliomyelitis

After the introduction of vaccination, all cases in the local and nation-wide outbreaks were seen in unvaccinated or incompletely vaccinated persons, all of whom (except for one 61-year-old man in the 1992-1993 outbreak) belonged to the orthodox reformed groups that reject vaccination for religious reasons. The absence of circulating poliovirus in non-epidemic periods means that no natural immunity can be acquired, and thus, once an outbreak occurs, unvaccinated persons can be infected at an older age. Then the chances of paralytic poliomyelitis due to poliovirus infection increase. At an older age, the symptoms are more severe; quadriplegy and bulbar paralysis are more often diagnosed (68). Eradication of the virus would be the ideal solution for the situation in our country, where groups that reject vaccination live socially and demographically clustered.
As the WHO has included adequate AFP surveillance as a criterion in the certification process as polio-free, the AFP surveillance will need to be continued and improved (65).

Invasive *Haemophilus influenzae* type b infections

Meningitis (with or without sepsis) is the foremost complication of the *Haemophilus influenzae* infections and was almost invariably caused by type b strains in the pre-vaccination era. The incidence of invasive Hib meningitis decreased quickly after vaccination was introduced in June 1993, as did the mortality, particularly in those younger than 5 years. No catch-up campaign was conducted for older children in the Netherlands. As a result, an

upward shift in age distribution of invasive Hib diseases was seen in the first years after the introduction of vaccination. The effect of Hib vaccination on epiglottitis and sepsis is (still) considerably less striking due to a higher age of peak incidence.

Invasive meningococcal infections
After a decrease in the late 1970s and early 1980s, a substantial increase in invasive meningococcal disease was observed from 1983 to the late 1980s and early 1990s. The rise in meningococcal disease is mainly caused by serogroup B. The absolute number of meningococcal meningitis and/or sepsis cases seems to have stabilised in the last few years, but because of the decrease in Hib disease as a result of vaccination, the proportional contribution of meningococcal disease has grown.

Invasive pneumococcal infections
The absolute number of pneumococcal meningitis cases has grown slightly in the last two decades, but pneumococcal bacteraemia/sepsis has shown a considerable increase. This increase is mainly due to an increase in age groups over 65 years. It seems that other presentations of pneumococcal disease are more frequently accompanied by bacteraemia and/or sepsis. Severe pneumococcal infections are a threat for the ageing population.
The increase in the proportional distribution of pneumococcal meningitis to bacterial meningitis is, for the most part, the result of a decline in incidence in *Haemophilus influenzae* meningitis as a result of Hib vaccinaton. The increase of pneumococcal sepsis does not seem to be caused by bias.
Looking forward to the availability of a pneumococcal vaccine for paediatric use, systems should be developed for the surveillance of other clinical presentations of pneumococcal infections, such as pneumonia and otitis media.

Additional future surveillance
Certain infections can be subclinical (e.g. poliomyelitis and measles) and such cases are not recognised and registered by the surveillance systems used in this report. Furthermore, we have seen that clinical cases are not always registered, so no accurate estimate of the incidence of most diseases can be made. Linking data from various registrations would enable us to get a better insight into the amount of underreporting of the surveillance systems. Unfortunately, linking data from different systems is almost impossible: it is illegal to provide data that can be traced to an individual. A fairly accurate linkage would be possible if all registrations included date of birth, gender, place (e.g. place of birth, residence) and time (year and date of first day of illness) (9).
Even though reliable laboratory diagnostic methods for all RVP target diseases are available, they are rarely used in cases of rash disease because of the usually self-limiting character of the disease, the lack of therapeutic consequences and the burden of blood sampling on children. In contrast to the relevance for the individual patient, laboratory confirmation is important for surveillance purposes. This is particularly true for an outbreak of a rash disease, since it is

difficult - particularly for inexperienced physicians from the post-vaccination era - to clinically distinguish rashes caused by different viruses.
For insight into the immunity of the population, the vaccination coverage is insufficient for several reasons. Vaccine failures occur in a small percentage of vaccinated persons and antibody levels wane in time for most diseases. The force of infection is low for most diseases so that booster opportunities for the immune system are not available. Furthermore, persons born before 1945 were not included in the RVP and some people may have received (additional) vaccinations in relation to travelling and military service.
In 1995/1996 in the so-called Pienter-project, a serum bank was established from a representative sample of the Dutch general population. This serum bank will be mainly used to estimate age-specific immunoprevalence for the infectious diseases in the RVP. Therefore, in the near future, age-specific data regarding the immunity of the Dutch general population to the RVP target diseases will become available (107).

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Appendix I Mortality and morbidity figures from the various data sources per disease

table I.1 Mortality of measles in the period 1901-1995 (source: CBS)

1901-1949

year	*total*	*year*	*total*
1901	2741	1926	889
1902	2430	1927	1019
1903	1223	1928	641
1904	2399	1929	359
1905	1182	1930	502
1906	1400	1931	408
1907	1477	1932	300
1908	1576	1933	174
1909	968	1934	292
1910	1176	1935	193
1911	1243	1936	132
1912	1163	1937	111
1913	1196	1938	302
1914	1277	1939	47
1915	945	1940	146
1916	1279	1941	179
1917	642	1942	110
1918	1179	1943	159
1919	1360	1944	77
1920	625	1945	54
1921	660	1946	385
1922	344	1947	20
1923	761	1948	119
1924	260	1949	53
1925	602		

1950-1995

year	*age*						
	0 yr	1-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr	total
1950	13	42	9	1	0	0	65
1951	39	111	31	8	2	1	192
1952	1	12	0	1	0	0	14
1953	22	60	17	3	0	1	103
1954	8	18	8	11	1	0	46
1955	7	24	8	0	1	0	40
1956	8	23	5	0	0	0	36
1957	1	10	2	0	0	0	13
1958	6	31	4	1	0	0	42
1959	4	28	6	0	1	0	39
1960	4	17	6	1	1	0	29
1961	1	8	4	0	0	0	13
1962	2	16	6	1	1	0	26
1963	3	14	0	2	0	1	20
1964	6	18	4	1	0	1	30
1965	2	13	3	0	0	0	18
1966	3	10	2	1	0	0	16
1967	2	7	0	0	0	0	9
1968	1	11	5	1	1	0	19
1969	0	7	2	0	0	0	9
1970	1	7	4	3	0	0	15
1971	1	4	0	0	0	0	5
1972	2	5	0	0	2	0	9
1973	0	2	0	0	0	0	2
1974	1	8	3	0	1	0	13
1975	0	1	0	0	0	0	1
1976	0	0	1	0	0	0	1
1977	0	2	3	0	0	0	5
1978	0	0	1	1	0	0	2
1979	0	0	0	0	0	0	0
1980	0	1	0	0	0	0	1
1981	0	0	0	0	0	0	0
1982	0	0	0	0	0	0	0
1983	0	1	0	0	0	0	1
1984	0	0	0	0	0	0	0
1985	0	0	0	0	0	0	0
1986	0	0	0	0	0	0	0
1987	0	1	0	0	0	0	1
1988	0	2	0	0	0	0	2
1989	0	0	0	0	0	0	0
1990	0	0	0	0	0	0	0
1991	0	0	0	0	0	0	0
1992	0	0	0	0	0	0	0
1993	0	0	0	0	0	0	0
1994	0	0	0	0	0	0	0
1995	0	0	0	0	0	0	0

table I.2 Notifications of measles in the period 1976-1996 (source: IGZ)

year	*age*						
	missing	0-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr	total
1976	80	1348	1012	53	17	2	2512
1977	38	908	785	64	17	0	1812
1978	0	66	56	9	2	0	133
1979	3	19	23	8	3	0	56
1980	1	52	110	11	4	0	178
1981	0	24	41	11	1	0	77
1982	0	26	29	32	10	1	98
1983	1	138	257	81	3	0	480
1984	3	32	28	17	2	0	82
1985	0	1	6	14	3	0	24
1986	0	24	34	29	3	0	90
1987	4	74	106	40	3	0	227
1988	5	524	554	411	25	0	1519
1989	1	29	45	42	7	0	124
1990	0	9	0	4	2	1	16
1991	0	16	14	24	5	0	59
1992	1	145	161	144	20	1	472
1993	2	181	199	64	22	0	468
1994	1	72	123	90	16	0	302
1995	0	61	72	35	12	0	180
1996	0	20	15	6	16	0	57

table I.3 Hospital admissions for measles in 1980-1996 (source: LMR)

year	*age*						
	0 yr	1-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr	total
1980	24	39	19	7	3	0	92
1981	8	33	8	3	0	0	52
1982	6	16	13	3	2	0	40
1983	4	47	38	9	3	1	102
1984	4	16	6	7	1	0	34
1985	4	6	4	7	3	0	24
1986	3	15	4	4	4	0	30
1987	6	16	21	7	4	0	54
1988	16	41	27	21	8	0	113
1989	1	5	0	8	1	0	15
1990	1	5	1	0	3	0	10
1991	2	3	2	1	4	0	12
1992	2	18	3	10	5	0	38
1993	6	18	1	6	9	1	41
1994	2	4	1	6	7	0	20
1995	2	4	1	6	5	0	18
1996	1	6	1	2	8	2	20

table I.4 Registered cases of measles in 1971-1996 (source: CMRN)

year	*age*				
	0 yr	1-4 yr	5-9 yr	10+ yr	total
1971	11	107	31	0	149
1972	0	26	14	4	44
1973	0	19	10	3	32
1974	3	104	77	7	191
1975	1	4	2	0	7
1976	6	47	34	0	87
1977	1	25	25	0	51
1978	0	3	1	0	4
1979	0	0	0	0	0
1980	1	0	1	0	2
1981	0	0	1	1	2
1982	0	0	0	1	1
1983	0	0	0	0	0
1984	0	0	0	0	0
1985	0	0	0	0	0
1986	0	0	0	0	0
1987	0	0	0	9	9
1988	0	0	2	1	3
1989	0	0	0	2	2
1990	0	0	0	0	0
1991	0	0	0	0	0
1992	0	1	0	0	1
1993	0	0	0	0	0
1994	0	0	0	0	0
1995	0	0	0	0	0
1996	0	0	0	0	0

table I.5 Number of positive serology or virus isolation for measles in 1981-1996 (source: clinical virological laboratories and RIVM)

year	*age*							
	missing	0 yr	1-4 yr	5-14 yr	15-24 yr	25-59 yr	60+ yr	total
1981	0	2	27	20	6	2	2	59
1982	0	7	23	17	8	4	0	59
1983	0	5	44	43	8	9	2	111
1984	3	2	17	11	7	4	0	44
1985	0	1	17	8	18	4	1	49
1986	3	2	16	29	8	9	3	70
1987	0	3	8	23	9	4	1	48
1988	0	10	32	51	45	15	1	154
1989	0	2	9	4	14	3	1	33
1990	0	1	9	8	3	6	5	32
1991	0	0	4	4	7	5	0	20
1992	3	3	17	18	34	11	0	86
1993	0	12	18	15	15	13	3	76
1994	0	8	3	5	7	5	2	30
1995	0	6	6	3	8	2	0	25
1996	0	3	0	0	0	0	0	3

table I.6 Mortality of mumps in the period 1950-1995 (source: CBS)

year	*age*						
	0 yr	1-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr	total
1950	1	0	1	1	1	5	9
1951	0	0	1	0	0	0	1
1952	0	0	0	0	0	2	2
1953	0	0	0	0	0	1	1
1954	0	0	0	1	1	4	6
1955	1	0	1	0	0	1	3
1956	0	2	0	0	0	0	2
1957	1	0	0	1	0	0	2
1958	0	0	0	1	0	0	1
1959	0	1	0	0	0	2	3
1960	0	0	0	1	0	1	2
1961	0	0	1	0	1	1	3
1962	0	1	0	0	0	1	2
1963	0	0	0	0	0	2	2
1964	0	0	0	0	0	0	0
1965	0	0	0	0	0	0	0
1966	0	1	0	0	0	1	2
1967	0	0	0	0	0	0	0
1968	0	1	0	0	0	1	2
1969	1	0	1	0	0	2	4
1970	0	1	1	1	0	0	3
1971	0	0	0	0	0	0	0
1972	0	1	0	0	0	1	2
1973	1	0	0	0	1	1	3
1974	0	1	0	0	0	0	1
1975	0	0	0	0	0	2	2
1976	0	0	1	0	0	2	3
1977	0	0	0	0	0	1	1
1978	0	0	0	0	1	0	1
1979	0	0	0	0	0	0	0
1980	0	0	1	0	0	0	1
1981	0	1	0	0	0	0	1
1982	0	0	0	0	1	0	1
1983	0	0	0	0	0	1	1
1984	0	0	0	0	0	0	0
1985	0	0	0	0	0	0	0
1986	0	1	0	0	0	1	2
1987	0	0	0	0	0	0	0
1988	0	0	0	0	0	1	1
1989	0	0	0	0	0	0	0
1990	0	0	0	0	0	0	0
1991	0	0	0	0	0	0	0
1992	0	0	0	0	0	0	0
1993	0	0	0	0	0	0	0
1994	0	0	0	0	0	0	0
1995	0	0	0	0	0	0	0

table I.7 Notifications of mumps in 1976-1996 (source: IGZ)

year	*age*						
	missing	0-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr	total
1976	15	470	494	76	67	7	1129
1977	17	615	682	132	99	5	1550
1978	10	488	461	73	68	5	1105
1979	4	175	214	49	27	1	470
1980	4	412	517	88	89	7	1117
1981	4	304	311	83	48	3	753
1982	0	167	170	28	37	3	405
1983	4	322	310	104	82	0	822
1984	0	102	115	51	31	8	306
1985	1	112	134	30	32	4	310
1986	3	181	180	41	51	1	458
1987	3	159	164	40	60	7	433
1988	0	35	38	14	8	4	99
1989	0	15	7	4	4	0	30
1990	0	10	5	3	2	1	21
1991	0	8	6	1	7	1	23
1992	0	20	14	6	11	2	53
1993	2	11	19	5	4	0	41
1994	0	9	6	8	16	1	40
1995	0	13	10	9	2	3	37
1996	0	13	13	4	4	2	36

table I.8 Hospital admissions for mumps in 1980-1996 (source: LMR)

year	*age*						
	0 yr	1-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr	total
1980	6	289	284	63	54	6	702
1981	4	145	140	45	27	4	365
1982	4	135	97	28	25	3	292
1983	9	330	294	80	66	3	782
1984	4	116	110	36	29	4	299
1985	10	147	135	31	27	1	351
1986	5	161	131	25	22	6	350
1987	3	151	152	37	32	6	381
1988	1	10	15	10	6	1	43
1989	0	5	5	1	7	0	18
1990	1	3	0	2	2	2	10
1991	0	4	3	1	2	1	11
1992	1	3	2	1	1	1	9
1993	0	2	1	0	1	0	4
1994	0	0	2	0	3	0	5
1995	0	1	2	1	2	0	6
1996	0	1	2	1	2	0	6

table I.9 Registered cases of mumps in 1971-1996 (source: CMRN)

year	*age*				
	0 yr	1-4 yr	5-9 yr	10+ yr	total
1971	0	4	4	3	11
1972	0	40	59	17	116
1973	0	10	5	6	21
1974	0	28	43	6	77
1975	0	17	13	4	34
1976	0	4	11	0	15
1977	2	36	38	8	84
1978	0	34	33	10	77
1979	0	9	4	1	14
1980	0	24	28	15	67
1981	0	6	5	12	23
1982	0	15	12	4	31
1983	0	30	14	5	49
1984	1	4	9	5	19
1985	0	17	11	3	31
1986	0	13	5	6	24
1987	0	14	4	6	24
1988	0	2	0	2	4
1989	0	2	0	0	2
1990	0	0	2	0	2
1991	0	0	1	0	1
1992	0	0	0	0	0
1993	0	0	0	0	0
1994	0	0	1	0	1
1995	0	0	2	0	2
1996	0	0	1	0	1

table I.10 Positive serology or virusisolation for mumps in 1981-1996 (source: clinical virological laboratories and RIVM)

year	*age*							
	missing	0 yr	1-4 yr	5-14 yr	15-24 yr	25-59 yr	60+ yr	total
1981	0	1	93	123	14	24	4	259
1982	1	7	69	78	16	23	1	195
1983	2	5	165	177	28	46	7	430
1984	4	4	53	65	18	22	1	167
1985	3	6	75	85	22	38	1	230
1986	0	10	97	108	22	35	1	273
1987	1	12	94	104	25	38	4	278
1988	0	2	26	19	8	16	3	74
1989	0	2	7	1	0	5	2	17
1990	0	0	5	6	2	9	5	27
1991	0	0	2	2	0	1	3	8
1992	0	1	3	6	0	6	2	18
1993	0	1	6	4	1	8	2	22
1994	0	6	1	5	1	3	0	16
1995	0	5	5	1	0	1	3	15
1996	0	1	0	0	0	0	0	1

table I.11 Mortality of rubella in the period 19501995 (source: CBS)

year	*age*						
	0 yr	1-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr	total
1950	0	1	1	0	0	0	2
1951	1	0	0	0	0	0	1
1952	0	1	0	0	0	0	1
1953	0	0	0	0	0	0	0
1954	0	0	0	0	0	0	0
1955	0	1	1	0	0	0	2
1956	0	0	0	0	0	0	0
1957	0	1	0	0	0	0	1
1958	0	0	0	0	0	0	0
1959	0	0	0	0	0	0	0
1960	0	0	0	0	0	0	0
1961	0	0	0	0	0	0	0
1962	0	0	0	0	0	0	0
1963	0	0	0	0	0	0	0
1964	0	0	1	0	0	0	1
1965	0	0	0	0	0	0	0
1966	0	0	0	0	0	0	0
1967	0	0	0	0	0	0	0
1968	0	0	0	0	0	0	0
1969	0	0	1	0	0	0	1
1970	1	0	0	0	0	0	1
1971	0	1	0	0	0	0	1
1972	0	0	0	0	0	0	0
1973	0	0	0	1	0	0	1
1974	0	0	0	0	0	0	0
1975	0	0	1	0	0	0	1
1976	0	0	0	0	0	0	0
1977	1	0	0	0	0	0	1
1978	1	0	0	0	0	0	1
1979	0	0	0	0	0	0	0
1980	0	0	0	0	0	0	0
1981	0	0	0	0	0	0	0
1982	0	0	0	0	0	0	0
1983	0	0	0	0	0	0	0
1984	0	0	0	0	0	0	0
1985	1	0	0	0	0	0	1
1986	0	0	0	0	0	0	0
1987	0	0	0	0	0	0	0
1988	0	0	0	0	0	0	0
1989	0	0	0	0	0	0	0
1990	0	0	0	0	0	0	0
1991	0	0	0	0	0	0	0
1992	0	0	0	0	0	0	0
1993	0	0	0	0	0	0	0
1994	0	0	0	0	0	0	0
1995	0	0	0	0	0	0	0

table I.12 Notifications for rubella and CRS in 1952-1996 (source: IGZ)

year	*age*							
	missing	0 yr	1-4 yr	5-9 yr	10-19 yr	20-29 yr	30+ yr	total
1952	0	173	1956	3089	884	314	388	6804
1953	0	57	208	182	69	15	18	549
1954	0	54	218	189	66	20	16	563
1955	0	28	2985	4520	1526	510	498	10069
1956	0	269	2019	2624	1163	293	345	6713
1957	0	57	251	116	35	8	7	474
1958	0	54	216	93	52	13	7	435
1959	0	76	482	487	134	28	31	1238
1960	0	144	1049	1239	379	88	93	2992
1961	0	113	841	818	258	59	64	2153
1962	0	67	357	255	76	31	18	804
1963	0	120	825	990	409	122	56	2522
1964	0	144	1841	2362	893	205	142	5587
1965	2	62	475	437	163	37	28	1204
1966	0	56	240	146	97	36	7	582
1967	0	64	481	464	144	44	21	1218
1968	0	129	1461	2269	722	238	116	4935
1969	0	67	675	976	309	97	33	2157
1970	4	61	544	726	261	54	33	1683
1971	3	91	867	1374	582	154	69	3140
1972	2	51	480	602	340	132	44	1651
1973	6	78	819	967	563	241	41	2715
1974	0	26	225	181	57	36	4	529
1975	0	69	410	478	218	133	17	1325
1976	83	89	1289	1736	662	460	46	4365
1977	11	41	312	259	74	62	9	768
1978	12	56	261	340	93	78	14	854
1979	27	66	866	1256	427	326	39	3007
1980	8	37	262	222	83	83	11	706
1981	10	36	186	148	60	47	18	505
1982	9	16	245	370	113	108	12	873
1983	3	25	129	99	27	47	5	335
1984	6	17	247	315	93	145	19	842
1985	2	8	41	39	14	19	5	128
1986	0	4	29	32	8	16	2	91
1987	5	15	76	117	29	61	17	166
1988	1	10	22	26	6	7	5	77
1989	0	3	14	7	3	2	0	29
1990	0	1	5	9	7	8	8	38
1991	1	3	4	2	19	25	3	57
1992	0	2	4	0	3	0	0	9
1993	1	4	5	2	0	2	2	16
1994	0	0	4	3	1	5	1	14
1995	0	3	4	4	3	1	6	21
1996	0	4	6	4	8	15	2	39

table I.13 Number of hospital admissions for acquired rubella (source: LMR)

year	*age*						
	0 yr	1-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr	total
1980	15	25	18	7	18	1	84
1981	11	14	5	6	4	0	40
1982	7	24	14	8	11	1	65
1983	7	19	9	2	7	2	46
1984	9	36	8	8	12	1	74
1985	8	7	7	2	3	1	28
1986	7	14	4	3	6	0	34
1987	6	20	12	2	4	1	45
1988	5	5	1	2	1	0	14
1989	4	3	0	0	0	0	7
1990	4	1	0	1	2	0	8
1991	1	3	0	1	1	0	6
1992	2	0	0	0	1	1	4
1993	2	3	0	1	1	0	7
1994	0	0	0	1	0	0	1
1995	1	0	1	2	3	0	7
1996	0	0	1	0	1	0	2

table I.14 Hospital admissions for CRS in 1980-1996 (source: LMR)

year	*age*						
	0 yr	1-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr	total
1980	27	9	3	0	1	0	40
1981	18	8	1	1	0	0	28
1982	18	3	2	1	0	0	24
1983	12	5	1	2	1	0	21
1984	14	5	1	0	0	0	20
1985	26	1	3	0	0	0	30
1986	4	4	1	1	0	0	10
1987	3	3	2	0	0	1	9
1988	12	5	0	1	2	0	20
1989	1	5	0	3	6	0	15
1990	0	7	0	3	3	0	13
1991	8	0	0	1	0	1	10
1992	7	0	2	1	0	0	10
1993	4	1	0	6	0	1	12
1994	2	3	0	1	4	0	10
1995	4	0	0	1	0	0	5
1996	2	0	0	0	0	0	2

table I.15 Hospital admissions for pregnant women with rubella infection, this being a complication during pregnancy, at delivery or after delivery period in 1980-1996 (source: LMR)

year	*age*		
	20-49 yr	50+ yr	total
1980	1	15	16
1981	0	13	13
1982	1	34	35
1983	0	20	20
1984	1	27	28
1985	0	17	17
1986	0	7	7
1987	1	18	19
1988	0	7	7
1989	0	1	1
1990	0	2	2
1991	0	2	2
1992	0	1	1
1993	1	3	4
1994	0	2	2
1995	0	3	3
1996	0	4	4

table I.16 **Number of registered cases of rubella (source: CMRN)**

year	*age*				
	0 yr	1-4 yr	5-9 yr	10+ yr	total
1971	2	12	12	4	30
1972	0	10	7	6	23
1973	0	34	43	22	99
1974	0	3	2	0	5
1975	3	4	2	1	10
1976	1	7	8	4	20
1977	0	2	2	1	5
1978	1	14	45	3	63
1979	0	16	15	14	45
1980	1	21	19	9	50
1981	2	0	0	1	3
1982	0	9	8	3	20
1983	1	8	7	1	17
1984	2	18	26	16	62
1985	0	5	0	0	5
1986	4	10	10	4	28
1987	1	11	3	6	21
1988	0	4	2	1	7
1989	0	3	3	0	6
1990	0	1	0	0	1
1991	1	1	1	1	4
1992	0	0	0	0	0
1993	0	0	0	0	0
1994	0	0	0	0	0
1995	0	0	0	0	0
1996	0	0	0	0	0

table I.17 Positive serology or virus isolation for rubella in 1981-1996 (source: clinical virological laboratories and RIVM)

year	*age*							
	missing	0 yr	1-4 yr	5-14 yr	15-24 yr	25-59 yr	60+ yr	total
1981	1	13	29	61	47	38	1	190
1982	7	16	73	193	97	158	2	546
1983	0	9	25	42	45	82	2	205
1984	4	23	56	148	103	225	2	561
1985	1	24	20	26	19	47	1	138
1986	1	5	13	29	15	40	1	104
1987	2	13	47	117	51	140	0	370
1988	1	7	9	9	12	13	0	51
1989	0	0	5	2	8	10	0	25
1990	0	1	5	2	32	23	0	63
1991	3	4	5	4	24	16	0	56
1992	0	2	0	1	5	7	0	15
1993	0	3	5	1	2	4	0	15
1994	0	4	4	3	7	6	0	24
1995	0	4	0	1	5	6	0	16
1996	0	2	0	0	0	0	0	2

table I.18 Mortality due to diphtheria from 1950-1995 (source: CBS)

year	*age*						
	0 yr	1-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr	total
1950	9	131	41	2	7	6	196
1951	5	95	45	6	6	2	159
1952	4	110	54	1	3	1	173
1953	3	75	57	5	6	2	148
1954	4	41	21	3	3	1	73
1955	0	17	18	2	6	3	46
1956	2	20	11	1	4	4	42
1957	0	15	18	1	2	0	36
1958	0	11	12	3	0	0	26
1959	0	14	19	5	1	0	39
1960	0	3	8	3	0	0	14
1961	0	0	1	0	1	0	2
1962	0	1	0	0	0	0	1
1963	0	0	0	0	0	0	0
1964	0	0	0	0	0	0	0
1965	0	0	0	0	0	0	0
1966	0	0	0	0	0	0	0
1967	0	0	0	0	0	0	0
1968	0	0	1	0	0	0	1
1969	0	0	0	0	0	0	0
1970	0	0	0	0	0	0	0
1971	0	0	0	0	0	0	0
1972	0	0	0	0	0	0	0
1973	0	1	0	0	0	0	1
1974	0	0	0	0	0	0	0
1975	0	0	0	0	0	0	0
1976	0	0	0	0	0	0	0
1977	0	0	0	0	0	0	0
1978	0	0	0	0	0	0	0
1979	0	0	0	0	0	0	0
1980	0	0	0	0	0	0	0
1981	0	0	0	0	0	0	0
1982	0	0	0	0	0	0	0
1983	0	0	1	0	0	0	1
1984	0	0	0	0	0	0	0
1985	0	0	0	0	0	0	0
1986	0	0	0	0	0	0	0
1987	0	0	0	0	0	0	0
1988	0	0	0	0	0	0	0
1989	0	0	0	0	0	0	0
1990	0	0	0	0	0	0	0
1991	0	0	0	0	0	0	0
1992	0	0	0	0	0	0	0
1993	0	0	0	0	0	1	1
1994	0	0	0	0	0	0	0
1995	0	0	0	0	0	0	0

table I.19 Notifications for diphtheria in the period 1940-1996 (source: IGZ)

year	*total*	*year*	*total*
1940	1733	1969	0
1941	3437	1970	2
1942	19407	1971	1
1943	56790	1972	0
1944	60400	1973	1
1945	50005	1974	0
1946	27003	1975	0
1947	10390	1976	0
1948	4313	1977	2
1949	3364	1978	1
1950	2985	1979	1
1951	2765	1980	0
1952	2805	1981	0
1953	2714	1982	0
1954	1512	1983	2
1955	745	1984	1
1956	576	1985	0
1957	446	1986	1
1958	217	1987	0
1959	387	1988	0
1960	112	1989	0
1961	16	1990	0
1962	15	1991	*1
1963	5	1992	0
1964	1	1993	0
1965	2	1994	0
1966	1	1995	**1
1967	0	1996	0
1968	3		

* 25-29 yr
** 50-54 yr

table I.20 Mortality due to tetanus in the period 1950-1995 (source: CBS)

year	*age*						
	0 yr	1-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr	total
1950	10	0	0	2	8	6	26
1951	4	3	5	4	6	7	29
1952	6	0	7	4	7	8	32
1953	3	2	7	1	4	5	22
1954	5	1	5	3	7	7	28
1955	1	2	6	6	9	7	31
1956	4	2	2	3	2	6	19
1957	3	0	5	5	2	4	19
1958	4	1	2	0	5	10	22
1959	0	1	1	2	6	3	13
1960	0	0	0	0	2	5	7
1961	0	0	1	1	1	11	14
1962	1	0	1	1	2	5	10
1963	2	1	0	1	3	2	9
1964	1	0	0	1	1	3	6
1965	1	0	0	1	1	8	11
1966	0	0	0	0	0	4	4
1967	0	0	0	0	2	4	6
1968	0	0	0	0	0	2	2
1969	0	0	0	0	1	7	8
1970	0	0	0	0	3	4	7
1971	0	0	0	0	1	6	7
1972	0	0	0	0	0	0	0
1973	0	0	0	0	0	1	1
1974	0	0	0	0	0	3	3
1975	0	0	0	0	0	3	3
1976	0	0	0	0	0	3	3
1977	0	0	0	0	0	2	2
1978	0	0	0	0	0	0	0
1979	0	0	0	0	0	0	0
1980	0	0	0	0	0	1	1
1981	0	0	0	0	1	0	1
1982	0	0	0	0	1	1	2
1983	0	0	0	0	0	1	1
1984	0	0	0	0	0	1	1
1985	0	0	0	0	0	2	2
1986	0	0	0	0	0	0	0
1987	0	0	0	0	0	0	0
1988	0	0	0	0	0	1	1
1989	0	0	0	0	0	1	1
1990	0	0	0	0	0	0	0
1991	0	0	0	0	0	1	1
1992	0	0	0	0	0	0	0
1993	0	0	0	0	0	0	0
1994	0	0	0	0	0	0	0
1995	0	0	0	0	0	2	2

table I.21 Notifications of tetanus in the period 1952-1996 (source: IGZ)

year	*age*		
	20-49 yr	50+ yr	total
1952			32
1953			18
1954			20
1955			28
1956			25
1957			26
1958			18
1959			31
1960			20
1961			21
1962			20
1963			21
1964			11
1965			10
1966			8
1967			14
1968			11
1969			7
1970			8
1971			11
1972			7
1973			5
1974			7
1975			9
1976			4
1977			7
1978			2
1979			2
1980			8
1981			2
1982			1
1983			9
1984	0	1	1
1985	1	2	3
1986	1	4	5
1987	0	2	2
1988	1	4	5
1989	0	3	3
1990	1	1	2
1991	0	2	2
1992	0	3	3
1993	1	1	2
1994	0	2	2
1995	1	2	3
1996	0	1	1

table I.22 Mortality due to pertussis in the period 1905-1995 (source: CBS)

1905-1949

year	*total*	*year*	*total*
1905	1226	1928	566
1906	1002	1929	563
1907	1035	1930	626
1908	1325	1931	387
1909	1002	1932	476
1910	1056	1933	425
1911	1104	1934	493
1912	1176	1935	323
1913	828	1936	406
1914	933	1937	334
1915	1227	1938	322
1916	1058	1939	257
1917	929	1940	434
1918	1198	1941	549
1919	1036	1942	231
1920	733	1943	556
1921	574	1944	423
1922	1027	1945	356
1923	761	1946	841
1924	576	1947	147
1925	538	1948	278
1926	917	1949	248
1927	771		

1950-1995

year	*age*						
	0 yr	1-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr	total
1950	88	50	4	1	0	2	145
1951	73	51	4	0	0	2	130
1952	79	45	3	0	0	0	127
1953	51	25	5	0	0	0	81
1954	16	6	1	1	0	0	24
1955	17	12	0	0	0	1	30
1956	16	18	1	0	0	0	35
1957	7	7	0	0	0	0	14
1958	14	7	0	0	0	0	21
1959	16	8	3	1	0	0	28
1960	1	1	0	0	0	0	2
1961	5	1	1	0	0	0	7
1962	6	1	0	0	0	0	7
1963	6	0	0	0	0	0	6
1964	0	0	0	0	0	0	0
1965	0	0	0	0	0	0	0
1966	0	0	0	0	0	0	0
1967	0	0	0	0	0	0	0
1968	0	0	0	0	0	0	0
1969	0	0	0	0	0	0	0
1970	2	0	0	0	0	0	2
1971	0	0	0	0	0	0	0
1972	0	0	0	0	0	0	0
1973	0	0	0	0	0	0	0
1974	1	0	0	0	0	0	1
1975	0	0	0	0	0	0	0
1976	0	0	0	0	0	0	0
1977	0	0	0	0	0	0	0
1978	0	0	0	0	0	0	0
1979	0	0	0	0	0	0	0
1980	0	0	0	0	0	0	0
1981	1	0	0	0	0	0	1
1982	0	0	0	0	0	0	0
1983	0	0	0	0	0	0	0
1984	0	0	0	0	0	0	0
1985	0	0	0	0	0	0	0
1986	0	0	0	0	0	0	0
1987	0	0	0	0	0	0	0
1988	0	0	0	0	0	0	0
1989	0	0	0	0	0	0	0
1990	0	0	0	0	0	0	0
1991	0	0	0	0	0	0	0
1992	0	0	0	0	0	0	0
1993	1	0	1	0	0	0	2
1994	0	0	0	0	0	0	0
1995	0	0	0	0	0	0	0

table I.23 Notifications for pertussis in the period 1976-1996 (source: IGZ)

year	*age*							
	missing	0 yr	0-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr	total
1976								4
1977								25
1978								1
1979								26
1980								30
1981								50
1982								80
1983								200
1984								534
1985								1522
1986								2159
1987								2709
1988	0	18	40	42	21	4	2	127
1989	0	91	90	182	48	15	8	434
1990	2	103	104	178	50	35	6	478
1991	2	35	39	54	20	5	5	160
1992	0	35	32	50	31	17	1	166
1993	1	71	78	77	39	23	5	294
1994	4	86	180	174	51	35	6	536
1995	0	43	106	96	36	28	10	319
1996	0	203	828	1113	361	236	78	2819

table I.24 Hospital admissions for pertussis in the period 1980-1996 (source: LMR)

year	*age*						
	0 yr	1-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr	total
1980	55	14	3	0	0	1	73
1981	56	15	8	1	0	0	80
1982	73	32	3	1	0	0	109
1983	153	61	20	8	0	0	242
1984	126	69	8	4	4	3	214
1985	182	97	47	14	6	5	351
1986	237	114	68	11	7	21	458
1987	324	81	65	20	24	28	542
1988	70	20	9	2	3	3	107
1989	163	41	24	5	2	1	236
1990	125	22	16	2	1	3	169
1991	50	21	8	6	0	1	86
1992	76	28	4	3	1	0	112
1993	245	55	13	4	1	1	319
1994	197	80	21	5	4	0	307
1995	108	47	20	5	1	1	182
1996	376	109	54	17	7	9	572

table I.25 Number of positive serological results (one-point and/or two-point serology) for *Bordetella (para)pertussis* in the period 1989-1996 (source: RIVM/LIS)

year	*positive serological results*
1989	2110
1990	1482
1991	1521
1992	1099
1993	1971
1994	2365
1995	1342
1996	9739

table I.26 Mortality due to poliomyelitis in the period 1905-1995 (source: CBS)

year	*age*						
	0 yr	1-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr	total
1950	0	3	2	0	7	1	13
1951	2	8	3	7	13	1	34
1952	1	19	10	15	29	0	74
1953	0	2	1	4	4	4	15
1954	0	0	1	2	5	1	9
1955	1	15	7	5	11	3	42
1956	3	26	15	7	20	3	74
1957	1	8	1	3	9	3	25
1958	0	1	1	2	6	1	11
1959	0	0	0	2	3	2	7
1960	0	1	1	1	2	1	6
1961	0	0	2	2	5	0	9
1962	0	0	1	1	5	1	8
1963	0	0	2	1	0	1	4
1964	0	1	0	1	2	0	4
1965	0	0	0	0	2	1	3
1966	0	0	0	0	2	2	4
1967	0	0	0	1	1	0	2
1968	0	0	0	1	0	0	1
1969	0	0	0	1	2	3	6
1970	0	0	0	0	2	2	4
1971	0	1	1	3	3	1	9
1972	0	0	0	0	0	3	3
1973	0	0	0	1	5	3	9
1974	0	0	0	0	1	2	3
1975	0	0	0	0	4	4	8
1976	0	0	0	0	0	3	3
1977	0	0	0	0	3	3	6
1978	1	0	0	0	0	3	4
1979	0	0	0	0	0	0	0
1980	0	0	0	0	0	0	0
1981	0	0	0	0	0	0	0
1982	0	0	0	0	0	0	0
1983	0	0	0	0	0	0	0
1984	0	0	0	0	0	0	0
1985	0	0	0	0	0	0	0
1986	0	0	0	0	0	0	0
1987	0	0	0	0	0	0	0
1988	0	0	0	0	0	0	0
1989	0	0	0	0	0	0	0
1990	0	0	0	0	0	0	0
1991	0	0	0	0	0	0	0
1992	1	0	0	0	0	1	2
1993	0	0	0	0	0	0	0
1994	0	0	0	0	0	0	0
1995	0	0	0	0	0	0	0

table I.27 Notifications of poliomyelitis in the period 1924-1996 (source: IGZ)

year	*total*
1924	39
1925	32
1926	49
1927	50
1928	75
1929	511
1930	599
1931	136
1932	242
1933	146
1934	197
1935	52
1936	101
1937	60
1938	687
1939	403
1940	111
1941	445
1942	196
1943	1931
1944	1218
1945	200
1946	357
1947	693
1948	81
1949	160
1950	77
1951	568
1952	1713
1953	167
1954	75
1955	481
1956	2206
1957	203
1958	39
1959	11
1960	29

year	*0 yr*	*1-9 yr*	*10-19 yr*	*20+ yr*	*total*
1961					83
1962					36
1963					33
1964					15
1965					3
1966					14
1967					2
1968					7
1969					16
1970					2
1971					39
1972					0
1973					4
1974					0
1975					0
1976					0
1977					1
1978					110
1979					0
1980					0
1981					1
1982					0
1983					1
1984					1
1985					0
1986					0
1987					0
1988					0
1989					0
1990					0
1991					0
1992	7	6	7	14	34
1993	0	7	11	19	37
1994					0
1995					0
1996					0

table I.28 Hospital admissions for poliomyelitis in the period 1980-1996 (source: LMR)

year	*age*						
	0 yr	1-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr	total
1980	0	1	0	0	3	0	4
1981	0	0	1	1	4	0	6
1982	0	2	1	0	1	1	5
1983	1	1	0	0	2	0	4
1984	0	0	1	1	1	0	3
1985	0	0	0	0	0	0	0
1986	0	1	0	0	0	1	2
1987	0	0	0	0	1	0	1
1988	0	0	0	0	0	0	0
1989	0	0	0	0	2	0	2
1990	0	0	0	0	0	2	2
1991	0	0	0	0	0	2	2
1992	10	4	9	14	20	3	60
1993	0	0	0	3	5	2	10
1994	0	0	0	0	2	2	4
1995	0	1	0	0	0	1	2
1996	0	0	0	0	0	0	0

table I.29 Number of positive serology or isolation for poliovirus type 1, 2, and 3 (source: clinical virological laboratories and RIVM)

year	*type of virus*		
	polio type 1	polio type 2	polio type 3
1981	1	6	4
1982	1	0	3
1983	5	3	7
1984	1	0	1
1985	1	0	0
1986	0	0	2
1987	5	1	1
1988	0	0	5
1989	0	1	0
1990	0	0	0
1991	2	3	0
1992	1	2	*72
1993	1	0	*11
1994	0	0	0
1995	0	0	1
1996	0	0	0

* polio type 3

year	*age*							
	missing	0 yr	1-4 yr	5-14 yr	15-24 yr	25-59 yr	60+ yr	total
1992	0	10	11	16	15	19	1	72

1993	0	0	1	5	1	4	0	11

table I.30 Hospital admissions for *Haemophilus influenzae* meningitis in 1980-1996 and sepsis in 1991-1996 (source: LMR)

meningitis

year	*age*						
	0 yr	1-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr	total
1980	43	113	3	4	2	0	165
1981	50	101	7	2	4	2	166
1982	72	98	5	2	3	0	180
1983	48	93	7	2	1	3	154
1984	47	80	9	0	0	2	138
1985	51	93	2	0	3	1	150
1986	74	120	6	1	2	0	203
1987	87	120	6	7	6	3	229
1988	67	140	2	0	5	6	220
1989	85	148	4	4	5	5	251
1990	81	155	3	0	3	3	245
1991	74	116	3	1	5	4	203
1992	81	135	5	0	0	1	222
1993	90	111	6	2	6	2	217
1994	11	96	8	0	7	1	123
1995	2	27	5	0	3	2	39
1996	12	9	0	0	4	5	30

sepsis

year	*age*						
	0 yr	1-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr	total
1991	8	7	0	0	1	5	21
1992	1	11	1	0	2	4	19
1993	6	10	1	2	1	4	24
1994	4	6	1	0	1	12	24
1995	0	4	1	0	1	7	13
1996	1	2	1	3	0	3	10

table I.31 *Haemophilus influenzae* isolates serotyped at the RBM in 1976-1996 by serotype (source: RBM)

year	*serotype*		*origin of isolate*		*total number of isolates*
	Serotype b	Serotype d,e,f and non-typable	CSF (or CSF and blood) isolates	blood isolates	
1976	71	1			72
1977	74	5			79
1978	89	7			96
1979	118	5			123
1980	153	10			163
1981	171	10			181
1982	171	12			183
1983	164	11			175
1984	154	12			166
1985	179	12			191
1986	246	11	228	29	257
1987	267	18	256	29	285
1988	229	21	210	40	250
1989	316	26	282	60	342
1990	269	24	243	50	293
1991	236	27	210	53	263
1992	294	21	241	74	315
1993	244	33	204	73	277
1994	148	28	112	64	176
1995	60	36	50	46	96
1996	30	58	28	60	88

table I.32 Mortality of meningococcal disease in 1979-1995 (source: CBS)

year	*age*						
	0 yr	1-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr	total
1950	22	27	3	2	7	5	66
1951	26	25	4	3	2	6	66
1952	35	19	3	1	3	6	67
1953	27	23	5	3	4	1	63
1954	19	26	4	1	3	5	58
1955	18	25	3	1	4	7	58
1956	20	19	3	3	4	9	58
1957	18	24	4	0	2	6	54
1958	13	11	5	0	2	9	40
1959	14	19	2	1	4	3	43
1960	4	18	0	0	1	3	26
1961	8	10	2	2	4	5	31
1962	11	8	2	2	1	2	26
1963	5	13	4	1	6	1	30
1964	8	9	3	2	1	1	24
1965	6	15	1	0	1	2	25
1966	9	22	5	1	2	5	44
1967	10	23	2	1	2	4	42
1968	10	16	0	2	4	2	34
1969	16	16	3	1	2	3	41
1970	16	23	1	6	0	3	49
1971	3	15	6	2	3	3	32
1972	13	11	3	1	0	6	34
1973	10	17	3	0	2	4	36
1974	7	10	3	4	3	6	33
1975	4	7	2	5	0	1	19
1976	4	2	2	1	2	4	15
1977	1	2	2	2	0	3	10
1978	5	6	0	2	2	0	15
1979	4	6	0	3	2	6	21
1980	2	4	3	1	3	4	17
1981	1	5	4	3	0	6	19
1982	3	5	3	0	3	3	17
1983	2	1	0	1	0	3	7
1984	4	4	2	4	2	2	18
1985	5	7	1	0	5	3	21
1986	6	8	1	8	5	3	31
1987	5	15	6	8	2	1	37
1988	8	10	4	7	4	3	36
1989	11	13	3	18	1	4	50
1990	3	16	2	9	4	4	38
1991	9	15	2	16	5	3	50
1992	4	18	2	8	6	9	47
1993	14	15	5	6	4	6	50
1994	8	16	3	12	2	1	42
1995	12	13	1	12	6	12	56

table I.33 Notifications of meningococcal meningitis in 1947-1996 and sepis in 1976-1996 (source: IGZ)

year	*meningitis*	*sepsis*
1947	956	
1948	337	
1949	296	
1950	282	
1951	321	
1952	333	
1953	313	
1954	331	
1955	349	
1956	352	
1957	214	
1958	156	
1959	174	
1960	118	
1961	149	
1962	162	
1963	183	
1964	156	
1965	170	
1966	516	
1967	303	
1968	253	
1969	211	
1970	183	
1971	202	
1972	248	
1973	171	
1974	161	
1975	95	
1976	88	41
1977	79	38
1978	165	21
1979	154	27
1980	143	33
1981	179	19
1982	114	22
1983	100	23
1984	113	31
1985	126	40
1986	150	55
1987	129	76
1988	169	67
1989	297	175
1990	269	243
1991	225	214
1992	291	224
1993	268	295
1994	181	241
1995	231	233
1996	234	247

table I.34 Hospital admissions for meningococcal meningitis and sepis in 1980-1996 (source: LMR)

meningitis

year	*age*						
	0 yr	1-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr	total
1980	47	78	20	58	35	9	247
1981	49	63	33	48	29	12	234
1982	32	58	23	33	23	9	178
1983	41	47	17	37	16	17	175
1984	33	66	30	46	25	13	213
1985	40	79	40	63	25	10	257
1986	57	87	50	91	45	28	358
1987	45	85	53	75	30	11	299
1988	50	109	51	82	45	23	360
1989	54	154	79	122	55	23	487
1990	50	125	55	166	49	20	465
1991	69	130	73	130	54	22	478
1992	84	158	77	151	84	39	593
1993	74	163	87	159	78	42	603
1994	74	150	77	88	55	29	473
1995	71	147	76	141	60	35	530
1996	75	175	92	128	54	39	563

sepsis

year	*age*						
	0 yr	1-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr	total
1980	17	29	11	12	3	3	75
1981	13	25	18	16	4	8	84
1982	8	20	8	14	5	3	58
1983	14	21	3	10	7	12	67
1984	16	33	20	20	6	7	102
1985	11	40	17	20	18	10	116
1986	23	32	31	38	17	18	159
1987	22	55	44	35	15	12	183
1988	32	66	39	43	16	15	211
1989	26	100	54	67	23	18	288
1990	26	93	48	76	25	19	287
1991	51	112	63	82	21	14	343
1992	36	140	58	68	39	37	378
1993	61	150	66	81	34	29	421
1994	52	139	57	65	22	22	357
1995	61	157	55	88	28	33	422
1996	54	166	77	67	32	19	415

table I.35 Meningococcal isolates typed at the RBM in 1986-1996 (source: RBM)

year	*CSF (or CSF and blood) isolates*	*blood isolates*	*total*
1985	223	31	254
1986	312	45	357
1987	281	56	337
1988	332	53	385
1989	420	99	519
1990	413	113	526
1991	419	112	531
1992	473	127	600
1993	480	162	642
1994	350	140	490
1995	445	148	593
1996	414	155	569

table I.36 Hospital admissions for pneumococcal meningitis and sepsis in 1980-1996 in the period 1980-1996 (source: LMR)

meningitis

year	*age*						
	0 yr	1-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr	total
1980	35	15	16	13	33	43	155
1981	22	13	7	12	32	29	115
1982	29	25	5	19	29	32	139
1983	34	26	15	16	26	42	159
1984	33	37	13	11	35	47	176
1985	17	27	7	10	34	41	136
1986	33	27	10	9	40	65	184
1987	26	27	8	14	28	68	171
1988	31	24	7	4	21	52	139
1989	22	23	6	9	38	69	167
1990	29	22	5	14	28	67	165
1991	34	20	3	9	32	68	166
1992	29	26	11	8	48	86	208
1993	37	21	17	12	68	86	241
1994	45	23	6	6	47	103	230
1995	54	27	12	2	41	111	247
1996	52	29	6	8	56	125	276

sepsis

year	*age*							
	missing	0 yr	1-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr	total
1980	0	10	21	7	3	12	45	98
1981	0	11	18	3	5	13	48	98
1982	0	10	14	6	4	20	66	120
1983	0	18	15	5	6	12	62	118
1984	0	10	13	3	4	18	85	133
1985	0	6	17	3	2	18	81	127
1986	0	22	27	2	1	19	90	161
1987	0	11	17	1	5	20	103	157
1988	1	21	16	2	1	15	97	153
1989	0	14	17	6	3	23	102	165
1990	0	14	17	11	3	24	101	170
1991	0	15	23	4	8	31	143	224
1992	0	14	16	8	0	40	158	236
1993	0	22	22	12	4	53	196	309
1994	0	16	17	1	5	34	220	293
1995	0	23	17	2	4	62	198	306
1996	0	31	20	12	6	66	295	430

table I.37 Pneumococcal isolates typed at the RBM in 1984-1996 (source: RBM)

year	*CSF (or CSF and blood) isolates*	*blood isolates*	*total*
1984	73	74	147
1985	141	112	253
1986	172	117	289
1987	171	147	318
1988	154	183	337
1989	172	164	336
1990	144	249	393
1991	165	274	439
1992	167	298	465
1993	193	430	623
1994	196	312	508
1995	193	447	640
1996	236	726	962

Appendix II Case definitions for notification used by the Medical Inspectorate of Health (IGZ)

MEASLES

Clinical case definition

An illness characterised by all of the following clinical features:

- generalised rash lasting ≥ 3 days
- temperature ≥ 38.3 C (101 F)
- cough, or coryza, or conjunctivitis

Laboratory criteria for diagnosis

- isolation of measles virus from a clinical specimen, or
- significant rise in measles antibody level by any standard serologic assay, or
- positive serologic test for measles IgM antibody

Case classification

Suspect: any rash illness with fever

Probable: meets the clinical case definition, has no or non-contributory serologic or virologic testing, and is not epidemiologically linked to a probable or confirmed case.

Confirmed: a case that is laboratory confirmed or that meets the clinical case definition and is epidemiologically linked to a confirmed or probable case. A laboratory-confirmed case does not need to meet the clinical case definition.

Comment

Two probable cases that are epidemiologically linked can be considered confirmed, even in the absence of laboratory confirmation. Only confirmed cases should be notified.

MUMPS

Notification after clinical diagnosis and/or positive serological confirmation.

NB For serodiagnosis of mumps the results are positive when a significant rise in titres in paired sera occurred (positive two-point serology)

RUBELLA

Notification after positive serological and/or clinical confirmation or solely on epidemiological grounds.
If exanthema is present and a rapid diagnosis is necessary (in case of pregnancy), confirmation can be acquired in case of presence of IgM antibodies against the rubella virus. These are present in all patients at the third or fourth day of exanthema during at least four weeks. In case of reinfection only IgG antibodies are present.

NB For serodiagnosis of rubella the results are positive when a significant rise in titres in paired sera occurred (positive two-point serology)

DIPHTHERIA

Notification after positive microbiological confirmation (isolation of the bacterium).

TETANUS

Positive diagnosis can usually only be made on clinical grounds. Sometimes *Clostridium tetani* can be isolated from wound material. Serological confirmation is not possible.

PERTUSSIS

1. Pertussis

1.1 Anamnestic one or more of the following symptoms:

a. A serious cough, with a duration of more than two weeks
b. Coughing attacks
c. Cough followed by vomiting

In combination with

1.2 One or more of the following signs, symptoms or findings:

a. For young infants a period of apnoea and cyanosis after long-term coughing
b. For pertussis characteristic cough with whooping
c. Subconjunctival bleeding
d. Contact with a individual suspected for pertussis or with a confirmed case with pertussis in the previous three weeks
e. The occurrence of a pertussis outbreak locally
f. Leucocytosis from ≥ 15,000 lymphocytes per ml

And in combination with

1.3 Positive bacteriological and/or serological findings in the patient, or in the index patient (epidemiological criteria included in case def. in 1992)

NB For serodiagnosis of pertussis the results are positive when a significant rise in titres in paired sera occurred (positive two-point serology)

2. Atypical pertussis
The diagnosis pertussis is made, when the patient coughs, and the criteria described in 1.1 and 1.2 were not met, but the criteria in 1.3 were met.

NB An individual without symptoms has not to be notified independently on microbiological or serological findings which indicate that the individual has a pertussis infection.

POLIO

Virus isolation:
- by means of pharyngeal swab in the first two or three days of illness.
- from faeces in the first three to six weeks or longer after the third day of illness.

Polio is a category A notifiable disease meaning that in case of suspicion of polio, a physician should contact the Public Health Service or the regional Medical Inspector of Health.

MENINGOCOCCOSIS

Isolation of the bacterium:
Isolation of *Neisseria meningitidis* from blood, CSF or pharynx.