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State of Infectious Diseases *in the Netherlands, 2016*

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Synopsis

State of infectious diseases in the Netherlands, 2016

The most notable infectious disease outbreak in 2016 was the large Zika virus outbreak in Latin America. During this outbreak it was discovered that the Zika virus can cause Guillain-Barré syndrome, and that infection during pregnancy can lead to severe congenital disorders. In the Caribbean Netherlands, the Zika virus is mainly spread by mosquitoes, while in the European Netherlands sexual transmission of the virus occurs via infected travellers. In 2016, Zika virus infection during pregnancy and severe cases of Zika virus disease became notifiable.

The first two cases of tick-borne encephalitis (TBE) infected in the Netherlands occurred in 2016. The virus causing this condition is spread by ticks and infection can lead to (meningo) encephalitis. The main infectious disease outbreaks in the Netherlands in 2016 were caused by *Salmonella*, hepatitis A virus and *Neisseria meningitidis* (meningococcal disease). In addition, relatively many Legionella infections occurred. From August 2015 to July 2016 low numbers of rotavirus diagnoses were reported in the virological surveillance, similar to the 2013/14 season. A normal season was observed n 2014/15 and 2016/17. These observations might indicate a transition from an annual rotavirus pattern to a biennial pattern in the Netherlands. With regard to international outbreaks, aside from the aforementioned Zika virus epidemic, the yellow fever outbreak in Angola and measles epidemics in several European countries were monitored in order to assess possible risks to the Netherlands.

These are some of the highlights of the annual State of Infectious Diseases in the Netherlands report by the Dutch National Institute for Public Health and the Environment (RIVM). This report provides insight into infectious disease developments for policy makers at the Ministry of Health, Welfare and Sports (VWS) and in municipal health services (GGD).

The thematic Chapter of the 2016 report reviews vaccination and the immune system during the life course. Certain populations, specifically young children, the elderly, pregnant women and people with a weakened immune system, become infected more easily and, if infected, they can experience a more severe disease course. Vaccination may be less effective for these groups. To protect vulnerable groups, maintaining herd protection through high vaccination coverage in the general population is essential.

Publiekssamenvatting

Staat van Infectieziekten in Nederland, 2016

In 2016 was de grote uitbraak van het zikavirus in Latijns Amerika de meest in het oog springende infectieziekte. Tijdens deze uitbraak werd ontdekt dat het zikavirus infectie Guillain-Barré syndroom kan veroorzaken en dat na een infectie tijdens de zwangerschap ernstige aangeboren afwijkingen kunnen ontstaan. In Caribisch Nederland wordt het zikavirus vooral verspreid via muggen. In Europees Nederland kan zikavirus verspreid worden door seksuele contacten met geïnfecteerde reizigers. In 2016 is een meldingsplicht ingesteld voor zwangeren met een zikavirusinfectie of als de ziekte ernstig verloopt.

Verder kwamen in 2016 de eerste twee gevallen van tekenencefalitis (TBE) aan het licht die in Nederland zijn opgelopen. Het virus dat deze aandoening veroorzaakt wordt via teken verspreid en kan hersen(vlies)ontsteking veroorzaken. De belangrijkste uitbraken van infectieziekten in Nederland in 2016 werden veroorzaakt door *Salmonella*, hepatitis A virus en *Neisseria meningitidis* (meningokokken). Daarnaast kwamen relatief veel Legionella-infecties voor. Van augustus 2015 tot juli 2016 werden lage aantallen rotavirus diagnosen gemeld in de virologische weekstaten. In 2013/14 werden eveneens lage aantallen gemeld, terwijl de gemelde aantallen in 2014/15 en 2016/17 normaal waren. Deze waarnemingen wijzen op een mogelijke verschuiving van een jaarlijks rotaviruspatroon naar een tweejaarlijks patroon in Nederland. Wat betreft buitenlandse signalen, zijn behalve de genoemde zikavirusepidemie, vooral de gele koorts-uitbraak in Angola en de mazelenepidemieën in verschillende Europese landen in de gaten gehouden om eventuele risico's voor Nederland te kunnen inschatten.

Dit blijkt uit de 'Staat van Infectieziekten' van het RIVM. Deze jaarlijkse rapportage geeft beleidsmakers bij het ministerie van VWS en GGD-en inzicht in ontwikkelingen van infectieziekten in Nederland en in het buitenland.

Het verdiepende thema is dit keer vaccinatie en het immuunsysteem in de verschillende fasen van een mensenleven. Sommige bevolkingsgroepen, te weten (jonge) kinderen, ouderen, zwangeren en mensen met een verzwakt immuunsysteem, lopen vaker infecties op. Ook kan het zijn dat bij hen infectieziekten ernstiger verlopen of dat vaccinaties minder goed werken. Om kwetsbare groepen te beschermen, is het van groot belang dat de groepsimmuniteit in de bevolking door een hoge vaccinatiegraad gehandhaafd blijft.

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1 Introduction

This report is the 11th edition of the State of Infectious Diseases in the Netherlands. This annual publication is primarily intended to inform policy makers at the Ministry of Health, Welfare and Sports (VWS), at municipal health services, and at the Centre for Infectious Disease Control at the RIVM. It provides an overarching summary of relevant alerts and (changing) trends in infectious diseases in the Netherlands. Detailed annual reports are available for specific fields (including respiratory infections, sexually transmitted infections, antimicrobial resistance, zoonoses and vaccine-preventable diseases).

This report starts with a chapter on the main national and international infectious disease events that occurred in 2016 (Chapter 2). This chapter includes the annual reported numbers of cases of notifiable diseases in the Netherlands up to 2016.

In Chapter 3, the results of virological surveillance in the Netherlands in 2016 are presented. These results are based on weekly reports of pathogen detections from sentinel laboratories across the Netherlands.

In Chapter 4, surveillance by general practitioners (GPs) in the Netherlands, as coordinated by NIVEL, is described. This chapter gives an overview of the type of data included in the GP surveillance system, the method of data collection, findings and the use and dissemination of the reported data.

In Chapter 5, we provide an overview of notifiable infectious diseases reported in asylum-seekers in the Netherlands in 2016. Numbers of notifications and the incidences of hepatitis B, tuberculosis and malaria in asylum-seekers residing in asylum-seeker centres are presented.

Chapter 6 contains updated estimates of the burden of infectious diseases in the Netherlands for the period 2012–2016. Estimates of disease burden can be informative for public health policy decisions regarding the prioritisation of interventions and preventive measures.

This year, our theme chapter (Chapter 7) reviews specific issues around vaccine-preventable diseases in four vulnerable groups: the young, the old, the pregnant and the immunocompromised ('YOPI'). People with a weakened immune system are at particular risk of infectious disease, but may also respond less well to vaccination. Challenges and opportunities for vaccination of the YOPI are discussed.

2 Notifications and signals

2.1 Introduction

In this chapter, we provide an overview of the reported number of cases of notifiable diseases and key infectious disease alerts (e.g. outbreaks and changing trends) in 2016, previously reported in the weekly reports by the Netherlands Early Warning Committee (http://signalen.rivm.nl/). These include both national and international signals.

Table 2.1 shows the number of notifications of all notifiable infectious diseases in the Netherlands by year of disease onset in the period 2009–2016. In Sections 2.2 to 2.4, we describe the most important signals concerning mandatory notifiable diseases under the Dutch Public Health Act [1]. No group A events were reported in 2016. Section 2.5 deals with signals regarding non-notifiable infectious diseases for the Netherlands. In Section 2.6, we discuss international signals that were included at least five times in the weekly reports of the Netherlands Early Warning Committee, as these constituted long-term outbreaks or were deemed to be of greater public health relevance. We have included information from the year 2017 only when the events started in 2016 and continued into 2017.

Table 2.1 Number of notifications of infectious diseases by year of disease onset, the Netherlands, 2009–2016[1]

Group*	Infectious disease	2009	2010	2011	2012	2013	2014	2015	2016
Group A	MERS-CoV					0[a]	2	0	0
	Polio	0	0	0	0	0	0	0	0
	Severe Acute Respiratory Syndrome (SARS)	0	0	0	0	0	0	0	0
	Smallpox	0	0	0	0	0	0	0	0
	Viral hemorrhagic fever	0	0	0	0	0	1	0	0
Group B1	Diphtheria	0	0	1	1	0	1	5	2
	Human infection with zoonotic influenza virus	0	0	0	0	0	0	0	1
	Plague	0	0	0	0	0	0	0	0
	Rabies	0	0	0	0	1	1	0	0
	Tuberculosis**	1157	1068	1004	956	845	815	861	889
Group B2	Cholera	4	0	3	3	0	3	1	1
	Clusters of foodborne infection***	39	48	42	48	36	28	29	29
	Hepatitis A	180	261	116	124	109	105	79	81
	Hepatitis B acute	215	196	156	175	146	141	108	112
	Hepatitis B chronic	1776	1573	1552	1319	1152	1072	1009	989
	Hepatitis C acute	39	30	72	54	64	53	70	44
	Invasive group A streptococcal disease	255	211	186	178	203	149	171	187
	Measles	11	20	51	35	2659	140	7	6
	Paratyphoid A fever	17	19	14	25	22	9	6	11
	Paratyphoid B fever	16	16	27	18	14	8	23	29
	Paratyphoid C fever	3	0	1	3	2	0	4	0
	Pertussis	6351	3696	7054	13851	3491	9056	6672	5562
	Rubella	7	0	3	1	57	2	1	0
	STEC/enterohemorragic E.coli infection	279	398	649	905	849	754	754	575
	Shigellosis	413	533	584	752	473	360	476	446
	Typhoid fever	27	24	20	17	25	20	17	18
Group C	Anthrax	0	0	0	0	0	0	0	0
	Botulism	0	0	0	2	0	0	0	2
	Brucellosis	3	6	1	3	6	1	9	5
	Chikungunya						61[c]	24	10
	Creutzfeldt-Jakob disease	20	27	27	31	30	25	25	25
	Variant Creutzfeldt-Jakob disease	0	0	0	0	0	0	0	0
	Dengue						13[b]	25	4
	Hantavirus infection	7	19	7	23	4	37	10	31
	Invasive Haemophilus influenzae type b infection	16	31	20	22	18	19	17	28
	Invasive pneumococcal disease (in children 5 years or younger)	42	57	48	43	28	39	43	43
	Legionellosis	256	473	315	308	311	370	438	464
	Leptospirosis	22	29	29	44	27	104	86	95
	Listeriosis	56	69	87	71	74	92	71	95

Table 2.1 (continued) Number of notifications of infectious diseases by year of disease onset, The Netherlands, 2008-2015[1].

Group*	Infectious disease	2009	2010	2011	2012	2013	2014	2015	2016
	MRSA-infection (clusters outside hospitals)	16	14	6	2	11	3	12	5
	Malaria	235	244	242	199	166	285	344	250
	Meningococcal disease	158	143	99	106	109	81	95	153
	Mumps	80	563	609	397	205	40	87	71
	Psittacosis	81	73	70	45	53	41	47	60
	Q fever	2424	411	77	63	20	26	20	14
	Tetanus	1	2	5	2	1	0	1	1
	Trichinosis	1	0	1	0	0	0	0	0
	Tularemia								3[d]
	West Nile virus infection	0	0	0	0	0	0	0	3
	Yellow fever	0	1	1	0	0	0	0	1
	Zika virus								8[d]

1 Until the year 2012, the allocation of a case to a specific year was based on the date of notification to the public health authorities. From 2012 onwards, the allocation of a case to a specific year is based on the date of disease onset or, if unknown, the date of diagnosis or, if unknown, the date of notification. As a result, the numbers presented in this table differ from the numbers presented for the same years in previous State of Infectious Diseases reports. The table was sourced from the Dutch notifiable infectious diseases database Osiris on 17 April 2017. The number of reported cases is subject to change as cases may be entered at a later date or retracted upon further investigation. The longer the time between the period of interest and the date this table is sourced, the more likely it is that the data are complete and the less likely they are to change.

* Notifiable infectious diseases in the Netherlands are grouped according to the legal measures that may be imposed. See http://www.rivm.nl/Onderwerpen/M/Meldingsplicht_infectieziekten for further information.

** The TB numbers presented in this table differ from the numbers presented for the same years in previous State of Infectious Diseases reports. This is due to the fact that TB notifications diagnosed abroad for which treatment in the Netherlands is continued, notifications of Mycobacterium Bovis BCG, and infections caused by non-TB mycobacteria are excluded.

*** Number of clusters, not number of cases.

a Not notifiable until 3 July 2013.

b Not notifiable until 1 July 2014.

c Not notifiable until 1 September 2014.

d Not notifiable until 1 November 2016.

2.2 Group B1 diseases

Human infection with zoonotic influenza virus

A school-aged patient with a history of mild eczema developed a respiratory tract infection in October 2016, a couple of days after visiting a pig farm [2]. The child had entered the pigsty but had not been in direct contact with pigs. The patient's condition deteriorated rapidly and the child required life support through extracorporeal membrane oxygenation. After the start of oseltamivir treatment and removal of mucus plugs, the patient recovered fully. The patient was diagnosed with swine influenza A(H1N1) virus of the Eurasian avian lineage. Pigs at the farm visited by the patient tested positive for the same swine influenza virus. In order to detect human-to-human transmission at an early stage, it was decided to contact all individuals that had been in close contact with the patient without wearing personal protective equipment, and monitor them for symptoms of possible swine influenza infection (cough, fever or conjunctivitis) for 10 days after exposure. In total, more than 80 contacts were monitored. Six contacts developed mild respiratory symptoms including cough, coryza and conjunctivitis during the monitoring period but all tested negative for influenza A virus. Sporadic cases of human infection with swine influenza have been reported worldwide since the late 1950s. Most of these were in individuals exposed to pigs.

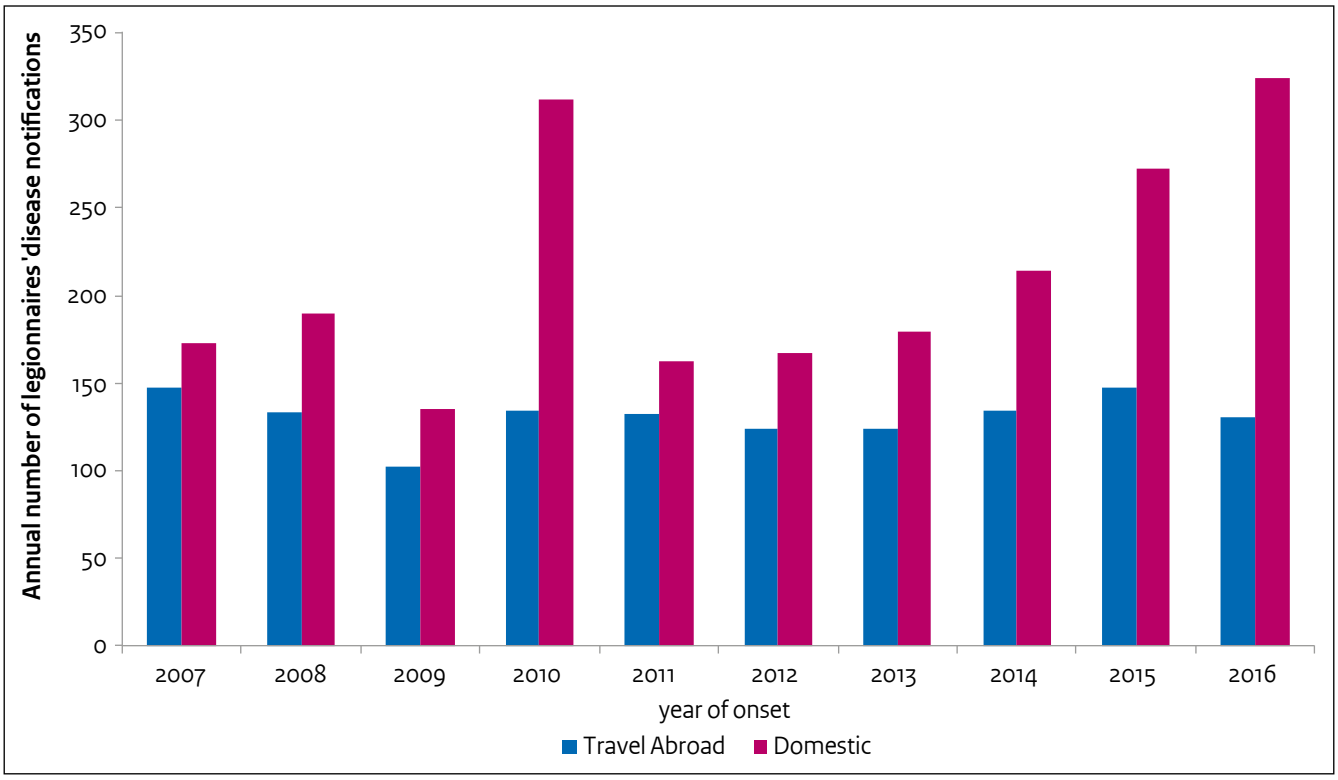
2.3 Group B2 diseases

Hepatitis A

On 19 September 2016, an outbreak investigation was initiated after the notification of two cases of hepatitis A in males, in their 30s and 40s, who fell ill in mid-September [3]. Both cases identified themselves as men who have sex with men (MSM) and reported having had anonymous sexual contact during the EuroPride, which took place in Amsterdam in July/August 2016. Sequencing showed that strains from both cases were identical. Given the international character of the EuroPride, alerts were placed on the Early Warning and Response System and on the ECDC's Epidemic Intelligence Information System for Food- and Waterborne Diseases to inform other European countries. Between 4 July 2016 and 10 May 2017, 124 cases of hepatitis A in males were reported nationally. Of these, 54 identified themselves as MSM. In 2013, 2014 and 2015, 56, 58 and 45 male cases of hepatitis A were reported each year in the Netherlands, respectively. Of these, none were classified as MSM.

Currently, three different hepatitis A strains co-circulate among MSM in the Netherlands and in other European countries. As of 28 April 2017, 13 countries (Austria, Belgium, Denmark, Finland, France, Germany, Ireland, Italy, the Netherlands, Portugal, Spain, Sweden and the United Kingdom (England, Scotland)) had reported 674 confirmed

Figure 2.1: Annual number of Legionnaires' disease notifications, 2007-2016



hepatitis A cases since the beginning of June 2016. Of the 665 cases with available information on gender, 531 were male. Among cases with available information on sexual orientation (n=425), the majority were MSM (n=353). Most cases were infected with a strain linked to the United Kingdom/Spain (n=336), followed by the strain linked to the EuroPride and Taiwan (n=286) and a strain first reported by Germany (n=70). The outbreak in Europe is currently still ongoing and Hepatitis A vaccination has been recommended to MSM as the main prevention measure (4).

STEC

In 2007, surveillance of Shiga toxin-producing Escherichia coli (STEC) O157 was expanded to non-O157 serotypes. This led to a steep increase in STEC notifications. Monitoring of these notifications showed that laboratory findings of STEC were not always associated with acute gastrointestinal disease. A study was undertaken to gain more insight into the relation between positive stool and gastrointestinal disease. Simultaneously, the first steps to optimise STEC surveillance were taken, decreasing the number of notifications. This process was finalised with new notification criteria in July 2016. The most important change in the criteria is that only laboratory-confirmed cases with acute onset of gastrointestinal disease should be notified (not more than 21 days between onset and laboratory test). As a result of these changes in notification criteria, a sharp decrease of cases was observed in 2016 compared with previous years.

2.4 Group C diseases

Zika virus

Zika virus (ZIKV) is a mosquito-borne flavivirus, which caused an extensive outbreak in Latin America with a large number of human infections. Between the start of the outbreak in Brazil in 2015 and March 2017, 61 countries and territories reported the emergence of autochthonous ZIKV cases due to vector-borne transmission. In addition, there were 18 countries with active transmission where the virus already had circulated before 2015, such as Indonesia and Thailand [1]. In the three Dutch Caribbean municipalities: Bonaire, St Eustatius and Saba, the first autochthonous cases were reported in January, June and May 2016, respectively. In 2016, Bonaire reported over 400 confirmed ZIKV infections, whereas St Eustatius and Saba reported a few dozen infections (imported and autochthonous). Curacao, St Martin and Aruba, which are Dutch constituent countries, also reported large numbers of infections. In continental Netherlands, over a hundred import cases of ZIKV infection have been reported, but this is a considerable underestimation since no routine surveillance system is in place for uncomplicated ZIKV infections.

ZIKV received much international attention due to its association with congenital anomalies, including microcephaly, and neurological complications. This led to the declaration of ZIKV as a Public Health Emergency of International Concern (PHEIC) by the World Health Organization (WHO) in February 2016. The PHEIC stressed the importance of enhanced ZIKV surveillance and timely reporting of neurological disorders, in order to gain knowledge on the mechanisms of ZIKV infection and to guide international control efforts [2]. In order to monitor the burden of complicated ZIKV infections in the Dutch Caribbean and continental Netherlands, selected ZIKV infections became notifiable (group C diseases) from 1 November 2016. These include probable and confirmed ZIKV infections in pregnant women, women who have had a (spontaneous) abortion, newborns with congenital anomalies, hospitalised persons, persons with Guillain-Barré syndrome (GBS) and cases who died within four weeks of infection.

Worldwide until March 2017, 31 countries had reported newborns with birth defects including microcephaly and other malformations of the central nervous system, potentially associated with (congenital) ZIKV infection [3]. (Preliminary) results from various Zika pregnancy registries are being published to disseminate the current knowledge with regard to the mechanisms of ZIKV infection during pregnancy and to guide clinicians in the diagnosis and monitoring of these cases [4, 5]. In the Netherlands (both continental and the Caribbean), several ZIKV infections during pregnancy have been reported since the start of the notification requirement. Most of the pregnant cases in continental Netherlands contracted the infection while travelling in a ZIKV-epidemic area in the first trimester of pregnancy. One case of congenital microcephaly has been reported in continental Netherlands, likely due to ZIKV infection. In addition, two cases of GBS likely caused by ZIKV infection were notified in the Netherlands [6]. Twenty-three other countries have reported GBS cases associated with ZIKV infection [3].

Sexual transmission of ZIKV is possible and is of particular concern during pregnancy or the periconceptional period. For countries outside the ZIKV-epidemic areas (i.e. where the main mode of transmission via *Aedes* mosquitoes is absent), comprehensive recommendations have been made for the prevention of sexual transmission of ZIKV in the context of (planned) pregnancy [7]. Since February 2016, 13 countries have reported person-to-person transmission, suspected to be sexual [2]. As well as transmission from male to female, male-to-male and female-to-male transmission have been described [8, 9]. Sexual transmission is not limited to persons having symptoms of ZIKV, given that three cases of sexual transmission originated from asymptomatic men. Although detection of ZIKV-RNA in semen for up to a year

after infection has been described, the longest serial interval between the onset of the disease in one partner and onset in the other in cases of probable sexual transmission is 44 days [10]. In the Netherlands, one case of male-to-female sexual transmission has been reported. Therefore, men who return to the Netherlands from a ZIKV-epidemic area are advised to use a condom for a period of two months to prevent sexual transmission to the (pregnant) partner [5].

Tularemia

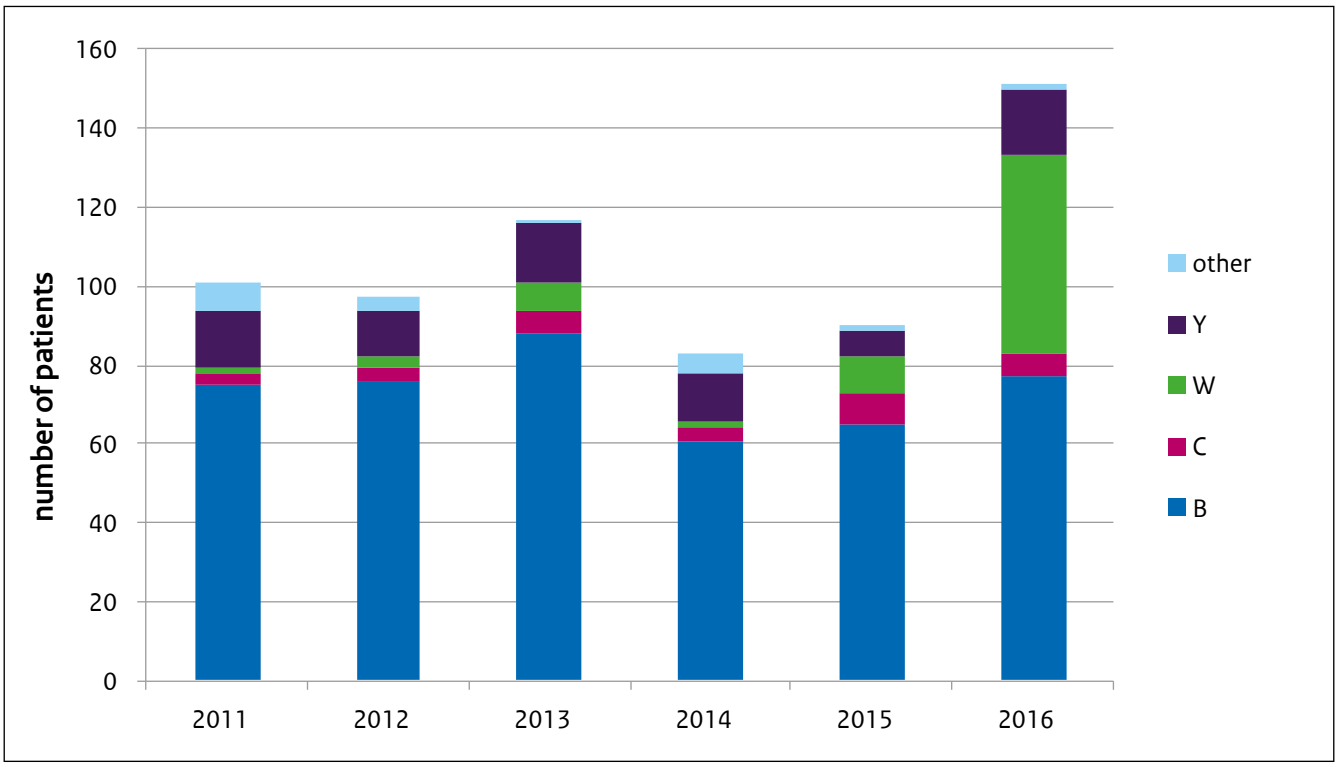
After being absent for decades, tularemia has re-emerged in the Netherlands in both hares and humans. Tularemia is a bacterial zoonosis caused by the bacterium *Francisella tularensis*. Tularemia is primarily a disease of rodents and hares, but the bacterium has been detected in more than 300 animal species, including other mammals, birds, amphibians, reptiles, fish and invertebrates. Humans can become infected through several routes, including tick and deer fly bites, skin contact with infected animals, ingestion of contaminated water or meat, and inhalation of contaminated aerosols or agricultural dust. The signs and symptoms of tularemia vary depending on the entry point of the bacteria.

Since 2011, 14 human cases of tularemia have been reported in the Netherlands, the majority (n=8) in 2016. Before that, the last reported human case was in 1953. Most cases were associated with direct contact with infected hares, or possible exposure to hares, mosquitoes or surface water. Tularemia became notifiable in November 2016 in order to allow source tracing in cases when e.g. hares are suspected to be involved as potential source of infection in order to prevent further cases and to gain more insight into transmission routes, potential reservoirs and vectors of *F. tularensis* in the Netherlands.

Legionellosis

From 2014 to 2016, there was an increasing trend in domestically acquired legionellosis (Legionnaires' disease) in the Netherlands. In 2016, a total of 468 notifications of legionellosis were received, of which 454 were cases of Legionella-pneumonia in Dutch residents. The increase in 2016 was observed only in domestic cases (infection acquired in the Netherlands). With 324 domestic cases in 2016, 273 cases in 2015 and 214 cases in 2014, the number of domestic cases in 2016 was the highest ever reported (Figure 1). The increase was spread over multiple Municipal Health Regions. No large outbreaks were detected that could explain the rise in domestic cases. Several small

Figure 2.2: Annual number of invasive meningococcal disease notifications by serogroup, 2011-2016



geographic clusters were observed in different regions, for which no source of infection was found. In May and June 2016, an increase in cases and clusters was associated with heavy rainfall in the area in the preceding weeks. However, other clusters could not be explained through an association with warm and wet weather. In addition to the increase in May and June, more cases than usual were observed during the winter months (January–February and November–December 2016). Part of the increase may be attributed to improved case detection, since the proportion of PCR-identified cases increased slightly. However, improved diagnostics can explain only a small part of the increase. In 29% of all cases, Legionella-pneumonia was acquired abroad, the most frequently reported country of infection being Italy.

Meningococcal disease

In 2016, 151 patients with invasive meningococcal disease (IMD) were reported in the Netherlands (Figure 2). This is a 50% increase over the average of the past five years (83-117 patients per year). This increase is mainly attributable to an increase in meningococcal serogroup W (MenW) cases. Over the past years, meningococcal serogroup B (MenB) has been responsible for the majority of cases. MenW has been a rare cause of IMD in the Netherlands, responsible for a few cases each year. In 2016, MenW cases increased, with a total of 50 cases reported. MenW was therefore responsible for 33% of all IMD cases in the Netherlands in 2016. Of the MenW cases in 2016, 42% were persons 65 years or older. A similar increase has been reported in the UK, where the number of cases has risen each year since 2009: in 2008/9 MenW accounted for only 1-2% of meningococcal cases; in 2014/15 MenW caused 24% of meningococcal cases in the UK.

In the Netherlands, in 91% of the MenW patients the strain causing disease was identified as W:P1.5,2:F1–1:cc11. In the UK, the clonal complex (cc) 11 strain is associated with severe illness, which often requires treatment in intensive care and a higher death rate than other strains of meningococcal disease (13% case fatality compared with 5-10%) (http://www.meningitis.org/menw). MenW is also associated with different clinical presentations from other serogroups. Rather than meningitis or septicaemia, patients with MenW infection more often present with septic arthritis or a severe respiratory tract infection, such as pneumonia, epiglottitis or supraglottitis. Several adolescents with MenW septicaemia have presented with mainly gastrointestinal symptoms, without the characteristic non-blanching rash, and progressed rapidly to death [6]

Botulism

Botulism is a rare disease in the Netherlands, with occasional reports every few years. In 2016 two unrelated cases of botulism were reported. The first case was a Polish man who presented at the emergency department with mydriasis and impaired swallowing. After being hospitalised, the patient showed progressive deterioration of his motor functions and developed potential life-threatening respiratory failure. Diagnosis, conducted by the Wageningen Bioveterinary Research, showed botulism caused by neurotoxin type B, after which antitoxin was administered. The man recovered fully. Although several products were tested, the source was not identified.

The second case was an elderly woman who was hospitalised due to dysphagia, visual impairment, vomiting and diarrhoea. The woman primarily ate natural products, had no refrigerator and preserved food by canning. On suspicion of botulism, antitoxin was administered. Faecal samples showed *Clostridium botulinum*-type E, which is known to occur in fish. She remembered eating salmon, but nothing was left to test. The woman recovered and was discharged from the hospital with mild dysphagia.

Botulinum toxins are neurotoxic and therefore affect the nervous system. Foodborne botulism is characterised by descending, flaccid paralysis that can cause respiratory failure. Early symptoms include marked fatigue, weakness and vertigo, usually followed by blurred vision, dry mouth and difficulty in swallowing and speaking. Vomiting, diarrhoea, constipation and abdominal swelling may also occur. The disease can progress to weakness in the neck and arms, after which the respiratory muscles and muscles of the lower body are affected. There is no fever and no loss of consciousness. The symptoms are not caused by the bacterium itself, but by the toxin produced by the bacterium. Incidence of botulism is low, but the mortality rate is high in the absence of prompt diagnosis and treatment. The disease is fatal in 5 to 10% of cases.

West Nile virus infection

In 2016, one case of West Nile virus infection was reported in a patient returning from Ontario, Canada.

A week after returning to the Netherlands, the patient was hospitalised with fever, confusion and meningitis. Based on IgM-positive ELISA, the patient was diagnosed with West Nile virus. During her stay in Canada, she had many mosquito bites. West Nile virus has been endemic to Canada since the beginning of the 21st century, with an average of 149 annual cases (range 21–428) in 2012–2016. Autochthonous West Nile virus infections have never been detected in the Netherlands, though sporadic import cases have been reported in recent years. However, the virus is seasonally present in some southeastern European countries, including Italy, Greece and Hungary. West Nile virus is transmitted to humans by mosquitoes. Most people who become infected with West Nile virus do not develop symptoms. About 1 in 5 people who are infected develop a

fever with other symptoms such as headache, body aches, joint pains, vomiting, diarrhoea or rash. Less than 1% of people who are infected develop a serious neurologic illness such as encephalitis or meningitis.

Hantavirus infection

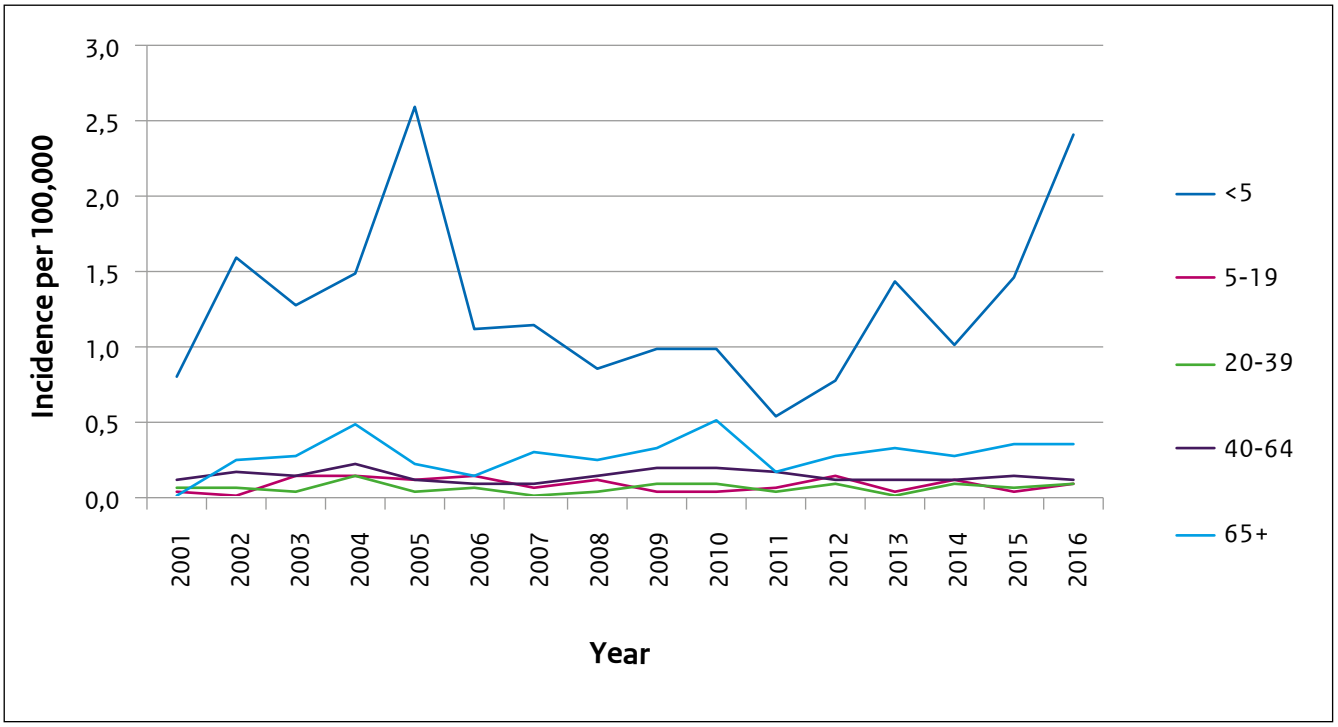
In 2016, the first case of autochthonous Seoul hantavirus infection in the Netherlands was reported. The patient showed clinical symptoms of vomiting, diarrhoea, lower back pain, malaise and elevated liver enzyme levels. The patient had not travelled abroad; he did, however, have extensive contact with rats. After leptospirosis testing was negative, he was tested for hantavirus. The patient showed high IgG and IgM levels against viruses from the Seoul serogroup. He kept feeder rats, of which six out of ten tested PCR-positive for Seoul hantavirus. The rats came from a rat-breeding farm, which was investigated by the Netherlands Food and Consumer Product Safety Authority (NVWA) and the RIVM for the Seoul hantavirus. The majority of the adult rats that were tested were PCR-positive for Seoul hantavirus. Preventive measures to ensure the safety of the employees of and visitors to the rat-breeding farm were undertaken.

Seoul hantavirus is carried and spread by the brown rat (*Rattus norvegicus*) or the black rat (*Rattus rattus*) and the virus has been found in both pet rats and wild rat populations around the world. Most infected humans do not develop symptoms or have very mild symptoms. In rare cases, infection can lead to a type of acute renal disease called haemorrhagic fever with renal syndrome (HFRS), which can include low blood pressure, acute shock and acute kidney failure. The mortality is low but complete recovery can take weeks or months.

Invasive Haemophilus influenzae *type b*

With 44 reported invasive *Haemophilus influenzae* type b (Hib) infections in 2016, the total number of cases was higher than in the past five years, when on average 29 cases were reported. The incidence of Hib infections was highest among children under the age of 5 years (Figure 3). In this age group the total number of Hib infections increased from 7 in 2012 (incidence 0.8/100,000) to 21 in 2016 (incidence 2.4/100,000). Hib vaccination was added to the National Immunisation Programme (NIP) in 1993 and vaccinations are scheduled at 2, 3, 4 and 11 months of age. Of the 21 Hib patients under the age of 5 years, three were too young to be vaccinated, nine were unvaccinated and nine were vaccinated with at least three doses.
The percentage of cases vaccinated and the estimated vaccine effectiveness (96%) are comparable to previous years. The cause of the increase in Hib infections is unknown. In 2005, a similar increase in Hib infections with an unknown cause was observed.

Figure 2.3: incidence of invasive *Haemophilus influenzae* type b infections by age group 2001-2016



2.5 Key signals related to non-notifiable infectious diseases

Tick-borne encephalitis virus

Until recently, tick-borne encephalitis virus (TBEV) was thought to be absent in the Netherlands and all cases of tick-borne encephalitis (TBE) were considered imported from endemic regions. However, on 30 June 2016, the RIVM reported that Dutch *Ixodes ricinus* ticks were RT-PCR positive for TBEV-Eu, without any autochthonous cases having been reported at that point. Subsequently, a person in their 60s without recent travel history suffered from neurological symptoms after a tick bite. TBEV serology was positive and the tick was PCR-positive for TBEV [7]. A few weeks later, a second case of TBEV was reported in a patient who lived near the Sallandse Heuvelrug and had no recent travel history either [8].

TBE is a viral infectious disease that attacks the central nervous system and can result in long-term neurological symptoms and even death. Approximately two-thirds of human TBEV infections are asymptomatic. The European subtype is associated with milder disease than the Far Eastern subtype, with mortality rates of 0.5–2%, and severe neurological sequels in up to 10% of patients. Ticks, specifically hard ticks of the family *Ixodidae*, act as both the vector and reservoir for TBEV. The main hosts are small rodents, with humans being accidental hosts. Large animals serve as feeding hosts for the ticks, but do not play a role in maintaining the transmission cycle of the virus [9].

Salmonella *Enteritidis*

Between May 2015 and March 2017, a large international outbreak of *Salmonella* Enteritidis with uncommon Multiple Locus Variable number tandem repeat Analysis (MLVA) profiles 2-9-7-3-2 and 2-9-6-3-2 was ongoing in multiple European countries. Two distinct clusters were identified using Whole Genome Sequencing (WGS), with similar MLVA profiles in both clusters. A total of 565 cases were notified, of which 202 (36%) were in the Netherlands. The majority of cases were reported in 2016 (n=174), with a sharp increase from May and a peak in September. A case-control study was conducted in the Netherlands to identify the source of the outbreak. Food questionnaires administered by municipal health services (GGD) showed that patients were more likely to have eaten in a restaurant or other food establishment than controls. No specific food item was identified from the questionnaires. Food trace-back investigations were performed by the Netherlands Food and Consumer Product Safety Authority (NVWA) in collaboration with the Netherlands Controlling Authority Eggs (NCAE) among cases who ate in food establishments, which led to the identification of eggs imported from Poland as the vehicle of infection. WGS confirmed that the strains isolated from the eggs were identical to those in both outbreak clusters. After control measures were implemented at farm and distribution level, the number of outbreak-related cases drastically decreased.
The collaboration between MHS, laboratories, the NVWA, NCAE and the RIVM was crucial in identifying the source of the outbreak, and highlighted the importance of the rapid exchange of information in stopping international outbreaks.

2.6 International key signals

Measles

In 2016, measles outbreaks were seen in a number of EU/EEA countries; and an increase in the number of cases continues to be observed in 2017. Since February 2016, a measles outbreak has been ongoing in Romania and cases continue to be reported despite implemented and ongoing reinforced vaccination activities. As of 17 February 2017, 3071 cases have been reported to the National Institute of Public Health in Romania. According to data reported to ECDC, in the 12-month period from 1 February 2016 to 31 January 2017, eight EU/EEA countries (Austria, the Czech Republic, France, Germany, Ireland, Italy, Spain and the United Kingdom) reported a total of 34 measles cases whose probable country of infection was Romania. Thirty of the cases were reported between September 2016 and 31 January 2017.

Yellow fever

In 2016, multiple yellow fever outbreaks have been ongoing globally. On 21 January 2016, the International Health Regulation (IHR) focal point in Angola notified the WHO about an ongoing yellow fever outbreak. Until 23 December 2016, when the end of the outbreak was declared, the Angolan Ministry of Health notified 4306 yellow fever cases, 884 of which were laboratory confirmed and 376 were fatal. The case–fatality ratio among confirmed cases was 13.7% (121 of 884). All provinces in Angola reported cases during the outbreak. Since April 2017, the number of new cases has declined.

Between 1 January 2016 and 26 October 2016, the Democratic Republic of Congo reported 2909 suspected cases of yellow fever and 78 confirmed cases, of which the majority had a recent history of travel to Angola. Of the 78 confirmed cases, 16 have died since the beginning of the outbreak in 2016. More than 30 million people were vaccinated in the two countries in emergency vaccination campaigns. This key part of the response included immunisation campaigns and preventive campaigns in remote areas up until the end of the year to ensure vaccine protection for as many people in all areas of risk as possible [10].

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3 Virological surveillance in the Netherlands – Virological weekly reports

3.1 Introduction

In this chapter we provide an overview of the laboratory diagnosis of pathogens, mainly viruses, reported in the virological weekly reports. Up to 21 medical microbiological laboratories, located throughout the country, provide data for this surveillance system (Figure 3.1). The weekly voluntary reporting of these data makes the surveillance system valuable for the early detection of outbreaks and monitoring of trends in viral infections [1]. Since 2016, partly in response to the Zika virus epidemic, considerable effort has been made to include virological laboratories in the Caribbean municipalities and the overseas territories of the Netherlands in the virological surveillance. We anticipate that the virological weekly reports will be a valuable tool for gaining insight into the circulation of viruses in that part of the Caribbean. However, to date, data from these laboratories are not yet available in the weekly reports.

Table 3.1 shows the number of positive diagnoses reported in the virological weekly reports in 2016, as well as for the seven previous years. In addition, Figure 3.2 shows the stacked numbers of positive diagnoses of the most frequently reported pathogens potentially causing respiratory (a) or gastrointestinal (b) complaints. In Section 3.2 we provide a short explanation of noteworthy events and observed trends in 2016.

Figure 3.1: The location of laboratories submitting data to the virological weekly reports (n=21)

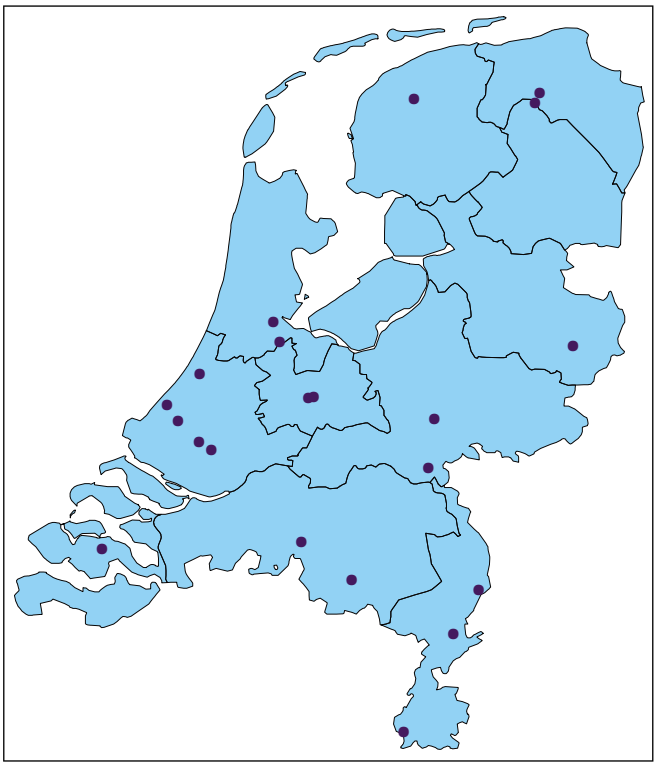

Table 3.1 Number of positive laboratory diagnoses reported in the virological weekly reports, summed by year

Pathogen	2009	2010	2011	2012	2013	2014	2015	2016
Viruses								
Adenovirus 40/41	229	296	185	142	141	155	128	141
Adenovirus non40/41	424	523	288	197	357	226	202	162
Adenovirus untyped	675	712	648	777	746	887	992	1309
Astrovirus[a]	-	-	15	55	81	85	95	124
Bocavirus[a]	-	-	107	136	111	107	114	159
Chikungunyavirus[b]	-	-	-	-	-	-	-	23
Coronavirus	192	429	288	307	377	318	575	712
Dengue virus	160	225	122	209	123	101	132	182
Enterovirus	1224	1499	1035	1212	786	1264	783	1156
Hantavirus	7	17	3	10	4	47	7	9
Hepatitis A virus	96	107	63	53	38	63	49	65
Hepatitis B virus	1553	1403	1377	1024	678	633	704	710
Hepatitis C virus	822	815	679	513	386	385	405	340
Hepatitis D virus	10	13	11	7	9	12	13	9
Hepatitis E virus	18	31	37	50	67	205	303	307
HIV 1	1173	1186	1135	886	739	677	698	688
HIV 2	5	6	5	2	3	1	3	1
hMPV	224	419	389	298	469	385	651	542
HTLV	3	3	3	4	1	2	2	2
Influenza A virus	7419	158	872	891	2333	899	3195	3128
Influenza B virus	120	63	466	64	981	47	698	1351
Influenza C virus	6	3	0	0	1	0	3	0
Measles virus	7	13	8	9	212	55	8	4
Mumps virus	22	144	190	95	65	24	45	43
Norovirus	1991	4063	2771	2898	2866	2836	2979	3774
Parainfluenza type 1	208	85	114	41	138	76	149	55
Parainfluenza type 2	127	65	56	53	74	66	72	108
Parainfluenza type 3	247	232	282	238	291	218	344	411
Parainfluenza type 4	84	65	51	36	76	53	122	65
Parainfluenza untyped	107	81	102	70	54	19	28	17
Parechovirus	373	706	329	397	187	354	227	298
Parvovirus	418	221	214	216	130	175	123	94
Rhinovirus	1994	1906	1987	1780	2049	2193	2410	2589
Rotavirus	1936	2180	1505	1288	1496	607	1323	680
RS-virus	2030	2778	2466	2043	1864	1455	1870	2085
Rubella virus	15	17	15	15	47	27	16	17
Sapovirus[a]	-	-	9	32	59	129	140	159
West-Nile virus	0	1	1	0	0	0	0	1
Zika virus[b]	-	-	-	-	-	-	-	26

Table 3.1 (continued) Number of positive laboratory diagnoses reported in the virological weekly reports, summed by year

Pathogen	2009	2010	2011	2012	2013	2014	2015	2016
Bacteria								
Chlamydia psittaci	30	29	37	23	23	16	18	32
Chlamydia pneumoniae	64	35	43	60	27	20	31	57
Chlamydia trachomatis	16,486	18,454	19,108	21,234	20,908	24,191	25,017	27,111
Chlamydia untyped	5	10	3	5	9	8	28	36
Coxiella burnetii	786	417	136	83	89	130	125	89
Mycoplasma pneumoniae	414	541	917	775	325	436	525	610
Rickettsiae	36	10	23	14	7	12	17	10
Total virological weekly reports annually	1096	1087	1082	1038	987	993	1068	1020
Annual number of laboratories which reported ≥50 weeks	20	21	20	18	16	16	20	17

Abbreviations: HIV = human immunodeficiency virus; hMPV = human metapneumovirus; HTLV = human T-cell lymphotropic virus; RS-virus = respiratory syncytial virus.

a Included in the virological weekly reports since 2011.

b Included in the virological weekly reports since 2016.

3.2 Signals based on data from the virological weekly reports in 2016

Gastrointestinal pathogens

A substantial increase in reported diagnoses of norovirus was observed starting in week 38 of 2016 (Figure 3.2b). The total number of reported diagnoses of norovirus in 2016 was 3774. Taking into account the slight annual fluctuation of reporting laboratories (see bottom of Table 3.1), this corresponds to an average of 3.7 positive norovirus diagnoses per laboratory per week. In 2015 and 2014, an average of 2.8 and 2.9 norovirus diagnoses were reported per laboratory per week, respectively. These numbers suggest that the norovirus season in 2016 had a higher incidence than in previous years. This observation from the virological weekly reports was confirmed by data on all-cause gastroenteritis consultations in children under 5 years of age from the Dutch sentinel general practice network (see Chapter 4).

In the 2013/14 rotavirus epidemiologic year (August 2013 to July 2014) the number of reported rotavirus diagnoses was unexpectedly low (Table 3.1) [1]. A total of 551 rotavirus diagnoses were reported, compared with an average of 1440 (range 1237–1577) in the three previous rotavirus seasons (August 2010–July 2013). In the next epidemiologic year, 2014/15, a fairly normal rotavirus season was observed in the virological data, with 1383 reported positive diagnoses [2]. In 2015/16, the number of reported diagnoses was again low (n=673). The current (2016/17) season follows the usual rotavirus season pattern. These observations might indicate a transition from an annual rotavirus pattern to a biennial pattern in the Netherlands.

Respiratory pathogens

Figure 3.2a clearly shows the seasonal variation in the prevalence of respiratory pathogens, mainly of influenza A and B virus and RS-virus, whereas the other respiratory pathogens display a more constant distribution over the year. In 2016, high numbers of influenza B virus (n=1351) were reported compared with previous years (Table 3.1, Figure 3.2a). This was also observed in the NIVEL influenza surveillance, where the Victoria lineage of influenza B virus appeared to be the main circulating lineage. This lineage was not included in the trivalent influenza vaccine in 2015–2016 [3].

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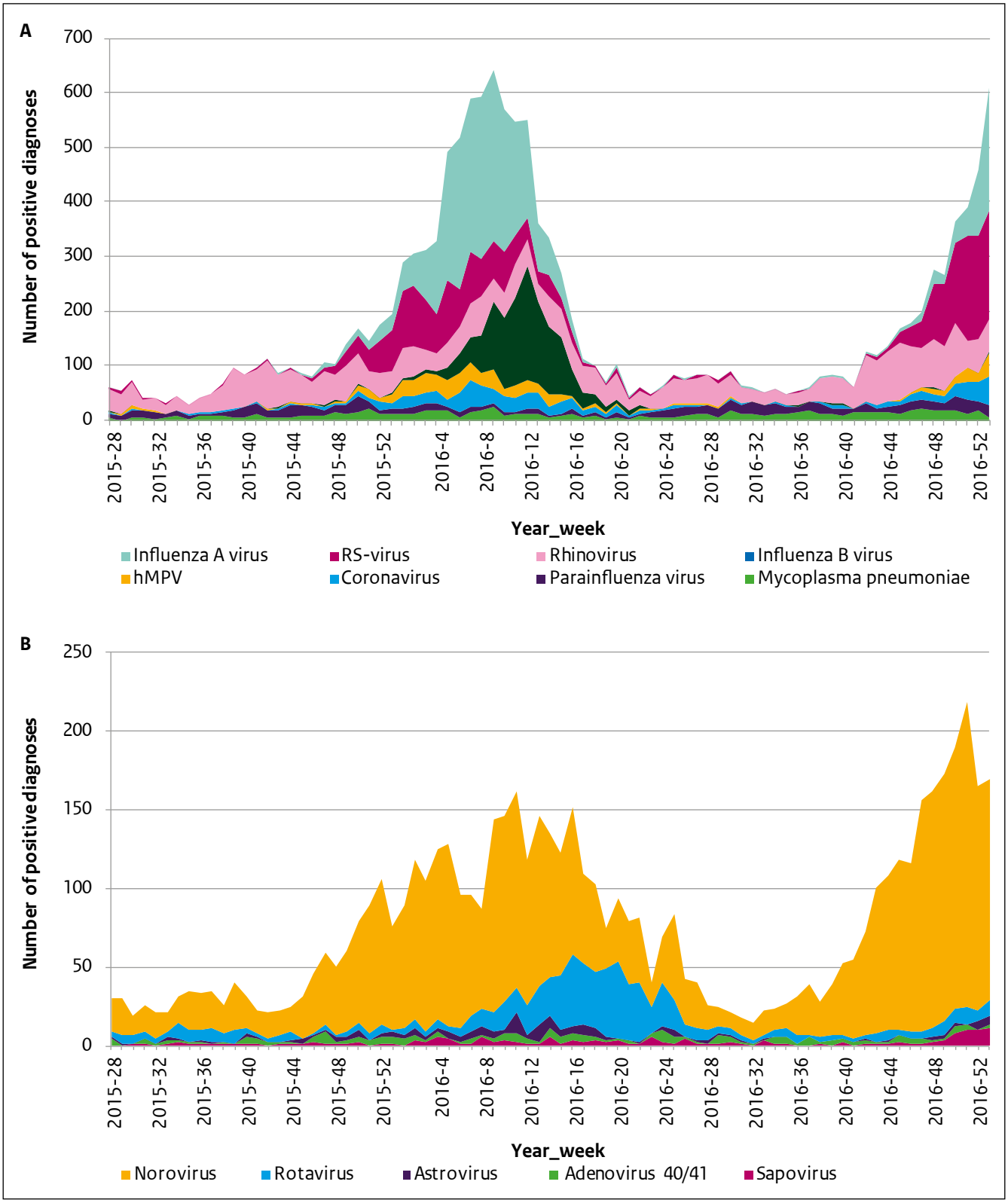
Figure 3.2: Weekly number of positive diagnoses of the eight most frequently reported pathogens potentially causing respiratory complaints (A) and the five most frequently reported pathogens potentially causing gastrointestinal complaints (B) in the period 2015 week 27 till 2016 week 52 (hMPV = human metapneumovirus, RS-virus = respiratory syncytial virus)



4 Surveillance of infectious diseases based on electronic medical records in primary care in 2016

4.1 Introduction

In the Netherlands, several sources of information are being used for the surveillance of infectious diseases, ranging from self-reported symptoms of respiratory infections (www.degrotegriepmeting.nl) to mandatory disease notifications by physicians and laboratories. A comprehensive overview of infectious disease surveillance systems in the Netherlands was published in the 2015 edition of the State of Infectious Diseases [1].

Electronic medical records (EMR) kept by general practitioners (GPs) provide a fairly complete picture of the population's health, since every Dutch citizen is required to be enlisted in a general practice and GPs act as gatekeepers for specialised, secondary health care. Clinical diagnoses, recorded as part of the routine care process, can be used for the surveillance of communicable and other diseases [2]. This kind of information is referred to as 'syndromic surveillance' [3].

4.2 NIVEL Primary Care Database

The NIVEL Primary Care Database comprises a near real-time (weekly) collection of longitudinal data from the EMR of a large sample of general practices and other primary health care providers in the Netherlands. About 300 of the 500 participating general practices use an information system that allows automatic weekly data extraction from medical records. They do not actively report patients and do not take laboratory samples for surveillance purposes, but make their EMR available for automatic, pseudonymised data extraction.

A subset of 38 general practices, the sentinel practices, actively report on patients who consult them for an acute influenza-like illness (ILI), defined according to the 'Pel criteria' [4]. The GP is asked to take a nose and throat swab from two ILI patients per week. The National Institute for Public Health and the Environment (RIVM) (Infectious Diseases Diagnostics and Screening Laboratory) tests the specimens for influenza and a selection of other respiratory viruses.

EMR data are extracted overnight every Monday/Tuesday and are processed at NIVEL on Tuesday mornings. After data quality checks and checks on deviations from normal patterns, results are published in the weekly 'NIVEL Surveillance Bulletin' on the NIVEL website on Tuesday afternoons: www.nivel.nl/surveillance. This bulletin summarises the most important results. An update with the results from the respiratory virus diagnostics on ILI patient specimens is published on Wednesday afternoons. About 80 professionals in infectious disease control and other interested parties have signed up to receive an email on the publication of a new bulletin.

Dutch GPs use the International Classification of Primary Care (ICPC, version 1) [5] to record symptoms and diagnoses of consulting patients. Weekly rates for specific diagnoses, as well as clusters of diagnoses, are calculated as the number of patients with one or more records for the health problem concerned, using the total number of patients enlisted in the practice as denominator (weekly prevalence rate). Stratified rates are calculated for each gender, various age groups, and the different geographic regions. In addition, age-standardised prevalence ratios are calculated for the geographic regions using the age distribution of the Dutch population (direct standardisation).

Figure 4.1: Geographical distribution of general practices contributing to the NIVEL Primary Care Database, 2016

Data from a general practice are included only if the practice is defined as 'active' during the week. This status is granted when the number of recorded diagnoses is at least 0.45% of the total number of enlisted patients during at least three days of the reported week, running from Monday to Sunday.

Weekly rates are visually inspected for unusual patterns of disease, while CUSUM (cumulative sum) algorithms are calculated for aberration detection [6]. Deviations from normal disease patterns, 'signals', are reported to the RIVM Early Warning Committee ('Signaleringsoverleg', see Chapter 2). Regional signals are notified to the municipal health services (GGD). Weekly numbers on ILI (sentinel practices) and ARI (EMR data) are submitted to the database hosted by the European Surveillance System (TESSy), jointly coordinated by the European Centre for Disease Prevention and Control (ECDC) and the WHO Regional Office for Europe, for the European influenza surveillance.

4.3 Privacy

Taking into account the privacy regulations in the Netherlands, a trusted third party (TTP) removes directly and indirectly identifying patient information and assigns each patient a pseudonym, before transferring data to NIVEL. Thus, NIVEL is never in the possession of personally traceable information. At NIVEL, the data are stored in a secured, NEN7510-certified database, from which weekly data extracts are generated after applying a second pseudonymisation step (two-way pseudonymisation) [7]. Dutch law allows the use of electronic health records for research purposes under certain conditions. According to this legislation, neither obtaining informed consent from patients nor obtaining approval from a medical ethics committee is obligatory for this type of observational study containing no directly identifiable data (Dutch Civil Law, Article 7:458) [8]. The privacy protocol and all agreements are laid down in a governance structure, providing stakeholders with control over the use of the data and its results.

4.4 Output and data use in 2016

In 2016, the mean number of reporting general practices was 303 (range 265–317) and the mean denominator population in these practices was 1.2 million (range 1.0–1.2, which accounts for 6–7% of the total Dutch population). The participating practices are well spread over the country, although the number of participants is limited in the South and South-West of the Netherlands (Figure 4.1). The age distribution of the enlisted population was representative of the general Dutch population.

In 2016, the NIVEL weekly surveillance bulletin reported on the following symptoms and diseases: influenza-like illness (reported by the sentinel practices), the diagnostic cluster |of acute respiratory infections, pneumonia, the cluster 'vomiting, diarrhoea or presumed gastrointestinal infection', fever, measles, viral exanthema, mumps, conjunctivitis, acute otitis media, whooping cough, strep throat/scarlet fever, and hay fever/allergic rhinitis. In addition, patterns of some other infectious diseases were explored ad hoc, based on a reported signal from other sources reporting to the Weekly Early Warning Committee (e.g. hepatitis, scabies).

4.5 Overview of results in 2016

- *Respiratory diseases:* GP consultation rates for acute respiratory infections followed the expected seasonal patterns (Figure 2a). During the last weeks of 2016, relatively high rates were observed for acute otitis media (data not shown) and pneumonia among children below the age of 5 years (Figure 2d). This was in line with relatively high incidences of ILI during these weeks (Figure 2b). Whooping cough and strep throat/scarlet fever consultations were comparable to previous years (not shown).
- *Gastrointestinal diseases:* consultation rates were highest for young children (0–4 yrs), as usual (Figure 2e). Rates were relatively low during the first weeks and relatively high during the last weeks of 2016 compared with previous years. A study on associations with rotavirus infections is in progress.
- *MMR:* Consultation rates for measles, mumps or rubella among 0–4-year-olds were low throughout the year (data not shown).
- *Fever:* From week 6, 2016, the consultation rate for fever started was statistically significantly higher ($p<0.01$ based on CUSUM rates) than the average rates in 2012–2015 among children aged 5 to 14 years (Figure 2f). The peak was reached in week 8, after which rates started to decline and remained at normal levels from week 15. The signal was not confirmed by other surveillance sources at the RIVM and the increased rates remained unexplained. Other surveillance sources at the RIVM could not verify this signal and the increased rates remained unexplained.

Figure 4.2: Selected results from NIVEL Primary Care Database – surveillance: weekly consultation rates (per 100,000 population), 2013–2016

a. Acute respiratory infections
(excl. pneumonia)
all ages

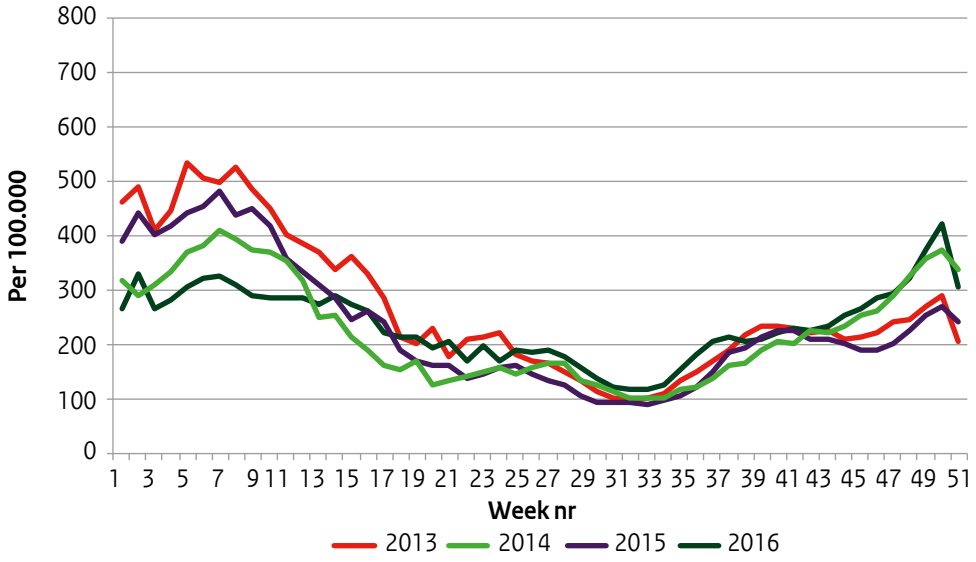
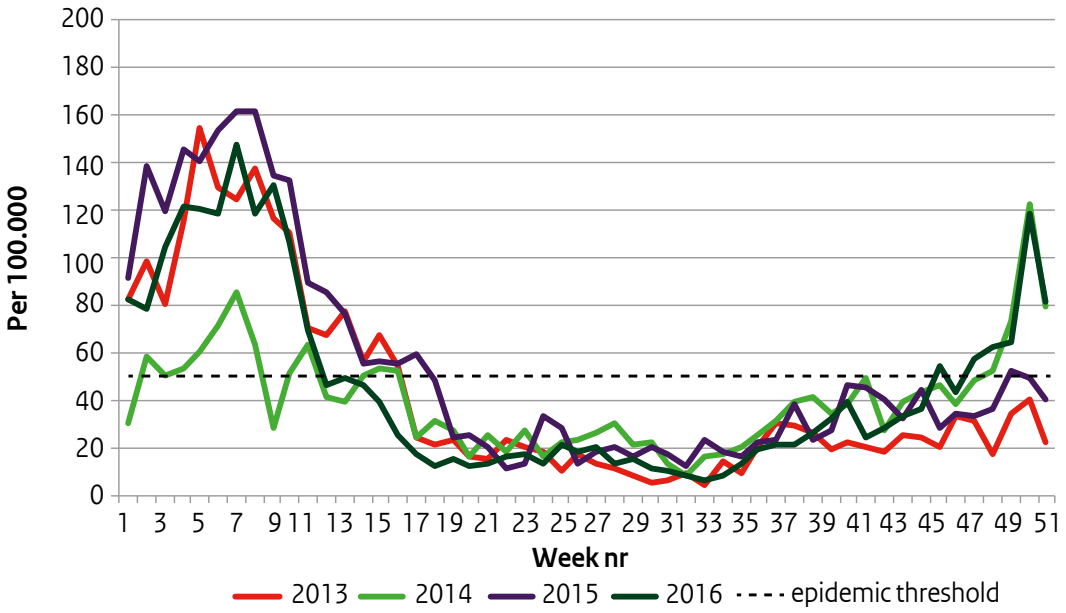


Figure 4.2: (continued) Selected results from NIVEL Primary Care Database – surveillance: weekly consultation rates (per 100,000 population), 2013–2016

b. Influenza-like illness (ILI)
all ages



c. Pneumonia
all ages

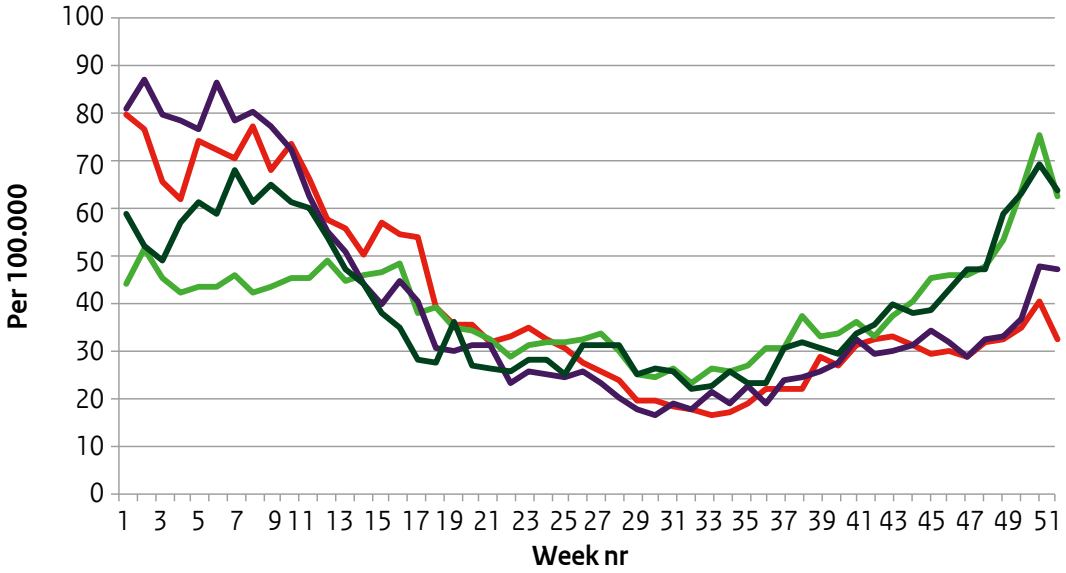
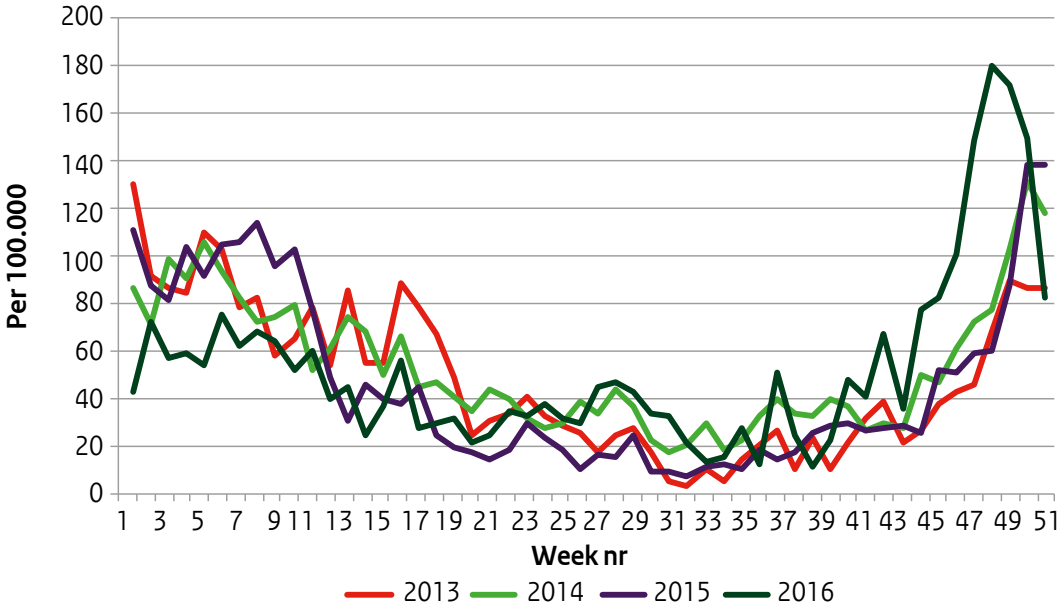


Figure 4.2: (continued) Selected results from NIVEL Primary Care Database – surveillance: weekly consultation rates (per 100,000 population), 2013–2016

d. Pneumonia
age 0–4 years



e. Vomiting, diarrhoea or gastro-intestinal infection
age 0–4 years

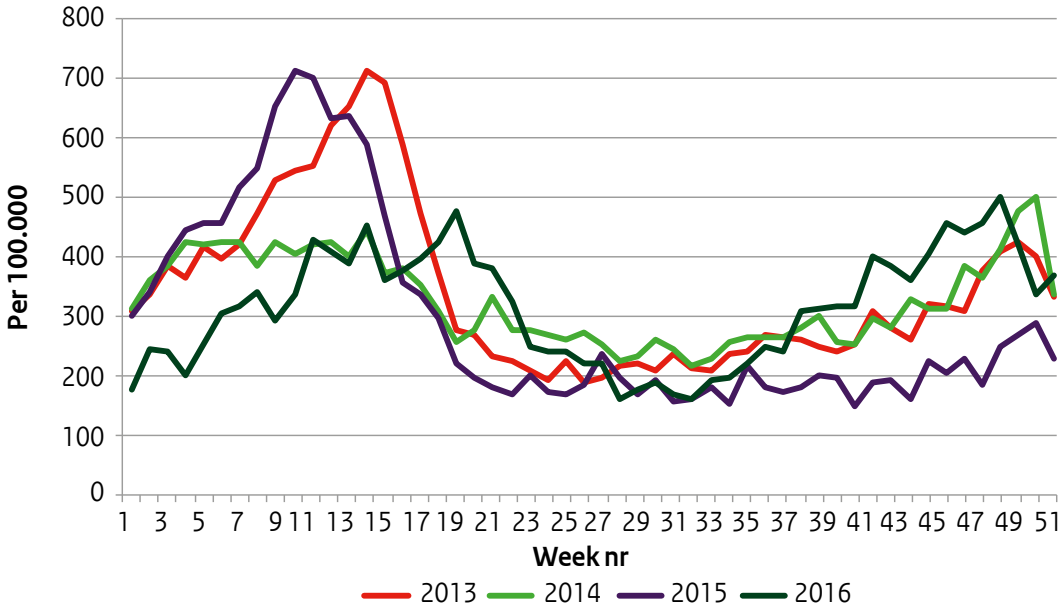
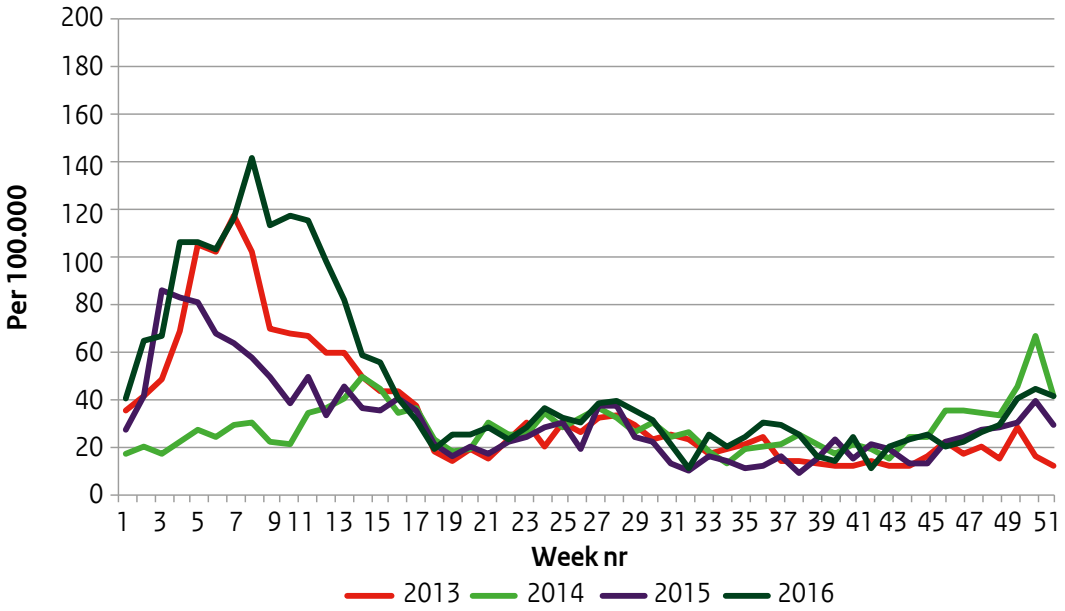


Figure 4.2: (continued) Selected results from NIVEL Primary Care Database – surveillance: weekly consultation rates (per 100,000 population), 2013–2016

f. Fever
age 5–14 years



4.6 Concluding remarks

The NIVEL Primary Care Database uses data from the electronic medical records of general practices for surveillance purposes. The strengths of this system are the professional basis of the clinical diagnoses, the use of routinely recorded information without additional burden for GPs, and the continuous, fully automated data extraction. The coverage of the surveillance system is substantial, with more than 1 million patients spread over most of the country. Although the focus of the NIVEL surveillance system is mainly on infectious diseases, all GP-recorded symptoms and diagnoses can be monitored on a weekly basis. However, local outbreaks may remain unnoticed due to relatively small numbers. Although the surveillance of clinical diagnoses by GPs may identify potential outbreaks earlier than laboratory surveillance, the lack of laboratory test information may hamper the interpretation of signals in symptoms like fever or cough or in broadly defined diagnoses like acute respiratory infections.

A strength of the Dutch infectious disease surveillance overall is the combination of different data sources. By combining information from different data sources, epidemiologists at the RIVM can gain a comprehensive view of the state of infectious diseases in the Netherlands.

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5 Notifiable infectious diseases in asylum-seekers in the Netherlands

5.1 Introduction

In the Netherlands, the number of people applying for asylum nearly halved in 2016 compared with 2015. In 2016, the Netherlands received approximately 35,000 asylum applications compared with 60,000 in 2015 (Figure 5.1). In 2016, the majority of asylum-seekers originated from Syria; this is comparable to 2015. There was, however, a shift in the most reported countries of origin. In 2015, Iraq and Iran were in the top five countries of origin. In 2016, we see more people coming from Albania and former Yugoslavia.

Since 2012, notifiable infectious diseases among asylum-seekers in the Netherlands have been monitored using Osiris, the Dutch notifiable infectious diseases surveillance system. Data on notifiable infectious diseases are collected by the municipal health services. The monitoring of tuberculosis in asylum-seekers using Osiris started in 2014 by adding a question whether or not the patient resides in an asylum centre. In this chapter, we provide an overview of notifiable infectious diseases reported in asylum-seekers residing in asylum centres in the Netherlands.

5.2 Methods

The surveillance of notifiable infectious diseases in asylum-seekers is based on disease notifications in asylum-seekers living in asylum centres and collective reception centres of the Central Agency for the Reception of Asylum-Seekers (COA). Infectious diseases in asylum-seekers not living in COA-centres (but in, e.g., municipal emergency shelters) and refugees with a residence permit living in the community (including family reunification) cannot be identified from this surveillance.

In this chapter, we have used the occupancy at COA-centres to calculate the prevalence of a disease. For the occupancy per year, we calculated the mean of the occupancy on the first day of each month from January of the given year until January of the year after. Even though fewer asylum-seekers were coming into the Netherlands in 2016, the mean occupancy at COA-centres was higher in 2016 than in 2015 (Figure 5.2). Due to the high influx in the second half of 2015, occupancy at COA-centres was high at the beginning of 2016. It decreased slowly during the course of the year.

Figure 5.1: Asylum applications in the Netherlands 2012–2016 by country of origin [1, 2]

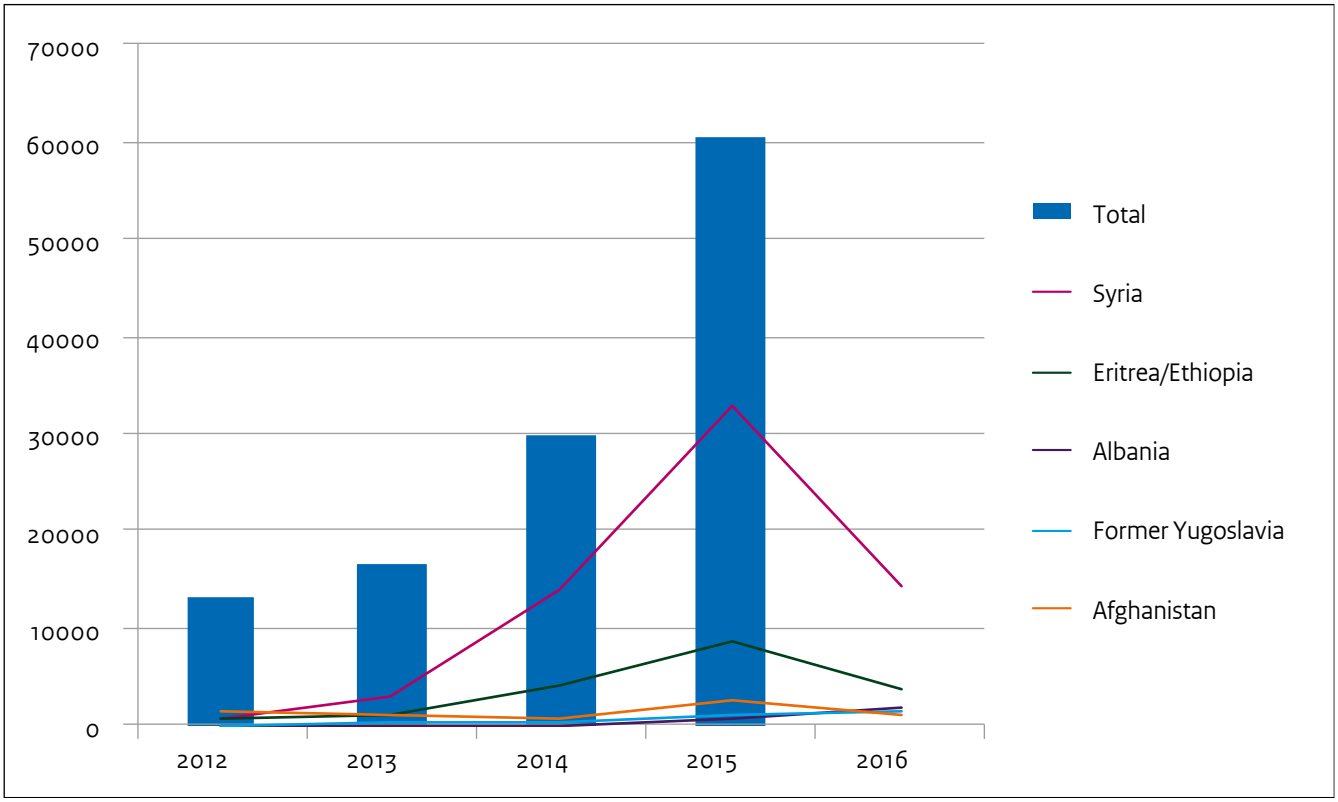
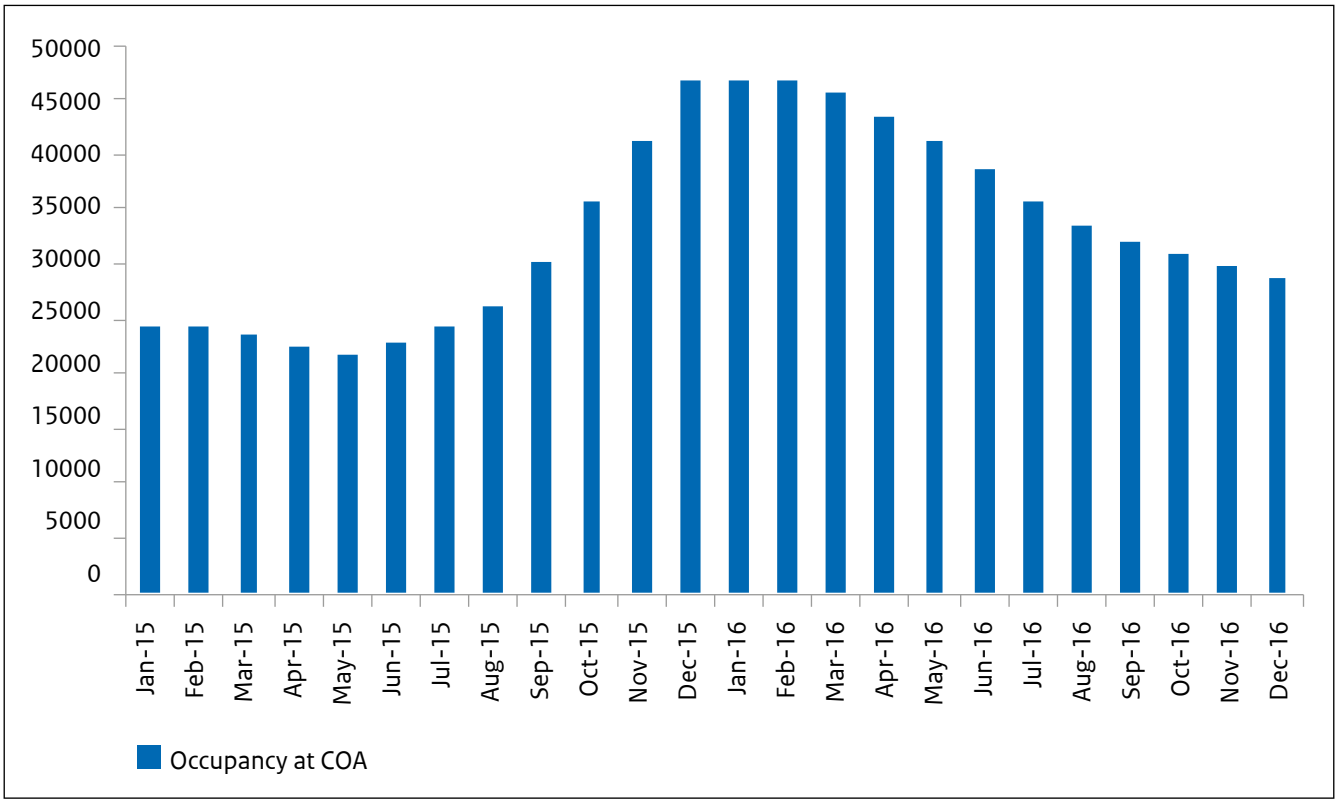


Figure 5.2: Occupancy at COA-centres January 2015–December 2016



5.3 Overview of notifiable infectious diseases in residents of COA-centres

Table 5.1 shows the number of notifications of infectious diseases reported in asylum-seekers living in asylum centres in the Netherlands by year of disease onset in the period 2013–2016. In this section, we discuss the most frequently reported infectious diseases in asylum-seekers: tuberculosis, chronic hepatitis B and malaria.

Table 5.1 Number of notifications of notifiable infectious diseases in asylum-seekers by year of disease onset and as percentage of total notifications in the Netherlands, 2013–2016*

Group**		2013 (%)	2014 (%)	2015 (%)	2016 (%)
Group A[1]		0	0	0	0
Group B1[2]	Tuberculosis[5]	n.a.	79 (9.7)	104 (12.1)	95 (10.7)
Group B2[3]	Hepatitis A	2 (<1.0)	2 (1.9)	9 (11.4)	4 (4.9)
	Hepatitis B Acute	3 (2.1)	2 (1.4)	1 (<1.0)	1 (<1.0)
	Hepatitis B Chronic	70 (6.1)	91 (8.5)	106 (10.6)	107 (10.8)
	Invasive group A streptococcal disease	0	2 (1.3)	1 (<1.0)	0
	Measles	1 (<1.0)	0	1 (14.3)	0
	Paratyphi C	0	0	1 (25.0)	0
	Pertussis	8 (<1.0)	19 (<1.0)	8 (<1.0)	6 (<1.0)
	STEC/enterohemorrhagic E.coli infection	0	1 (<1.0)	1 (<1.0)	2 (<1.0)
	Shigellosis	0	3 (<1.0)	4 (<1.0)	2 (<1.0)
	Typhoid fever	0	0	2 (11.8)	1 (5.6)
Group C[4]	Brucellosis	0	0	1 (11.1)	0
	Hantavirus infection	0	1 (2.7)	0	0
	Invasive pneumococcal disease (in children 5 years or younger)	0	0	1 (2.3)	0
	Legionellosis	0	0	1 (<1.0)	0
	Malaria	6 (4.2)	106 (37.2)	126 (36.3)	42 (16.8)
	Meningococcal disease	0	1 (1.2)	0	2 (1.3)
	Mumps	0	0	1 (1.1)	0
	Psittacosis	0	1 (2.4)	0	0

* The table was sourced from the Dutch notifiable infectious diseases database Osiris on 24 April 2017. The number of reported cases is subject to change as cases may be entered at a later date or retracted on further investigation. The longer the time between the period of interest and the date this table is sourced, the more likely it is that the data are complete and the less likely they are to change.

** Notifiable infectious diseases in the Netherlands are grouped in accordance with the legal measures that may be imposed.

1 0 cases for MERS-CoV, polio, SARS, smallpox and viral haemorrhagic fever.

2 0 cases for diphtheria, human infection with zoonotic influenza virus, plague and rabies.

3 0 cases for cholera, clusters of foodborne infection, hepatitis C acute, paratyphi A, paratyphi B and rubella.

4 0 cases for anthrax, botulism, chikungunya, Creutzfeldt-Jakob disease, Variant Creutzfeldt-Jakob disease, dengue, invasive haemophilus influenza type b infection, leptospirosis, listeriosis, MRSA infection (clusters outside hospitals), q fever, tetanus, trichinosis, West Nile virus and yellow fever.

5 It was not until 2014 that the question 'whether or not the patient is living in an asylum centre' was added to the tuberculosis questionnaire.

N.a. = not available

Tuberculosis

All asylum-seekers from countries with a TB incidence of more than 50 per 100,000 population are screened for TB within a week of arrival in the Netherlands. Asylum-seekers and other immigrants from countries with an incidence of more than 200 per 100,000 population as estimated by the WHO and from otherwise specified high-risk countries, such as Eritrea, are invited for follow-up chest X-ray screening every six months for two years [3]. In addition, systematic testing and treatment of latent TB infection is being piloted in at-risk populations such as asylum-seekers from high-incidence countries.

In 2016, 95 cases of tuberculosis (TB) in asylum-seekers staying at COA-centres were notified, accounting for 10.7% of all TB notifications in the Netherlands. This is a slight decrease compared with 2015, when 104 cases of TB were notified, accounting for 12.1% of all TB notifications in the Netherlands (Table 5.1). The largest group of asylum-seekers notified with TB originated from Eritrea/Ethiopia, with 55 cases in 2016 and 68 cases in 2015 (Table 5.2). Since 2013, most asylum-seekers have originated from Syria and among the latter TB is relatively uncommon. The incidence of TB notifications per 100 asylum-seekers staying at COA-centres in 2015 and 2016 was 0.3. In 2016, the incidence of TB notifications in asylum-seekers from Eritrea/Ethiopia (1.2%) was slightly lower than in 2015 (Table 5.2). In 2016, TB was almost exclusively reported in asylum-seekers in the age groups 5–17 and 18–50. This is comparable to previous years (Table 5.3).

In 2016, 20 of 95 (21%) asylum-seekers with TB living in asylum centres in the Netherlands were diagnosed with infectious pulmonary TB. This is a decrease compared with 2015, when 27 of 104 (26%) asylum-seekers with infectious pulmonary TB were reported. Between 2010 and 2016, the proportion of infectious pulmonary TB cases in the total number of TB patients in the Netherlands varied between 19% and 26%.

Table 5.2 Tuberculosis notifications in asylum-seekers by country of birth and occupancy at COA-centres by country of origin, 2014–2016

Country of birth	2014			2015			2016		
	Notifications	Occupancy COA	Notifications per 100 persons	Notifications	Occupancy COA	Notifications per 100 persons	Notifications	Occupancy COA	Notifications per 100 persons
Eritrea/Ethiopia	45	2957	1.5	68	5205	1.3	55	4778	1.2
Syria	2	5398	0.0	8	12,861	0.1	4	15,201	0.0
Afghanistan	0	1321	0.0	6	1399	0.4	8	3048	0.3
Somalia	14	1568	0.9	7	853	0.8	10	622	1.6
Other	18	8308	0.2	15	9680	0.2	18	13,285	0.1
Total	79	19,552	0.4	104	29,998	0.3	95	36,934	0.3

Table 5.3 Tuberculosis notifications in asylum-seekers: age distribution by occupancy at COA-centres, 2014–2016

Age groups	2014			2015			2016		
	Notifications	Occupancy COA	Notifications per 100 persons	Notifications	Occupancy COA	Notifications per 100 persons	Notifications	Occupancy COA	Notifications per 100 persons
0–4	1	1821	0.1	0	2337	0.0	0	2710	0.0
5–17	14	4115	0.3	13	6037	0.2	19	6804	0.3
18–50	64	12,530	0.5	88	20,132	0.4	73	25,360	0.3
50+	0	1087	0.0	3	1492	0.2	3	2061	0.1
Total	79	19,552	0.4	104	29,998	0.3	95	36,934	0.3

Chronic hepatitis B

Asylum-seekers in the Netherlands are not systematically screened for chronic hepatitis B virus (HBV), but GPs from the Asylum-seekers Health Centres (GCA) occasionally offer tests for chronic HBV. Pregnant women are screened for HBV infection through antenatal screening, which is in place throughout the Netherlands.

In 2016, 107 chronic HBV infection cases in asylum-seekers were notified, accounting for 10.8% of all notified chronic HBV infection cases in the Netherlands. This is similar to 2015, when 106 chronic HBV infection cases in asylum-seekers were notified, accounting for 10.6% of all cases (Table 5.1).

Over the last three years, most notified chronic HBV cases originated from Syria and Eritrea (Table 5.4). In the years prior to that, most cases originated from Somalia, Syria and Sierra Leone. The total number of chronic HBV notifications per 100 asylum-seekers staying at COA-centres in 2016 was 0.3. This is a slight decrease compared with 2015, when 0.4 HBV notifications per 100 asylum-seekers were reported.

In 2016, a slight decrease was observed in chronic HBV notifications in asylum-seekers from Eritrea/Ethiopia (0.3) and Somalia (0.2) compared with 2015 (Table 5.4). Over the past four years, the number of chronic HBV notifications per 100 asylum-seekers was highest in the age group 18–50 years (Table 5.5).

Preliminary results from a serosurvey in 2016 among 622 asylum-seekers from Syria, Afghanistan, Iraq, Iran and Eritrea show a prevalence of chronic HBV infection of 1.1%. The prevalence ranged from 0% in asylum-seekers from Iran and Iraq, to 5.4% in asylum-seekers from Eritrea (I. Veldhuijzen, personal communication).

The incidence of acute HBV infection in the general population in the Netherlands has been declining for more than 10 years, and has been below 1 per 100,000 since 2013. This suggests that the increasing influx of refugees from higher prevalence countries is not associated with an increasing transmission of HBV within the Dutch population.

Table 5.4 Chronic hepatitis B notifications in asylum-seekers by country of birth and occupancy at COA centres by country of origin, 2013–2016

Country of birth	2013			2014			2015			2016		
	Notifications	Occupancy COA	Notifications per 100 persons	Notifications	Occupancy COA	Notifications per 100 persons	Notifications	Occupancy COA	Notifications per 100 persons	Notifications	Occupancy COA	Notifications per 100 persons
Syria	7	1089	0.6	14	5398	0.3	26	12,861	0.2	28	15,201	0.2
Eritrea/Ethiopia	6	721	0.8	11	2957	0.4	24	5205	0.5	14	4778	0.3
Somalia	11	1840	0.6	3	1568	0.2	4	853	0.5	1	622	0.2
Sierra Leone	6	250	2,4	3	277	1.1	2	257	0.8	3	214	1.4
Afghanistan	3	1868	0.2	3	1321	0.2	5	1399	0.4	7	3048	0.2
Unknown/Other	48	10,777	0.4	60	9599	0.6	49	10,276	0.5	54	13,071	0.4
Total	70	14,705	0.5	91	19,552	0.5	106	29,998	0.4	107	36,934	0.3

Table 5.5 Chronic hepatitis B notifications in asylum-seekers: age distribution by occupancy at COA-centres, 2013–2016

Age groups	2013			2014			2015			2016		
	Notifications	Occupancy COA	Notifications per 100 persons	Notifications	Occupancy COA	Notifications per 100 persons	Notifications	Occupancy COA	Notifications per 100 persons	Notifications	Occupancy COA	Notifications per 100 persons
0–4	0	1593	0.0	1	1821	0.1	0	2337	0.0	1	2710	0.0
5–17	18	3281	0.5	7	4115	0.2	5	6037	0.1	8	6804	0.1
18–50	50	8910	0.6	75	12,530	0.6	98	20,132	0.5	90	25,360	0.4
50+	1	921	0.1	8	1087	0.7	3	1492	0.2	8	2061	0.4
Total	69	14,705	0.5	91	19,552	0.5	106	29,998	0.4	107	36,934	0.3

Malaria

After a sharp increase in malaria cases among asylum-seekers in 2014 and 2015, a decrease was observed in 2016, both in the number of cases reported in asylum-seekers and in the total number of malaria cases. In 2016, 42 malaria cases in asylum-seekers were notified, accounting for 16.8% of all malaria cases in the Netherlands (Table 5.1). This is a decrease of 67% compared with the 126 malaria cases in asylum-seekers that were notified in 2015. As in 2014–2015, most malaria in asylum-seekers was caused by *Plasmodium vivax* infections (40/42 cases) [4]. A further 11 *P. vivax* malaria notifications were specified as being among Eritrean asylum-seekers (not residing in COA-centres), which is the same number as in 2015. In 2014–2016, over 90% of asylum-seekers with malaria were born in Eritrea or Ethiopia (Table 5.6). The total number of malaria notifications per 100 asylum-seekers at COA-centres decreased from 0.4 in 2015 to 0.1 in 2016. This decrease was also observed in the notifications per 100 asylum-seekers from Eritrea/Ethiopia, from 2.2 in 2015 to 0.8 in 2016 (Table 5.6). In 2016, the number of malaria notifications per 100 asylum-seekers was highest in the age groups 5–17 and 18–50 (Table 5.7). This is comparable to previous years.

Table 5.6 Malaria notifications in asylum-seekers by country of birth and occupancy at COA-centres by country of origin, 2013–2016

Country of birth	2013			2014			2015			2016		
	Notifications	Occupancy COA	Notifications per 100 persons	Notifications	Occupancy COA	Notifications per 100 persons	Notifications	Occupancy COA	Notifications per 100 persons	Notifications	Occupancy COA	Notifications per 100 persons
Eritrea/Ethiopia	4	721	0.6	96	2957	3.2	118	5205	2.3	39	4778	0.8
Unknown/Other	2	13,984	0.0	10	16,595	0.1	8	24,793	0.0	3	32,156	0.0
Total	6	14,705	0.0	106	19,552	0.5	126	29,998	0.4	42	36,934	0.1

Table 5.7 Malaria notifications in asylum-seekers: age distribution by occupancy at COA-centres, 2013–2016

Age groups	2013			2014			2015			2016		
	Notifications	Occupancy COA	Notifications per 100 persons	Notifications	Occupancy COA	Notifications per 100 persons	Notifications	Occupancy COA	Notifications per 100 persons	Notifications	Occupancy COA	Notifications per 100 persons
0–4	0	1593	0.0	0	1821	0.0	0	2337	0.0	1	2710	0.0
5–17	0	3281	0.0	39	4115	0.9	36	6037	0.6	20	6804	0.3
18–50	6	8910	0.1	67	12,530	0.5	89	20,132	0.4	21	25,360	0.1
50+	0	921	0.0	0	1087	0.0	1	1492	0.1	0	2061	0.0
Total	6	14,705	0.0	106	19,552	0.5	126	29,998	0.4	42	36,934	0.1

5.4 Concluding remarks

The influx of asylum-seekers into the Netherlands nearly halved in 2016 compared with 2015. However, the mean occupancy at COA-centres was higher in 2016 than in 2015. This is mostly due to the fact that the high influx of asylum-seekers started in the second half of 2015 and occupancy decreased slowly during 2016. The most frequently reported notifiable infectious diseases in asylum-seekers in the Netherlands were tuberculosis, chronic hepatitis B and malaria. Even though the influx of asylum-seekers decreased in 2016 compared with 2015, the number of notifications for chronic hepatitis B and TB stayed more or less the same. However, a sharp decrease in malaria cases was observed.

The risk of autochthonous malaria in the Netherlands is negligible due to the low vector capacity and (very) limited contact rates between infectious malaria patients and native mosquitoes [5]. There is no evidence of significant transmission of TB or chronic HBV to the Dutch population.

Although the large influx in asylum-seekers is mainly attributable to the increase of Syrian asylum-seekers, most infectious diseases reported in asylum-seekers are from people originating from the Horn of Africa. The prevalence of infectious diseases varies according to the country of origin, as well as to the countries visited en route and conditions there.

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6 Burden of infectious diseases in the Netherlands, 2012–2016

6.1 Introduction

To allow comparison of the health impact of different infectious diseases for policy and research prioritisation, the burden of disease needs to be expressed in a single measure. Disease burden is expressed in disability-adjusted life years (DALY), which is an estimate of the number of healthy years lost due to ill health, disability or early death [1]. Here, burden estimates are presented for 38 infectious diseases in the Netherlands in the years 2012–2016.

6.2 Methods

DALY

To estimate disease burden in DALY, an incidence- and pathogen-based approach was applied to quantify the burden due to illness, disability and premature mortality associated with all short- and long-term consequences of infection. The underlying outcome trees, disease progression probabilities and models used have been described elsewhere [2–4]. DALY estimates incorporate both years of life lost (YLL) due to premature mortality and years lived with disability (YLD) [1]. YLD were calculated by multiplying the number of acute cases by the duration of the health state and the disability weight of the health state. The disability weight is a value between 0 (perfect health) and 1 (death). In contrast to the disease burden estimates presented in previous editions of this report, we used the newly available European disability weights by Haagsma et al. [5]. These disability weights were derived from a survey of over 30,000 European citizens, using a system developed for the Global Burden of Disease (GBD) study 2010. These disability weights are incorporated in the BCoDE toolkit [6]. The selection of the disability weights per health state was discussed with disease and burden experts at the RIVM. For acute infections that comprise a range of separate health states (e.g. acute measles with pneumonia, diarrhoea, encephalitis or otitis media) a syndromic approach was taken to obtain an average disability weight for this acute syndrome. In the same spirit, one duration was applied to all health states belonging to an acute infection. A full overview of the disability weights and durations that we used in our disease models can be found in the Appendix.

Another difference in methodology compared with the previous edition of this report is the use of the life expectancy table as determined for the GBD 2010 study [7] (note that the previously used table was from the GBD 1990 study). This is the projected frontier remaining life expectancy in 2050 per age group. Equal life expectancies are assumed for men and women.

Incidence

The multiplication factor applied to psittacosis notifications was updated to 22.7 (95% CI 12.2–64.8) [8]. For all other diseases, models as first described in the State of Infectious Diseases 2013 and model modifications as reported in State of Infectious Diseases 2015 were maintained for the current estimations [3, 4].

We extended previously published methods for estimating the incidence of seasonal influenza by combining all relevant data sources via Bayesian evidence synthesis [9]. As an improvement on the method, we estimated incidence for each season through specification of an evidence synthesis model that recognised that ILI incidence over multiple seasons should be considered as dependent data.

We estimated disease burden ascribed to infections occurring in 2012, 2013, 2014, 2015 and 2016 separately. No time discounting was applied. For sexually transmitted diseases reliable data were not yet available for 2016; therefore, we report disease burden estimates up to 2015. We omitted Lyme disease estimates because yearly incidence data were not available. We estimated the burden of seasonal influenza for respiratory seasons (week 40 to week 20) from 2011/12 to 2015/16.

6.3 Results

Figure 6.1 shows the estimated disease burden for 38 infectious diseases in DALYs per year for the period 2012–2016 in the Netherlands. Table 6.1 shows the estimated DALY per year with 95% uncertainty intervals and the average DALY per 100 infections, which is a measure of the disease burden at the individual patient level. The influence of outbreaks on disease burden is apparent from Figure 6.1 and Table 6.1. The 2013/14 measles outbreak is clearly visible, as are those of rubella in 2014 and salmonellosis in 2012 (i.e. the outbreak of *Salmonella* Thompson in salmon) and, less prominently, in 2016 (i.e. *Salmonella* Enteritidis in imported eggs). Rabies and tetanus are rare, but due to their severity, the burden for those sporadic cases is high. Pertussis incidence is known to surge every few years, which is also visible from Figure 6.1. For hepatitis B and Q fever, a clear downward trend is visible due to decreasing incidence.

In Figure 6.2, infectious diseases are ranked by the estimated annual disease burden in 2012–2016, split by YLD (years of life lost due to morbidity) and YLL (years of life lost due to premature mortality). Influenza and invasive pneumococcal disease are by far the leading drivers of infectious disease burden in the Netherlands, both estimated to cause over 10,000 DALY lost annually in the Netherlands, mainly by YLL. While the disease burden of invasive pneumococcal infections is fairly constant (see Figure 4.1), the health impact of influenza highly varies between seasons.

6.4 Discussion

This chapter presents updated estimates of infectious disease burdens for the years 2012 to 2016. The burden of each disease is attributed to the year in which the infection occurred. For interpretation of the results, this means that all (future) burden is attributed to the year in which the infection occurred. As in the estimates presented in the State of Infectious Diseases 2015 report, influenza and invasive pneumococcal disease cause the highest disease burden, with over 10,000 DALY per year. The influence of outbreaks of infectious diseases (e.g. measles) is apparent from Figure 6.1: this emphasises the importance of ongoing prevention efforts such as the NIP.

Two methodological changes have influenced disease burden estimates since the last State of Infectious Diseases report: the application of new disability weights and the use of a different life expectancy table. The currently used disability weights are derived from a single study among citizens of four European countries including the Netherlands. In previous estimates, disability weights from different studies, derived from different methods and populations, were applied. The new disability weights are well applicable to the Netherlands and mark an important improvement in the comparability of diseases. This has resulted in a more robust ranking of burden of infectious diseases in the Netherlands. The new disability weights are generally lower than the disability weights previously applied (see Appendix). However, the application of a longer life expectancy (i.e. more recent estimates of 'optimum' remaining life expectancy) results in higher estimates for YLL and also influences the YLD of long-term sequelae. As a result, DALY estimates for diseases with high mortality rates and/or a large number of cases experiencing long-term sequelae are relatively high. For example, HIV infection, which is a chronic condition, is now ranked higher than pertussis, for which the disease burden is mainly suffered in the acute phase. Considering the parameter adaptations, the ranking of infectious diseases by burden is remarkably similar to our previous estimation, which was also led by influenza and invasive pneumococcal disease (Figure 6.2) [3]. The most notable differences in the ranking of infectious diseases in the Netherlands are the much lower position for chlamydia and gonorrhoea. This is due to the disability weight given to female infertility, which was 0.18 previously and 0.007 in the current estimates. As has been discussed elsewhere, the burden suffered as a result of infertility is likely to be very complex and variable between individuals [3].

The influenza burden estimate is based on an improved method of estimating influenza incidence. Previously, influenza incidence per age group was calculated by multiplying influenza-like illness (ILI) incidence from GP

Figure 6.1 Annual disease burden in DALY attributable to infectious diseases in the Netherlands, 2012–2016 (2012–2015 for STD). FBD = foodborne disease; RES = respiratory disease; STD = sexually transmitted disease; VPD = vaccine-preventable disease; i. = invasive

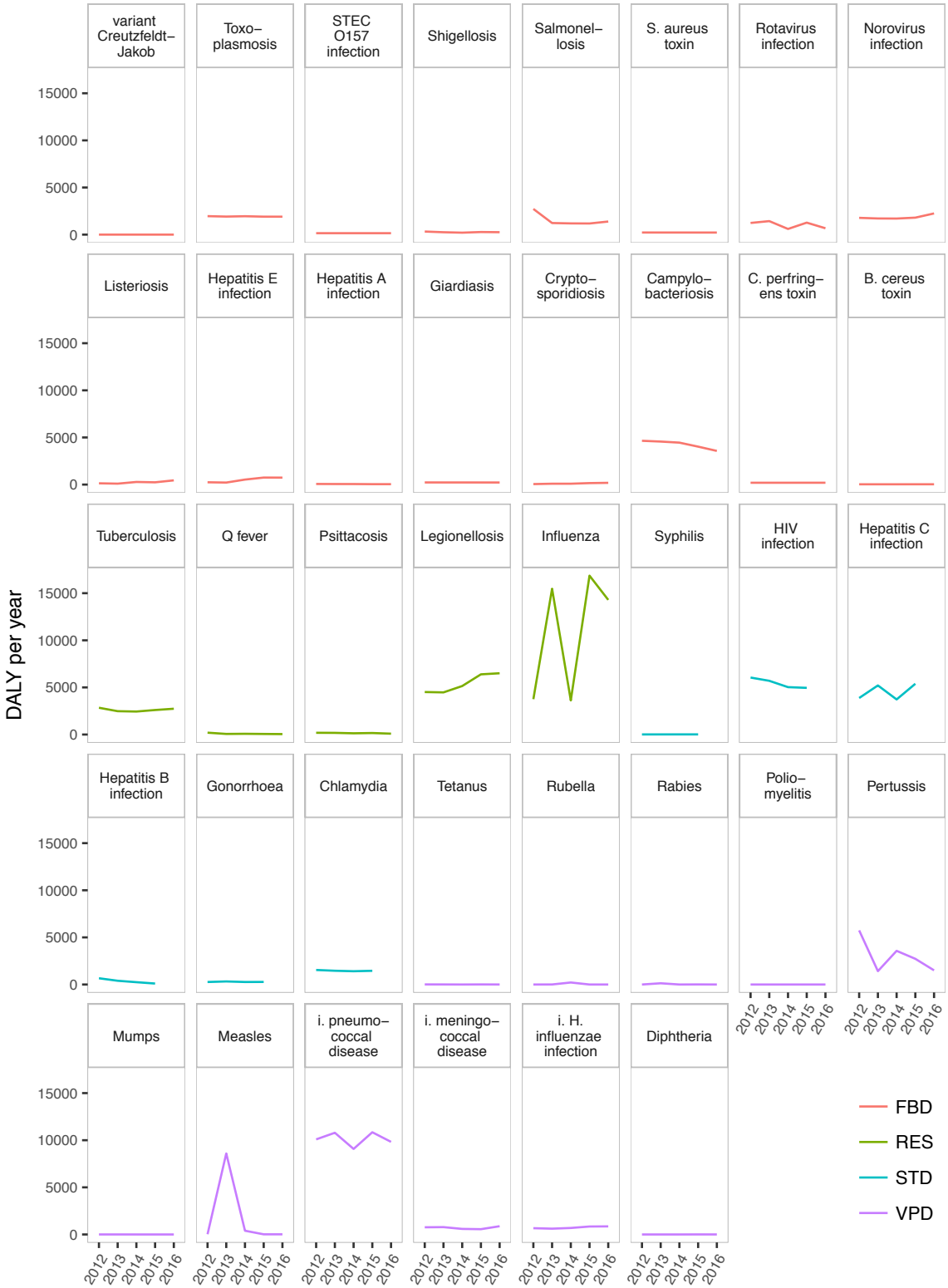
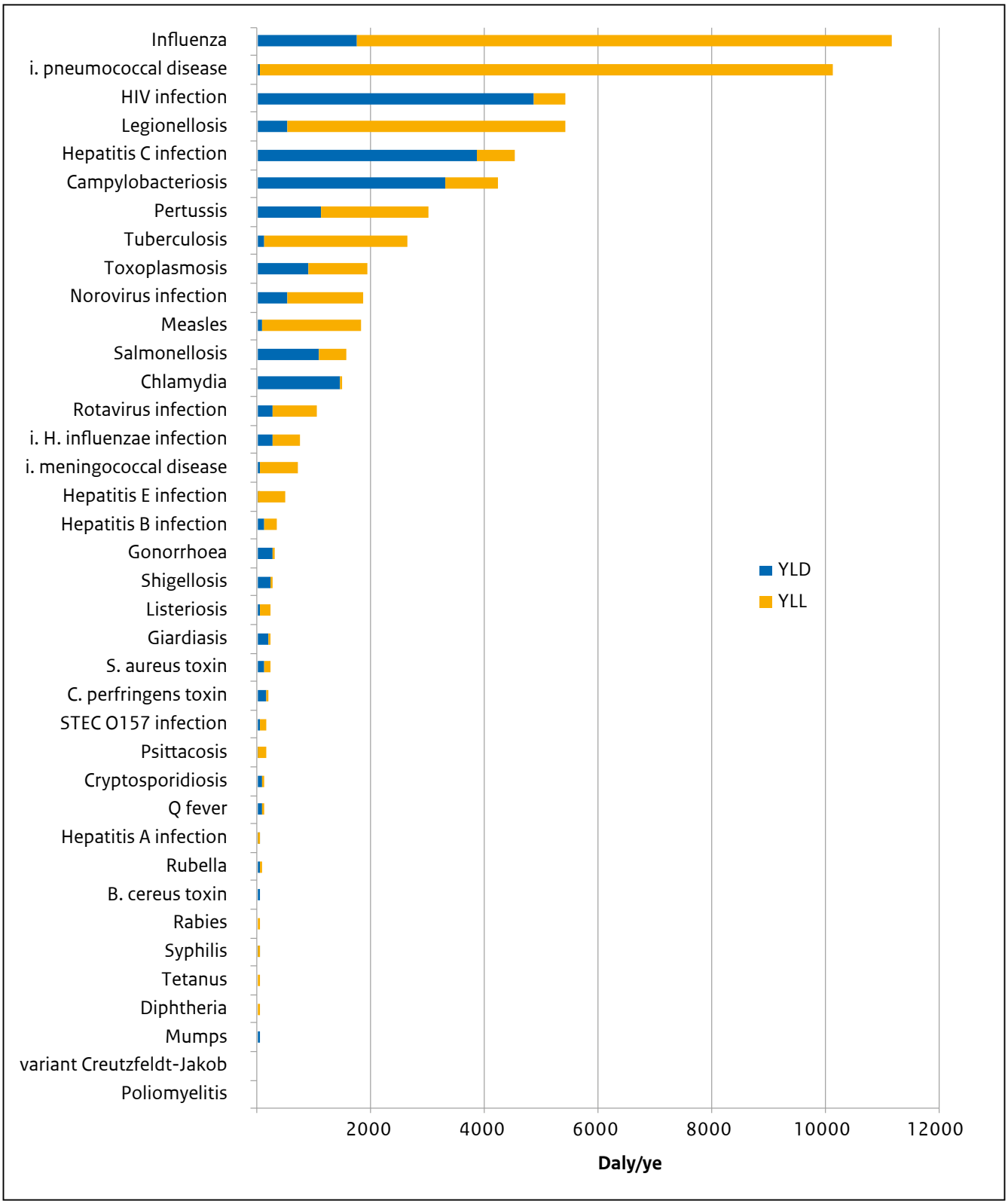


Figure 6.2 Average annual disease burden in DALY, split by YLD and YLL, attributable to infectious diseases in the Netherlands, 2012–2016 (2012–2015 for STD)



surveillance data by the influenza positivity rate from sampled patients, per age. This method did not take into account the considerable uncertainty surrounding these estimates due to the limited number of samples per age group. In the currently applied method, a model was employed to quantify this uncertainty. This has resulted in a much wider uncertainty interval (Table 6.1) compared with the interval presented last year, which was based only on uncertainty for disease progression probabilities. A further change is the presentation of influenza burden per season (week 20–40) instead of per calendar year, as the influenza burden is highly dependent on the season (see Figure 6.1). We chose not to include influenza burden outside the respiratory season, as the influenza positivity rates in ILI patient swabs during this period are too low to indicate influenza burden with any certainty.

The incidence of legionellosis was higher than usual in 2015 and 2016, which is reflected in the burden estimates. A decrease in acute hepatitis B incidence resulted in lower burden estimates for recent years. This decrease in incidence follows adjustments to the vaccination programme, with vaccination of risk groups since 2002 and universal infant vaccination since 2011. However, prevalent chronic hepatitis B infections are not included in the current burden estimate although this disease can carry a high disease burden due to cirrhosis or hepatocellular carcinoma. It was recently estimated that mortality from chronic hepatitis B sequelae was stable around 200 deaths per year in 2008–2015 [10]. Except for sporadic outbreaks, the long-term trend in the burden from foodborne diseases is either decreasing or stable, except for hepatitis E and cryptosporidiosis. The incidence of these two diseases has increased in recent years, and studies are ongoing to determine the reasons behind this.

Table 6.1 Estimated disease burden in DALY (with 95% uncertainty intervals) per year in the Netherlands for 2012–2016, by disease category in order of highest to lowest DALY in the most recent estimate, and DALY per 100 infections in the most recent estimate (2016, 2015 for STD)

Disease	DALY (95% uncertainty interval)					DALY/ 100 infections
	2012	2013	2014	2015	2016	
Foodborne diseases						
Campylo-bacteriosis	4646 (2563–9076)	4565 (2521–8914)	4450 (2438–8749)	4025 (2209–7905)	3573 (1955–7039)	4.5 (3.3–8.7)
Norovirus infection	1778 (969–2963)	1714 (927–2870)	1704 (914–2863)	1800 (958–3035)	2248 (1188–3808)	0.3 (0.2–0.5)
Toxoplasmosis	1960 (1320–2848)	1914 (1290–2781)	1950 (1314–2835)	1906 (1285–2768)	1903 (1283–2763)	248 (179-375)
Salmonellosis	2726 (1271–6133)	1230 (578–2752)	1190 (549–2688)	1181 (546–2664)	1389 (636–3165)	4.3 (3.2–11)
Hepatitis E infection	244 (82–521)	214 (72–456)	529 (178–1128)	744 (250–1587)	738 (248–1574)	40 (15–77)
Rotavirus infection	1237 (516–2416)	1432 (590–2813)	602 (252–1178)	1270 (516–2515)	673 (278–1329)	0.5 (0.3–0.9)
Listeriosis	135 (104–168)	98 (82–114)	277 (265–289)	239 (228–250)	448 (432–465)	467 (450–484)
Shigellosis	327 (266–397)	252 (200–306)	206 (163–253)	274 (219–331)	257 (205–310)	3.6 (3.5–3.7)
Giardiasis	227 (128–421)	225 (127–419)	224 (126–416)	222 (125–415)	221 (124–413)	0.3 (0.2–0.4)
S. aureus toxin	223 (75–569)	222 (74–567)	221 (73–564)	220 (73–563)	220 (73–563)	0.1 (0–0.2)
C. perfringens toxin	195 (59–486)	195 (59–484)	195 (59–484)	196 (59–485)	196 (59–486)	0.1 (0.1–0.2)

Table 6.1 (continued) Estimated disease burden in DALY (with 95% uncertainty intervals) per year in the Netherlands for 2012–2016, by disease category in order of highest to lowest DALY in the most recent estimate, and DALY per 100 infections in the most recent estimate (2016, 2015 for STD)

Disease	DALY (95% uncertainty interval)					DALY/ 100 infections
	2012	2013	2014	2015	2016	
Crypto-sporidiosis	53 (19–145)	92 (31–265)	91 (30–263)	158 (49–465)	185 (57–550)	0.2 (0.1–0.4)
STEC O157 infection	152 (101–235)	152 (101–235)	152 (101–235)	152 (101–235)	152 (101–235)	7.1 (1.6–71)
Hepatitis A infection	65 (40–108)	59 (36–98)	57 (35–94)	43 (27–72)	44 (27–73)	11 (7.8–15)
B. cereus toxin	31 (11–71)	31 (11–73)	31 (11–74)	32 (11–74)	32 (11–75)	0.1 (0.1–0.1)
Variant Creutzfeldt–Jakob	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	n.a.
Respiratory diseases						
Influenza	3755 (3127–4489)	15,435 (14,417–16,539)	3605 (3049–4245)	16,836 (15,537–18,193)	16,316 (15,169–17,501)	2.0 (2.0–2.0)
Legionellosis	4511 (4019–5083)	4474 (4007–4994)	5148 (4606–5762)	6388 (5698–7152)	6503 (5806–7304)	110 (102–119)
Tuberculosis	2842 (2332–3364)	2477 (2018–2958)	2441 (2012–2887)	2602 (2121–3099)	2737 (2253–3255)	20 (16–24)
Psittacosis	187 (141–239)	177 (137–224)	131 (102–165)	161 (122–205)	92 (70–118)	9.7 (7.9–12)
Q fever	198 (172–225)	64 (55–74)	80 (68–92)	62 (52–72)	46 (36–56)	24 (19–29)
Vaccine–preventable diseases						
invasive pneumococcal disease	10,090 (9447–10,735)	10,791 (10,151–11,448)	9075 (8534–9618)	10,847 (10,195–11,503)	9827 (9179–10,440)	350 (328–372)
Pertussis	5744 (5329–6186)	1416 (1324–1513)	3572 (3307–3869)	2726 (2525–2951)	1502 (1397–1613)	1.1 (1.1–1.2)
invasive meningococcal disease	761 (610–925)	779 (630–943)	588 (463–731)	560 (437–696)	875 (728–1041)	549 (499–600)
invasive *H. influenzae* infection	666 (629–704)	615 (580–650)	690 (653–730)	844 (797–890)	857 (803–909)	401 (377-424)
Measles	26 (17–35)	8597 (6316–11,060)	396 (312–486)	15 (10–20)	16 (10–22)	23 (14–32)
Diphtheria	1 (1–1)	0 (0–0)	1 (1–2)	4 (3–5)	2 (2–3)	122 (97–147)
Tetanus	11 (9–12)	6 (5–7)	0 (0–0)	9 (7–10)	2 (2–2)	174 (167–181)

Table 6.1 (continued) Estimated disease burden in DALY (with 95% uncertainty intervals) per year in the Netherlands for 2012–2016, by disease category in order of highest to lowest DALY in the most recent estimate, and DALY per 100 infections in the most recent estimate (2016, 2015 for STD)

Disease	DALY (95% uncertainty interval)					DALY/ 100 infections
	2012	2013	2014	2015	2016	
Mumps	3 (3–3)	2 (1–2)	0 (0–0)	1 (1–1)	1 (1–1)	0.4 (0.4–0.4)
Rubella	0 (0–0)	4 (3–5)	213 (171–260)	0 (0–0)	0 (0–0)	n.a.
Rabies	0 (0–0)	35 (35-35)	49 (49-49)	0 (0-0)	0 (0–0)	n.a.
Poliomyelitis	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	n.a.
Sexually transmitted diseases						
Hepatitis C infection	3875 (2413–5356)	5211 (2950–7602)	3726 (2357–5173)	5386 (3363–7481)		244 (152–339)
HIV infection	6047 (6007–6088)	5700 (5661–5737)	5029 (4996–5062)	4953 (4919–4986)		564 (561–568)
Chlamydia	1540 (1032–2296)	1459 (979–2153)	1409 (943–2081)	1454 (980–2130)		0.5 (0.3–0.8)
Gonorrhoea	265 (183–391)	324 (224–460)	265 (189–378)	271 (194–378)		1.2 (0.9–1.7)
Hepatitis B infection	663 (621–702)	396 (367–424)	246 (231–261)	101 (94–107)		19 (18–21)
Syphilis	11 (8–14)	13 (10–17)	16 (13–22)	15 (12–17)		0.4 (0.4–0.5)

n.a. = not applicable, due to no cases occurring in 2016.

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7 Vaccination and immune status throughout life: a public health perspective

Each stage in the human life course is associated with a particular risk of exposure to and vulnerability to infections. Some parts of the population are particularly vulnerable to either contracting an infection or suffering a severe course of disease once infected. A term often used to describe vulnerable parts of the population is 'YOPI': the (very) young, the old, the pregnant and the immunocompromised. As these groups all have a particular immune status, they are especially vulnerable to certain infectious diseases. Moreover, their altered immunity often diminishes vaccine responses, rendering these groups at double risk of contracting vaccine-preventable diseases (VPDs). In such cases, adequate herd protection is of the essence to protect the vulnerable against infections. The National Immunisation Programme (NIP) was originally set up, in 1957, to prevent specific childhood diseases. Nowadays, vaccination of older children, adults and the elderly is an increasingly common practice, both within and outside the NIP. In this chapter, the challenges and opportunities relating to the protection of YOPI from infectious diseases via immunisation are discussed and recommendations for public health surveillance are made.

7.1 Immune status and vaccination: the young, the old, the pregnant and the immunocompromised

The young

Emerging from the relatively sterile environment of the amniotic fluid, the newborn child is suddenly exposed to a world full of antigens. The neonatal immune system needs to tolerate the many bacteria quickly colonising the skin and mucosae, in order to establish a healthy commensal flora. Infant immune responses tend to be tolerogenic, and develop during the first year of life. Newborn babies have a developing immune system and are less able to mount effective and long-lived antibody responses to many vaccinations and infections than older children or adults [1]. This renders infants particularly susceptible to infection. Another implication of the characteristics of the newborn immune system is that more vaccine doses may be needed to reach adequate immunity. Designing an appropriate infant vaccination scheme means balancing the minimisation of the risk of infectious disease in the very young (warranting early vaccination) against the need for the infant to generate better antibody responses, i.e. need fewer vaccine doses (postponing vaccination).

Nature's way of providing some immunity to infants is through the transfer of maternal antibodies. IgG, the predominant class of antibodies against infection, is actively transferred across the placenta to the foetus. Due to this active transport, the concentration of these antibodies can even be higher in newborns than in the maternal circulation. Placental antibody transport is hampered when the mother is infected with e.g. HIV or malaria [2]. Maternal IgG antibodies can persist in the infant for up to 6 to 12 months, depending on the antibody levels at birth [3]. In addition, IgA antibodies, which inhabit the mucosae and strengthen these barriers against infection, are transferred in breastmilk. Colostrum, the first milk produced after birth, is a particularly rich source of IgA, which may provide further protection of the infant mucosae against pathogens [4].

The persistence of maternal antibodies in the young infant provides some protection against infection, but on the other hand interferes with infant vaccination by blunting the immune response mounted after vaccination [3, 5]. This is the case with measles, for example. This means that children who still have circulating maternal measles antibodies when the vaccine is administered produce fewer antibodies in response. However, studies have found that measles vaccine effectiveness is still high (>90%) for children vaccinated early (6 to 9 months), suggesting that lower antibody levels are largely sufficient to protect against disease [6, 7] (see Box 7.1). The optimal timing of infant immunisation depends on the type of vaccine, the disease burden and epidemiology, the development of the infant immune system and the timing of maternal antibody waning.

To summarise, the vaccination of infants is complicated by two factors: the developing immune system and the presence of maternal antibodies. To make use of the maternal antibody phenomenon, vaccinating women during pregnancy rather than the infant is a possibility. IgG antibodies induced in the mother after vaccination are also actively transferred to the foetus and can persist in the infant for some months. When the mother chooses to breastfeed her child, the infant may further benefit from the maternal vaccination through transfer of IgA, although evidence for this is scarce (8). Through these routes, maternal vaccination can help to protect children against infection, even when they are too young for effective infant

Figure 7.1 Vaccination schedule of the NIP from 2014 onwards

Vaccination schedule National Immunisation Programme

Phase 1	Injection 1	Injection 2
6-9 weeks	DTaP-IPV Hib HBV	PCV
3 months	DTaP-IPV Hib HBV	
4 months	DTaP-IPV Hib HBV	PCV
11 months	DTaP-IPV Hib HBV	PCV
14 months	MMR	MenC

Phase 2	Injection 1	Injection 2
4 years	DTaP-IPV	

Phase 3	Injection 1	Injection 2
9 years	DT-IPV	MMR

Phase 4	Injection 1	Injection 2
12 years	HPV*	HPV* (6 months later)

Meaning of the abbreviations

D	Diphtheria	HBV	Hepatitis B	MenC	Meningococcal C disease
aP	Pertussis (whooping cough)	PCV	Pneumococcal disease	HPV	Human papillomavirus
T	Tetanus	M	Mumps		
IPV	Poliomyelitis	M	Measles	*	Only for girls
Hib	Haemophilus influenzae type b	R	Rubella		

BOX 7.1: Timing of measles vaccination

The first dose of vaccine against measles, mumps and rubella (MMR) is given at 14 months of age in the Netherlands (Figure 7.1). Research has shown that MMR vaccination from 6 months onwards is safe and warranted in the context of a measles outbreak [6, 7, 14], although the WHO advises countries not to administer the first dose of MMR vaccine below 9 months of age in routine schedules, due to lower immunogenicity. However, the WHO has recently decided to advise measles vaccination for 6-month-old infants in several contexts, such as during an outbreak [15].
Low vaccination coverage and measles outbreaks in (parts of) the Netherlands can pose risks to children below the age of 14 months – the age at which routine measles vaccination is being offered. Measles is an exceptionally contagious disease, with great potential to emerge when herd protection dwindles. The risk of children below 14 months contracting measles due to falling vaccination coverage has spiked controversy in society and the media.
Besides measles, other VPDs (pneumococcal disease, meningococcal disease, invasive *Haemophilus influenzae*) are rare in children below the age of the first scheduled vaccination as a result of herd protection. This emphasizes the importance of maintaining herd protection.

vaccination. Furthermore, the immunisation of the mother can prevent transmission of a pathogen from the mother to the infant. Maternal immunisation has already been shown to be a potent strategy for eliminating neonatal tetanus, and for preventing pertussis and influenza in infants [3] (see Table 7.1 and Box 7.3).

The Dutch NIP starts early in the first year of life, with routine vaccination at 2 months of age. The primary series of vaccinations against diphtheria, tetanus, pertussis, polio, hepatitis B, *Haemophilus influenzae* type b and *Streptococcus pneumoniae* consists of three doses given at 2, 3 and 4 months (two doses, at 2 and 4 months, for *S. pneumoniae*) and a booster dose at 11 months (see Figure 7.1). This programme results in early and effective protection of infants against these illnesses. However, 2–3 doses of infant pertussis vaccines are necessary before adequate protection is reached and circulation of *Bordetella pertussis* is high in the Dutch population [9, 10]. Children below the age of 4 months are therefore at considerable risk of *B. pertussis* infection. Pertussis disease is at its most severe in infants under 3 months, leading to hospitalisation and in rare cases even death. Last year, the Health Council therefore advised maternal vaccination against pertussis [11]. Implementation of maternal immunisation may have implications for the effectiveness and optimal timing of subsequent infant vaccination (which may possibly be postponed until maternal antibodies have waned to a certain level). This is currently being investigated by the RIVM [12].

Infants born preterm or with congenital anomalies are generally at even higher risk of contracting infectious diseases. Two potentially vaccine-preventable viruses causing severe disease in such vulnerable infants are respiratory syncytial virus (RSV) and rotavirus. RSV is a highly circulating pathogen that is known for causing particularly severe disease in young infants, especially those born preterm. At present, preterm infants and infants with comorbidity are eligible to receive monoclonal antibodies during the winter season to prevent RSV infection. RSV vaccines are currently under development or being tested [13]. Like RSV, rotavirus is a seasonal pathogen causing the most severe symptoms in preterm infants and infants with underlying conditions. Rotavirus is an enteric pathogen, and the vaccine is administered as oral droplets. The Health Council is to review the need for rotavirus vaccination in the Netherlands in 2017.

The old

The elderly form a large and growing population with affected immunity. In 2016, 3,085,000 people in the Netherlands were aged 65 years or older, which is more than 18% of the total population. Within this group, 749,000 were 80 years or older (0.4% of the total population). With ageing, the phenomenon of immunosenescence occurs. Immunosenescence entails many alterations to the amount and function of immune cells, resulting in less active immune responses.
The repertoire of naïve T cells starts to diminish around 50 years, and with ageing the proportion of memory cells increases relative to naïve cells [16]. This results in the older immune system mounting less effective responses to vaccination and puts the elderly at higher risk of contracting any infectious diseases they are exposed to. From a public health perspective, both the incidence and the severity of infections are higher in the elderly. This is illustrated by an increased mortality in older age groups coinciding with seasonal epidemics of influenza and RSV, viruses mostly causing mild disease in younger adults [17]. As the proportion of elderly people in the Dutch population is increasing with improvements in life expectancy, the public health impact and mortality of common infections is expected to grow considerably. In addition, the clinical presentation of infectious diseases may be less typical in older adults, especially with comorbidities in

place. This may lead to (initial) misdiagnosis and/or inappropriate use of antibiotics.

As with the youngest infants, the oldest adults are the most vulnerable to (severe) infectious disease but will generally mount the least effective vaccine responses. The age at which vaccination should be offered to older adults is therefore a case of balancing effectiveness (likely to be lower at higher age), duration of protection and the disease burden that often increases with age. It is important to administer the vaccine before immunosenescence has deteriorated the immune system's abilities to mount effective immunity. Vaccination at a slightly younger age might be considered if this results in higher vaccine effectiveness and if the duration of protection is long enough to prevent disease in old age [18].

Seasonal influenza vaccination is offered free of charge in the Netherlands to people aged 60 years or older and to patients with chronic diseases. Influenza vaccine uptake among this at-risk population is below the recommended 75% and has decreased steadily since 2008 [19]. High mortality rates in the elderly are observed to coincide with influenza seasonality [17]. However, the benefit of seasonal influenza vaccination for the elderly may be perceived as modest, as vaccine effectiveness is highly variable [20]. Moreover, recent studies have found that repeated vaccination against seasonal influenza might decrease its effectiveness [21, 22]. If this phenomenon is further understood and confirmed, it may have implications for influenza vaccination policy.

Further potentially vaccine-preventable diseases causing considerable morbidity and mortality among the elderly include pneumococcal disease and herpes zoster (18, 23).

Streptococcus pneumoniae infection causes a considerable disease burden in elderly people, and can present as pneumonia or invasive pneumococcal disease. Since the implementation of infant vaccination against 7 *S. pneumoniae* serotypes in 2006 (10 since 2011), the incidence among the elderly of pneumococcal disease caused by the serotypes included in the vaccine has decreased. This points to herd protection; the vaccination of infants has reduced the transmission of vaccine-type *S. pneumoniae*, indirectly protecting the elderly as well. Unfortunately, invasive infections by serotypes not included in the vaccine are increasing in the elderly, although case-fatality is lower for these serotypes [24]. Further protection of the elderly against pneumococcal disease may be achieved by including more serotypes in the infant vaccine or by vaccinating the elderly themselves. A large randomised placebo-controlled trial in the Netherlands showed a reasonable vaccine efficacy of a 13-valent conjugate vaccine (75% against invasive disease by vaccine serotypes) in immunocompetent adults above the age of 65 [25]. Even more serotypes [23] are included in an unconjugated pneumococcal polysaccharide vaccine, which has similar effectiveness against invasive disease [26, 27]. However, polysaccharide vaccines have important limitations, including a relatively short duration of protection [28] (see Box 7.2).

Herpes zoster also causes a considerable disease burden in the elderly [23]. Primary infection with varicella zoster virus generally presents as a mild disease in young children, but reactivation of the virus in older age can cause herpes zoster and post-herpetic neuralgia. It has been theorized that repeated exposure to the virus reduces the chance of developing herpes zoster in older age; childhood vaccination against varicella would then be undesirable, as it reduces virus circulation and may thereby increase the risk of herpes zoster in unvaccinated people [29]. A licensed vaccine is available and can be used by older adults to prevent herpes zoster. However, both effectiveness and duration of protection are limited [30, 31]. This is one of the reasons why the Health Council concluded that vaccination against herpes zoster should not be included in the national Dutch NIP [32]. The development of more effective vaccines

BOX 7.2: Polysaccharide vaccine-induced hyporesponsiveness

Bacteria such as *Streptococcus pneumoniae, Haemophilus influenzae* type b and *Neisseria meningitidis* are surrounded by a polysaccharide capsule, which is not very immunogenic. Mounting an immune response against these bacterial capsules is important in preventing disease. While B cells can produce antibodies against polysaccharides, T cells do not respond to non-amino acid antigens and can therefore not stimulate B cells to form memory cells in response to polysaccharide antigens. Low and fast decreasing levels of antibodies in response to pneumococcal polysaccharide vaccine have been found in children, older adults and immunocompromised patients [34]. Moreover, studies have shown that repeated exposure to polysaccharides (by a booster dose after primary vaccination, for example) actually reduces antibody responses [34–36]. This hyporesponsiveness phenomenon is observed in both children and adults, and can occur not only as a consequence of vaccination but also after recent disease from or carriage of the pathogen [34]. Conjugate vaccines, combining polysaccharide antigen with an immunogenic protein, can induce long-lasting effective responses including T cell involvement against encapsulated bacteria.

BOX 7.3: Timing of vaccination in pregnancy

The vaccination of pregnant women can have three primary aims, which determine the optimal timing of vaccination.

1. When vaccination is used to protect the mother against infectious disease, the vaccine should be given before or early in pregnancy. In the case of seasonal influenza vaccination for pregnant women, vaccination at the onset of the influenza season is warranted, regardless of the pregnancy stage.
2. When vaccination is intended to prevent congenital disease, it is essential to administer the vaccine before, or at least very early in, pregnancy, before the mother can become infected or vertical transmission to the foetus can occur.
3. Maternal immunisation aimed at protecting the infant after birth, such as maternal pertussis immunisation, is more effective in mid- to late pregnancy [45]. As the transplacental transport of IgG occurs mainly in the third trimester, the optimal timing of maternal vaccination would be in the late second or early third trimester [2]. It takes the mother some time to mount a high antibody response, after which as much IgG as possible is transferred to the foetus before (possibly pre- or early term) birth.

providing longer-lasting immunity might make routine vaccination of the elderly against herpes zoster worthwhile in the future [33].

Pregnant women

Another life stage influencing immunity is pregnancy. Circa 1% of the Dutch population was pregnant at some time in 2016 [37]. Significant immune alterations, both local and systemic, are induced by pregnancy hormones and are necessary to tolerate the foetus while maintaining the mother's defence against infection. It has been proposed that type1 immunity (a pro-inflammatory immune profile) is associated with unsuccessful pregnancy and a more type-2 (or tolerogenic) profile is needed to complete gestation, although not all research data support this theory [38]. While the mechanisms are not completely elucidated, pregnancy is undoubtedly a state of intricate immune modulation. Still, this altered immune status does not seem to increase susceptibility to infection across the board. Moreover, vaccine responses are not hindered by pregnancy [39]. This enables routine vaccination of pregnant women; to protect either them or their foetus via the transplacental transfer of antibodies (see Box 7.3 and Table 7.1).

Nevertheless, due to physiological changes, pregnancy can increase women's susceptibility to specific pathogens, such as *Plasmodium falciparum* (malaria) and *Listeria monocytogenes*, which infect the placenta [38]. Changes in lung capacity, blood volume and the urinary tract can also affect the risk or course of infectious disease in pregnant women. While pregnancy is not associated with increased influenza incidence, the course of the infection has been found to be more severe in pregnant women during influenza pandemics [38, 39]. In many countries, seasonal influenza vaccination is recommended for pregnant women. In the Netherlands, this is not the case. The Dutch Health Council has advised not to implement routine influenza vaccination for pregnant women, contrary to the WHO recommendation, as studies showing that pregnant women suffer a higher burden of seasonal influenza are lacking [40, 41]. In the context of pandemic influenza, the Health Council has, however, advised the vaccination of pregnant women [42, 43]. Table 7.1 shows vaccines for pregnant women that are currently available or expected to become available soon.

Table 7.1. Infections for which vaccination during pregnancy is currently implemented or expected in the near future. Based on [44]

Pathogen	Primary aim	Status
Tetanus	Elimination of neonatal tetanus	Implemented in developing countries
Influenza	Prevention of disease during pregnancy	Implemented. In the Netherlands advised only for pandemic influenza outbreaks
Pertussis	Prevention of neonatal infection	Implemented in Belgium, UK, US and Australia Advised to be implemented in the Netherlands
Respiratory syncytial virus	Prevention of neonatal infection	Vaccine under development (phase 3)
Streptococcus group B	Prevention of invasive neonatal infection	Vaccine under development (past phase 2)

Another potential objective of vaccination in pregnancy is the prevention of congenital disease after vertical transmission of infections. Infection with rubella, *Toxoplasma*, varicella and cytomegalovirus (CMV) during pregnancy can cause congenital diseases. Recently, Zika virus has also shown its ability to have devastating developmental effects. No vaccines are available against CMV infection or toxoplasmosis, although some are under development. Rubella vaccine is contra-indicated during pregnancy, due to its live attenuated nature. Vaccines against Zika virus are under development, but would be indicated only for Dutch women (and their partners) living in or travelling to endemic areas.

Vaccines to prevent congenital disease or disease in pregnancy could be integrated in pre-conception consultations, which currently focus on lifestyle advice and folic acid supplementation.

The immunocompromised

The immunocompromised form a heterogeneous group. Primary immune deficiency is a rare and innate affliction, resulting from genetic defects in the immune system. Fewer than 700 people with primary immune deficiency are registered in the Netherlands [46]. Secondary immunodeficiency can be acquired due to disease or drug treatment, such as a glucocorticoid, TNF-α-blocker or other immunosuppressant. The national influenza prevention programme defines 1.9% of the population as having reduced immune function [47]. The number of patients with a secondary immunodeficiency due to medication or chronic conditions such as chronic inflammatory disease, cancer or a haematological disorder is steadily increasing. Another form of immune deficiency is asplenia, which can either result from splenectomy or diseases impairing spleen function (functional asplenia). In the Netherlands, around 1,000 splenectomies are performed annually [48].

For patients using immunosuppressive drugs, both their condition and their (dose of) medication can influence vaccine responses. Ideally, immunocompromised patients would receive a personalised vaccination recommendation, based on their age, sex, condition, travel plans and medication regimen and be vaccinated before the initiation of immunosuppressive drugs that may interfere with the response to vaccination. Not enough evidence is yet available to design such specific recommendations for each patient category or predict vaccination outcome with each combination of immunosuppressive drugs when patients are vaccinated during immunosuppression.
This year, the RIVM will publish on its website a guidance document on the vaccination of immunocompromised patients based on the available evidence and expert consensus. Aside from providing guidance to clinicians, this project has identified evidence gaps and is expected to lead to further research on vaccine responses in patients using immune suppressants. As immunocompromised patients are generally excluded from vaccine trials, vaccine efficacy is mostly unknown for this population [25, 33].
(Functional) asplenia carries the risk of asplenic sepsis, whereby encapsulated bacteria are not cleared from the circulation, resulting in sepsis, with high mortality rates [48]. As infection with the bacteria causing post-splenectomy sepsis is often vaccine-preventable (mainly *Streptococcus pneumoniae*), vaccination is an important measure to prevent mortality in asplenic patients. If possible, vaccines should be administered several weeks before a splenectomy [49].

Chronic diseases that are not primarily immune disorders can also be marked by reduced immunity against infection. For example, both type 1 and type 2 diabetes may increase the risk of sepsis, osteomyelitis, urinary tract infections and skin and soft tissue infections [50]. Concerning VPDs, invasive pneumococcal disease is known to occur more often in diabetic patients. A recent study in the Netherlands

BOX 7.4: Anti-inflammatory medication during pregnancy and infant vaccine responses

If a woman uses immunosuppressive drugs during pregnancy, this can have consequences for infant immunisation. When a pregnant woman has a chronic inflammatory condition such as psoriasis or inflammatory bowel disease, both the inflammatory condition and the medications needed to control it can affect foetal health and immunity [52]. When monoclonal IgG antibodies such as anti-TNF-α are used as therapy against inflammatory disease, these can cross the placenta and enter the foetal circulation. This may reduce vaccine responses in infancy and even increase infection risk and severity. If live attenuated vaccines are administered while these monoclonal antibodies are still in the circulation of the infant, disseminated infection with the vaccine strain may occur. A case has been described of an infant, born after infliximab use during pregnancy, receiving the live attenuated BCG vaccine at 3 months and subsequently dying of disseminated BCG infection [53]. As (maternal) therapeutic monoclonal antibodies seem to persist in infants as long as maternally produced antibodies, live vaccine administration should be withheld until these antibodies have waned. Ceasing monoclonal antibody therapy during the third trimester might prevent these monoclonal antibodies from persisting in the child [54]. Much remains unknown about the effects of medication during pregnancy on the foetus, as randomised controlled trials are not feasible for ethical reasons.

BOX 7.5: Travelling while 'YOPI'

The National Coordination Centre for Travellers' Health Advice (LCR) gives advice on travel vaccinations for YOPI travellers.

The young: Young infants travelling to a country with a high risk of measles may receive an early MMR vaccination (between 6 and 14 months of age), after which (if it is given before the age of 12 months) the usual vaccination schedule should be followed at 14 months and 9 years of age. When the early MMR is given between 12 and 14 months of age, a second dose at 9 years of age completes the schedule.

The old: The elderly are advised to get vaccinated at least 2 weeks before travel, to allow for the slower development of the immune response in older adults.

Pregnant women: During pregnancy, live vaccines are contra-indicated.

The immunocompromised: Patients taking immune suppressants are advised to get vaccinated before starting immune suppressant medication, because an intact immune system is necessary for an adequate immune response to vaccination. If medication is already started or patients are immunocompromised for another reason (e.g. HIV, haematological disease or metastatic tumours), live attenuated vaccines are contra-indicated. For certain vaccines (e.g. hepatitis A and B or rabies), an antibody titer determination is necessary 4 to 6 weeks after vaccination to assess protection of the traveller.
Patients with asplenia are advised to always carry broad-spectrum antibiotics with them while travelling, because they have a higher risk of a complicated course of disease after an infection with encapsulated bacteria. Patients with asplenia are therefore also advised to make sure they have received the pneumococcal, meningococcal, Hib and influenza vaccination (https://www.lcr.nl/Bijzondere-reizigers).

showed adults under 65 years with diabetes to have a 6 times higher risk of invasive pneumococcal disease than people without a chronic predisposing condition. Other chronic metabolic and pulmonary diseases also significantly increase the risk of invasive pneumococcal disease [51]. As chronic notifiable conditions such as diabetes and chronic pulmonary or vascular disease are highly prevalent, the public health impact of this increased risk is considerable. These findings may warrant vaccination in specific adult risk groups, just as patients with chronic diseases such as diabetes or cardiovascular disease are offered seasonal influenza vaccination in the Netherlands.

7.2 Surveillance of vaccine-preventable diseases in people with impaired immunity

As shown in Chapter 6, influenza and invasive pneumococcal disease cause the highest burden of infectious disease in the Netherlands in recent years. These are the two infections that cause the most (severe) disease in immunocompromised groups, and they are partly vaccine preventable. Determining the share of the infectious disease burden suffered by immunocompromised patients would greatly aid public health surveillance and intervention planning. In the event of an outbreak or a change in the trend in occurrence of a VPD, it is important to know the patient characteristics in order to plan targeted interventions. Moreover, it is of the essence that type-specific surveillance data are collected, along with immune status data, to assess whether specific types (possibly not covered by the vaccine) cause disease in specific risk groups [51].

Currently the Dutch surveillance system for notifiable diseases includes information on whether or not a patient is immunocompromised for invasive *Haemophilus influenzae* disease, invasive meningococcal disease and invasive pneumococcal disease (in children born after 2009). For these VPDs, information is requested on whether the patient has a e.g. chronic illness, impaired immunity, complement deficiency or history of splenectomy via the notification questionnaire. In young children, the existence of an immunocompromising condition might be unknown and can present primarily as vaccine failure. Surveillance via notifications is supplemented by surveillance data from the Netherlands Reference Laboratory for Bacterial Meningitis, which adds surveillance data for pneumococcal disease for children born before 2009 and adults, but does not include information on immune status. However, retrospective studies on serotype epidemiology and patient characteristics are carried out regularly [24].

Systematically gathering more surveillance data on immune status, i.e. specific categories of immunodeficiency, for all ages and all VPDs is also indicated to optimise control efforts.

A foreseeable development in the near future is the implementation of maternal immunisation in the Netherlands, first for pertussis and possibly later for RSV and other infections. When maternal immunisation is implemented, gathering data on the vaccination status of both child and mother will be a necessary part of VPD surveillance. Information on pregnancy duration and the exact timing of maternal immunisation are also important in this context, to monitor the extent of antibody transfer during gestation. Post-implementation, enhanced surveillance of both vaccine safety and effectiveness of maternal immunisation is required. Certainly, the effects on infectious disease epidemiology should be closely monitored after changes in the immunisation programme.

7.3 Concluding remarks

The young, the old, the pregnant and the immunocompromised form a large and growing part of the Dutch population. The influenza vaccine target population (those aged 60+ and those with chronic disease) already comprises over 37% of the total Dutch population [19]. In addition, pregnant women and babies constitute 2% of the population. Around 280,000 patients are estimated to use immune suppressants, which is about 0.2% of the Dutch population. As immunosuppressive drugs are increasingly prescribed, the prevalence of chronic conditions keeps rising and the Dutch population ages, even more people will fall under the 'YOPI' classification in the future.

These developments also bring new target populations into focus for vaccination, which will have consequences for health promotion and communication. While vaccination coverage is high for the child vaccination schedule in the Netherlands, additional vaccines for specific target groups (such as seasonal influenza) do not currently reach such high uptake numbers.

As pregnant women are currently not a target group for vaccination in the Netherlands, their (and their caregivers') attitudes towards maternal vaccination are largely unknown. Maternal pertussis vaccination uptake was around 50–65% in 2014 in the United States and Belgium [55, 56]. In England, vaccine coverage among pregnant women increased in 2016 to 75% [57]. The Netherlands has a unique perinatal health care system, with a large proportion of pregnancies and births attended by midwives and not taking place in a hospital setting [58]. A study confirmed the notion that Dutch women fear over-medicalisation of pregnancy and birth, which may contribute to the more widespread reluctance towards pharmaceutical intervention during pregnancy [59, 60].

Although the elderly (60+) currently do form a target group for vaccination, less than 50% of healthy elderly people got their 'flu jab' in 2013 [19]. Seasonal influenza vaccine uptake is lowest (and decreasing) for the age group 60–65 without medical indication [47]. This group has been included as a target group for influenza vaccination since 2008, but this may not be concordant with the perceptions of influenza risk for healthy 60–65-year-olds [19]. Factors in vaccine acceptance specific to the elderly include notions of aging 'naturally' and seeing pneumonia as an 'acceptable' cause of death, but also a low perceived risk for the otherwise healthy elderly [61]. General practitioners share some of these views, including that of pneumonia as 'the old man's friend' [62]. Practical barriers to vaccination of the elderly should be kept as low as possible by, if possible, uniform risk group classifications and combination vaccines [62].

The heterogeneous nature of the immunocompromised patient population might make this the most difficult group to reach for vaccination. As the specific care of these patients is often undertaken by medical specialists, such as rheumatologists, internal medicine specialists or oncologists, many medical professional groups need to be able to advise on and administer vaccines. Communication and collaboration between these professional groups and municipal health services (where travel health advice and vaccination are embedded) might make it easier to give appropriate vaccine advice and administer the appropriate vaccines to patients.

Maintenance of herd protection, by high vaccination coverage throughout the Netherlands, remains essential to protect vulnerable parts of the population against specific VPDs. Moreover, as health care workers come into close contact with vulnerable patients, vaccination coverage among professionals is important to prevent nosocomial transmission of VPDs. Unfortunately, seasonal influenza vaccine uptake remains low in this group. In the context of insufficient herd protection (either by low vaccination coverage or low vaccine effectiveness), the strategy of cocooning may be employed. Cocooning entails the vaccination of (household) contacts of the vulnerable person, such as infants too young to be fully immunised against pertussis. However, studies have shown limited effects of cocooning, and most adults (with an altered immune status) will have far too many contacts for cocooning to be feasible.

As new vaccines are being developed and marketed, new opportunities for immunisation arise. Vaccination schedules may become increasingly personalised, depending on age, (travel) behaviour, morbidity and medication, and immunisation may become part of personalised medicine. However, from a public health perspective, ensuring herd protection through high (and uniform) vaccination coverage across the Netherlands remains essential to protect the most vulnerable among us.

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