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The State of infectious diseases in the Nether

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2012

State of infectious disease in the Netherlands 2012

P. Bijkerk
J. Kemmeren
K. Kardamanidis
L. Mollema
E.B. Fanoy
H.E. de Melker

Colophon

Editors: P. Bijkerk[1], J. Kemmeren[1], K. Kardamanidis[1], L. Mollema[1], E.B. Fanoy[1,2], H.E. de Melker[1].

Contact:
Paul Bijkerk
Epidemiology and Surveillance Unit
paul.bijkerk@rivm.nl

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K. Kardamanidis[1], E.B. Fanoy[1,2], P. Bijkerk[1]

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J. Kemmeren[1]/ Paul Bijkerk[1], L. Mollema[1], H.E. de Melker[1]

1. Epidemiology and Surveillance, Centre for Infectious Disease Control, RIVM, Bilthoven
2. Public Health Service Midden-Nederland, Zeist

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Rapport in het kort

Staat van Infectieziekten in Nederland, 2012

De uitbraken van kinkhoest en *Salmonella* Thompson in 2012 waren de meest in het oog springende infectieziekten van dat jaar. Dit blijkt uit de Staat van Infectieziekten in Nederland 2012, die inzicht geeft in ontwikkelingen van infectieziekten bij de Nederlandse bevolking. Daarnaast worden ook de ontwikkelingen in het buitenland beschreven die voor Nederland relevant zijn. Met deze jaarlijkse uitgave informeert het RIVM beleidsmakers van het ministerie van Volksgezondheid, Welzijn en Sport (VWS).

Elk jaar komt er een thema aan bod; dit keer de ontwikkelingen in vaccins en vaccinatieprogramma's en de relevantie daarvan voor de Nederlandse volksgezondheid. De meeste vaccinaties worden gegeven vanuit nationale vaccinatieprogramma's, zoals het Rijksvaccinatieprogramma (ongeveer 2 miljoen prikken per jaar) en het Nationale Griep Preventieprogramma (ongeveer 3,5 miljoen prikken per jaar). Daarnaast wordt gevaccineerd bij onder andere reizigers, medische risicogroepen zoals mensen zonder milt en werknemers die een verhoogd risico hebben om een infectieziekte tijdens het werk op te lopen, zoals personeel in de zorg en in laboratoria. Per vaccinatieprogramma is in kaart gebracht in welke mate de ziekten voorkomen, wat het percentage gevaccineerden is en het aantal gegeven vaccins. Het percentage gevaccineerden bij reizigers, medische risicogroepen en werknemers is onbekend.

Veranderingen in de maatschappij zorgen ervoor dat bepaalde groeperingen kritisch staan ten opzichte van vaccinaties. In het jaaroverzicht staat ook beschreven welke groepen afzien van vaccinatie, zoals orthodox-gereformeerden (circa 250.000 mensen) en antroposofen. Ook wordt de motivatie en houding van ouders besproken om hun kind wel of niet te laten vaccineren. Daarnaast komt de toename van het aantal ouderen en chronisch zieken aan bod. Hun gevoeligheid voor infecties maakt hen een belangrijke groep om (nieuwe) vaccinaties te overwegen.

Trefwoorden:
Staat van Infectieziekten, vaccinatieprogramma, vaccinatie, infectieziekten, meldingsplichtige infectieziekten.

State of Infectious Diseases in the Netherlands, 2012

In 2012, outbreaks of pertussis and Salmonella Thompson were the most important events concerning infectious diseases in the Netherlands. These outbreaks are described in the State of Infectious Diseases in the Netherlands in 2012. The purpose of this annual report is to provide insight into developments and trends of infectious diseases in the Dutch population. In addition, developments in other countries that are relevant for the Netherlands, are described. The annual report is compiled for policymakers at the Ministry of Health, Welfare and Sport (VWS).

Each year, one particular topic is highlighted. This time the focus is on developments in vaccines and vaccination programmes and their relevance for the Dutch public health. Many vaccines are given through countrywide vaccination programmes, such as the National Immunization Programme (approximately 2 million vaccinations each year) and the National Influenza Prevention Programme (approximately 3,5 million vaccination each year). In addition, vaccinations are given to travellers, medical risk groups, such as people without a spleen, and employees who have an increased risk for an infectious disease through their vocation, such as health care and laboratory personnel. The epidemiology, the mortality and morbidity, and vaccine coverage are described per vaccination programme. Vaccine coverage in travellers, employees and medical risk groups is largely unknown.

Changes in society ensure that certain groups are critical to vaccinations. In this report we describe groups who refuse vaccination, such as members of Reformed Congregations and people with an anthroposophical lifestyle. Also, the attitude and motivation of parents to have their child vaccinated or not is discussed. Finally, we describe the increase in the number of elderly and chronically ill people. Their susceptibility to infections makes them an important group to consider (new) vaccinations.

Keywords:
State of Infectious Diseases, vaccine preventable diseases, vaccines, infectious diseases, notifiable diseases.

Contents

1 Introduction

This report is the eighth edition of the State of Infectious Diseases in the Netherlands. The annual publication of this report is written in order to inform policy makers at the Ministry of Health, Welfare and Sports (VWS) and at the Centre of Infectious Diseases at RIVM. As from this year, this report will be published in English to broaden our readership internationally.

This State of Infectious Diseases in the Netherlands starts with a chapter of main national and international infectious diseases events that occurred in the Netherlands in 2012. This chapter includes the table with annual numbers of notified diseases in the Netherlands.

One particular topic is highlighted each year. This year the focus is on developments in vaccines and vaccination programmes and their relevance for the Dutch public health. Many vaccines are given through national immunization programmes. In paragraph 3.2 we describe briefly the different programmatic vaccination (National Immunization Programme, National Influenza Prevention Programme of both specific risk group vaccination programmes against Hepatitis B and tuberculosis) by aim and target group, content, coordination and organization and financial aspects and individual based vaccination options. In paragraph 3.6, an overview is given of the registered vaccines in the Netherlands with their indication and target group.

In population-wide vaccination programmes such as the NIP, the interplay between host, pathogen, vaccine and population determines the eventual impact of vaccination on population level. In paragraph 3.3 we give an overview of relevant concepts with potential impact on long-term effects of population-based vaccination programmes and examples of their impact on the occurrence of vaccine-preventable diseases included in routine vaccination programmes. In addition, other factors that may affect the impact of the vaccination programme, such as the occurrence of adverse events and other non-specific effects, are described.

In paragraph 3.4 we describe two important changes in population and society in relation to vaccination. First, we describe the more critical views on vaccination nowadays and the effects on the willingness to be vaccinated. In the second part, we describe the ageing of the population, its effect on infectious diseases and the opportunities to protect the elderly by vaccination. Furthermore, we describe the increasing numbers of immune compromised patients, due to ageing and to developments in the field of immune modulatory drugs. Immunosuppressive drugs are extensively used.

The development of vaccines is an important achievement in medical history. However, vaccines are still unavailable for many of the infectious diseases that plague humankind. In paragraph 3.5, we describe the history of vaccine development and the different stages the candidate vaccine has to go through before it can be licensed. Furthermore, we will give an overview of the most important progresses in vaccine development and vaccination programme development.

2 The state of infectious diseases in the Netherlands, 2012

K. Kardamanidis, E.B. Fanoy and P. Bijkerk

2.1 Introduction

In this chapter, we provide an overview of key infectious diseases events in 2012 previously reported in weekly reports of the Dutch early warning committee. These include both national and international events. Table 2.1 shows the number of notifications of all notifiable diseases in the Netherlands in 2005-2012. In paragraphs 2.2 to 2.5 we describe the most important events concerning mandatory notifiable diseases under the Dutch Public Health Act (1). Paragraph 2.6 deals with notable occurrences regarding non-notifiable infectious diseases for the Netherlands, including events in the rest of Europe and the rest of the world. We included information from the year 2013, in case an outbreak or unusual event started in 2012 and continued into 2013. We have not included information about outbreaks that started or events that occurred in 2013.

2.2 Group A-diseases

Polio

In 2012, 223 patients with poliomyelitis were reported to the World Health Organization (WHO) globally. Of these, 217 (97%) were reported from the last 3 countries were poliomyelitis is endemic (Nigeria 122 patients, Pakistan 58 patients, and Afghanistan 37 patients). The other 6 patients were reported from Chad (5) and Niger (1). In 1988 the World Health Assembly resolved to eradicate the disease. Since then, the number of polio cases worldwide has largely decreased from 350,000 cases in 1988, to 1,294 in 2010, 650 in 2011 and 223 in 2012. The number of endemic countries has decreased from over 125 in 1988 to just three by the beginning of 2012. The virus has however re-established transmission in three countries which were previously polio-free. These countries are Angola, Chad and the Democratic Republic of the Congo (http://www.polioeradication.org/). In addition, since February 2013, wild polio virus type 1 (WPV1) has been detected in 96 sewage samples from 27 sampling sites in southern and central Israel. Three positive environmental samples were also collected from the West Bank and Gaza. For the first time, these findings indicate widespread wild polio virus circulation without identified cases of clinical disease. As Israel is a popular destination for European Union travellers and vice versa, there is a risk of WPV importation and re-establishment (particularly within unvaccinated groups) in EU countries. (http://www.ecdc.europa.eu/en/publications/Publications/Communicable-disease-threats-report-21-sep-2013.pdf). In the Netherlands, the last

Table 2.1 Number of infectious disease notifications, the Netherlands, 2005-2012.

Group*	Infectious disease	2005	2006	2007	2008	2009	2010	2011	2012
Group A	Smallpox	0	0	0	0	0	0	0	0
	Polio	0	0	0	0	0	0	0	0
	Severe Acute Respiratory Syndrome (SARS)	0	0	0	0	0	0	0	0
Group B1	Human infection with zoonotic influenza virus				0[a]	0	0	0	0
	Diphtheria	0	0	0	0	0	0	1	1
	Plague	0	0	0	0	0	0	0	0
	Rabies	0	0	0	1	0	0	0	0
	Tuberculosis**	1128	1030	999	1013	1158	1068	1003	958
	Viral haemorrhagic fever	0	0	0	1	0	0	0	0
Group B2	Typhoid fever	34	23	22	29	20	33	20	17
	Cholera	4	3	3	5	3	1	3	3
	Hepatitis A	222	258	168	183	176	274	134	123
	Hepatitis B Acute	282	267	223	225	202	219	197	178
	Hepatitis B Chronic	1536	1512	1563	1640	1743	1788	1760	1286
	Hepatitis C Acute	28	30	44	45	52	48	78	51
	Pertussis	6759	4163	7374	8704	6504	4348	7568	13675
	Measles	3	1	4	109	11	21	52	10
	Paratyphi A	10	20	10	10	12	24	14	25
	Paratyphi B	9	15	21	26	14	17	28	18
	Paratyphi C	2	0	2	1	3	0	1	3
	Rubella	362	13	4	2	7	0	3	1
	STEC/enterohemorragic *E.coli* infection	61	45	96	141	265	398	695	879
	Shigellosis	415	268	384	356	465	573	626	740
	Invasive group A streptococcal disease				2[a]	252	222	205	177
	Clusters of foodborne infection***	92	91	100	84	36	49	52	44
Group C	Anthrax	0	0	0	0	0	0	0	0
	Mumps				7[a]	32	568	671	395
	Botulism	0	1	1	7	0	0	0	2
	Brucellosis	5	6	5	8	4	6	1	3
	Creutzfeldt-Jakob disease	20	14	18	18	8	28	40	24
	Creutzfeldt-Jakob disease - Variant	1	0	1	0	0	1	0	0
	Yellow fever	0	0	0	0	0	0	0	0
	Invasive *Haemophilus influenzae* type b infection				0[a]	0	45	22	21
	Hantavirus infection				0[a]	8	18	8	23
	Legionellosis	280	452	325	341	240	477	351	308
	Leptospirosis	29	22	37	37	25	30	34	45
	Listeriosis				3[a]	47	74	95	70
	Malaria	310	251	210	225	243	251	276	195
	Meningococcal disease	260	168	195	162	153	153	112	108
	MRSA-infection (clusters outside hospitals)				0[a]	10	17	10	1
	Invasive pneumococcal disease (in children age 5 years or younger)				0[a]	35	60	57	43
	Psittacosis	48	76	52	85	72	72	88	43
	Q fever	5	10	132	1013	2317	547	94	63
	Tetanus				0[a]	1	1	6	2
	Trichinosis	0	0	0	1	1	0	1	0
	West Nile virus infection				0[a]	0	1	1	0

* Notifiable infectious diseases in The Netherlands are grouped according to the legal measures that may be imposed (2)

** Numbers received from KNCV Tuberculosis fund

*** Number of clusters, not number of cases

[a] not notifiable until 1 December 2008, so the number for 2008 is for one month only

poliomyelitis epidemic occurred in 1992-1993 affecting 71 patients who were all but one unvaccinated for religious reasons.

2.3 Group B1-diseases

Rabies

In 2012, a case of rabies in an animal was reported in the Netherlands. An 8 week old rabid puppy dog was imported from Morocco via Spain by a Dutch couple. This led to a resource-intensive and costly joint action between the public health authorities and the Dutch Food and Consumer Product Safety Authority (NVWA), in order to identify and trace all people and animals with possible exposure to the rabid puppy. The puppy was euthanized, as well as two cats which had been in contact with it. A total of 43 Dutch residents and five people in Morocco and Spain who had also been in contact with the dog received rabies post-exposure prophylaxis. Rabies is endemic in Morocco (3). In the Eastern part of Europe, rabies affected wildlife has been reported from the Russian Federation, Ukraine, Romania, Poland, Belarus, Croatia, Turkey, and Moldova (4). Since the end of 2012 there have been several reports about rabies positive foxes and dogs in Northern Greece which had a rabies free status since 1987. Surveillance was scaled up and domestic and stray dogs and cats were vaccinated. In the Netherlands, since the beginning of surveillance for rabies, three people have been notified with this disease, one each in 1962, 1996 and 2008. Two had been bitten by a dog while abroad and one had been bitten by a bat in Kenya (5).

Tuberculosis

In 2012 there were 958 notifications of tuberculosis in the Netherlands, of which 511 were of pulmonary tuberculosis. Of the pulmonary tuberculosis patients, 177 had smear positive tuberculosis, the most infectious type of tuberculosis. The number of tuberculosis patients has decreased by 32% since 2002 and the decrease continues into 2013. The incidence rate in 2012 was 5.7 per 100,000 inhabitants. The decrease was more pronounced in the group of people with pulmonary tuberculosis compared to those with extra-pulmonary tuberculosis (42% vs. 17%). Nearly three quarters (73%) of tuberculosis diagnoses in 2012 originated from people born abroad. Of these patients, the largest group (18%) was born in Somalia. Patients from Somalia relatively often present with lymph node tuberculosis. In 2012, there were 11 notifications of multidrug-resistant (MDR)-tuberculosis cases. There have not been any notifications of cases with extreme drug-resistant (XDR)-tuberculosis since 2009, in which year 3 cases were notified. In 2011, the percentage of patients who successfully completed their treatment was on average 87% (http://www.rivm.nl/Documenten_en_publicaties/Algemeen_Actueel/Uitgaven/Infectieziekten/Tuberculose/Tuberculose_in_Jaarrapportage_Surveillance_Respiratoire_Infectieziekten_2012). In the European Region, the incidence of tuberculosis varies among and within the countries, from a range of less than one tuberculosis case per 100,000 inhabitants, to above 200 cases per 100,000. The 53 countries of the WHO European Region account for around 4.4% of the world's cases, representing an estimated 380,000 individuals with a new episode of tuberculosis, or 42 cases per 100,000 inhabitants (http://www.ecdc.europa.eu/en/publications/Publications/Tuberculosis-surveillance-monitoring-2013.pdf).

2.4 Group B2-diseases

Pertussis

In the Netherlands pertussis re-emerged suddenly in 1996. Since then, high peaks in notifications have been observed every 2 to 3 years (Figure 2.1). A particularly large pertussis epidemic occurred in the Netherlands in 2012, with a total of 13,675 notifications compared to an average of 6,900 notifications per year in the previous 5 years (Figure 1). The epidemic started in the winter months of 2011, which was unusual, as normally a decrease in pertussis notifications is seen at the end of the year. The epidemic reached its highest level in July 2012 after which the number of notifications decreased. During this latest epidemic, three infants died from pertussis. They had not yet received vaccination due to their young age. Cases occurred in all age groups, but the age specific incidence was highest in the age categories 0-2 months and from 8 years onwards. The relatively high incidence in the age category 8-12 years suggests that immunity, conferred by a booster dose with acellular vaccine given at the age of 4 years, starts to wane after 4 years. An unexpected limited duration of immunity conferred by acellular vaccines has also been observed in Australia and the USA (6). The resurgence of pertussis has been observed in a number of countries with highly vaccinated populations. Research suggests that the increase in pertussis observed since 1996, is associated with the emergence of P3 strains which produce more pertussis toxin. The P3 strain has spread globally, largely replacing the resident *Bordetella pertussis* population (7, 8). More recently strains have emerged which do not produce pertactin, a component of 3 and 5 component pertussis acellular vaccines (9-11) (12). Based on these observations, the resurgence of pertussis could be due to a combined effect of waning immunity and pathogen adaptation (13). Measures to decrease the burden of pertussis, especially for infants for whom pertussis is most severe, even life threatening need to be considered (14). Some countries offer an adolescent or adult booster dose. This is not only done to protect young infants but also to reduce the burden of disease in adolescents and adults themselves. In

Figure 2.1 Number of pertussis notifications, the Netherlands, 1989-2012.

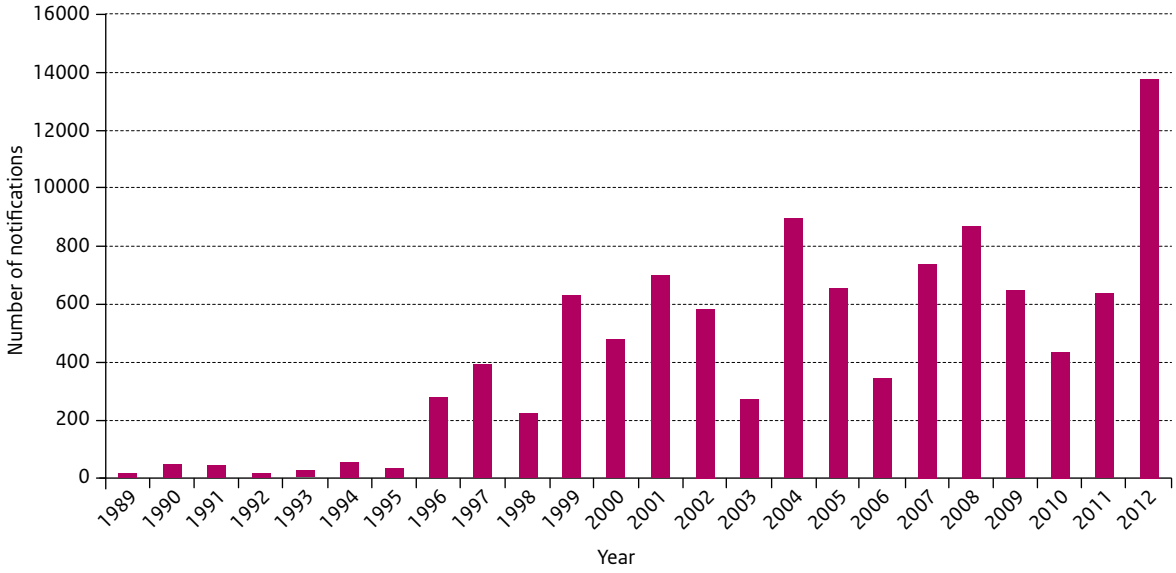
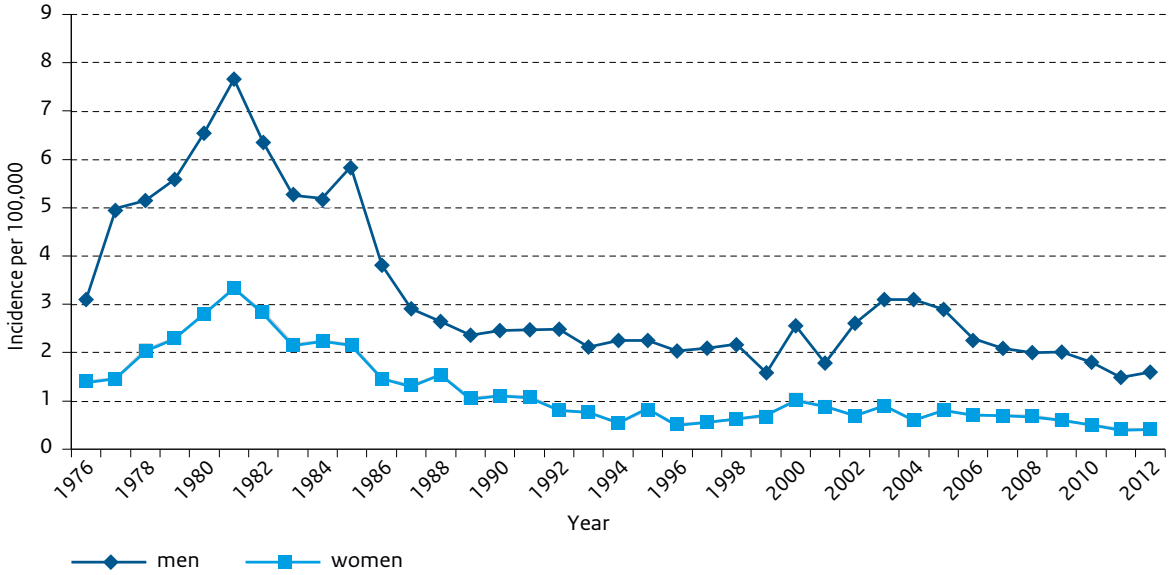


Figure 2.2 Incidence of hepatitis B notifications in men and women (per 100,000 inhabitants), the Netherlands, 1976-2011.

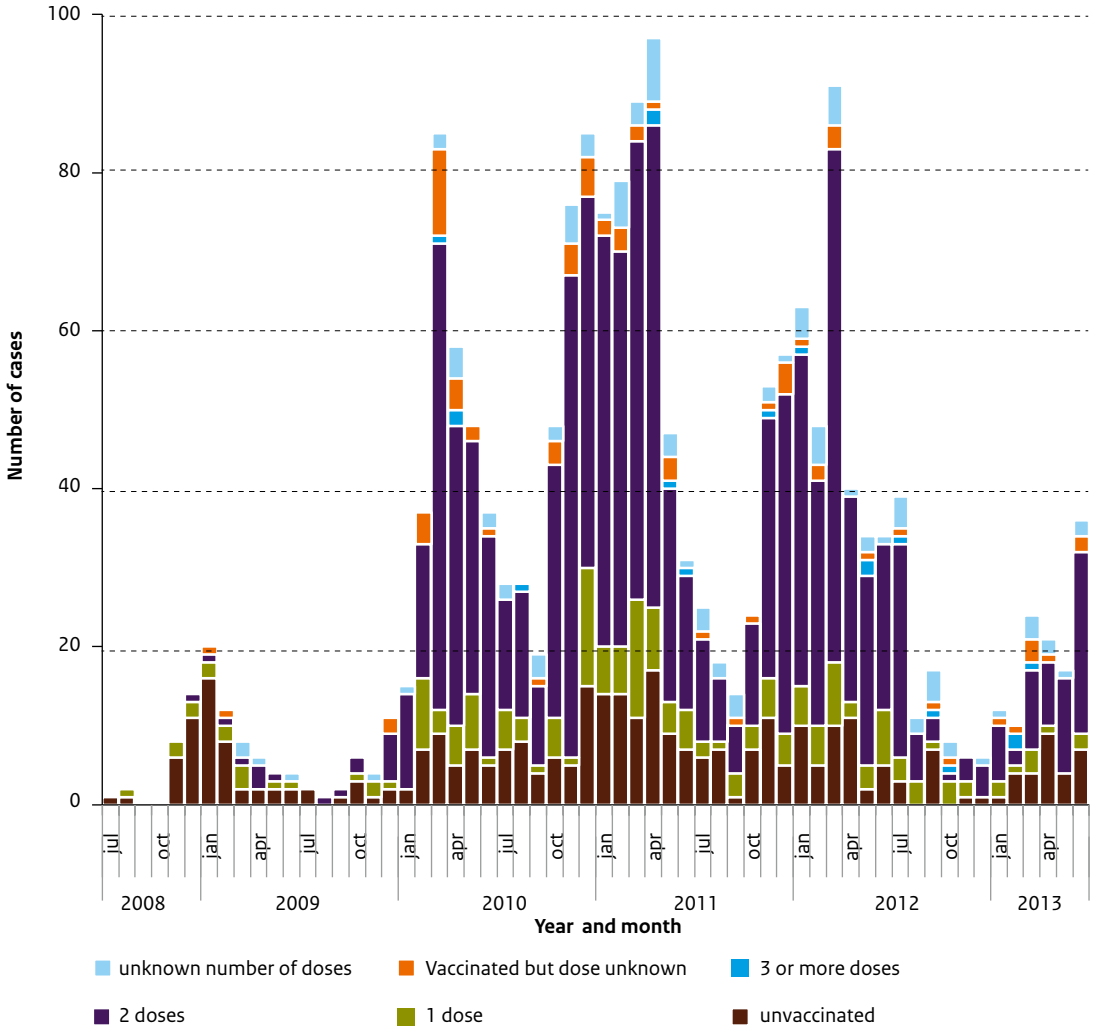


Australia the aim of cocooning (offering a booster vaccination to parents and other adults who have close contact with newborn babies) was to reduce disease in young infants. However, this policy has been discontinued because no effect on infants was noticeable (15). The USA and UK advise pregnant women to be vaccinated. In the UK, however, this is a temporary measure only, to stop the 2012 outbreak (16). In the Netherlands the Health Council will advise on possible additional measures to protect newborns in the near future.

Hepatitis B

In 2012, the incidence of acute hepatitis B virus (HBV) infections in the Netherlands reached its lowest point since 1970, when laboratory diagnostics became possible (see Figure 2.2). In men, the incidence decreased from 3.1/100,000 inhabitants in 2004 to 1.5/100,000 in 2011. In women, the incidence remained stable between 2004 and 2008 (0.7/100,000 inhabitants), then decreased to 0.4/100,000 in 2011. In both males and females, the most frequently reported risk factor for contracting acute HBV

Figure 2.3 Mumps notifications (n=1,795) by vaccination status, the Netherlands, 1 July 2008 - 30 June 2013.



infection was unprotected sexual contact. In 1989, the Netherlands initiated a national screening programme for HBV carriage for all pregnant women. From 2002, there has also been a vaccination programme in place for men who have sex with men (MSM), drug users (injecting as well as oral), and male and female commercial sex workers. These are groups that have a higher risk of contracting a HBV infection. From 2012, drug users are no longer part of the vaccination programme as HBV vaccination is now provided by drug treatment centres. From 1 August 2011, vaccination against HBV of all newborn babies has been included in the National Immunisation Programme. The decrease in incidence from 2004 can largely be explained by the 51% decrease of infections in men who have sex with men (MSM). The decrease can be attributed to the vaccination programme for MSM. The number of cases in people with no reported risk factors also decreased by 50%. Part of this decrease may also be due to the selective vaccination programme (17, 18).

2.5 Group C-diseases

Mumps

Since December 2009, an outbreak of mumps has been ongoing in the Netherlands, mainly affecting university students. The outbreak started in the university cities Utrecht, Delft and Leiden and subsequently spread to other university cities. In 2010 and 2011 there were 568 and 671 cases respectively. In 2012 the outbreak declined with 395 cases notified (see Figure 2.3). Most cases had been vaccinated, usually twice. A total of 137 patients (8.3%) developed complications of which 121 were orchitis (12.3% of males). Possible causes of the outbreak were waning vaccine immunity, and introduction of the virus in a

student network of close contacts. In addition to this, the circulating wild-type mumps virus genotype G is known to cause large outbreaks of mumps in the vaccinated population. Mumps outbreaks in students and in vaccinated populations have been described in other European countries, and in the United States of America and Canada as well (19-24).

Botulism

In 2012, two cases of infant botulism were notified in the Netherlands. One case concerned a two months old breast-fed baby who had consumed some amount of honey. The other case concerned a four-months-old baby in whom the source was never identified. The *Clostridium botulinum* toxine types that affected the babies were different (A and B respectively), indicating a separate source. Honey is a known reservoir for spores of *C. botulinum* and a known risk factor for infant botulism. Spores of *C. botulinum*, which are commonly found in the environment (soil and dust) may be picked up by bees and brought to the hive. The Dutch health authorities advise against the consumption of honey in children under the age of 1. Since 1976, when infant botulism was first described, more than 1500 cases have been reported, mainly in the United States of America. In the Netherlands, botulism (food borne, infant, and wound botulism) became a notifiable disease in 1985. Human cases of botulism in the Netherlands are rare. In 2008, there was a cluster of 7 botulism cases in participants of a mini-cruise in Turkey. Black olives were the most likely source of infection (25, 26).

Leptospirosis

In 2012, there were 45 cases of leptospirosis notified in the Netherlands compared to a 7 year average of 31 cases (2005-2011). As in previous years however, most cases acquired the infection abroad, usually during vacation in tropical countries. Different serovars of the bacteria favour different host animals such as rats, swine, cattle, and dogs. Leptospirosis is an endemic zoonotic disease in the Netherlands - the main infecting serogroup is Icterohaemorrhagiae, with rats as the most important host, causing the more severe Weil disease (27). Infections in humans in the Netherlands are mainly caused by recreational activities which involve contact with water. From the end of the 1950s, the proportion of imported infections gradually increased, reaching its peak in 2005. Most imported infections nowadays are associated with outdoor activities and adventurous holidays (28).

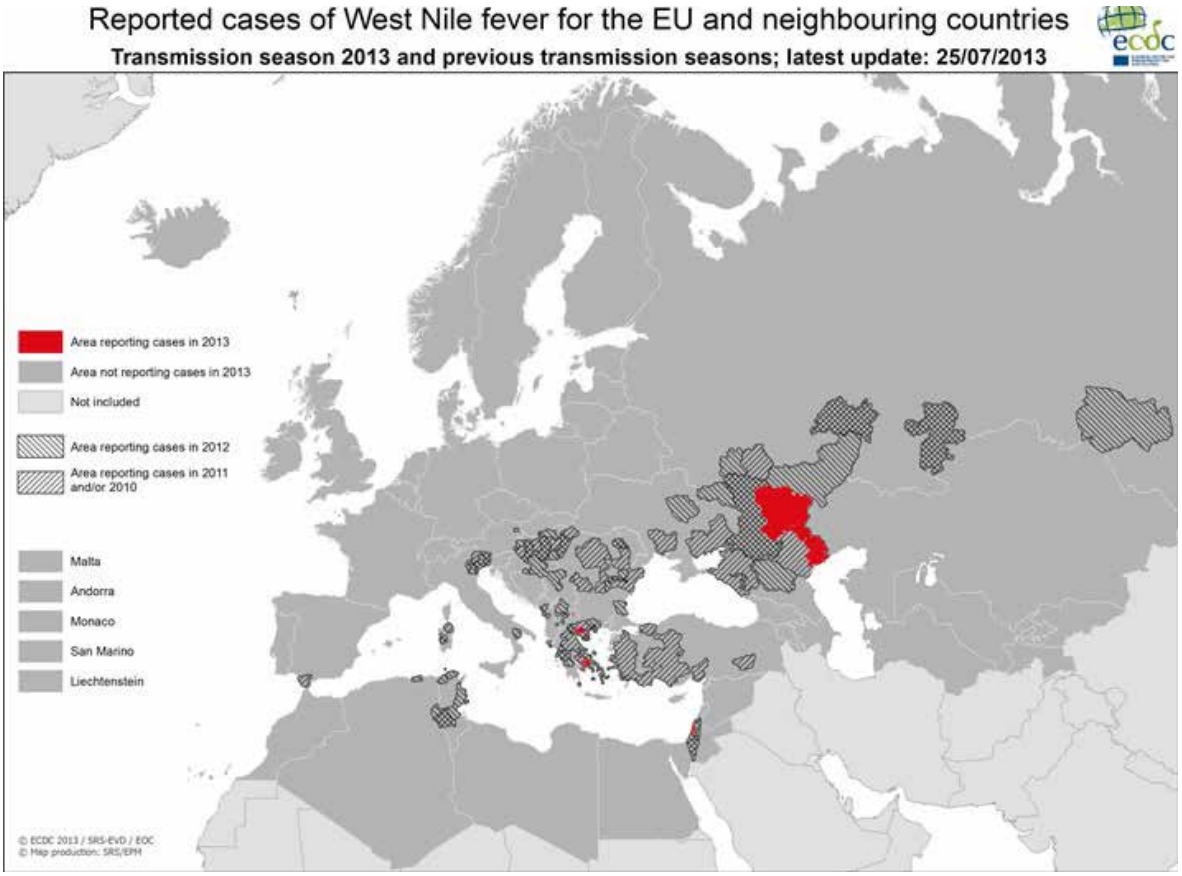
Anthrax

In 2012, there was an international outbreak of anthrax infection affecting 14 injecting drug users. Patients were identified in several European countries: the United Kingdom (5 in England, 1 in Scotland and 1 in Wales), Germany (4), Denmark (2), and France (1 patient). The patients probably used contaminated heroin. Another case was reported from England in the beginning of 2013. The source of the contaminated heroin has not been found. Anthrax infection caused by injection was first described in 2000 in an injecting heroin user in Norway(29). In 2009/2010 there was also a large outbreak of anthrax infection in injecting heroin users with 52 cases in the United Kingdom and 3 in Germany. The multi-locus variable-number tandem repeat analysis (MLVA) and single nucleotide polymorphism (SNP) analysis of isolates from 2009-2010, 2012 and the first case in Norway in 2000, show that all cases were affected by the same strain. This indicates the probability of the fact that contamination of the heroin is caused by a single source, and that the outbreak has been lasting for at least a decade (29). In the Netherlands, so far no cases of anthrax among injecting drug users have been reported. Since it became notifiable in the Netherlands in 1976, 7 cases have been reported with the last 2 cases in 1994.

Large outbreak of West-Nile virus in the United States of America

The Centers for Disease Control and Prevention (CDC) in the United States of America (USA) reported the largest number of West-Nile virus (WNV) infections in the USA since 2003, when the first outbreak of WNV was described, with 5,674 cases in 2012. The majority (92%) of cases in this large multistate outbreak had an illness onset in the summer months of July to September with a peak in August (30). Over half of the cases (51%) were suffering from neuro-invasive diseases (encephalitis, meningitis and acute flaccid paralysis). 3,491 (62%) patients were hospitalized and 286 (5%) subsequently died (30). It is not clear why there was an epidemic of WNV in the USA in 2012: the occurrence of outbreaks are dependent on a complex ecology of weather, the number of birds that maintain the virus, the number of mosquitoes spreading the virus, and human behaviour. These factors make it difficult to explain and predict outbreaks (30). Originally, WNV was endemic on the African continent only. Nowadays, WNV is endemic in areas around the Mediterranean Sea, India and America. The European Centre for Disease prevention and Control (ECDC) monitor the number of cases of WNV in European Union member states and neighbouring countries, in the summer months between June and November (see figure 2.4). In the 2012 transmission season, 237 probable and confirmed cases were reported in the EU and 670 cases in neighbouring countries (31). During the transmission season of 2012, the Netherlands asked blood donors who had traveled to these parts of Europe to abstain from blood donations until 4 weeks after their return. In order to monitor where patients acquired the infection, and to ensure that no patients have contracted the virus in the Netherlands,

Figure 2.4 Reported cases of West Nile fever for the EU and neighbouring countries (source: ECDC).



WNV has been a notifiable disease in the Netherlands since 2008. Nine genera of mosquitoes potentially capable of transmitting WNV are endemic in the Netherlands.

Hantavirus pulmonary syndrome amongst visitors of the Yosemite National Park in the United States of America

In November 2012, the Yosemite National Park in California in the USA, reported a cluster of 10 confirmed cases of Sin Nombre hantavirus infections, of which three were fatal. Nine of the cases probably became infected during their stay in tent cabins in the park (32). Several Dutch travellers stayed at these tent cabins and were contacted through public health authorities: there were no cases amongst them. Rats and mice are the reservoir for hantaviruses. Deer mice (*Peromyscus maniculatus* see Figure 2.5) were most likely the source of infection for this cluster of Sin Nombre virus infections. The Sin Nombre hantavirus does not occur in the Netherlands, but the Puumalavirus, another type of hantavirus, does. Puumalavirus is the predominant human pathogenic hantavirus species in western, central and northern Europe (33). From October 2011 to April 2012 there was an outbreak of puumalavirus infection in Germany with 852 human cases. It is thought that this was due to a beech mast year in 2011, followed by an early and massive reproduction of the bank vole (Myodes *glareolus*, a type of mouse) population during winter 2011 and spring 2012 (34). During mast years, deciduous trees produce exceptionally high quantities of seeds, an important food source for bank voles. The Puumalavirus causes a relative mild illness in about 10% of infected people. In 2012, there were 23 reported cases of hantavirus infections in the Netherlands. Most cases live in areas in the Netherlands where hantavirus is endemic (35).

Figure 2.5 Deer mouse (*Peromyscus maniculatus*). Source: http://www.cedarcreek.umn.edu/mammals/cricetidae.html

2.6 Other relevant events related to non-notifiable infectious diseases

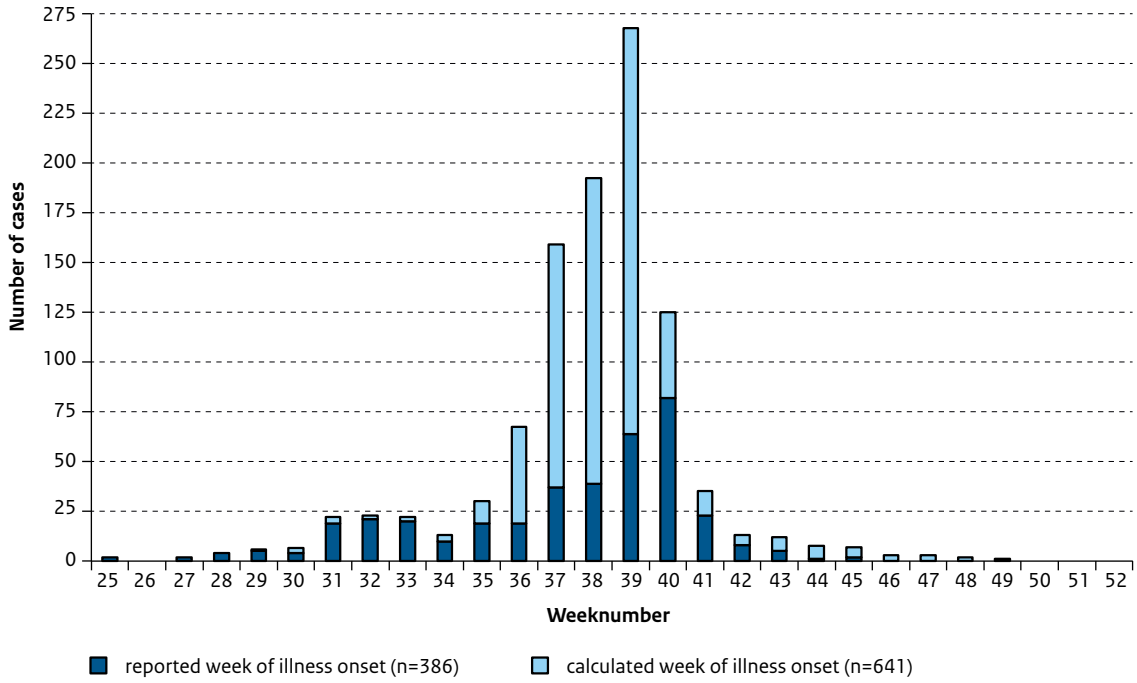
Outbreak of *Salmonella* Thompson caused by the consumption of smoked salmon

Between August and December 2012 there was a large outbreak of salmonellosis in the Netherlands, with 1,149 confirmed cases of *Salmonella* Thompson (see Figure 2.6). Cases were reported from all over the Netherlands in people with a median age of 45 years, and mostly in females (65%). Four elderly people were reported to have died from the infection. Salmonellosis is not a notifiable disease in the Netherlands, but stool specimens positive for *Salmonella* can be sent to the RIVM for serotyping. A case-control study pointed to smoked salmon as a possible source of infection and several supermarkets were reported significantly more often than others. These supermarkets turned out to have the same supplier. Trace-back of the smoked salmon by the Dutch Food and Consumer Product Safety Authority (NVWA) led to one fish processing company. An environmental investigation was conducted at the fish processing site and 4 of 9 batches of smoked salmon products tested positive for S. Thompson. Molecular typing by means of pulsed-field gel electrophoresis (PFGE) showed that strains from the patients and the smoked salmon were indistinguishable. Dishes used to transport the salmon within the processing line turned out to be porous and thus absorbing the *Salmonella* bacteria. How the dishes initially got contaminated remains unknown. All smoked salmon and products containing smoked salmon from this producer were recalled. After withdrawing the salmon from the supermarkets, the number of reported cases decreased. There was no concurrent increase in *Salmonella* Thompson cases in other European countries. In the United States there was a cluster of S. Thompson infections. At first, microbiological results indicated a similar pulsed-field gel electrophoresis (PFGE) pattern. Later, significant differences between the strains were detected by whole genome sequencing. Investigation revealed no particular exposures, and no connection was found between the outbreak in the Netherlands and the cluster in the United States (36).

Discovery of a novel coronavirus

In September 2012, a new coronavirus was identified post-mortem from a patient suffering from acute pneumonia and subsequent renal failure in Saudi Arabia (37). Internationally this novel virus has since been named Middle East Respiratory Syndrome-coronavirus (MERS-CoV). From September 2012 to August 2013, WHO had been informed of a total of 94 laboratory-confirmed cases of infection with MERS-CoV, including 46 deaths, globally

Figure 2.6 Number of *Salmonella* Thompson cases by (reported or calculated*) week of disease onset, the Netherlands, 2012.



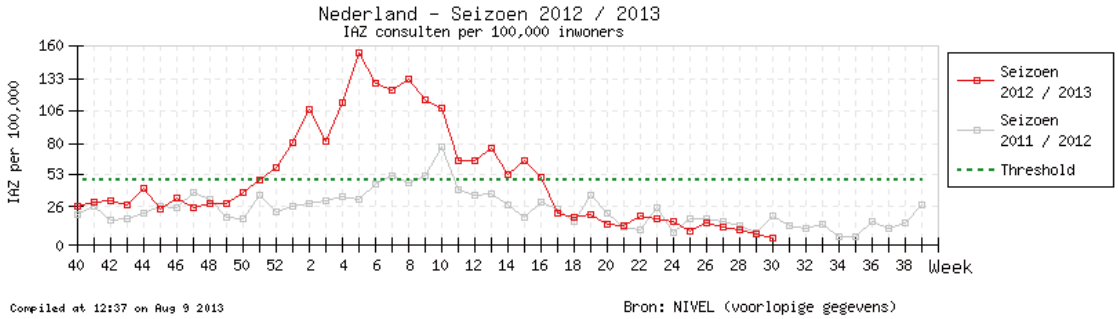
* Calculated for cases where the date of disease onset was unknown as follows: Firstly for cases where date of disease onset and date of laboratory confirmation was known, the median number of days between the two dates was calculated. Subsequently, for cases where disease onset was unknown, the median number of days was subtracted from the date of laboratory confirmation. Cases where both dates were unknown (n=122) were not included in this figure.

(http://www.who.int/csr/don/2013_08_01/en/index.html). All cases have been directly or indirectly linked, through travel or residency, to 4 countries in the Middle East: Saudi Arabia, Qatar, Jordan, and the United Arab Emirates. This includes cases reported from Germany, the United Kingdom, France, Italy and Tunisia. There has been transmission from person-to-person on a small scale amongst people who had close contact with cases, for example by sharing a household or work place, or by caring for a patient in a health care setting. In Saudi Arabia a cluster of 23 cases was investigated and 21 of these 23 cases acquired the infection through person-to-person transmission in hemodialysis units, intensive care units, or in-patient units in three different health care facilities (38). Coronaviruses are a large family of viruses including viruses that may cause a range of illnesses in humans, from the common cold to severe acute respiratory syndrome (SARS). Viruses of this family may also cause a number of diseases in animals. There is very limited information available about transmission, severity, and clinical impact of the MERS-CoV because of a relatively small number of cases that have been reported thus far. Camels from different countries have high prevalence of antibodies against MERS-CoV, suggesting that these animals are a potential reservoir (39). A role for bats as reservoir has also been suggested (40). On the 3rd of July 2013 MERS-CoV became a notifiable disease in the Netherlands as happened in many other countries worldwide, in order to identify cases early and prevent transmission. In July 2013, the World Health Organization (WHO) International Health Regulations Emergency Committee determined that, at least at that moment in time, MERS-CoV did not meet criteria for a "public health emergency of international concern," but was nevertheless of "serious and great concern".

Outbreak of autochthonous Dengue virus on the island of Madeira, Portugal

In October and November 2012 an outbreak of Dengue virus occurred on the Portuguese island of Madeira. This was the first time autochthonous infections of Dengue virus were seen on Madeira. Also, it was the first epidemic of Dengue virus in Europe. In total 1357 cases were reported, of which 669 were confirmed. Eighty-nine cases were hospitalized (http://www.ecdc.europa.eu/en/publications/publications/dengue-outbreak-madeira-

Figure 2.7 General practice consultations for ILI (number/100,000 inhabitants), the Netherlands, seasons 2011-2012 and 2012-2013.



mission-report-nov-2012.pdf). Other European countries, not including the Netherlands, reported imported cases of Dengue virus infections in travellers to Madeira (41). The most effective vector for the transmission of the Dengue virus, the *Aedes aegypti* mosquito, has been present on the island since 2005. *Aedes aegypti* is not seen on the European mainland, although the climate of Southern Europe seems suitable for the mosquito (42). Another mosquito species, *Aedes albopictus*, which is a less effective vector for the transmission of the Dengue virus, has been found in 20 European countries. This mosquito is responsible for the autochthonous transmission of the Dengue virus from imported Dengue virus cases to persons who did not visit an endemic country (43, 44).

Outbreaks of vancomycin resistant *Enterococcus faecium* in 6 hospitals

During 2012, 6 outbreaks of vancomycin resistant *Enterococcus faecium* (VRE) were reported by 6 hospitals across the Netherlands. Enterococci are commensal bacteria of the human gut and are intrinsically resistant to most antibiotics. VRE are also resistant to vancomycin, considered a 'last-resort' agent, and usually also to aminoglycosides. VRE almost exclusively cause nosocomial infections, mostly in patients with prolonged hospitalization, especially in ICU, receiving enteral feeding, after liver or stem cell transplantation, and after extensive antibiotic-exposure. Based on findings from research using multi-locus sequence typing (MLST), almost all VRE hospital outbreaks in the world are caused by a specific clonal lineage that is also characterized by resistance to ampicillin. So-called ampicillin-resistant *Enterococcus faecium* (ARE), that are still susceptible to vancomycin, have emerged in Dutch hospitals during the last 10 years. The VRE outbreaks of 2012 may have been caused by pre-existing ARE subtypes that adopted a transposon with a vancomycin resistance gene (vanA or vanB) (45). *E. faecium* usually does not cause infections in healthy people, but is capable of doing so in immunocompromised patients, in which case it needs to be treated with antibiotics. Vancomycin is the most appropriate antibiotic to treat infections with antibiotic resistant enterococcus but VRE are less, or no longer sensitive to it. Alternative choices of antibiotics for VRE infections are linezolid and daptomycin. The theoretical possibility of horizontal transfer of the vancomycin resistance gene from VRE to multi-resistant *Staphylococcus aureus* (MRSA) was long considered a major threat, but the occurrence of such events appears to be very unlikely. The Dutch surveillance system for antibiotic resistant bacteria in institutions (ISIS-AR) has recorded a total of 7,152 clinical *E. faecium*-isolates in 2012 of which 6,102 were ARE (85%) and 127 (1.8%) were VRE. These proportions have been stable over time since 2008 when surveillance started (86% ARE and 1.4% VRE in 2008) (https://www.isis-web.nl/).

Influenza epidemic in the Netherlands

In 2012/2013 the Netherlands saw the most prolonged influenza epidemic of the past 25 years. The epidemic threshold of 51 cases of influenza like illnesses (ILI) per 100.000 inhabitants was reached in week 51 of 2012 (see Figure 2.7). The disease rate fell to below the threshold in week 16 of 2013, 18 weeks later. The epidemic started 10 weeks earlier than the much smaller, and shorter lasting epidemic of 2011/2012 (46). Most of the ILI cases in the 2012/2013 epidemic were caused by the influenza A H1N1pdm09 and H3N2 viruses, and by the influenza-B (Yamagata strain) virus. These had all been included in the 2012 influenza vaccine (47). Other European countries reported the same prevalent influenza strains (48, 49). A reason for the long duration of the epidemic in the Netherlands might be the fact that the winter was relatively cold and dry, which may have contributed to the survival of the influenza virus in aerosols, an important route of transmission.

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3 Developments in vaccination

J. Kemmeren / P. Bijkerk, L. Mollema and H.E. de Melker

3.1 Introduction

Vaccines are among the most effective interventions in modern public health medicine. In 1796, Edward Jenner used a vaccine against smallpox for the first time. Today, more than 70 vaccines have been licensed worldwide for use against approximately 25 pathogens (1, 2). In the Netherlands, population wide use of vaccinations in a national programme started in 1957. Overall, the programme has led to reduction of the target diseases, making them less visible in the population. Impact on the infectious disease dynamics will only be evident in the long run and will need continuous evaluation. Recently, vaccines against new target diseases have been included in the programme. Over the past decades progress has been made in technical opportunities for vaccine development. The aim of this chapter is to give an overview of the current status and state of the art regarding vaccination and vaccination programmes focusing on the Netherlands. First, we summarize the current use of vaccines, which protect not only the individual but also the population at large (paragraph 3.2). We will give an overview of the interaction between host, pathogen and population and of the developments in society in relation to vaccination (paragraphs 3.3 and 3.4), since these factors contribute to the impact of vaccination. Finally, aiming to address possible future perspectives, we describe the progress in vaccine and vaccination programme development (paragraphs 3.5 and 3.6).

3.2 Overview of vaccination programmes and other use of vaccines

Below we describe briefly the aim and target group, content, coordination and organization and financial aspects of both the programmatic vaccination (National Immunization Programme, National Influenza Prevention Programme, specific risk group vaccination programmes against Hepatitis B and tuberculosis) and individual based vaccination options. More detailed information on each of these programmes can be obtained from referenced publications (3, 4). In paragraph 3.6, an overview is given of the registered vaccines in the Netherlands with their indication and target group.

3.2.1 National Immunization Programme

Since 1957, Dutch infants and children have been offered vaccination against infectious diseases, free of charge and on a voluntary basis through the National Immunization Programme (NIP). The overall aim of the programme is to protect the society against serious infectious diseases

Table 3.1 Current vaccination schedule of the NIP.

Age of child	Vaccination*
At birth**	HBV
2 months	DTaP-HBV-IPV/Hib + pneumo
3 months	DTaP-HBV-IPV/Hib + pneumo
4 months	DTaP-HBV-IPV/Hib + pneumo
11 months	DTaP-HBV-IPV/Hib + pneumo
14 months	MMR + MenC
4 years	DTaP-IPV
9 years	DT-IPV + MMR
12 years***	HPV

* HBV, Hepatitis B virus vaccine; DTaP-HBV-IPV, diphtheria-tetanus-acellular pertussis-Hepatitis B virus-inactivated poliovirus vaccine; Hib, conjugated *Haemophilus influenzae* type B vaccine; pneumo, 10-valent pneumococcal conjugate vaccine; MMR, measles-mumps-rubella vaccine; MenC, Conjugated Meningococcal C vaccine; DTaP-IPV, diphtheria-tetanus-acellular pertussis-inactivated poliovirus vaccine; DT-IPV, diphtheria-tetanus-inactivated poliovirus vaccine; HPV Human papillomavirus vaccine.
** Only for children born to mothers who tested positive for HBsAG.
*** Only for girls, three doses of HPV vaccine.

through vaccination. Initially, target diseases included only diphtheria, whooping cough, tetanus and poliomyelitis. Later, the programme was extended with vaccination against measles, rubella, mumps, hepatitis B (the latter first only for risk groups but since 2011 as universal infant vaccination), invasive infection by *Haemophilus influenzae* type b, serogroup C meningococcal disease and invasive pneumococcal disease. In 2009, the NIP was extended with human papillomavirus (HPV) vaccination for teenage girls (5). The Minister of Health makes decisions to include new vaccines in the NIP based on the advice of the Health Council of the Netherlands. The Health Council of the Netherlands developed a set of criteria to review scientific data in order to assess whether a vaccine should be part of the NIP (6) (see also paragraph 3.6). Table 3.1 gives an overview of the current vaccination schedule of the NIP. The costs are paid from public funding, through the AWBZ, the Exceptional Medical Expenses Act ('Algemene Wet Bijzondere Ziektekosten').

NIP organization

The vaccinations of the NIP are delivered through child health care for children 0-4 years old at baby well clinics ('consultatiebureaus') and for 5-19-year-olds at Public Health Services (PHS). The implementation of the NIP is carried out by many organizations: home care ('thuiszorgorganisaties'), Public Health Services, children's centres ('Centra voor Jeugd en Gezin'), obstetric practitioners, paediatricians and general practitioners. Since 2005, the Centre of Infectious Disease Control of the National Institute of Public Health and the Environment (RIVM) is responsible for management of the programme (NIP Programme management).
RCP/IOD ('Regionale Coördinatie Programma's – Inkoop, Opslag en Distributie') coordinates the implementation of the national vaccination programmes: they procure, store and distribute the necessary vaccines and immunoglobulins and take care of the vaccination database Praeventis.

Epidemiology, mortality and morbidity of NIP target diseases

In the first half of the 20th century, vaccine preventable diseases caused high morbidity and mortality, especially in children. In the 30s, mortality and morbidity in children started to decline. The main reasons for this were the availability of safe potable water, improvement in sanitation, construction of sewage, improvement of the nutritional status, better housing conditions and improvement of hygiene measurements in the production of food.
After introduction of vaccination programmes in the 50s, the mortality and morbidity in children declined further. The burden of disease of poliomyelitis decreased dramatically after introduction of the poliomyelitis vaccination in 1957. Since the introduction of the poliomyelitis vaccination there were several small outbreaks in the 60s and 70s. The last 2 epidemics occurred in 1978 (110 cases) and 1993 (71 cases) in people who refuse vaccination on religious grounds (7).
Due to vaccination, the number of deaths from diphtheria dropped to zero. For diphtheria only sporadic import cases are reported, and so the burden virtually disappeared.
Tetanus is a rare disease nowadays, with only a few cases in elderly persons who were not eligible for vaccination earlier and did not receive proper tetanus post-exposure prophylaxis being wounded.
Deaths from pertussis declined from 1000 cases each year to almost zero after introduction of universal vaccination in 1957. However, pertussis remains an endemic disease in the Netherlands and since 1996 epidemics occur every 2 to 3 years. From 1996 till 2012 13 deaths have been registered,

almost all among infants too young to be vaccinated.
After the introduction of the vaccination against measles, the number of measles cases declined from 2500 each year to just a few cases. However, large outbreaks of measles continue to occur in unvaccinated population subgroups. In an outbreak in 1999/2000, three children died as a result of measles virus infection (8). The incidence of measles and rubella is generally lower than 1 per 1,000,000 inhabitants per year. In 2013, another large measles outbreak started among orthodox protestant groups with low vaccination coverage. In October 2013 over 1600 cases and one death had been reported (9). In 2004/2005 a rubella outbreak occurred in the same group; 32 pregnant women were infected and 9 cases of babies with congenital disorders associated with congenital rubella syndrome were born (10, 11).
Before vaccination against mumps, yearly 300 to 800 children were hospitalized with mumps meningitis. In recent years the number of hospitalizations due to mumps amounted between 2 (1999) and 44 (2008). In 2009, when mumps became notifiable, an outbreak of mumps started among mostly adequately vaccinated students. The outbreak peaked in 2011, but is still continuing at low level into 2013. It was most likely caused by a combination of waning of vaccine induced immunity and intense exposure (12, 13).
The introduction of vaccination against *Haemophilus influenzae* type b in 1993 had a clear effect on the disease in children; it decreased from 294 cases in 1991 to 30 cases in 1996.
Introduction of vaccination against meningococcal C in 2002 has strongly decreased the number of cases: from 285 in 2001 to 2 in 2012.
The introduction of vaccination against pneumococcal disease in 2006 has led to a considerable reduction in the number of invasive pneumococcal disease cases in the vaccinated cohorts. A reduction was also observed in elderly people. Although the reduction of vaccine types has been partly counterbalanced by an increase of non-vaccine type invasive pneumococcal disease, the overall incidence is lower than in the pre-vaccine area.

Universal vaccination against hepatitis B has been implemented in 2011. Before 2011 only high-risk children and behavioural risk groups among adults were vaccinated against hepatitis B in the NIP: children with one or two parents from endemic countries and children of mothers chronically infected with hepatitis B virus (HBV). Since in the Netherlands most HBV infections are acquired at adult age, the impact of infant vaccination is not yet visible.

Coverage

The coverage of the NIP has been high from the beginning. A major reason for the high vaccine coverage is the organization of vaccination through children's clinics and youth health departments of Public Health Services (PHS). Furthermore, in the Netherlands there is a linkage between the vaccination registry and the population register (GBA) (14).
At present, the average participation for all vaccinations included in the NIP is 92 to 99%. Exception is the participation for HPV vaccination against cervical cancer (58%) (15). There are clear geographical differences. For example, in parts of the country with high numbers of orthodox reformed Christians, some of whom have principled objections to vaccination, the vaccination rate is well below the national average. The orthodox reformed Christians are socio-geographically clustered and are therefore at risk of epidemics such as currently observed for measles (9). More information on the acceptance of vaccination is given in paragraph 3.4.

Procured vaccines

The number of vaccines, which were procured for the national immunization programme over 2010 to 2012, is shown in Table 3.2. Vaccines are procured by RCP/IOD (see Textbox).

TEXTBOX

RCP/IOD coordinates the implementation of the National Immunisation Programme and two national perinatal screening programmes. It takes care of the supply of vaccines for the national influenza prevention programme, the hepatitis B vaccination programme for risk groups, tuberculosis vaccination programme, pandemic flu resources, and other national amenities. The department procures the vaccines and immunoglobulins. It manages the stocks of these materials and distributes them to the field organisations responsible for the actual delivery of the programmes. It records and reports on the uptake rate for screening and vaccination. The department also maintains a stock of less common vaccines and serums (the National Serum Depot) for use in case of an emergency, like treatment after bites by snakes, scorpions or spiders.

Table 3.2 The number (#) of different vaccines, which were procured for the National Immunization Programme by RIVM-RCP/IOD from 2010 through 2012 (Source: 'Nacalculaties AWBZ met accountantsverklaring 2010 t/m 2012').

Vaccine*	2010 # of vaccines	2011 # of vaccines	2012 # of vaccines
DT-IPV	200,952	196,589	193,532
DTaP-IPV	199,029	179,404	178,269
DTaP-IPV/Hib	577,959	492,302	74,081
DTaP- HBV-IPV/Hib	158,105	221,661	616,378
Hepatitis B	9,299	9,251	8,217
MenC	206,057	185,267	182,687
MMR	404,256	377,589	372,354
HPV	n/a	184,314	187,153
Pneumo	735,332	713,660	689,194

* HBV, Hepatitis B virus vaccine; DTaP-HBV-IPV, diphtheria-tetanus-acellular pertussis Hepatitis B virus-inactivated poliovirus vaccine; Hib, conjugated *Haemophilus influenzae* type B vaccine; Pneumo, 10-valent pneumococcal polysacchagaride conjugated vaccine; MMR, measles-mumps-rubella vaccine; MenC, Conjugated Meningococcal C vaccine; DTaP-IPV, diphtheria-tetanus-acellular pertussis-inactivated poliovirus vaccine; DT-IPV, diphtheria-tetanus-inactivated poliovirus vaccine; HPV Human papillomavirus vaccine.

3.2.2 National Influenza Prevention Programme

Next to the National Immunization Programme for childhood vaccination, the Dutch National Influenza Prevention Programme (NPG) was established in 1997. The aim of this programme is to protect people from complications and death from influenza. People at risk are invited by their general practitioner for a free of charge vaccination. The target population, as defined by the Health Council of the Netherlands, is people at the age of 60 years or older, and all individuals of 6 months or older with certain medical conditions (i.e. cardiovascular diseases, diabetes mellitus, lung diseases, serious kidney conditions, and poor resistance due to other illnesses or medical treatment such as chemotherapy).The costs are paid for by the Ministry of Health, Welfare and Sport (Rijksbegroting; Subsidieregeling Publieke Gezondheid). Since 1997, the 'Stichting Nationaal Programma Grieppreventie (SNPG)' coordinates the implementation of the programme. Procurement, storage and distribution are done by RCP/IOD. The National Institute of Public Health and the Environment is responsible for management of the programme.

Epidemiology, burden and mortality of influenza

Seasonal incidences on influenza like illness (ILI) are available from the sentinel network of general practitioner. They ranged from 87 / 10.000 inhabitants – 221 / 10.000 inhabitants in the period 2002 – 2012. The incidence of ILI consultations has declined over the last two decades (16). Assessing the impact of seasonal influenza is complicated, because in the large majority of patients with influenza-like illness no laboratory test is done. Therefore, virology data based on selective sampling in a GP sentinel surveillance for ILI is used to estimate what the proportion of ILI is associated with influenza virus. Seasonal influenza mortality estimates are also based on statistical models in which part of the excess of all-cause mortality during influenza epidemics is attributed to influenza. In a study by Van den Wijngaard et al. annual influenza-attributed deaths were estimated by age category for seasonal influenza from 1999 through 2009. The total number of influenza-attributed deaths ranged from 87 – 3,634 per year. The average number over 10 seasonal influenza years was 1,956 deaths (17). In the Netherlands, there is no registry available for hospitalizations and deaths associated with influenza (3).

Coverage

In 2012, 62.4% of the target population was vaccinated against influenza, which is 19.8% of the total Dutch population. The vaccination rate of people with diabetes mellitus is 76.3%, of people with cardiovascular diseases 74.5% and of people with lung diseases 66.4% (http://www.rivm.nl/dsresource?objectid=rivmp:218698&type=org&disposition=inline). The overall vaccination coverage is declining, especially in the age group of 60 to 65 years: from 56.2% in 2011 to 49.8% in 2012. Nevertheless, the coverage of seasonal influenza vaccination in the Netherlands remains high compared to other European countries (18).

Procured vaccines

The number of vaccines, which were procured for the National Influenza Prevention Programme over 2010 to 2012, is shown in Table 3.3.

Table 3.3 The number (#) of influenza vaccines, which were procured for the National Influenza Prevention Programme by RIVM-RCP/IOD from 2010 through 2012 (Source: SNPG jaarverslag 2012 en rekentool CvB).

Vaccine	2010 # of vaccines	2011 # of vaccines	2012 # of vaccines
Influenza	3,789,930	3,628,472	3,490,841

Table 3.4 The number (#) of vaccines, which were procured for the hepatitis B risk groups programme by RIVM-RCP/IOD from 2010 through 2012 (Source: SAP).

Vaccine	2010 # of vaccines	2011 # of vaccines	2012 # of vaccines
Hepatitis A/B	4,660	3,079	2,980
Hepatitis B	16,990	10,960	9,390

3.2.3 Hepatitis B vaccination for specific risk groups

Outside the NIP, several groups are targeted for HBV vaccination in the Netherlands, including health care workers, certain patient groups and individuals who are at risk due to their behaviour patterns. In 2002, selective vaccination of behavioural high risk groups was started, including men having sex with men (MSM), commercial sex workers (CSW) heterosexuals with frequent partner change and drug users. Currently, only MSM and CSW are targeted within this programme. Vaccination of drug users is now provided through drug treatment services. From 2009, RIVM has been responsible for coordination of the programme, in cooperation with GGD Nederland and Soa Aids Nederland. This programme is funded by the Dutch Ministry of Health.

Epidemiology, burden and mortality of hepatitis B

In 2012, 1,513 cases of hepatitis B virus (HBV) infection were notified. Of these, 1,317 (87%) were chronic infections, 171 (11%) acute and 25 had an unknown status. The incidence of notified acute HBV infections dropped in 2011 to an all-time low level since hepatitis B could first be diagnosed. This decrease is mainly attributable to a decreasing number of cases reported in men who have sex with men. The number of cases with no information on risk exposure also declined (4, 15). There was, however, a small increase in the number of notified acute HBV infections in 2012.

Coverage

From 1998 to 2011, about 105,000 individuals received at least one HBV vaccination within the programme. Of these, one-third were MSM. 73.7% of the HBV-susceptible MSM completed the series of three doses (19). Modelling of HBV transmission among MSM in the Netherlands estimated that, with a vaccination coverage of 2% per year, the HBV incidence among MSM could be halved in 10 years if specifically MSM at high-risk for HBV were vaccinated (20). The number of reported cases in MSM was halved in 9 years of programmatic HBV vaccination. This suggests that the programme is successful in reaching high-risk MSM (19).

Procured vaccines

The number of vaccines, which were procured for the national hepatitis B risk group vaccination programme over 2010 to 2012, is shown in Table 3.4. Hepatitis B vaccination given in the NIP is given in Table 3.2.

3.2.4 Tuberculosis vaccination for specific risk groups

In the Netherlands, vaccination against tuberculosis is indicated for children younger than 12 years of age, born in the Netherlands, of whom at least one parent originates from a country with a high incidence of tuberculosis (more than 50 tuberculosis cases per 100,000 inhabitants per year).
This is related to the expected regular visits to the country of origin of the parent(s). Such children receive an invitation from the Public Health Services for the BCG vaccination between the sixth and twelfth month of their life. The KNCV Tuberculosis Foundation provides the national guideline 'Tuberculosis BCG vaccination'. The starting point to determine the country incidence is based on the WHO estimation or the registered incidence. For some countries or areas there are no official WHO figures available and the incidence is estimated based on the incidence in neighbouring countries. For removing or adjusting the indication, the condition of an incidence below 50 cases per 100,000 inhabitants has to be met for a continuous period of at least two years.

Epidemiology, burden and mortality of tuberculosis

In 2012, in the Netherlands, the total number of notified TB patients dropped to 958. The number of tuberculosis

Table 3.5 The number (#) of BCG vaccines which were procured for the tuberculosis risk groups programme by RIVM-RCP/IOD from 2010 through 2012 (Source: SAP RCP/IOD).

Vaccine	2010 # of vaccines	2011 # of vaccines	2012 # of vaccines
BCG	6,051	5,458	4,660

patients has declined with 32% in the last 10 years. The majority (73%) concerns immigrants (http://www.rivm.nl/dsresource?objectid=rivmp:218822&type=org&disposition=inline).

Procured vaccines
There is no data available on uptake or coverage of BCG vaccination. However, the number of vaccines, which were procured for the BCG vaccination strategy are available and are shown in Table 3.5 for the years 2010-2012.

3.2.5 Preventive vaccination for health care workers

Because of their contact with patients or infective material from patients, many health-care workers (HCWs) (e.g., physicians, nurses, emergency medical personnel, dental professionals and medical and nursing students, laboratory technicians, hospital volunteers and administrative staff) are at risk of exposure to and possible transmission of vaccine-preventable diseases. Maintenance of immunity is therefore an essential part of prevention and infection control programmes for HCWs. Optimal use of immunizing agents safeguards the health of HCWs and protects patients from becoming infected through exposure to infected HCWs. Consistent immunization programs could substantially reduce both the number of susceptible HCWs in hospitals and health departments, and the attendant risks for transmission of vaccine-preventable diseases to other HCWs and patients. Any medical facility or health department that provides direct patient care is encouraged to formulate a comprehensive immunization policy for all HCWs (http://www.cdc.gov/mmwr/preview/mmwrhtml/00050577.htm). In addition to HCWs in hospitals and health departments, these recommendations apply to those in private physicians' offices, nursing homes, schools, day-care facilities and laboratories, and to first responders.
No consistent / systematic information is available about the coverage of these recommendations. For influenza, coverage of health care workers in general hospitals in 2010 was only 17.7% (21). The Health and Safety Act ('Arbowet') prescribes that each employee with a risk to develop an infectious disease through work should be protected by vaccination and that the employer has to carry the costs of the offered vaccination.

3.2.6 Travel vaccination

People who are travelling outside the Netherlands may need to be (re)vaccinated against some of the serious diseases that are found in other parts of the world. These vaccines can be divided into three categories: routine, recommended, and required. Routine vaccines are necessary for protection from diseases that are still common in many parts of the world; even though they rarely occur in the Netherlands. Recommended vaccines will protect travellers from illnesses present in other parts of the world and prevent the importation of infectious diseases across international borders. Which vaccinations are recommended depends on a number of factors including the destination, duration of travel, whether the traveller will be spending time in rural areas, intended type and intensity of interaction or contact with the local population, the season of travelling, age, health status and previous immunizations. The only vaccine required by International Health Regulations is yellow fever vaccination for travel to certain countries in sub-Saharan Africa and tropical South America. Meningococcal vaccination is required by the government of Saudi Arabia for annual travel during the Hajj. The Dutch National Coordination Centre for Travellers Health Advice ('Landelijk Coördinatiecentrum Reizigersadvisering (LCR)') provides the national guidelines on vaccinations and other preventive interventions such as anti-malaria measures, and disseminates these to Public Health Services, travel clinics and general practitioners performing travel vaccinations. In the Netherlands, there are over a 100 large travel vaccination clinics that purchase vaccines directly from vaccine manufactures. Additionally, vaccines are described by GP's and hospitals and are delivered through pharmacies. For commercial reasons, vaccine producers do not provide sales data on their traveller's vaccines. SFK (Foundation for Pharmaceutical Statistic, The Hague) registers the number of all vaccines delivered by pharmacies (see paragraph 3.2.9).

Vaccinations given at travel clinics
In order to gain insights into vaccine use in travellers we sent a small questionnaire to all travel clinics at the 25 Public Health Services (PHS) in the Netherlands. In this questionnaire, we asked for information on the number of vaccines given in 2012. We also asked to obtain the number of residents living in the PHS region. Because PHSs are not the only organisations to have travel clinics,

Table 3.6 Number (#) of travel vaccines given, reported by 20 of 25 Public Health Services in the Netherlands in 2012.

The reported number of inhabitants of the 20 PHS regions was 10,930,396. The 20 PHS reported to have 54 locations in which they provide travel vaccinations.

Vaccine	2012 # total of vaccines
DT-IPV	70,974
Früh Sommer Meningo-Encephalitis (child dose)	216
Früh Sommer Meningo-Encephalitis (adult dose)	1,063
Hepatitis A (child dose)	11,714
Hepatitis A (adult dose)	70,180
Hepatitis A/B (child dose)	10,855
Hepatitis A/B (adult dose)	28,621
Hepatitis B (child dose)	1,339
Hepatitis B (adult dose)	22,398
Japanese Encephalitis	255
Meningococcal ACWY	4,208
MMR	2,647
Rabies	10,051
Typhoid fever	36,373
Yellow fever	25,496

Table 3.6 does not provide a national overview. Twenty of the 25 PHS returned the questionnaire. The total number of inhabitants of the 20 PHS regions is 10,930,396. The 20 PHS reported to have 54 locations in which they provide travel vaccinations.

3.2.7 Prescribed vaccines in primary health care

We obtained Dutch data of vaccine use in primary health care from the SFK (foundation for pharmaceutical statistics, The Hague). The SFK collects data from 95% of the Dutch community pharmacies (serving 91.5% of the Dutch population) and extrapolates their data to 100%. The data are expressed in the number of prescriptions. Data are presented in Table 3.7 as the number of prescriptions per vaccine per year. From the data it is not clear whether a prescription stands for a complete immunization (for example three vaccine doses for hepatitis B) or for one vaccine. Furthermore, it is not registered why the vaccine was actually prescribed. Some of the vaccines are given in the context of travelling (i.e. yellow fever), in case of an injury, or to protect groups of patients with underlying medical conditions. Vaccines given in national vaccination programmes are not included in the SFK but are reported as above procured by the RCP/IOD.

3.2.8 Rabies vaccination after high-risk exposure

In the Netherlands, bats can be infected with rabies virus related EBLV-1 and EBLV-2, which potentially can infect humans and cause rabies. People who professionally may be exposed to bats are eligible for preventive vaccination. Volunteers participating in bat working groups should also be given pre-exposure prophylaxis. Persons, who have been potentially infected by bites or scratches from bats in the Netherlands, or by (potential) rabid animals outside the Netherlands, for example during holidays, are entitled to get rabies post-exposition prophylaxis. This means a vaccination course of 5 vaccines, with, depending on the type of wound, human anti-rabies immunoglobulins (MARIG).

Epidemiology, burden and mortality of rabies

Since 1962, 4 cases of human rabies were notified. All patients got sick after bite incidents abroad. In 2007 a Dutch woman died after a bat bite in Kenya (22). In 2013 a Dutch man died after being infected through a rabid dog in Haiti. None of the patients had received pre-exposure vaccination. The patients from 2007 and 2013 did also not receive post-exposure treatment in the respective countries. All four patients subsequently died.

Table 3.7 Use (in number of prescriptions #) of different registered vaccines in the Netherlands in primary health care from 2010 through 2012 (Source: SFK).
n/a: data not available.

Vaccine	2010 # of prescriptions	2011 # of prescriptions	2012 # of prescriptions
BCG	4	3	3
Cholera	169	78	124
DT-IPV	74,758	65,084	57,872
DTaP-IPV	339	258	416
DTaP-IPV-Hib	132	276	521
DTaP-IPV-Hib-HepB	110	129	160
FSME	722	858	894
Hib	2,108	2,159	2,204
Hepatitis A	118,992	99,448	84,366
Hepatitis A/B	28,191	26,991	23,591
Hepatitis B	24,771	26,612	25,451
Influenza	17,290	14,077	10,467
Japanese Encephalitis	n/a	102	134
Meningococci ACWY	n/a	608	762
Meningococci C	1,528	1,468	1,462
MMR	2,237	2,051	2,451
Human Papillomavirus type 16/18	426	207	224
Human Papillomavirus type 6/11/16/18	1,731	1,046	1,023
23-valent non-conjugated Pneumococci	5,501	5,484	5,566
7, 10 and 13-valent conjugated Pneumococci	489	675	750
Poliomyelitis	89	80	65
Rabies	2,374	2,562	2,787
Tetanus	75,737	80,323	84,122
Typhoid fever oral	2,374	2,563	2,787
Typhoid fever parental	28,087	27,491	21,348
Varicella	208	210	266
Varicella Zoster	35	26	23
Yellow Fever	6,189	6,559	6,435

3.2.9 Post-exposure tetanus vaccination for injuries

Treating physicians may give a dose of tetanus toxoid-containing vaccine in the case of an injury. The need for tetanus post-exposure prophylaxis (i.e. vaccination and immunoglobulin) were reviewed by the Health Council in 2003 and is based on the vaccination history of the patient and whether they were eligible for the NIP based on their age (23).

Epidemiology, burden and mortality of tetanus

Tetanus is a rare disease in the Netherlands, with only some cases in elderly persons who were not eligible for vaccination in the past.

Coverage

No accurate information is available on the coverage of tetanus vaccination in case of an injury. From Table 3.8 it is clear that tetanus vaccination is one of the vaccines often prescribed through prescription. Furthermore, a recent study on use of guidelines of post-exposure tetanus prophylaxis reported that both GPs and Emergency Departments regularly administer tetanus vaccination in their daily practice (24).

Key points of overview of vaccination programmes and other use of vaccines

- After introduction of the National Immunization Programme mortality and morbidity on target diseases declined further.
- Many vaccines in the Netherlands are distributed through programmatic prevention programmes, including National Immunization Programme, National Influenza Prevention Programme, (tuberculosis) vaccination for specific risk groups, and hepatitis B for behavioural high risk groups.
- In addition to these programmes vaccines are used in case of specific risks like travelling, injury, and bite incidents by rabid animals. Vaccines are also used for employees and health care workers.
- Monitoring of vaccine coverage among target populations is only routinely carried out for programmatic vaccination. Uptake of other vaccines in e.g. travellers, employees, medical risk groups and outpatients, is largely unknown.

3.3 Interaction between host, pathogen and population in relation to vaccination

In population-wide vaccination programmes such as the NIP, the interplay between host, pathogen, vaccine and population determines the eventual impact of vaccination on population level. After a concise introduction about immunity and how vaccines work, we give below a short overview of relevant concepts with potential impact on long-term effects of population-based vaccination programmes and examples of their impact on the occurrence of vaccine-preventable diseases included in routine vaccination programmes. In addition, other factors that may affect the impact of the vaccination programme, such as the occurrence of adverse events and non-specific effects, will be described.

3.3.1 Immunity and how vaccines work

Immunity can be defined as the ability of the human body to protect itself from infectious disease. Immunity involves a non-specific and an adaptive component. Non-specific immunity, or innate immunity, is the natural resistance with which a person is born. This system is important for the first line of defense against micro-organisms but does not confer long-lasting immunity against a pathogen. For the second line of defense the adaptive immunity is allowed for a stronger immune response as well as for immunological memory, where a specific pathogen is "remembered" by a signature antigen (25). Adaptive immunity is often sub-divided into two major types, depending on how the immunity was introduced. Naturally acquired immunity occurs through contact with a disease causing agent, when the contact was not deliberate, whereas artificially acquired immunity develops only through deliberate actions such as vaccination (26).

The adaptive immune system may be divided into two main parts: humoral immunity, which is involved in specific antibody production, and cellular immunity, with white blood cells that are able to deal with infected body cells or indirectly help other immune cells. The antibodies produced by differentiated B-cells, plasma cells, will bind to the specific pathogens which subsequently will be removed by innate immune cells.

The immune system uses several defence mechanisms. Blood contains white or immune cells, for eliminating pathogens. These white cells consist primarily of B-lymphocytes, T-lymphocytes, granulocytes and macrophages (25, 27):

- Phagocytes (granulocytes and macrophages) are white blood cells that identify and eliminate pathogens, either by attacking larger pathogens through contact or by engulfing and then killing micro-organisms. Macrophages also act as antigen-presenting cells that activate the adaptive immune system. The macrophages leave behind parts of the pathogen, i.e. antigens.
- Antibodies attack the antigens left behind by the macrophages. Antibodies are produced by defensive white blood cells i.e. B-lymphocytes.
- Several T-lymphocytes are another type of defensive white blood cells.

The first time the body encounters a pathogen, it can take several days to make and use all the mechanisms needed to get over the infection. After the infection, the immune system remembers what it had learned about how to protect the body against that disease. The body keeps a certain low level of T- and B-lymphocytes, called memory cells that go into action quickly if the body encounters the same pathogen again. Altogether the body is able to react much faster in comparison with a first time of encounter (27). Vaccines are designed to provide immunity similar to that induced by the natural disease-causing pathogen but without causing the disease. Vaccination helps to

stimulate and strengthen the immune system to produce T-lymphocytes and antibodies, and to generate long lasting immunity. Immunological memory by 'memory'-T-lymphocytes and B-lymphocytes allows the immune system to recognise and respond stronger and more rapidly to natural infection upon exposure and to prevent or limit the effect of that disease. Vaccines are made from inactivated (killed) or attenuated live organisms, purified secreted products, recombinant components, purified proteins or synthesised peptides (part of proteins). Vaccines must contain sufficient antigenic mass to stimulate a desired response. Some vaccines provide life-long protection against disease, some provide partial protection and some must be re-administered at regular intervals to provide protection (28).

3.3.2 Concepts in vaccinology

Vaccine efficacy and vaccine effectiveness

Vaccine efficacy is defined as the reduction in the incidence of a disease among people who have received a vaccine, compared to the incidence in unvaccinated people. Vaccine efficacy differs from vaccine effectiveness: vaccine efficacy is measured in randomized controlled trials and shows how effective the vaccine could be given ideal circumstances and 100% vaccine uptake in the target group; vaccine effectiveness is measured in observational studies and measures how well a vaccine performs in reducing diseases when used in routine circumstances in the community (29). From public health perspective vaccine effectiveness data are preferred, although it can be difficult to distinguish vaccine-related effects from non-vaccine related factors that affect outcomes of vaccine effectiveness analyses (30).

Primary vaccine failure

Primary vaccine failure occurs when a vaccination does not result in a predetermined immune response, which is assumed to correlate with protection in the vaccinated person. If such an individual gets infected, this is defined as a primary vaccine failure. Reasons for primary vaccine failure can be manifold and may be host-related (i.e. immune deficiency, insufficient or suboptimal immune response, age-related maturation and senescence of immune responsiveness, interference due to other infectious agents, immunological interference) or vaccine-related (vaccine is not 100% efficacious, incomplete coverage of strains or serotypes, antigenic interference or manufacturing-related) (31, 32).

Secondary vaccine failure

Secondary vaccine failure occurs when following an adequate initial immune response, the immunological response of a vaccinated person has declined over time to below a level that confers protection ('waning immunity'), for example because (natural) boosting was needed but did not occur. If infection occurs following an initial adequate response, this is defined as secondary vaccine failure. While antibody levels generally decline over time, a more rapid loss of immunity below protective levels than expected for that vaccine can be considered secondary vaccine failure. Whether protection remains intact is also dependent on the total immune mechanism involved, i.e. role of innate and cellular immunity in addition to humoral immunity (31).

Failure to vaccinate

Failure to vaccinate occurs when an indicated vaccine was not administered appropriately for any reason. This may be caused by usage issues (administration errors, vaccination series incomplete, non-adherence with recommended schedule including lack of recommended booster vaccination(s), storage-related, vaccine beyond expiry date when used) or by immunization programme-related issues (suboptimal recommendations regarding number and time points of vaccinations, shortage of vaccine leading to no or incomplete vaccination) (31, 33).

Matching of vaccine and circulating strains

Vaccines are likely to be most effective when there is a good match between the circulating pathogen strain and the strain used in the vaccine. Mismatching of vaccines and circulating strains may be due to escape mutation. For example, the current upsurge in pertussis may also be partly explained by the presence of mutations in circulating strains (34). For influenza vaccines it is known that it requires periodical replacement of viral antigens in order for the vaccines to keep matching the constantly evolving influenza viruses. Twice annually, WHO organises consultations with an advisory group of experts to analyse influenza virus surveillance data generated by the WHO Global Influenza Surveillance and Response System (GISRS), and issues recommendation on the composition of the influenza vaccines for the following influenza season. These recommendations are used by the national vaccine regulatory agencies and the pharmaceutical companies to develop, produce, and licence influenza vaccines (35).

Serotype replacement

Serotype replacement is defined as an increase in prevalence of non-vaccine serotypes after broad-scale vaccine introduction, which may lead to a reduction of the benefits of vaccination. For example, the pneumococcal population has changed since widespread introduction of multivalent pneumococcal heptavalent pneumococcal conjugate vaccine (PCV7). This vaccine targets seven of the more than 92 serotypes ("vaccine types") of *Streptococcus pneumonia*. After introduction of PCV7, non-vaccine types have increased among asymptomatic carriers, and to a

lesser extent, non-vaccine types have increased as causes of invasive pneumococcal disease. Although the reported magnitude of this increase of non-vaccine types has been relatively modest in most countries, such changes have the potential to dampen the overall public health benefit of the vaccine (36).

Unmasking

Unmasking is an apparent increase in disease due to non-vaccine types when the vaccine types disappear because of vaccine-induced immunity and thereby stop 'masking' the types not included in the vaccine. So, the reduction in prevalence of vaccine types by vaccination has made it easier to detect non-vaccine types present in the population but undetected in the absence of vaccination. In some instances, this may lead to overestimation of the overall impact of vaccination. (37, 38).

Cross-protection

Cross protection means that immunization with a certain vaccine type provides clinically significant protection against infection or disease (or both) due to other serotypes. Data on HPV vaccination for example strongly suggest that both the bivalent and quadrivalent vaccine can have a variable level of cross protection against HPV serotypes genetically and antigenically-closely related to vaccine serotypes (39).

Herd immunity

Herd immunity (or community immunity) describes a form of immunity that occurs when the vaccination of a significant portion of a population (or herd) provides a measure of protection for individuals who have not developed immunity (40). Herd immunity theory proposes that, in contagious diseases that are transmitted from individual to individual, chains of infection are likely to be disrupted when large numbers of a population are immune or less susceptible to infection. The greater the proportion of individuals who are resistant, the smaller the probability that a susceptible individual will come into contact with an infectious individual (41). Based on the herd immunity concept, the elimination of an infectious disease from a population can be achieved even if it is not possible to vaccinate the entire population (42). The relationship between transmission dynamics of an infectious disease and herd immunity is the key to an effective control programme for universal vaccination. Herd immunity can be achieved by universal vaccination against infections that are transmitted directly from person to person (such as measles, pertussis, and poliomyelitis). On the contrary, for those infections that are not transmitted from person to person and when humans are not the single reservoir for disease (tetanus), the concept of herd immunity does not apply.
Most of the initial theoretical work is based on the concept of 'herd immunity threshold', which assumes that vaccines induce solid immunity against infection in a randomly mixed population (43). The key determinant is the basic reproduction number Ro, which is the average number of susceptible individuals which each infected individual will infect in a population without immunity against the disease. In order to eliminate an infection (or eradicate a disease) the proportion of immune individuals in a population should then be equal to or greater than (1-1/Ro). For example, if a person in a naive population infects four individuals, vaccine coverage should be 75% to prevent outbreaks in this population. However, recent work further developed the theoretical concept of herd immunity and added the complexities of imperfect immunity, heterogeneous populations, non-random vaccination, and unvaccinated individuals. Groups that are highly interconnected will dominate transmission, resulting in a higher value of Ro and therefore requiring a larger vaccination threshold.

3.3.3 Concepts applied to (current) vaccinations

Although by far not exclusive, the above mentioned concepts and their interactions determine to what extent a vaccine will be successful or not in reducing incidence and morbidity of a specific infection. The best vaccination efforts have been able to either eradicate (wipe out worldwide) or eliminate (eradicate within national or regional boundaries) a given disease, such as the eradication of smallpox and the progress in eradication of polio and in elimination of measles and congenital rubella. On the other hand, the presence of other factors may lead to the (re)occurrence of vaccine-preventable diseases. Examples are mumps and pertussis which remain endemic diseases with epidemic peaks, despite vaccination.

Eradication of smallpox

Smallpox was officially declared eradicated in 1980 (44) - a feat that remains one of the greatest public health triumphs to date. As smallpox is the only infectious disease that has been eradicated, the smallpox vaccination campaign was exceptional in many ways. The circumstances surrounding this disease and the vaccine were unique, and it should not be taken for granted that future vaccination programmes will be able to duplicate this success.
Smallpox was a good candidate for eradication by vaccines for several reasons. It was represented by only a single strain, it lacked an environmental reservoir, and the symptoms of disease were easy to identify. Moreover, the smallpox vaccine was inexpensive, large groups of people could be immunized in a short time, it could be manufactured in the field, and post-exposure prophylaxis was possible (45).

Progress in eradication of poliomyelitis and in

elimination of measles

Poliomyelitis has been eliminated from most countries. Three countries remain endemic for indigenous transmission of wild polio virus: Nigeria, Pakistan and Afghanistan. Additionally, in 2013 the Horn of Africa was affected by an outbreak of wild polio virus, with cases confirmed in Kenya, Somalia and Ethiopia. Because of the routes of poliovirus spread in previous Horn of Africa outbreaks, neighbouring countries are considered at high risk of re-infection (46). Furthermore, in 2013 wild poliovirus type 1 was again isolated from sewage samples in Israel. Israel has been free of indigenous wild polio virus transmission since 1988 (47). Recently wild poliovirus type 1 is isolated in several cases in the Syrian Arab Republic. Wild poliovirus had not been detected in this country since 1999. Given the current situation in the Syrian Arab Republic, frequent population movements across the region and sub-national immunity gaps in key areas, the risk of further international spread of wild poliovirus type 1 across the region is considered to be high (48). The last polio outbreak in the Netherlands was in 1992/1993 with 79 cases (49). The presence of a large, socially clustered population that rejects vaccination on religious grounds, however, is a risk factor for renewed spread of the virus. Therefore, during an international expert meeting organised by the RIVM in 2011, the strategy during an outbreak, vaccine choice, and target group for vaccination are documented in a roadmap.

In the mid-1980s, it was decided that mass vaccination programmes would be necessary to interrupt polio transmission — routine infant immunization would not be sufficient to achieve this goal. Poliomyelitis was originally targeted for global eradication by the year 2000, but this has been postponed due to failure in some regions to implement universal vaccination (45). However, the goal of the WHO is still to interrupt wild poliovirus transmission globally by 2014, resulting in eradication poliomyelitis by 2018 (50). Eradication is possible since cheap and effective vaccines are available to prevent polio, and because the oral polio vaccine is easy to administer. Massive oral polio vaccine use decreased already the number of polio-endemic countries from >125 countries in 1988 to only 3 in 2012 and led to a >99.9% decrease in polio incidence in the corresponding period (51). However, to eliminate the risk of vaccine-derived poliovirus leading to a complete eradication of poliomyelitis, oral polio vaccines will be phased out and inactivated polio vaccines will be gradually introduced (51-54).

Measles is eliminated from certain areas such as the Americas. Elimination of a disease from a specific region is not the same as eradication, since the disease can return if the infectious agent is reintroduced into an area where vaccination coverage has been too low. Vaccines have interrupted measles transmission in the western hemisphere, but outbreaks in Europe and Japan still occur from time to time, generally in regions with comparatively low vaccine coverage in populations with anti-vaccine sentiments, or in hard-to-reach groups like Roma's and Sinti. In the Netherlands, high-risk groups for a measles outbreak are anthroposophist's and people who refuse vaccination for religious reasons. In May 2013 an outbreak of measles started among the orthodox reformed population with low vaccine coverage. The previous measles outbreak in the Netherlands was in 1999/2000 with about 3,200 reported cases. In developing countries, low measles vaccine coverage and outbreaks are products of spotty access to healthcare. Measles may never be eradicated without increased access to vaccines, enhanced surveillance, and a long-term financial commitment (45).

Mumps vaccination

A vaccine against mumps has been available for decades and has resulted in decreased incidence of (complications of) mumps. However, the disease continues to spread to various parts of the world, including the Netherlands. It is reported mostly among adolescents and adults with intense contacts such as university students. Waning immunity and intense social contact are probably the primary causes of resurgence.

In the Netherlands vaccine coverage has been high (96%) since the introduction of vaccination in 1987 (15). However, in 2009, a mumps outbreak occurred among students (age 18-24 years). According to the large-scale population-based seroprevalence study, a small drop in seroprevalence was observed in the age cohort 15-21 years. The seroprevalence was just below the herd immunity threshold of 86-92% (55). The number of students within the 15-21 year age cohort susceptible for an infection could have been large enough to account for an outbreak. Furthermore, since only limited spread occurred outside the student population, the homogenous contact patterns of these students and crowding at parties might have initiated such outbreaks. Moreover, mumps-virus is transmitted via droplets for which close contacts between persons is necessary. In addition to these factors another factor may play a role: circulating wild type mumps-virus is a genotype G, and this differs from the vaccine strain (genotype A), possibly inducing lower neutralizing antibody levels against wild type mumps-virus (55).

Pertussis vaccination

DTP-IPV containing whole-cell pertussis vaccine has been used since the 50s and since 2005, a safer acellular vaccine has been introduced in the Netherlands. Although there has been high vaccine coverage in recent years, there have been increases in whooping cough both in adults and in infants too young to be vaccinated. Waning immunity is one of the main factors driving the pertussis epidemiology, and it might interplay with changes in circulating *B.*

pertussis-strains (vaccine mismatch and more virulent strains). It is hypothesized that the bacteria can maintain itself in vaccinated populations where immunity is waning, because of antigenic variation and higher toxin production (34).
A booster vaccination programme has been implemented in the Netherlands including vaccination of preschool children at 4 years of age, resulting in a decrease of incidence rates of notifications and hospitalizations (56). Although the vaccine effectiveness of acellular vaccines is higher compared to the Dutch whole-cell vaccine used until 2005 (4, 56), it was also observed that the estimated vaccine effectiveness of the acellular vaccine declined after about four years. This suggests only a limited period of protection by the preschool booster. Furthermore, pertussis rates in adolescents and adults steadily increased probably resulting in increased transmission to infants, who are at risk for contracting severe pertussis. Therefore, additional measures such as maternal vaccination or cocooning must be considered to protect this group and to reduce the pertussis burden (56, 57).

3.3.4 Adverse Events

Vaccines are generally considered as being safe and effective, and most 'scares' have not been substantiated by rigorous scientific studies (58). But it is never possible to guarantee that each vaccine is perfectly safe and adverse events following immunisation (AEFI) can occur. Therefore, there is a need for close post-marketing monitoring.
Local reactions in the form of pain, redness and swelling are common. For example, after vaccination with the bivalent HPV vaccine, girls aged 13–16 years reported particularly pain at the injection site (i.e. 84% after the first dose) (59). A less common but still frequently occurring side effect is redness and swelling of the entire upper arm after the fifth acellular pertussis vaccination at 4 years of age in children primed with aP compared to children primed with whole cell pertussis (60, 61). Besides this, also very rarely more serious reactions may be observed like idiopathic thrombocytopenic purpura after MMR vaccination (62, 63). Sometimes it is difficult to determine whether there really is a causal relation between the occurrence of an event and vaccination. For example in several countries an association has been found between narcolepsy and the pandemic H1N1 vaccination. It is still unclear whether this reflects a true increase in affected individuals or a hastening of disease onset in individuals who would otherwise have developed narcolepsy later (64).
Given the large number of subjects exposed to a vaccine, even a low risk of a particular reaction can result in a high absolute number of afflicted individuals (65). Specific antigens may cause adverse effects, but also other components of vaccines like adjuvants, preservatives included in inactivated vaccine formulations or stabilizers play a role (62, 66, 67).
Before they are licensed, vaccines are subject to controlled clinical trials to detect any adverse effects. However, the size of these studies is limited and may be too small to detect important, but very rare, adverse effects. Once vaccines are introduced into general use, careful monitoring of vaccine safety is required to better measure the frequency of known adverse reactions and to enable the detection of new ones. Pharmacovigilance of vaccines relies on three steps: detecting 'signals' that suggests that an AEFI is associated with a vaccine, rather than a chance occurrence; developing hypotheses about a possible causal relation between the AEFI and vaccination; and testing those hypotheses through (epidemiological) studies. Passive and active surveillance are major tools to properly investigate signals and hypotheses. In the Netherlands, the passive surveillance is done by Lareb, while the active surveillance is mainly performed by the RIVM.
Results from epidemiological studies are important to inform the target vaccination group and clinicians adequately which type of events may be expected after vaccination. Improved knowledge of adverse events may help to keep or increase confidence in vaccination in the Netherlands. Besides this, for many infections, vaccines have an additional effect in protecting even unvaccinated individuals through reduced transmission rates of the target pathogen in the whole population. In such cases, the greatest impact is obtained if there is high and sustained vaccination coverage, and this can only be achieved if the vaccines are acknowledged to be very safe and effective by the great majority of the population (68). So, public trust in vaccine safety is a key factor to the success of vaccination programs.

3.3.5 Non-specific effects

There is an on-going debate about potential non-specific effects apart from more direct adverse effects as described above, of several vaccines or vaccination schedules routinely given to infants on long-term morbidity and mortality outcomes. Non-specific effects are effects not explained by the intended effect on infections that are targeted by the vaccines. A possible explanation of these non-specific effects is that (components of) vaccines or vaccine schedules affect susceptibility to other (infectious) diseases, thereby potentially increasing or decreasing morbidity or (all-cause) mortality. Variations in the immune response can be attributed to certain recent environmental exposures, concurrent disease states, sex, and adjuvants that influence immune responses. For example, it is shown that 1-year-old infants who engage in social mixing with other children have an enhanced

immune response to a single dose of a pneumococcal conjugate vaccine at 1 year of age compared with infants who have less exposure to other young children. If infections can alter the immunological milieu, vaccines might also do so. Direct evidence that vaccines may have an effect on responses to subsequent vaccines comes from Ota et al who found that BCG vaccine influences the immune responses to hepatitis B vaccine, resulting in higher antibody levels. Various studies by Aaby et al in resource-limited countries have shown that measles vaccine may reduce mortality from infections other than measles, and DTP vaccine may reduce mortality from diphtheria, tetanus and pertussis, but increase mortality from other infections (69-71). If vaccines indeed have such non-specific effects they may have a substantial impact, in addition to the direct effects, on morbidity and on life expectancy, in particular in countries with high child mortality. Generally, the reported non-specific effects of vaccines have been stronger in girls and are largely determined by the last vaccine administered (72). Immune responses vary by gender and may explain differences in disease incidence for autoimmune disease and responses to vaccines (73-80). Generally, females demonstrate more vigorous humoral and cellular immune responses to vaccination, compared with males (75, 77).

Key points of interactions between host, pathogen and population in relation to vaccination

- Infectious disease dynamics after vaccination change as results of interplay between host, pathogen, and population. Examples of factors that play a role are vaccine efficacy, herd immunity and changes in the pathogen.
- Vaccine safety is a key factor to the success of vaccinations programmes.
- The impact of non-specific effects of vaccines or vaccination schedules is under debate.

3.4 Changes in population and society in relation to vaccination

In this paragraph we describe two important changes in population and society in relation to vaccination. First, we describe the more critical views on vaccination nowadays and the effects on the willingness to be vaccinated. Furthermore, we describe different groups who decline vaccination and the attitudes and motivations towards vaccination.

In the second part, we describe the ageing of the population, its effect on infectious diseases and the opportunities to protect the elderly by vaccination. Furthermore, we describe the increasing numbers of immune compromised patients, due to ageing and to developments in the field of immune modulatory drugs. Immunosuppressive drugs are extensively used. Specific vaccinations are recommended to these patient groups in addition to generally recommended vaccinations. At last, we describe patients with diabetes mellitus and patients without a functional spleen, as examples for specific patient groups where vaccination should be considered. Diabetes was chosen because the number of patients is growing, and the group of patients without a functional spleen was chosen as an example of a group of patients which is vulnerable for severe infections of vaccine preventable infections.

3.4.1 Resistance against vaccination

Vaccination uptake in particular among young children has been high for decades and amounts to at least 95% in the Netherlands (15). On the other hand, through all times, certain people have resisted the idea of vaccination, both in the industrialized and developing world (81-83). Already in the nineteenth-century resistance against the introduction of smallpox vaccination was coming from various sources: effective traditional ways of preventing smallpox by way of variolation, religious objections, fear of side effects and disapproval of the leading role of the state (84-86). In the UK, after a 1974 report ascribing 36 neurological reactions to whole-cell pertussis vaccine, persistent television and press coverage resulted in the interruption of a successful vaccination programme. A prominent public health academic, claimed that the protective effect of the vaccine was marginal and did not outweigh its danger. Major epidemics occurred in 1977 and 1981; 1978 saw over 68,000 notifications and 14 deaths (http://www.patient.co.uk/doctor/whooping-cough-vaccination). Confidence was restored after publication of a national reassessment of vaccine efficacy. Among other things, provision of financial incentives for general practitioners who achieved the target of vaccine coverage contributed to the recovery (87). In 1998 Andrew Wakefield and colleagues published a paper where they detailed a case series of 12 children presenting, within a few days of receiving the MMR vaccine, with inflammatory bowel symptoms and a loss of language and other basic skills. That paper, since discredited on methodological and ethical grounds (http://www.gmc-uk.org/news/7115.asp), caused substantial and sustained media attention around the intended link (http://www.esrc.ac.uk/ESRCInfoCentre/Images/Mapdocfinal_tcm6-5505.pdf) (88). This was sufficient to create fear and uncertainty in a generation of parents (89, 90) and a drop in coverage with still on-going

measles transmission and outbreaks all over the United Kingdom (http://www.ecdc.europa.eu/en/publications/Publications/Measles-rubella-monitoring_June_2013.pdf).

3.4.2 Groups who refuse vaccination

Although vaccine coverage in infants is high in the Netherlands (15), previous studies have identified groups who refuse (some) vaccinations. One group consists of members of Reformed Congregations who believe that vaccination is contrary to the providence of God (91, 92). This group (estimated at about 250,000 members) is at risk for epidemics as a result of socio-geographical clustering, which has been observed for poliomyelitis, measles, mumps and rubella (8, 10, 11, 93, 94). Another group consists of people with an anthroposophical lifestyle (the anthroposophical society in the Netherlands counts about 4,300 members), who believe that experiencing some childhood diseases may contribute to strengthening body and mind (92, 95, 96). Anthroposophists do not refuse all vaccines, and they are scattered throughout the Netherlands, but clustering in anthroposophic schools is present. The increased risk of epidemics has been observed for measles; in 2008, an outbreak occurred at several anthroposophic schools in the Netherlands and in anthroposophic communities abroad (97-99). Furthermore, there is the 'Nederlandse Vereniging Kritisch Prikken' (NVKP - Dutch Association for Conscientious Vaccination with about 1600 members), who is formed by members critical towards childhood vaccination and who have different objections to vaccinations, mainly based on doubts about the safety of vaccines. In addition, other less well-identified groups or individuals may exist that have doubts concerning the risks and benefits of vaccination.

3.4.3 Attitude and motivation towards vaccination

Recent studies observed that the intention to vaccinate their children among the general population was most strongly determined by attitudes (95, 96, 100). The belief that vaccination is safe and the best way to protect children against infectious diseases, was positively associated with parents' positive attitudes. The idea that children receive too many vaccines simultaneously and that vaccination interferes with natural development (i.e. anthroposohical lifestyle) had a negative effect on parents' attitudes. Among the members of Reformed Congregations family tradition, apart from religious arguments, also plays an important role in decision-making on vaccination. A subgroup of these parents do not make a deliberate decision on vaccination and just follow the tradition within their family, and especially within this minority, the tradition is frequently not to vaccinate (101). Medical arguments, like the effectiveness or side–effects of vaccination, are less important to this group. Some groups also accept vaccination by using religious arguments to justify why vaccination is allowed (101). Some Dutch parents believed that doctors only inform them about the benefits of vaccination and disregard possible drawbacks (100). In the absence of visible vaccine-preventable diseases in the community, some parents did not perceive that their child is potentially at risk of exposure. Without fear of these diseases, the fear about possible side effects of vaccination will increase (102). Paulussen et al. observed that 81% of parents reported not having thought thoroughly whether to vaccinate their child or not (100). The authors hypothesized that these parents could therefore more easily be influenced by negative publicity about vaccination. Factors from outside the NIP can influence and alter attitudes towards vaccination quickly, e.g. epidemics, media attention, disagreeing professionals, and anti-vaccination lobbying. Therefore, it would be desirable to get insight in the determinants that influence parents (changing) intention to vaccinate or not. To get insight in these determinants, qualitative and quantitative studies are and have been performed to set-up a system to monitor the determinants associated with the acceptance of vaccination for both parents and childhood vaccine providers (CVPs). Recent studies found that CVPs are the most important source of information about vaccination for parents of young children (103). A qualitative assessment showed that CVPs were mainly positive toward the NIP, except that they had doubts to future NIP plans to vaccinate against diseases with a low perceived burden. The CVPs perceived a responsibility to promote vaccines and discuss the pros and cons of childhood vaccination with parents, although the discussion was usually not taken place if parents readily accepted the vaccination. Besides that, CVPs indicated to have limited time and not enough information about the NIP to discuss vaccinations with parents. Lastly, they reported that their relationship with parents was crucial and mainly based on communication to establish trust (104, 105).

3.4.4 Ageing and morbidity

The Dutch population is ageing. Between 1900 and 2013 the number of persons aged 65 years and older has risen from 0.3 million to 2.8 million. Forecasts of Statistics Netherlands (CBS) estimates that by 2050 there will be 4.5 million persons aged 65 years or over (25% of the total population). In 2008, this proportion was 15%. Apart from overall population growth, the main reason for the increase is that life-expectancy at birth has risen steadily over the last half-century. This change in the age distribution of the population has impact on the

occurrence of infectious diseases (http://statline.cbs.nl/statweb/).
Morbidity and mortality caused by infections increases from the age of 50 years onwards (106, 107). This is caused by the natural age-related changes in the innate and adaptive immune system, collectively termed 'immunosenescence', by anatomic and physiological changes of the body, and by underlying chronic diseases (108). Another reason for a higher morbidity and mortality among frail elderly is that they are living together in nursing homes or hospitals, with an increased probability of transmission of infectious diseases. According to Statistics Netherlands, the number of elderly people living in hospitals or nursing homes will rise (http://statline.cbs.nl/statweb/). In addition, healthy elderly will be more actively engaged in society and will be travelling more, also resulting in an increased chance of transmission of infectious diseases. Vaccination is an efficient measure to prevent infectious disease and can thereby contribute to strategies to keep elderly people healthy. The increased vulnerability to infection of the elderly and the development in new vaccines for specific target diseases in the elderly makes them an important target population for vaccination.

3.4.5 Effects of ageing and vaccination on immunity

Many processes which play a role in the transmission of infectious diseases are age related, such as risk behaviour and contact patterns. Changes in the age distribution of the population will have an impact on the transmission of infectious diseases. There are also cohort effects, in which an age group with a specific characteristic (e.g. immunity against a disease) moves to an older age group. In the case of hepatitis A it is known that nowadays the majority of the elderly have natural immunity against the disease, because this virus was circulating when they were young (109). With ageing of cohorts that did not acquire immunity to hepatitis A virus through natural infections, there is an increasing risk, once exposed, of outbreaks, especially if they would be living clustered in nursing homes (110).
Elderly people are more susceptible to for example tuberculosis and diphtheria, because of age-related changes in the immune system. In a situation where there is circulation of a pathogen in the population, immunity levels will be maintained, through regular exposure followed by natural boosting of immune responses. However, when universal immunization programs reduce the circulation of pathogens, immunity levels may decrease over time. This negative effect of immunization programmes can cause more susceptibility to certain pathogens in older age groups.

3.4.6 Vaccination of all age groups

The vulnerability of the elderly to adverse outcomes of vaccine preventable infectious diseases makes them a relevant target population for vaccination. On the other hand, most vaccines are less immunogenic and efficient in elderly people compared to healthy adults because of 'immunosenescence', affecting both innate and adaptive immunity. It highlights the need for more immunogenic vaccine formulations for the elderly. This might be achieved by making vaccines more potent, by using adjuvants to enhance immunity, by using higher antigen dosing, by applying immune modulators or by other interventions to alter host immunity generally.
In the Netherlands, vaccination against seasonal influenza is the only recommended vaccination for all people of 60 years and older. The Dutch Health Council expects that the elderly might become a target population for more vaccination programmes in the public domain in the future and will evaluate vaccines against pneumococcal disease (conjugated vaccine) and herpes zoster in the near future (5).
It is possible that vaccination of other age groups will have a positive effect on the elderly because of herd immunity. This effect has been observed in pneumococcal disease after introduction of vaccination in the NIP (111).
Vaccination of younger age groups could also have a possible negative effect on elderly because of diminishing circulation. For example introduction of varicella vaccination in childhood will lead to diminishing exogenous boosting which might result in lower immunity levels over time ('the exogenous boosting hypotheses') among those previously exposed to varicella zoster virus (112). Some predict an increase of zoster as a result of this decrease of exogenous boosting (113). However, up to now no consistent outcomes have been found in various studies with regard to the incidence of herpes zoster after introduction of vaccination. In general, decreasing boosting opportunities might imply lower protection after childhood and need for additional measures such as revaccination. The current national immunization programme is now mainly targeting children. An immunization programme encompassing guidelines for vaccination opportunities over the full life-span was recommended by the Health Council in 2007 (5).

3.4.7 Vaccinations in specific patient groups

Immune-mediated inflammatory diseases
The extensive use of immune modulatory and immune suppressive drugs in transplant recipients and in patients with autoimmune conditions has caused a steady increase in the number of people living with immune suppressive conditions. It is estimated that 5 to 7% of the Western population have immune-mediated disease that are

treatable with immune suppressive or immune modulatory drugs (114). Numbers from the Netherlands are lacking.
Immune-mediated inflammatory diseases describe a group of diverse medical conditions that may share inflammatory pathways, such as rheumatoid arthritis, inflammatory bowel diseases or multiple sclerosis. Vaccinations in patients with such autoimmune diseases are well capable of preventing infectious diseases. However, vaccination may lead to lower protection rates than in healthy people, although they are at increased risk to acquire vaccine preventable diseases (115). Not only does the immunosuppressive therapy that these patients undergo reduce vaccine effectiveness, but also some of these diseases associated with an intrinsic deterioration in immune response (116, 117). On the other hand, some autoimmune reactions are possibly vaccine-associated, for example immune thrombocytopenic purpura after a MMR-vaccination. Moreover, inactivated vaccines can induce a worsening of disease activity in patients with multiple sclerosis, rheumatoid arthritis or insulin-dependent diabetes mellitus, for reasons yet unknown (118, 119). Patients undergoing immunosuppressive treatment should be vaccinated, in addition to commonly recommended vaccines, risk-specific vaccinations against influenza and pneumococcal disease (120-123). Vaccinations should preferably be given before immunosuppression. Antibody testing may be considered to evaluate vaccine response in immune compromised patients.

Diabetes mellitus

Diabetes mellitus is a chronic metabolic disorder, which is associated with high levels of glucoses in the blood. The number of diabetes patients is growing in the Netherlands (http://www.nationaalkompas.nl/gezondheid-en-ziekte/ziekten-en-aandoeningen/endocriene-voedings-en-stofwisselingsziekten-en-immuniteitsstoornissen/diabetes-mellitus/trend/). Type 1 diabetes mellitus is an autoimmune disease that involves the progressive destruction of the insulin-producing beta cells in the islets of Langerhans. It is a complex process that results from the loss of tolerance to insulin and other beta-cell-specific antigens (124). The risk of and mortality from infectious diseases is higher in people with diabetes mellitus and therefore diabetic patients are a target group for the National Influenza Prevention Programme. Certain rare infections are more common among diabetic patients. Diabetes predisposes patients to comorbidities, such as foot ulcers that increase susceptibility to infection, whereas some infections, such as hepatitis C, may predispose individuals to developing diabetes (125). Furthermore, diabetes increases the risk of adverse outcomes, such as bacteraemia and mortality following pneumococcal pneumonia (126). Complications after infections are rare, but can have far-reaching consequences in the patient with diabetes mellitus (127).

Splenectomy / asplenia

People without a spleen have a higher risk of severe infections by encapsulated bacteria, because the number of IgM producing B cells is decreased and filtering of non-opsonized encapsulated bacteria is impossible. Each year, up to a 1000 splenectomies are performed in the Netherlands. Aside from patients without a spleen, there is also a large group of patients with hyposplenism or functional asplenia due to other primary diseases. All these patients are at risk of developing severe infections, such as post-splenectomy sepsis (PSS) caused by pneumococcal, meningococcal or *Haemophilus influenzae* bacteria, which is associated with very high mortality. The incidence of PSS is estimated to be 2-5 per 1000 patients without a functional spleen each year (128). However PSS can partly be prevented by taking simple measures such as immunizations and prophylactic or early use of antibiotics. Healthcare professionals in first and secondary care in the Netherlands are generally not well informed about which preventive measures should be taken to prevent these infections, resulting in often suboptimal management of patients. Recently recommendations were given on vaccination and administration of antibiotics to prevent severe infections such as PSS in this group of patients (129).

Key points of changes in the population and society in relation to vaccination

- Resistance against vaccination has been present through all times.
- To maintain a high vaccine uptake, a monitoring system for acceptance of vaccination can give timely insight in changes in the determinants associated with acceptance of vaccination.
- Elderly are an important target for vaccination given the growing number and the increased vulnerability to infectious diseases.
- Vaccination of groups at risk as a result of a specific disease needs consideration.

3.5 Vaccine development and vaccination programme development

The development of vaccines is an important achievement in medical history. However, vaccines are still unavailable for many of the infectious diseases that plague humankind. In the present chapter, we will shortly describe the history of vaccine development and the different stages the candidate vaccine has to go through before it can be licensed. Furthermore, we will give an overview of the most important progresses in vaccine development.

3.5.1 Vaccine development in a historical perspective

A vaccine is a biological preparation that can generate immunity to a particular disease at the individual level and at population level. A vaccine typically contains an agent that immunologically resembles a disease-causing microorganism, and is often made from weakened or killed forms of the pathogen, its detoxified toxins or one of its surface proteins.
The agent stimulates the body's immune system to recognize the agent as foreign, destroy it, and "remember" it in the form of antibodies and T-cells, so that the immune system can more easily recognize and destroy any of these micro-organisms that it later encounters (130).
In 1796, Edward Jenner performed the first vaccination. Taking pus from a cowpox lesion on a milkmaid's hand, Jenner inoculated an eight-year-old boy. Six weeks later Jenner variolated two sites on the boys arm with smallpox, yet the boy was unaffected by this as well as subsequent exposures. Through conscientious worldwide application of this vaccine, smallpox was eradicated and immunization stopped (131). Louis Pasteur's 1885 rabies vaccine was the next to make an impact on human disease. Aware of Jenner's cowpox inoculation experiments, Pasteur devised a different method of immunization by reducing the virulence of the pathogenic organism and thereby inoculating the attenuated form of the virus to induce active immunity against the rabies virus (132). In the twentieth century, several successful vaccines were introduced, including those against tetanus, diphtheria, measles, mumps, and rubella. A major achievement is the development of polio vaccines in the 1950s allowing the eradication of poliomyelitis which WHO aims to be realized before 2018 (50).
Today, the main challenges include developing or improving vaccines against as yet undefeated pathogens with rapid identification and response to emerging diseases. Emerging infectious diseases are a key threat to public health and the majority is caused by zoonotic pathogens (133). Aids, malaria and tuberculosis are three of the most challenging infectious diseases still affecting humans. New conceptual and technological advances indicate that it might be possible to develop vaccines against these diseases within the next 10 years (134).

3.5.2 Stages of vaccine development

Generally, a commercial manufacturer begins the process of vaccine development when scientific research has yielded promising results and when ''proof of principle" (the point in Research and Development when the feasibility of a particular product or process is determined) has been established. The decision to invest in this process takes into account two critical factors: the technical feasibility and complexity of developing the vaccine, and market considerations. These market considerations include the likelihood of an anticipated rate of return on investment, the availability of patent protection (and freedom from third-party patent rights), and the potential costs of liability exposure Investing (135). Only a small percentage of candidate vaccines progresses to licensing.
Development of vaccines can be simplified into two broad stages:

1. Pre-clinical development is research carried out in the lab and on animals. It includes:
   - Identification (discovery) of relevant antigens
   - Creation of the vaccine concept
   - Evaluation of vaccine efficacy in vitro and in animals
   - Manufacture of the vaccine to Good Manufacturing Practice standards
2. Clinical development is when the vaccine is tested in humans. It covers four stages over several years, from initial clinical trials in humans (phase I) right through to introduction and beyond (phase IV). Clinical development is built on rigorous ethical principles of informed consent from volunteers, with an emphasis on vaccine safety as well as efficacy.

Phase I clinical trials are small-scale trials to assess whether the vaccine is safe in humans and what immune response it evokes. Phase II clinical trials are larger and mainly assess adequate vaccine dosage and administration schedule and the efficacy of the vaccine. Vaccine safety, side effects and the immune response are also studied. Vaccines that progress to phase III clinical trials are studied on a large scale of many hundreds to thousands of subjects across several sites, in order to evaluate efficacy under natural disease conditions. If the vaccine retains safety and efficacy over a defined period, the manufacturer is able to apply to the regulatory authorities for a license to market the product for human use.
The final phase IV happens after the vaccine has been licensed and introduced into practice. Also called post-marketing surveillance, this stage aims to detect rare

Table 3.8 Vaccines under development relevant for the Netherlands.

Sexually transmitted infections	HIV/AIDS
Respiratory infections	RSV
	Tuberculosis
	Pseudomonas aeruginosa
Enteric infections	Noroviruses
Nosocomial agents	*Staphylococcus aureus*
	Clostridium difficile
Other viruses	Hepatitis C
	Cytomegalovirus
Other bacteria	Group B Streptococci

adverse effects as well as to assess long-term effectiveness. Manufacturers are obliged to do this (136).

3.5.3 Vaccine production

Vaccine production has several stages. First, the antigen itself is generated. Antigens can be immunogenic proteins from viruses or bacteria, whole viruses or bacteria, which are killed chemically, or live whole viruses or bacteria, which have been processed to be severely attenuated in infectivity. Viruses are grown either on primary cells such as chicken eggs (e.g., for influenza), or on continuous cell lines such as cultured human cells (e.g., for hepatitis A). Bacteria are grown in bioreactors (e.g., *Haemophilus influenzae* type b). Immunogenic proteins can be generated in yeast, bacteria, or cell cultures. After the antigen is produced, it is isolated and purified. Finally, the antigen, which is now the vaccine, is formulated by adding adjuvant, stabilizers, and preservatives when needed. The adjuvant enhances the immune response of the antigen, stabilizers increase the storage life, and preservatives allow the use of multidose vials (137). Combination vaccines are harder to develop and produce, because of potential incompatibilities and interactions among the antigens and other ingredients involved (138).

3.5.4 Progress in vaccine development

New Vaccines

During the last 30 years, vaccine development has accelerated due to improved understanding of microbial pathogenesis and the human immune response (139). Breakthroughs in biotechnology also resulted in new vaccine development. Conjugation technology, for example, has spurred new conjugate vaccines, which stimulate the type of immune cells needed to create a long-lasting memory of the pathogen. Adjuvant technology also has evolved. Progress in understanding how the human immune system recognizes the molecules carried by pathogens has led to the development of new vaccines (140). Examples of recently developed vaccines are vaccines against HPV, meningococcal disease, pandemic and pre-pandemic influenza virus, pneumococcal disease, rotavirus diarrhoea, and shingles caused by varicella zoster virus.

Novel approaches using live bacterial and viral vectors could allow for mucosal delivery of vaccines and prime-boost regimens that may also be useful for therapeutic vaccines. The use of non-living antigen delivery systems like proteasomes, lipids, cochleates, virus-like particles, and genes (e.g. replication incompetent vectors and replicons) also shows great potential for improving vaccines (45).

Advances in immunology and microbiology could improve vaccine efficacy. New technologies offer alternative products. For example, innovation in manufacturing has allowed a shift from egg-based methods to cell-based or recombinant methods. Transgenic plants might be used to produce antigens. However, high technical hurdles must be overcome before adequate yield and purity can be achieved (45, 141). In addition, the social climate for introduction of such vaccines should be taken into account.

For many infectious agents, new vaccines are currently under development (142); some of them are relevant for the Netherlands (see Table 3.8) (143).

New forms of administration of vaccines

Advanced delivery technologies, including needle-free strategies, could simplify immunizations schedules, and are supported by WHO and (E)CDC (144-146). Alternative vaccine delivery systems through the oral, nasal, trans- or intradermal route can improve antigen passage through relevant biological barriers, such as the intestinal and nasal mucosa and hold some promise towards the generation of needle-free vaccines. Regarding the oral route, the size of the delivery carrier is a fundamental parameter for adequate immune stimulation. Over the last decade the trend observed is that the smaller the particle size, the greater their ability to transport antigens across the intestinal barrier, although this is also affected by surface

composition and release properties (147).
The nasal route is another promising alternative for needle-free administration due to its particular physiological characteristics and immunological features. The nasal mucosa has a limited enzymatic activity and a relatively leaky epithelium accompanied by specialized cells (M cells) that harvest the antigens present in the mucosa and deliver them to associated lymphoid tissues (147).
Besides the mucosal routes, the transdermal route is also progressively becoming a feasible option for vaccination. The skin is one of the largest immune organs and is rich in potent antigen-presenting cells such as Langerhans cells in the epidermis and dendritic cells in the dermis. These cells can efficiently initiate primary immune responses both *in vitro* and *in vivo*.
Another strategy under evaluation is the use of intradermal delivery of vaccines, which has been shown to in dose sparing with some vaccines. Notably, dose sparing has been demonstrated for inactivated poliovirus vaccine, yellow fever vaccine, seasonal influenza vaccines, and rabies vaccine, although for vaccines against measles, diphtheria, tetanus, pertussis and hepatitis B, no such effect is found (148). Currently available vaccines have been selected to induce a robust humoral response. It is now clear, however, that for some infections a robust T-cell immune response is also necessary to achieve effective immunity (149). This will need appropriate delivery of vaccine compounds. So, new devices or easier, more reliable ID delivery are being developed, including adapters for traditional needles and syringes that control the depth and angle of needle penetration, mini-needles, micro needles, and disposable-syringe jet (148, 149).

Adjuvants
Following the discovery that addition of foreign material could enhance immune response to vaccines, alum (aluminium sulphate salts) was identified in 1926 as a potent adjuvant. For many years subsequently, alum remained the only adjuvant in general use for vaccine formulation. Recent advances in the fields of immunology and molecular biology, such as the identification and characterization of host pattern recognition receptors, have led to the discovery of new adjuvants like emulsions, liposomes and immune-stimulating complexes, and the potential for even more (150, 151). A new approach in vaccine/adjuvant design represents a coalescence of significant findings in the area of innate immunity and how it influences the adaptive immune response. In this new approach, the objective is to select an adjuvant or design a combination of adjuvants that will achieve certain immunologic objectives. These objectives are defined by an understanding of the candidate vaccine antigen and what type of host response is required to achieve optimal and long-lasting protection with the vaccine. This approach was used to launch recent vaccines targeting infectious diseases such as human papillomavirus (150).
Once a new vaccine is licensed, careful monitoring of vaccine safety is mandatory to measure the frequency of known adverse reactions and also to enable the recognition of not yet identified adverse events.

3.5.5 Vaccinomics and personalized vaccines

The current medical practice in vaccinology is to universal administering the same set of vaccines to everyone in the population. The major weakness of this approach is that it ignores individual variability in disease risk immunologic response, and any genetic propensity for reactogenicity, as well as differences in dose amount needed to generate immunity (32). Therefore, a new 'tension' is developing in the field of vaccinology, i.e. vaccinomics.
Vaccinomics refers to the integrated use of data enabled multi-omics approaches to understand the mechanisms responsible for heterogeneity in humoral, cell-mediated, and innate immune responses to vaccines at both the individual and population level (32, 152). This new science will inform the development of personalized vaccines. Rapid advances in developing such data are already occurring for hepatitis B, influenza, measles, mumps, rubella, anthrax and smallpox vaccines.

3.5.6 Progress in vaccination programme development

In 2007 the Health Council of the Netherlands introduced a framework for the assessment of vaccine candidates for inclusion in the NIP (5). Seven criteria were defined:
1. Infectious diseases cause a considerable disease burden within the population.
2. Vaccination may be expected to considerably reduce the disease burden within the population.
3. Any adverse reactions associated with vaccination are not sufficient to substantially diminish the public health benefit.
4. The inconvenience or discomfort that an individual may be expected to experience *in connection with his/her personal vaccination* is not disproportionate in relation to the health benefit for the individual concerned and the population as a whole.
5. The inconvenience or discomfort that an individual may be expected to experience *in connection with the vaccination program as a whole* is not disproportionate in relation to the health benefit for the individual concerned and the population as a whole.
6. The ratio between the cost of vaccination and the associated health benefit compares favourably to the cost-benefit ratio associated with other means of reducing the relevant disease burden.

7. The provision of vaccination may be expected to serve an urgent or potentially urgent public health need.

The current practice in Dutch immunization programmes is rooted in collective preventive programmes. Vaccines that are not (yet) included in a routine vaccination programme are only used on a very limited scale. Examples of diseases for which safe and effective vaccines are available, are chicken pox, gastroenteritis by rotavirus infection and shingles. In particular, risk groups vaccination against some disorders could be considered part of adequate health care. Because of their potential health benefits, wider use of vaccines is advocated. Since more vaccines become available by new technologies, the Dutch Health Council has recently proposed guidelines for the use of vaccines within and outside public vaccination programmes (153). In this, they propose to develop one general assessment framework for all vaccinations, irrespective the age of the potential target group. A starting point could be the whole spectrum of vaccination care: from health care financed by the individual or company, through collectively funded essential healthcare, to public vaccination programmes free of charge. A general assessment framework can be derived relatively easy from existing framework, as the Health Council proposes. This would allow to evaluating not only vaccinations with an explicit public objective, but also vaccinations with more individual benefits. Also for vaccinations which are considered to be more of individual benefit, an assessment is needed of the potential effects on the general population. For example, if vaccination against chickenpox would be an individual option, and only a part of the children is vaccinated, one has to take into account the potential of increased age of infection with a higher complication rate for chicken pox as well as the potential increase of zoster, as both infections are caused by the same virus.
In addition to the Health Council's recommendation there are initiatives from the ministry to modernize vaccination care. Creating a greater scope for vaccination outside public health programmes can help to ensure that this approach and content are more effectively safeguarded.

Key points of vaccine development and vaccination programme development

- For more than two centuries health benefits have been achieved through the use of vaccines.
- The use of innovative technology will contribute to the development of new vaccines.
- Vaccines are increasingly susceptible to individualization or personalization.
- The Dutch Health Council has recently proposed guidelines for the use of vaccines within and outside public vaccination programmes, this could led to optimal usage of safe and effective vaccines.

3.6 Appendix

List of registered vaccines in the Netherlands, (medical) indication and utilization in immunization programmes.

Vaccine against	(Medical) indication	Used in immunization programme
Diphtheria, pertussis, tetanus, polio, *Haemophilus influenzae* B, hepatitis B (DTaP-IPV-Hib-HepB)	Active immunization of infants against diphtheria, pertussis, tetanus, polio, *Haemophilus influenzae* B and hepatitis B.	National Immunization Programme – at 2, 3, 4, 11 months of age.
Diphtheria, pertussis, tetanus, polio, *Haemophilus influenzae* B (DTaP-IPV-Hib)	Primary vaccination and revaccination of new-borns against diphtheria, pertussis, tetanus, polio and *Haemophilus influenzae* type B.	
Diphtheria, pertussis, tetanus, polio, (DTP-IPV), reduced dose	Booster or primary vaccination of adolescents and adults against diphtheria, pertussis, tetanus and polio.	
Diphtheria, pertussis, tetanus, polio (DTP-IPV)	Booster vaccination against diphtheria, pertussis, tetanus, polio for persons (age ≥ 3 years).	National Immunization Programme – at 4 years of age.
Diphtheria, tetanus, polio (DT-IPV)	Active immunization against diphtheria, tetanus and polio. DT-IPV vaccine can be used for primary immunization and for re vaccination.	National Immunization Programme – at 9 years of age.
Haemophilus influenzae B	Active immunization of infants (> 2 months) and toddlers against *Haemophilus influenzae* type b (causing invasive infections like bacterial meningitis, sepsis, epiglottitis, cellulitis en arthritis).	
Hepatitis A	Active immunization against hepatitis A infection for person with a high risk of exposure to hepatitis A virus.	
Hepatitis B	Vaccination against hepatitis B virus for people with kidney disease (including patients with pre haemodialysis or haemodialysis). Active immunization against hepatitis B infection for person with a high risk of exposure to hepatitis B virus.	Hepatitis B vaccination for specific risk groups.
Hepatitis A + B	Active immunization against hepatitis A and B for persons (> 1 year) with a high risk of exposure to hepatitis A virus and/or hepatitis B virus.	
Seasonal Influenza	Vaccination against influenza for persons with a high risk of complications after an influenza infection.	National Influenza Prevention Programme - All people of 60 years of age and older, elderly living in nursery homes and specific risk groups.
Japanese encephalitis	Active immunization for adults against Japanese encephalitis.	
Conjugated Meningococci A, C, W135, Y	Active immunization against meningococcal disease caused *Neisseria meningitidis* serogroups A, C, W135 and Y.	
Conjugated Meningococci C	Active immunization against meningococcal disease caused by *Neisseria meningitidis* serogroup C.	National Immunization Programme - at 14 months of age.
Mumps, Measles, Rubella	Active immunization against mumps, measles and rubella for children (> 12 months); sometimes it is advisable to vaccinate children of age 6 – 12 months.	National Immunization Programme – at 14 months and 9 years of age.
Human papillomavirus type 16 and 18	Immunization against high grade cervical intra epithelial neoplasia (CIN 2 and 3) and cervical cancer caused by human papillomavirus (HPV) types 16 and 18.	National Immunization Programme – at 12 years of age (only girls).

Vaccine against	(Medical) indication	Used in immunization programme
Human papillomavirus type 6, 11, 16 and 18	Prevention of pre malign genital lesions (cervical, vulvar, vaginal, anal), cervical and anal cancer, and genital warts caused by human papillomavirus (HPV) types 6, 11, 16 and 18.	
23-valent polysaccharide Pneumococci	Immunization against pneumococcal disease for people with a high risk on morbidity and mortality caused by a pneumococcal pneumonia (e.g. persons without a spleen or with a dysfunctional spleen, with chronic diseases like diabetes mellitus, a dysfunctional heart, lungs, liver and/or kidneys and hiv-positive persons). People with Hodgkin disease can be vaccinated 10 days before treatment with chemotherapeutics or radiotherapy. Vaccination for children younger than 2 years is not indicated.	
10 and 13-valent conjugated Pneumococci	Immunization against pneumococcal disease (like sepsis, meningitis, bacterial pneumonia, bacteraemia and acute otitis media) caused by pneumococcal types in the vaccine. For specific risk groups in older people.	National Immunization Programme – at 2, 3, 4, 11 months of age.
Poliomyelitis	Active immunization against polio.	
Rabies	Active immunization against rabies. Pre exposure vaccination: for people with high risk jobs or persons living or visiting endemic countries. Post exposure vaccination: after bites or licking of infected animals or humans.	
Rotavirus	Active immunization against rotavirus for new-borns from 6 to 24 weeks of age.	
Tick-borne encephalitis ('Früh Sommer Meningo-encephalitis')	Active immunization against tick born meningo- encephalitis for persons living or visiting endemic countries. Risk assessment is based on official recommendations.	
Tetanus	Primary vaccination of adults. Re vaccination of adults. Prevention of tetanus after trauma.	
Tetanus / vaccine and immunoglobulin	Primary vaccinations and re vaccination of adults. Prevention of tetanus after wounding.	
Typhoid fever parenteral	Oral, active immunization against typhoid fever for persons travelling to endemic countries. Active immunization against typhoid fever.	
Tuberculosis	Active immunization against tuberculosis for children (< 12 years) with one or both parents from a high endemic country (incidence > 50/100.000).	Tuberculosis vaccination programme for specific risk groups.
Varicella	Active immunization against varicella zoster. Prevention of infection or to influence disease outcomes within 3 days after exposure to varicella zoster virus.	
Varicella Zoster	Prevention against herpes zoster and post herpetic neuralgia caused by herpes zoster virus.	
Yellow fever	Active immunization against yellow fever for people travelling to endemic countries and/or to countries asking for an international vaccination certificate and for (laboratory) personnel working with potential infectious material.	

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