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State of Infectious Diseases *in the Netherlands, 2015*

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Publiekssamenvatting

Staat van Infectieziekten in Nederland 2015

De meest in het oog springende infectieziekte in 2015 was de griepepidemie in de winter van 2014-2015, die met 21 weken de langstdurende griepepidemie was die ooit in Nederland is gemeten. De instroom van asielzoekers uit vooral Syrië en Eritrea zorgde ervoor dat opvangcentra extra alert waren op infectieziekten onder asielzoekers. De meest voorkomende meldingsplichtige infectieziekten bij asielzoekers waren tuberculose, malaria en chronische hepatitis B. Dit blijkt uit de Staat van Infectieziekten in Nederland 2015. Deze jaarlijkse rapportage geeft beleidsmakers van het ministerie van VWS inzicht in ontwikkelingen van infectieziekten onder de Nederlandse bevolking. Daarnaast worden relevante ontwikkelingen in het buitenland gemeld.

Het thema van deze editie is de surveillance van infectieziekten in Nederland: de gegevensverzameling over hoe vaak en waar infectieziekten voorkomen. Deze gegevens worden verzameld om bijvoorbeeld een uitbraak van een infectieziekte op te sporen, om trends in infectieziektes te volgen, of om de effectiviteit van een vaccinatieprogramma te bepalen. Door surveillancegegevens uit de vele beschikbare gegevensbronnen te combineren en te analyseren ontstaat meer inzicht in de epidemiologie van infectieziekten.

In deze editie zijn nieuwe ziektelastschattingen gemaakt van 35 infectieziekten in Nederland tussen 2012 en 2014. Deze ziektelast geeft de hoeveelheid jaren weer die mensen niet meer in goede gezondheid doorbrengen vanwege een infectieziekte. Sommige infectieziekten, zoals maagdarminfecties, komen vaak voor maar veroorzaken over het algemeen geen ernstige klachten. Andere infecties, bijvoorbeeld tetanus, komen slechts zelden voor maar veroorzaken relatief veel sterfgevallen. Een gezondheidsmaat die deze aspecten van ziekten combineert is de Disability Adjusted Life Year (DALY).

De gemiddelde jaarlijkse ziektelast voor de totale Nederlandse bevolking was het hoogst voor griep (8653 DALY's/jaar). De laagste ziektelast werd geschat voor difterie (0,6 DALY's/jaar). Deze ziektelast is zo laag dankzij het Rijksvaccinatieprogramma.

Trefwoorden: Staat van infectieziekten, infectieziekten, surveillance, meldingsplichtige infectieziekten, ziektelast

Synopsis

State of Infectious Diseases in the Netherlands 2015

The most notable infectious disease outbreak in 2015 was the flu epidemic in the winter of 2014-2015, which at 21 weeks was the longest ever recorded in the Netherlands. As a result of the influx of refugees from Syria and Eritrea in particular, reception centres were especially vigilant in detecting infectious diseases among asylum seekers. The most common notifiable infectious diseases among asylum seekers were tuberculosis, malaria, and chronic hepatitis B. These are some of the highlights of a report on infectious diseases in the Netherlands in 2015. These reports are published every year by the Dutch National Institute for Public Health and the Environment (RIVM), and provide policy-makers at the Ministry of Health, Welfare and Sport (VWS) with insight into infectious disease trends in the Dutch population. The report also covers relevant developments abroad.

The theme of this year's report is the surveillance of infectious diseases in the Netherlands, based on data about disease incidence and distribution. These data are collected in order to detect an outbreak of an infectious disease, to monitor trends in infectious diseases, and to determine the effectiveness of vaccination programmes, for instance. By combining and analysing surveillance data from the many data sources available, insight into the epidemiology of infectious diseases is enhanced.

In this edition, the disease burden has been re-estimated for 35 infectious diseases in the Netherlands in the 2012-2014 period. The disease burden provides an indication of the number of years that people suffer poor health due to an infectious disease. Some infectious diseases, such as gastroenteric infections, occur frequently in the population, but do not generally cause serious symptoms. Other infections, such as tetanus, are rare but cause relatively high numbers of fatalities. One health indicator that combines both aspects is the Disability Adjusted Life Year (DALY).

The average annual disease burden for the entire Dutch population was the highest for flu (8,653 DALYs per year). Diphtheria was estimated to have the lowest disease burden (0.6 DALY per year). The low disease burden for diphtheria is the result of the Dutch National Vaccination Programme.

Keywords: State of Infectious Diseases in the Netherlands, infectious diseases, surveillance, reportable infectious diseases, disease burden

Contents

1 Introduction

This is the tenth edition of the report on 'State of Infectious Diseases in the Netherlands'. This annual publication is primarily written to inform policy makers at the Ministry of Health, Welfare and Sports (VWS), at Municipal Health Services, at the Centre of Infectious Diseases at RIVM.

This State of Infectious Diseases in the Netherlands starts with a chapter on the main national and international infectious diseases events that occurred in the Netherlands in 2015 (Chapter 2). This chapter includes the table with annual numbers of notified diseases in the Netherlands.

In chapter 3, the theme of this year's report is presented. Here we give an overview of surveillance in the Netherlands, with a focus on different methods and applications.

In chapter 4, the virological surveillance in the Netherlands is described. This chapter gives an overview of the type of data included in the virological weekly reports, the method of data collection, results and the use and dissemination of the reported data.

In chapter 5, new estimates of the national burden of disease are presented for 35 infectious diseases in the period 2012-2014. The highest average annual burden is observed for influenza (8653 DALYs/year). Estimates of disease burden can be informative for public health policy decisions regarding the prioritisation of interventions and preventive measures.

In chapter 6, we provide an overview of notifiable infectious diseases reported in asylum seekers in the Netherlands. In 2015, the number of asylum application in the Netherlands was twice as high compared to the previous year. The increase in the Netherlands is mainly attributable to the increase of Syrian asylum seekers. Poverty, human rights abuses and deteriorating security are also prompting people to set out from countries such as Eritrea, Somalia, Morocco, Iran and Pakistan.

2
The state of infectious diseases in the Netherlands, 2015

2.1 Introduction

In this chapter, we provide an overview of notifiable diseases and key infectious disease signals (e.g. outbreaks and new trends) in 2015, 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 2008-2015. In section 2.2 to 2.4, we describe the most important signals concerning mandatory notifiable diseases under the Dutch Public Health Act (1). Section 2.5 deals with signals regarding non-notifiable infectious diseases for the Netherlands. We have included information from the year 2016 only when the signal started in 2015 and continued into 2016. We have not included information about signals that started in 2016.

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

Group*	Infectious disease	2008	2009	2010	2011	2012	2013	2014	2015
Group A	Middle East Respiratory Syndrome (MERS-CoV)						0 [b]	2	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	1	0	0	0	0	0	1	0
Group B1	Diphtheria	0	0	0	1	1	0	2	4
	Human infection with zoonotic influenza virus	0 [a]	0	0	0	0	0	0	0
	Plague	0	0	0	0	0	0	0	0
	Rabies	0	0	0	0	0	1	1	0
	Tuberculosis	1042	1198	1117	1046	986	886	858	900
Group B2	Cholera	5	4	0	3	3	0	3	1
	Clusters of Foodborne infection**	85	39	48	42	48	36	28	29
	Hepatitis A	185	180	261	116	124	109	105	79
	Hepatitis B Acute	225	215	196	156	175	146	141	107
	Hepatitis B Chronic	1592	1776	1573	1552	1319	1151	1071	998
	Hepatitis C Acute	28	39	30	72	54	64	53	68
	Invasive group A streptococcal disease	27 [a]	255	211	186	178	203	149	169
	Measles	110	11	20	51	35	2659	140	7
	Paratyphi A	9	17	19	14	25	22	9	6
	Paratyphi B	26	16	16	27	18	14	8	23
	Paratyphi C	1	3	0	1	3	2	0	4
	Pertussis	8135	6351	3696	7054	13851	3491	9055	6651
	Rubella	2	7	0	3	1	57	2	1
	STEC/enterohemorrhagic *E. coli* infection	154	279	398	649	905	849	753	752
	Shigellosis	438	413	533	584	752	473	360	477
	Typhoid fever	27	27	24	20	17	25	20	17
Group C	Anthrax	0	0	0	0	0	0	0	0
	Botulism	7	0	0	0	2	0	0	0
	Brucellosis	5	3	6	1	3	6	1	9
	Chikungunya							61 [d]	24
	Creutzfeldt-Jakob disease	15	20	27	27	30	29	25	17
	Creutzfeldt-Jakob disease - Variant	1	0	0	0	0	0	0	0
	Dengue							13 [c]	25
	Hantavirus infection	2 [a]	7	19	7	23	4	37	10
	Invasive *Haemophilus influenza* type b infection	0 [a]	16	31	20	22	18	19	16
	Invasive pneumococcal disease (in children 5 years or younger)	5 [a]	42	57	48	43	28	39	43
	Legionellosis	339	256	473	315	308	311	370	436
	Leptospirosis	29	22	29	29	44	27	104	86
	Listeriosis	8	56	69	87	71	74	92	71

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

Group*	Infectious disease	2008	2009	2010	2011	2012	2013	2014	2015
	MRSA-infection (clusters outside hospitals)	4 [a]	16	13	6	2	11	3	8
	Malaria	221	235	244	242	199	166	285	356
	Meningococcal disease	155	158	143	99	106	109	81	94
	Mumps	25 [a]	80	563	609	397	205	39	87
	Psittacosis	79	81	73	70	45	53	41	45
	Q fever	1003	2424	411	77	63	20	26	20
	Tetanus	0 [a]	1	2	5	2	1	0	1
	Trichinosis	1	1	0	1	0	0	0	0
	West Nile virus infection	0 [a]	0	1	1	0	0	0	0
	Yellow fever	0	0	0	0	0	0	0	0

[1] Up 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 has been 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 tables from previous 'State of Infectious Disease' reports. The Table was sourced from the Dutch notifiable infectious diseases database 'Osiris' on 09 May 2016. 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 was 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 depending on the legal measures that may be imposed.

** Number of clusters, not number of cases.

a Not notifiable until 1 December 2008, so the number for 2008 is for one month only.

b Not notifiable until 3 July 2013.

c Not notifiable until 1 July 2014.

d Not notifiable until 1 September 2014.

2.2 Group A-diseases

Polio

Globally, 74 patients with poliomyelitis were reported to the World Health Organization (WHO) in 2015 (www.polioeradication.org). All cases were reported from the last two poliomyelitis-endemic countries: Pakistan (54) and Afghanistan (20). In 2015, there were less cases in fewer places than ever before. In 2015, seven countries reported cases of circulating vaccine derived poliovirus (cVDPV) (Box 2.1). Circulating VDPV type 1 was detected in Madagascar (10), Lao PDR (8) and Ukraine (2); circulating VDPV type 2 was detected in Guinea (7), Myanmar (2), Pakistan (2) and Nigeria (1). In 1988, the World Health Assembly committed to eradicate the disease. Since then, the number of cases has considerably decreased. Of the three types of wild polioviruses, type 2 is considered to be eradicated, as the last case was reported in 1999. The last case of wild poliovirus type 3 was reported in November 2012. In 2016, every country in the world currently using oral poliovirus vaccine (OPV) has to withdraw the trivalent vaccine and replace it with the bivalent vaccine, containing live poliovirus type 1 and 3. This will continue to protect infants from poliovirus types 1 and 3. By withdrawing the type 2 component, the risk of seeding new type 2 circulating vaccine-derived poliovirus is avoided. With replacement of the trivalent OPV with bivalent OPV, the immunity against type 2 is induced by including at least one trivalent IPV dose in the vaccination schedule (http://www.polioeradication.org/).

In 2015, a case of VDPV-type 3 (Box 2.1) was detected in a child from Syria in the Netherlands, which showed negative results for poliovirus in follow-up samples. The VDPV was detected because the child showed symptoms of diarrhea, and fecal testing was conducted. This showed STEC STX2 and enterovirus. Because of enterovirus-surveillance, the latter was typed showing a poliovirus type 3 strain. Further sequence analysis of the complete VP1 gene showed a unique VDPV-3. The GGD in collaboration with the RIVM and the hospital conducted source and contact tracing. The child arrived in the Netherlands in 2014 and had probably received trivalent oral polio vaccination on the journey from Syria to the Netherlands. The child showed no polio symptoms. Multiple follow-up samples showed negative results for poliovirus. Fecal examinations of the family were also negative for poliovirus. Sewage surveillance was conducted in the area where the child lives, showing no poliovirus. As all follow up samples were negative, the VDPV was identified as an ambiguous VDPV (aVDPV).

MERS-CoV

In September 2012, a new coronavirus was identified post-mortem from a patient suffering from acute pneumonia and subsequent renal failure in the Kingdom of Saudi Arabia (3). Internationally, this novel virus has since been named Middle East Respiratory Syndrome-coronavirus (MERS-CoV). As of 29 April 2016, the WHO has been notified of 1733 laboratory-confirmed cases of infection with MERS-CoV, including 624 related deaths since the beginning of the outbreak (4) (Figure 2.1). All cases

Box 2.1: Vaccine-derived polioviruses

Vaccine-derived polioviruses are rare strains of poliovirus that have genetically mutated from the Sabin strain contained in the oral polio vaccine. When a child is vaccinated, the weakened vaccine-virus replicates in the intestine and enters into the bloodstream, triggering a protective immune response in the child. As with wild poliovirus, the child excretes the vaccine-virus for a period of two to eight weeks. Importantly, some of the excreted viruses may no longer be the same as the original vaccine-virus, as they have genetically altered during replication. This is called a vaccine-derived poliovirus. Very rarely, vaccine-derived poliovirus can cause paralysis. Vaccine-associated paralytic poliomyelitis occurs in an estimated 1 in 2.7 million children receiving their first dose of oral polio vaccine (2).

Types of Vaccine-derived polioviruses

- Circulating vaccine-derived poliovirus (cVDPV)
  On rare occasions, if a population is seriously under-immunized, there are enough susceptible children for the excreted VDPV to begin circulating in the community. These viruses are cVDPVs.

- Immunodeficiency-related vaccine-derived poliovirus (iVDPV)
  In a small number of people with immune deficiency disorders, prolonged replication of the vaccine strain may lead to accumulation of mutations and result in iVDPVs.

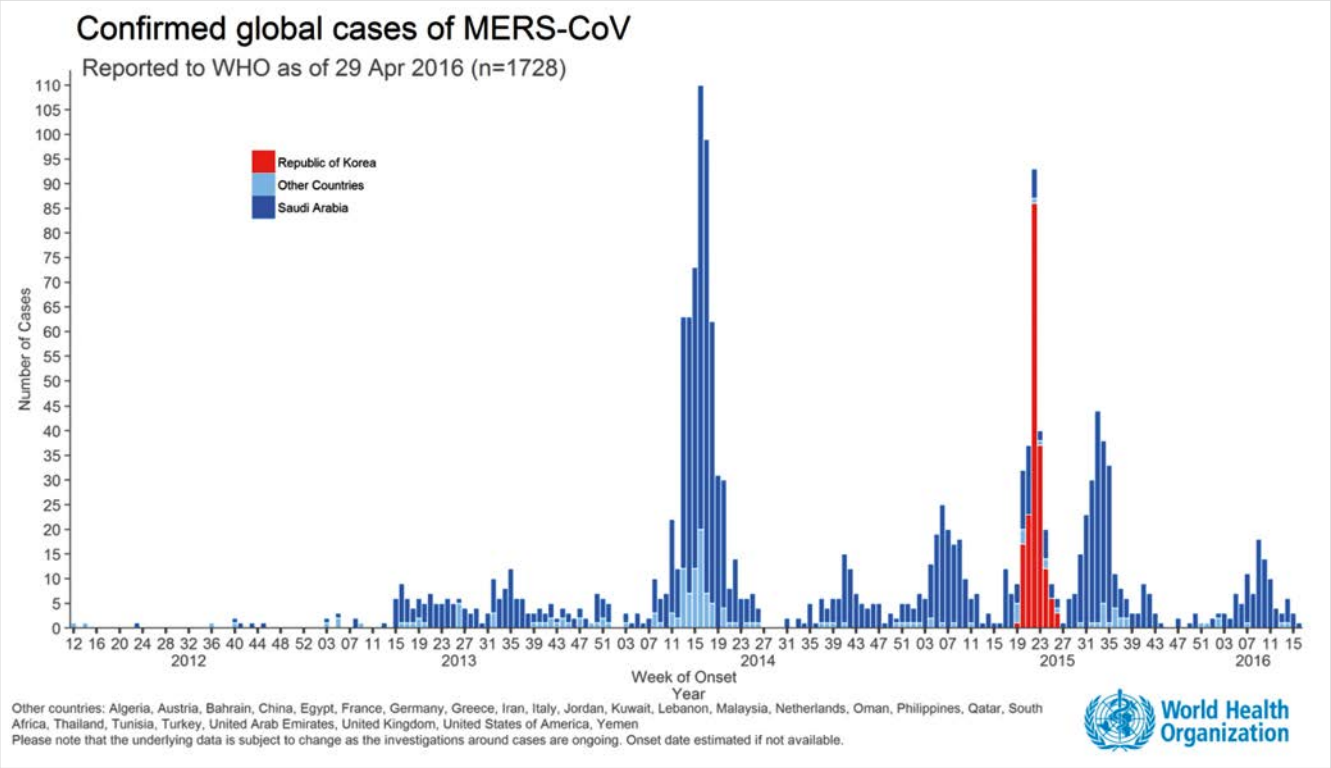
- Ambiguous vaccine-derived poliovirus (aVDPV)
  aVDPVs are VDPVs that cannot be classified as iVDPV or cVDPV.

have (in)directly been linked, through travel or residency, to the Arabian Peninsula. The majority of cases (>85%) have been reported from Saudi Arabia.
In May 2015, South Korea reported the first case of MERS-CoV. The index case was a 68-year old male with travel history to several countries in the Arabian Peninsula. A few days after returning to South Korea, he developed symptoms after which he visited four separate health care facilities before being diagnosed with MERS-CoV nine days later. Nosocomial transmission occurred and by the end of the outbreak in July 2015 186 patients were laboratory confirmed, including 36 deaths. Most cases were secondary contacts that had been in contact with the index case; in a few instances it was tertiary transmission.
In August 2015, a sharp rise in MERS-CoV cases was observed in Saudi Arabia, where a large healthcare-associated outbreak occurred related to a hospital in Riyadh. However, the upsurge in cases decreased from September as significant efforts were made to strengthen infection prevention and control measures.
In 2015, no cases of MERS-CoV were notified in the Netherlands. In 2014, two Dutch patients were diagnosed with MERS-CoV infection. Both had visited Saudi Arabia and recovered after their return to the Netherlands.

Ebola

Mid-March 2014, the Ministry of Health in Guinea notified the WHO about an outbreak of Ebola viral disease (EVD). By May 2014, the disease had spread to Sierra Leone and Liberia and subsequently to Nigeria, Senegal and Mali. The outbreak rapidly evolved and by August 2014, the WHO declared the Ebola outbreak in West Africa to be a Public Health Emergency of International Concern (PHEIC). A total of 28,610 suspected, probable, and confirmed cases of EVD were reported to WHO, including 11,308 deaths. In March 2016, the WHO declared that the Ebola outbreak no longer constituted a PHEIC. Even though all known chains of transmission had been stopped in West Africa, the WHO stated that flare-ups can be expected, and that strong surveillance and response systems will be critical in the months to come. At the beginning of 2016, new clusters of Ebola cases were reported but transmission was limited because of rapid response. Ebola virus is highly transmissible by direct contact with infected blood, secretions, tissues, organs and other bodily fluids from dead or living infected persons (5). The principal mode of transmission in human outbreaks is person-to-person transmission through direct contact with a symptomatic or dead EVD case. The incubation period is 2 to 21 days.

Figure 2.1 Confirmed global cases of MERS-CoV (4).



Humans are not infectious until they develop symptoms. First symptoms are the sudden onset of fever, fatigue, muscle pain, headache and sore throat. This is followed by vomiting, diarrhea, rash, symptoms of impaired kidney and liver function, and in some cases, both internal and external bleeding.
In 2015, no cases of Ebola were notified in the Netherlands. In 2014, one medical evacuation to the Netherlands of a confirmed Ebola-infected patient took place, and two persons exposed to Ebola, who then tested negative, were repatriated to the Netherlands.

2.3 Group B2-diseases

Hepatitis A
For the fourth consecutive year, the total number of hepatitis A cases in the Netherlands has slightly decreased, reaching a record low. In 2015, 79 cases were reported compared to 105 cases in 2014 and 109 cases in 2013. Approximately 60% of the cases acquired the infection abroad, of which most cases in Morocco (28%). In 2015, 13 patients with hepatitis A infection were reported in patients staying at an asylum seeker center in the Netherlands. This included two family clusters, both with two cases. Hepatitis A strains were identical within the clusters but not between the clusters. All strains were type 1B with most likely area of origin the Middle East. The typing results suggest that transmission occurred during their journey to the Netherlands. The decrease in hepatitis A cases could possibly be explained by the improvement of hygienic measures taken in other countries. Another hypothesis for the decrease in cases is that travelers take better precautions before going abroad (e.g. higher uptake of hepatitis A vaccination).

Pertussis
In the Netherlands, there is a persistent pertussis disease burden among infants too young to be (fully) protected by vaccination. In the period from 2005-2014, 1,711 cases of pertussis (1,279 among children aged 5 months and under), 1,126 hospital admissions (1,020 among children aged ≤5 months) and 5 deaths were reported among infants. Vaccination during pregnancy is an effective and safe addition to the existing infant vaccination programme. A model developed based on recent insights and data, indicates that vaccination of pregnant women can potentially reduce the number of cases of pertussis among infants aged five months and under (a large number of whom require hospitalization) from an average of 128 per year without maternal vaccination to an average of 26 per year with maternal vaccination. A further decline in the mortality rate, which is already low, can also be expected to result from the vaccination of pregnant women. This led the Dutch Health Council to advise in December 2015 that vaccination against pertussis should be made available to pregnant women. The minister of Health, Welfare and Sports is expected to take a decision on the implementation later this year.

2.4 Group C-diseases

Mumps
The incidence of mumps notifications increased compared to 2014, from 39 cases in 2014 to 87 cases in 2015. The incidence was lower compared to 2010-2013, when an average annual incidence of 444 cases was reported. Some small clusters among students were reported. One outbreak occurred in a field hockey team, with a total of 11 cases. Additional reported clusters were related to a bar and to an MBO-school. The latter was, based on molecular typing, linked to the field hockey cluster. Almost half of the cases in 2015 were students. Of all mumps cases in 2015, 71% were vaccinated, the majority of them (85%) received two vaccinations.

Legionellosis
The total number of legionellosis notifications has increased for the third consecutive year to 436 cases in 2015, of which 419 were cases of legionella-pneumonia in Dutch residents. Seventy percent of cases were male, which is common in legionellosis. The increase in cases was mainly observed in autochthonous cases, with a 46% increase compared to 2011-2014. Cases were spread throughout the country and no large clusters or notable sources were identified. The highest number of autochthonous cases was seen in summer (August and September). Additionally, during the winter months (January to March) and October, more cases than usual were observed. This increase may be attributed to a mild winter and a warm summer with heavy rainfall. In 35% of all cases, legionella-pneumonia was acquired abroad, with the most frequently listed countries of infection being Italy and France.

Leptospirosis
In 2014, the incidence of autochthonous human leptospirosis cases in the Netherlands increased 4-fold compared to 2010-2013, possibly related to favorable meteorological conditions, enabling rodents and excreted *Leptospira* to survive. This increase of leptospirosis cases was also observed in 2015, when a total of 86 leptospirosis cases were reported, of which 40 were autochthonous and 46 acquired the disease outside the Netherlands. Autochthonous cases mainly contracted the disease through surface water contact or (indirect) contact with rats. Imported cases mainly acquired the disease in Southeast Asia, of which the majority (n=22) in Thailand.

Malaria

In 2015, an increase in malaria cases was reported in the Netherlands. The increase is largely accounted for by the increase of cases in asylum seekers; representing 126 of the 356 cases (Chapter 6). Of the cases other than asylum seekers, approximately 42% of the cases were migrants visiting friends and family in their home country. Other groups that accounted for parts of the malaria cases included tourists and those working abroad. In Dutch residents travelers, most infections were acquired in Ghana, Nigeria, the Gambia and Guinea.

2.5 Key sIgnals related to non-notifiable infectious diseases

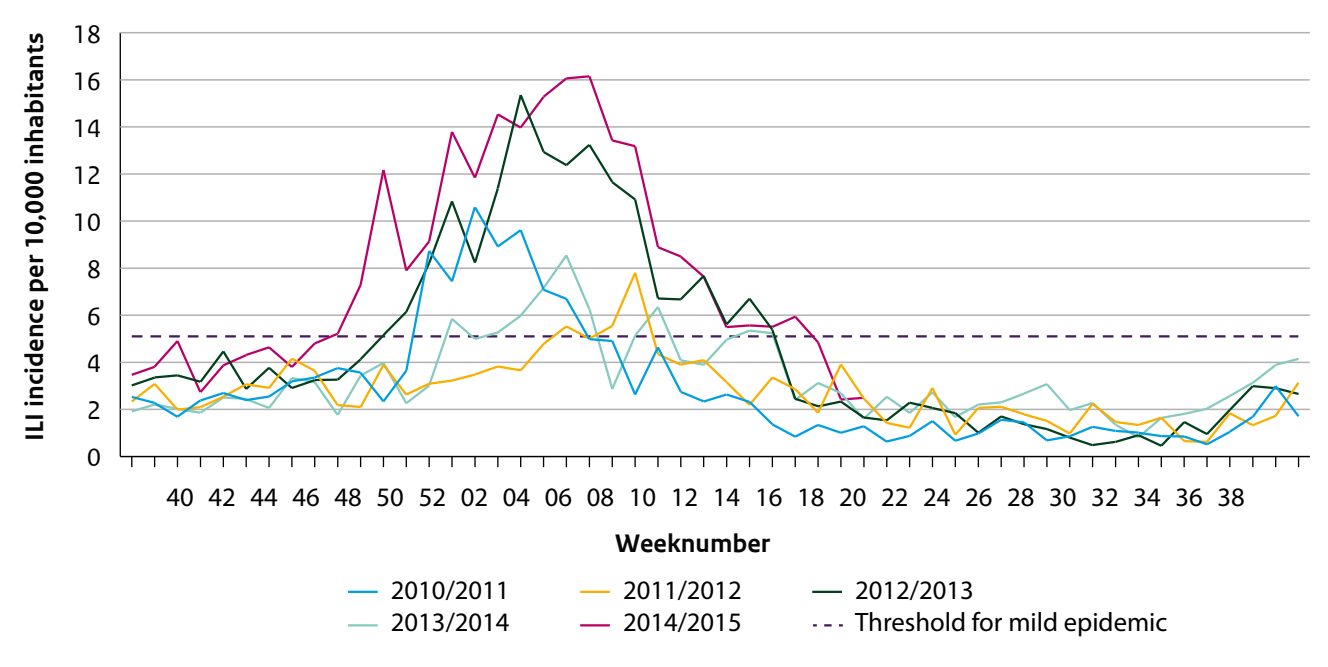
Influenza

From week 49 of 2014 through week 17 of 2015, a 21-week lasting influenza epidemic in the Netherlands was observed and, as such, this was the longest epidemic ever recorded in the Netherlands (Figure 2.2). The maximum peak of weekly influenza-like illness (ILI) incidence reported by sentinel GPs was high (16.1/10,000) compared to the previous four seasons. Additionally, the cumulative seasonal incidence was 264.8/10,000 inhabitants, this was also higher compared to the previous four seasons. The ILI incidence was highest among children aged 4 and younger, followed by the elderly (65 and older). In this season, half of the circulating A(H3N2) viruses (of HA genetic clade 3C.2a) showed antigenic differences with the vaccine A(H3N2) virus. Also, the B viruses that circulated in higher proportions later in the season were not optimally comparable with the vaccine components. In addition, these viruses were also antigenic-drifted compared with the viruses circulating in previous seasons, resulting in reduced immune protection in the general - not vaccinated – population (6).

Zika virus

Zika virus (ZIKV) is a mosquito-borne flavivirus, which emerged in South and Central America in 2015, causing large numbers of human infections. Most ZIKV infections remain asymptomatic; about 20% of the infections result in a mild and self-limiting febrile illness associated with fever, maculopapular rash, headache and conjunctivitis. ZIKV is endemic in Central and West Africa as well as South and South-East Asia. The virus was not considered a relevant human pathogen until outbreaks occurred on Yap Island and Federal States of Micronesia in 2007, in French Polynesia in 2013, and in other countries in the Pacific Region in 2013-2014. In Brazil, ZIKV circulation was confirmed in May 2015 (7). Since then, the virus has spread exponentially to other countries in South and Central America. As of 11 May 2016, 49 countries and territories reported active local transmission, which implies that health authorities had reported autochthonous human cases within the last three months (8) (Figure 2.3). Local transmission was also reported on Curacao, Bonaire, Aruba

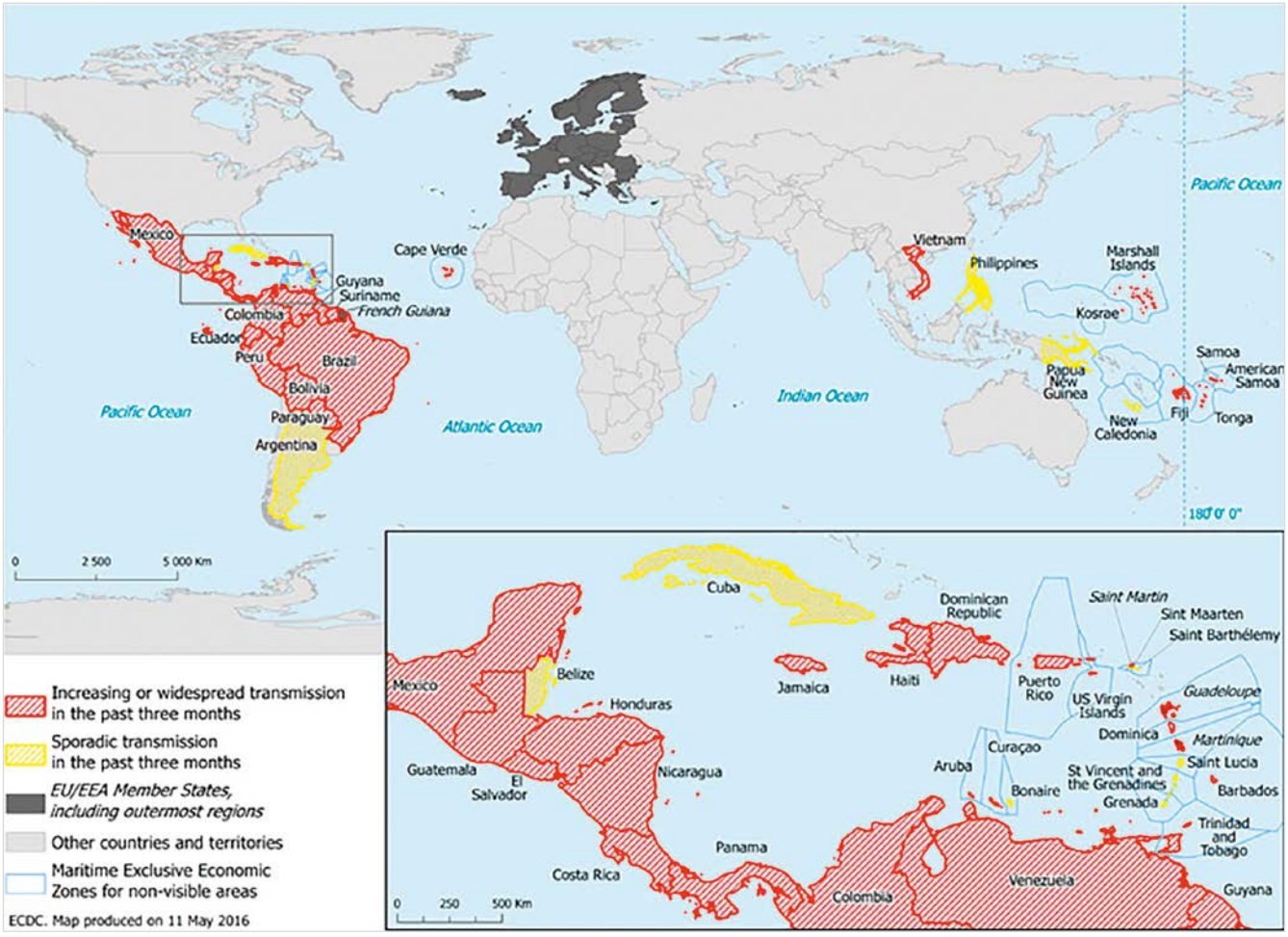
Figure 2.2 Weekly ILI incidence during the respiratory seasons 2010/2011 - 2014/2015 (through week 20 2015) (Source: NIVEL Primary Care Database).



and Sint-Maarten. Until May 2016, approximately one hundred human infections were reported from these islands, mainly from Curacao. In addition, about 50 cases of imported ZIKV infections were reported in the Netherlands. Most cases likely acquired the infection in Suriname.

Due to increasing numbers of reported cases of microcephaly in Brazil since late 2015, and multiple cases of Guillain-Barré syndrome (GBS) in the outbreak areas, a potential association between ZIKV infection and these disorders was suggested. Hence, on 1 February 2016, the World Health Organization (WHO) declared the recent clusters of microcephaly and other neurological disorders and the possible association with ZIKV a Public Health Emergency of International Concern (PHEIC) (9). Based on multiple case reports of adverse pregnancy and birth outcomes, the Centers for Disease Control and Prevention (CDC) concluded in April 2016 that a causal relationship exists between prenatal ZIKV infection and microcephaly and other brain disorders (10). Furthermore, an association of ZIKV infection with GBS has been observed in a case-control study in French Polynesia (11). ZIKV is transmitted to humans by *Aedes* spp. mosquito vectors, mainly *Ae. aegypti*, which is widespread in (sub)tropical regions and which is also one of the main vectors of dengue and chikungunya. In addition, the virus has been detected in *Ae. albopictus,* which has been shown to be a moderately competent vector for ZIKV by experimental infection (12). In Europe, *Ae. albopictus* has been established in multiple countries, including Italy, Southern France and Spain, whereas *Ae. aegypti* has only been established on the island of Madeira and in Northeastern Turkey (13). Given the history of autochthonous cases of chikungunya and dengue in some European countries in the past, limited local transmission of ZIKV after introduction of a viremic traveler cannot be excluded in regions where a suitable vector is present. In addition to mosquito-borne transmission, other transmission routes have been suggested, including trans-placental and blood-transfusion mediated transmission (10, 14). Unlike other arboviruses, sexual

Figure 2.3 Countries or territories with reported confirmed autochthonous cases of Zika virus infection in the past three months, as of 11 May 2016 (8).



transmission of ZIKV is also possible and is of particular concern during pregnancy (14). Zikavirus has been detected in semen of symptomatically infected males, and multiple case reports have been published of probable cases of sexual transmission from infected males to their otherwise unexposed sexual partners (14). In September 2016, the notification requirements for ZIKV will be implemented in the Netherlands as well as the overseas Dutch territories, Bonaire, Sint Eustatius and Saba. The notification requirement will be restricted to confirmed ZIKV infection during pregnancy, in a woman who has undergone (spontaneous) abortion, in newborns with congenital disorders, in hospitalized ZIKV-infected persons, fatal ZIKV infections, and in persons who developed GBS as a result of ZIKV infection.

Febris recurrens

Two cases of febris recurrens (louse borne relapsing fever (LBRF)), were laboratory confirmed in two asylum seekers from Eritrea. Both patients were admitted to the ICU for supportive treatment and recovered fully without further complications. Control measures were taken in the asylum center constituting of washing clothes and bed linen, and doctors from the Asylum Seekers Health Center were informed to be alert for LBRF cases. Twenty-seven confirmed cases of LBRF were diagnosed in EU countries and Switzerland between July and October 2015. Almost all diagnosed cases were refugees from countries of the Horn of Africa. LBRF is highly endemic in northeastern Africa. LBRF is caused by the spirochaete *Borrelia recurrentis*. The onset of symptoms is usually sudden. Symptoms include high fever, general malaise, chills and sweats, headache, meningism, myalgia/arthralgia and non-specific gastrointestinal symptoms (nausea and vomiting), but can also include mucocutaneous symptoms and cardio-respiratory symptoms. The symptoms increase in intensity over five days on average (range: 2–7), then subside as the pathogenic agent disappears from the blood. After a first remission, spirochetes reappear in the blood and symptoms recur. The disease can be severe, and death occurs in 10% to 40% of cases in the absence of appropriate treatment, and in 2-5% of treated patients. After initiation of treatment there is a high risk (90%) of developing a (severe) Jarisch Herxheimer reaction. Primary prevention of LBRF relies on measures for avoiding infestation with body lice. These infestations are linked to low socioeconomic status, overcrowding, and poor personal hygiene. Historically, major outbreaks of LBRF occurred in Eurasia and Africa, but currently the disease is primarily found in northeastern Africa. No cases of LBRF infections acquired in the Netherlands have been reported since 1990.

2.6 Literature

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3 Infectious disease surveillance: overview, methods and applications in the Netherlands

3.1 Introduction

Infectious disease surveillance is a cornerstone of effective infectious disease control. In this chapter, we give an overview of surveillance, with a focus on the different methods and applications used in the Netherlands. We start by presenting an historical overview of the development of surveillance from an early form of surveillance in the 14th century, when surveillance was implemented by placing exposed people in quarantine as a measure to control the spread of pneumonic plaque, to surveillance in the 20th century as the cornerstone of infectious disease treatment, prevention and control. In the first section, we describe the different infectious disease surveillance systems in the Netherlands. Subsequently, we focus on how the collected data are used to detect outbreaks, to control infectious diseases, and to inform policy makers. We discuss commonly used methods and provide examples. In the concluding section, we summarize strengths and limitations of surveillance methodology, and discuss future challenges in this area.

3.2 Surveillance overview

The emergence of pneumonic plague, also known as the Black Death, in 1348 in Europe resulted in Venice in the appointment of three guardians of public health by the Venetian Republic to detect and exclude ships which had infected people on board. This was possibly the first form of surveillance which led to public health measures being taken by a government in Europe. The detention of travelers from plague-infected areas for 40 days in Marseille and Venice resulted in the birth of quarantine as a means of controlling the spread of infectious diseases (1). Another early example of surveillance was that during plague epidemics in London in the seventeenth century. Prior to this, in plague years, data were collected centrally and sporadically. At the beginning of the seventeenth century, London clerks produced regular weekly reports on the number of burials and the cause of death. This information was interpreted and disseminated in a weekly 'Bill of Mortality'. This early surveillance system illustrates the main principles of surveillance, which are still in use: systematic, ongoing data collection and analysis, interpretation to provide information, and timely dissemination of that information for action (1).

During the eighteenth century, surveillance was recognized as an integral part of the provision of public health. William Farr, a medical statistician, was the first to systematically analyze surveillance data. He used mortality data to monitor infectious disease epidemics over time. He was convinced that the knowledge gained by his work was essential to understand and control infectious disease outbreaks. He is recognized as the founder of the modern concept of surveillance (2). In the twentieth century, the concept of surveillance expanded with the development of many different surveillance systems. Methods of collection, analyses and dissemination of data have diversified since then, and methods have been enhanced.

Figure 3.1 William Farr (Source: Wikipedia).

Table 3.1 Timeline of national and international developments in public health surveillance adopted from Declich et al (1) and supplemented with developments in the Netherlands.

1755	First registry of causes of death in The Hague
1865	First national mandatory reporting of communicable diseases
1866	First national statistical overview of six different causes of death
1899	Establishment of Statistics Netherlands (CBS)
1901	Establishment of the first municipal health service in Amsterdam
1951	International Sanitary Regulations adopted by WHO (pre version of the International Health Regulations (IHR)
1957	Start of the Dutch National Immunization Programme
1965	First edition of the 'GHI-bulletin' to disseminate surveillance data on a monthly basis
1966	First publication of Communicable Disease Surveillance Reports by the WHO
1967	Development of a General Practitioners' sentinel surveillance system
1969	Revised International Sanitary Regulations renamed International Health Regulations
1989	Establishment of the Dutch Virological Weekly Reports
1990	First edition of the Dutch Infectious Disease Bulletin ('Infectieziekten Bulletin') to disseminate surveillance data on monthly basis
1995	First national serology survey in the Netherlands ('serosurveillance')
1998	EU decision to set up a network for surveillance within all EU countries (Decision No 2119/98/EC)
1999	Start of the Netherlands Early Warning Committee
2000	Establishment of Early Warning and Response System (EWRS) in Europe
2005	Revised WHO International Health Regulations
2005	Establishment of the European Centre for Disease Prevention and Control (ECDC)
2005	Start of Dutch Centre for Infectious Disease Control at the National Institute for Public Health and the Environment (RIVM/CIb)
2009	Revised Public Health Act in the Netherlands to implement the revised WHO International Health Regulations
2013	EU decision that each country must maintain infectious disease surveillance (Decision No 1082/2013/EU)

Definition of surveillance

In 1950, Alexander D. Langmuir (CDC Atlanta, USA, 1910-1993) defined surveillance as 'Surveillance, when applied to disease, means the continued watchfulness over the distribution and trends of incidence through the systematic collection, consolidation and evaluation of morbidity and mortality reports and other relevant data. Intrinsic in the concept is the regular dissemination of the basic data and the interpretations to all who have contributed and to all others who need to know.' In 1968, at the World Health Assembly Technical Discussions, the definition of surveillance was simplified and summarized in 'surveillance: information for action' (3), to emphasize the difference between surveillance and monitoring.

Objectives of surveillance

Surveillance is one of the three methodological corner stones of the epidemiology of infectious diseases, besides outbreak investigation and epidemiological/methodological research. The different goals of surveillance are (4):

- to detect outbreaks (epidemics);
- to enable public health action;
- to monitor / evaluate trends in endemic disease;
- to identify clues about disease etiology;
- to plan and monitor / evaluate prevention programs;
- to evaluate an intervention;
- to predict outbreaks (epidemics);
- to estimate disease burden and future impact;
- to generate hypotheses for further research.

Sources of data and data collection

Many sources of data can be used for infectious disease surveillance. The traditional list of data sources includes, for example, mortality data, morbidity data, epidemic reporting, laboratory reporting, individual case reports, epidemic field investigation, surveys, animal reservoir and vector distribution studies, vaccine coverage, demographic data, and environmental data (5). Mortality registration is the oldest form of public health reporting. Since 1968, additional sources of data have become available. Most of these data are collected for other purposes, but they may be utilized in supplementing routine surveillance data or in evaluating special disease situations. These data sources are, for example, hospital or medical care statistics, general practitioner data/ reports, public health laboratory reports, disease registries, drug and biologics utilization and sales data, absenteeism reports from school or work, health and general population

Box 3.1 Definitions relevant for Public Health Surveillance (adopted from Principles & Practice of Public Health Surveillance. Lisa M. Lee, Steven M. Teutsch, Stephen B. Thacker, and Michael E. St. Louis).

Active surveillance: This can be defined by a set of activities, including regular active prompting/reminding reporters to report cases, the provision of a stimulus to health care workers in the form of individual feedback or other incentives; monitoring of reporting frequency by individual health workers; provision of specific feedback to health workers who consistently fail to report or complete the forms incorrectly to improve their performance; incentives for complete reporting; and zero-reporting.

Enhanced surveillance: is active surveillance which is intensified by e.g. putting emphasis on completeness and timeliness of data, or by requesting additional information for cases reported.

Laboratory surveillance: Laboratory-based surveillance uses on data produced in clinical and/or public health laboratories.

Passive surveillance: Passive surveillance often gathers disease data from all potential reporting health care workers. Health authorities do not stimulate reporting by reminding health care workers to report disease nor by providing feedback to individual health workers.

Sentinel surveillance: A sample of general practitioners, hospitals or laboratories in a country report certain disease/pathogen occurrences.

Surveillance (Langmuir definition): the continued watchfulness over the distribution and trends of incidence through the systematic collection, consolidation and evaluation of morbidity and mortality reports and other relevant data. Intrinsic in the concept is the regular dissemination of the basic data and the interpretations to all who have contributed and to all others who need to know (3).

Surveillance (WHO definition): Information for action (3).

Surveillance surveys: A survey is a collection of data at a single point in time from a specific population.

Syndromic surveillance: Applies to surveillance using health-related data that precede diagnosis and signal a sufficient probability of a case or an outbreak to warrant further public health response.

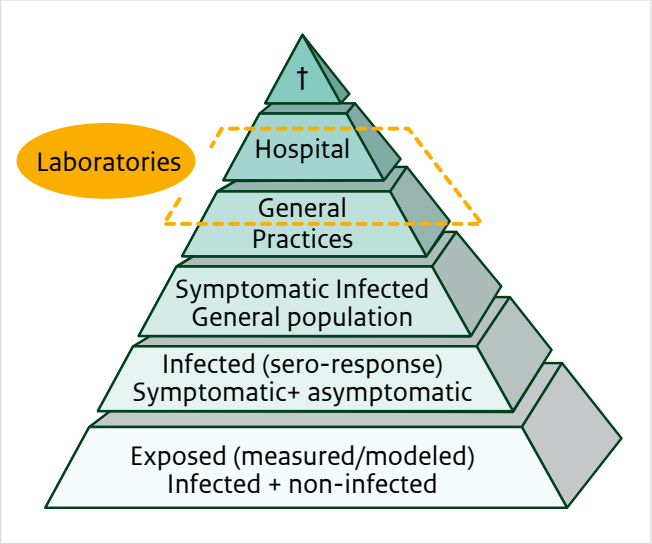
Zero-reporting: the requirement to also report absence of cases.

surveys, newspaper and news broadcasting reports, and genomic and/or molecular sequence data of pathogens. The collection of data is usually the most costly and difficult component of a surveillance system. The quality of a surveillance system is as good as the quality of the data collected. There are different methods to collect data: passive surveillance, active surveillance, enhanced surveillance, sentinel surveillance, syndromic surveillance, laboratory surveillance, surveillance surveys and investigations (see Box 3.1). The complexity of the data and the multitude of sources of data necessitate the development of new methods for linking (big) data, for analyses and for reporting and visualization of results.

Surveillance pyramid

The surveillance pyramid (figure 3.2) illustrates why surveillance data does usually not include all occurrences of an infection of an infectious disease in the population. It illustrates the steps that must occur for an episode of illness in the population to be registered in a surveillance system. The surveillance pyramid is a model for understanding infectious disease reporting. Most people do not seek health care for their illnesses, and even among individuals who seek care, many do not have a laboratory test. Laboratory testing does not always identify a pathogen, and even when a specific microorganism is identified, this may not be the cause of the disease, and physicians may not report all illnesses to public health authorities. Further, it may not be evident that patients are connected to a common exposure, so outbreaks could go undetected and unreported. Many surveillance systems focus on the top of the surveillance pyramid where data are often more readily available.

Figure 3.2 Surveillance pyramid.



Methods of data analysis, interpretation and dissemination

Surveillance data initially can be descriptively analyzed in terms of time, place, person and pathogen. Analysis of surveillance data primarily involves comparing current data with an expected value, identifying differences between them and assessing the importance of these differences. Data analysis is followed by interpretation. Interpretation involves considerations of whether the apparent deviating disease occurrence, within a specific population at a particular time and place, represents relevant deviation. These aspects are described and discussed in the following sections.

Dissemination of surveillance data to relevant parties is a critical component of a surveillance system. Recipients should at least include those who provide reports, those who collect data, and for the relevant parties regarding administrative or program planning and decision-making purposes (1). A summary of the current situation, appropriate analyses and presentation of the data (with meaningful interpretation and discussion of trends or other important features) are the basic elements of a surveillance report.

Current infectious disease surveillance systems

Tables 3.2 and 3.3 give an overview of national infectious disease surveillance systems in the Netherlands.

Table 3.2 Main sources of data for infectious disease surveillance in the Netherlands used by the National Institute of Public Health (RIVM/CIb).

Data source	Goal	Population under surveillance
Mandatory disease notification	With mandatory disease notification, the (local) government can implement preventive and control measures. At national level, the data is used to monitor trends, support the development of guidelines and policies such as vaccination program.	All residents of and visitors to the Netherlands.
Virological laboratory surveillance	To monitor trends of viral infections.	Population served by 21 laboratories.
NIVEL Primary Care database	The monitor developments in health and the use of primary health care.	Approximately 4% of Dutch population (6).
[Sentinel] surveillance at general practitioners who participate in NIVEL Primary Care Database	To monitor trends of disease syndromes in general care in the Netherlands, in particular influenza like illness.	Approximately 0.7% of Dutch population (6).
Sentinel surveillance of severe acute respiratory infections (3 pilot hospitals)	To monitor severe acute respiratory infections in hospitals	Patients in hospitals.
STI Centers	To monitor trends in sexually transmittable diseases Dutch STI centers.	All STI clinic attendees.
Gonococcal Resistance to Antimicrobials Surveillance programme	To monitor resistance trends in gonococci in the Netherlands.	Gonorrhea patients diagnosed at STI clinics.
Antenatal screening	To protect pregnant women and prevent transmission to their offspring for a selection of congenital infections	All pregnant women.
National sentinel surveillance network for infectious diseases in nursing homes (SNIV)	The aim of the SNIV network is to provide systematic year-round surveillance data on the incidence of infections in nursing homes for local interventions and national policymaking, and for the development of infection control guidelines.	Approximately 4% of residents of Dutch nursing homes.
Surveillance of antibiotic resistance (ISIS-AR)	The aim is to monitor resistance trends in the Netherlands and early detection of multi institutional outbreaks or increase trends of resistant microorganisms.	Patients whose bacterial infection is diagnosed and tested for antibacterial susceptibility.
PREZIES	PREZIES aims to monitor trends in nosocomial infections in hospitals in the Netherlands to support local and national infection prevention and control policy.	Patients in participating hospitals with post-operative wound infections or catheter related bloodstream infections.

Table 3.2 (continued) Main sources of data for infectious disease surveillance in the Netherlands used by the National Institute of Public Health (RIVM/CIb).

Data source	Goal	Population under surveillance
Pathogen surveillance, for example: • *Neisseria meningitidis* • *Streptococcus pneumoniae* • *Listeria monocytogenes* • *Leptospira*-species • Poliovirus • *Mycobacterium tuberculosis* • Methicillin resistant *Staphylococcus aureus* • Shiga toxigenic *Escherichia coli* (STEC) • Creutzfeldt-Jakob disease • *Trichinella*-species • Influenza virus • HIV	To monitor trends in pathogens, subtyping, and antimicrobial resistance patterns	Patients in primary care and hospitals whose infection is laboratory confirmed.
Laboratory Surveillance of Infectious Diseases (LSI)	To monitor trends on *Campylobacter, Shigella* and *Salmonella*	Approximately 52-64% of Dutch population (7).
Mortality	To monitor mortality trends in the Dutch population	All Dutch residents.
Immuno-surveillance	To monitor the immune status of the Dutch population	Sample of population.
Vaccination uptake	To monitor national vaccination uptake	Population targeted in the National Immunization Program.
Surveillance of adverse events following immunization	To monitor adverse events following immunization and vaccine safety	Population targeted in the National Immunization Program.

Table 3.3 The main sources of surveillance data and output in the Netherlands per disease category.

Disease category	Main sources of surveillance data	Most recent output
Vaccine-preventable diseases	• Mandatory disease notification, • Hospital admissions • Mortality • Vaccination uptake • Surveillance of adverse events • Immuno-surveillance • Pathogen surveillance / Virological laboratory surveillance	Annual report: The National Immunization Program in the Netherlands. Surveillance and developments in 2014-2015 (8) Vaccinatiegraad Rijksvaccinatie-programma Nederland verslagjaar 2015 (9). In Dutch only. Bijwerkingencentrum Lareb: Meldingen van mogelijke bijwerkingen Rijksvaccinatieprogramma: Rapportagejaar 2014 (10). In Dutch only.
Respiratory tract infections	• Sentinel surveillance at general practitioners who participate in NIVEL Primary Care Database • Mortality • Sentinel surveillance of severe acute respiratory infections (two pilot hospitals) • Sentinel surveillance network for infectious diseases in nursing homes • Pathogen surveillance • Virological laboratory surveillance • Mandatory disease notification • Vaccination uptake	Annual report: Surveillance of influenza and other respiratory infections in the Netherlands: winter 2014/2015 (6) Staat van Zoönosen (13) In Dutch only.
HIV, Sexually Transmitted Infections and viral Hepatitis	• STI Centers • Sentinel surveillance at general practitioners who participate in NIVEL Primary Care Database • Pathogen surveillance • Mandatory disease notification (only hepatitis B and C) • Virological laboratory surveillance • Antenatal screening • Vaccination uptake • Gonococcal Resistance to Antimicrobials Surveillance programme • HIV treatment clinics (by HIV monitoring foundation)	Annual report: Sexually transmitted infections including HIV in the Netherland in 2014 (11)
Food- and water-borne diseases	• Mandatory disease notification • Pathogen surveillance • Virological laboratory surveillance • Laboratory Surveillance of Infectious Diseases (LSI) • Immuno-surveillance	Surveillance van shigatoxine-producerende Escherichia coli (STEC) in Nederland, 2013 (12). In Dutch only. Registratie van voedselinfecties en -vergiftigingen in 2014 (13). In Dutch only. Surveillance van Listeria monocytogenes in Nederland, 2013 (14). In Dutch only. Staat van Zoönosen (7). In Dutch only.
Antimicrobial resistance and healthcare-associated infections	• Pathogen surveillance • ISIS-AR • PREZIES • Gonococcal Resistance to Antimicrobials Surveillance programme • Sentinel surveillance network for infectious diseases in nursing homes • Dutch Foundation for Pharmaceutical Statistics (SFK)	Annual report: Nethmap 2015: Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in the Netherlands / Maran 2015: Monitoring of antimicrobial resistance and antibiotic usage in animals in the Netherlands in 2014 (15)
Emerging and vector-borne disease	• Mandatory disease notification • Pathogen surveillance	Annual Report: Staat van Zoönosen 2014 (7). In Dutch only.

International perspective on surveillance

In 1998, the European Parliament and the European Council made a formal decision to set up a network for the epidemiological surveillance and control of communicable diseases in the EU. Subsequently, epidemiological surveillance and an Early Warning and Response system for prevention and control of infectious diseases were established. In 2005, the European Centre for Disease Prevention and Control (ECDC) was founded. The ECDC collect, analyze and disseminate surveillance data for 52 communicable diseases and related special health issues from all European Member States. Furthermore, countries are obliged, under the International Health Regulations (IHR) established by the World Health Organization (WHO), to notify to the WHO certain infectious diseases (e.g. a single case of poliomyelitis due to wild type polio virus) or certain outbreaks of diseases (e.g. an unexpected increase of dengue fever) that may constitute a public health emergency of international concern (PHEIC). The most recent PHEIC was declared on February 1, 2016 by the WHO due to the clusters of microcephaly and other neurological abnormalities that may be caused by the Zika virus in Brazil. This designation was also applied to the recent Ebola outbreak in West Africa. The WHO has the authority to decide whether a very serious event constitutes a PHEIC. Under the IHR, the WHO is at the center of global surveillance of national events or diseases with potential international implications.

In the next sections, we focus on different infectious disease surveillance methodology. Dutch surveillance data is mostly used in respect to the detection of outbreaks, monitoring trends in endemic disease, estimating disease burden, and planning and monitoring disease prevention programs. We describe the background of the different methods and give examples from the Netherlands. Finally, some methodological challenges are described.

3.3 Outbreak detection

The WHO defines a disease outbreak as "the occurrence of cases of disease in excess of what would normally be expected in a defined community, geographical area, or season" (16). Timely detection of outbreaks is needed for implementation of timely control measures to prevent further cases and spreading of the disease. Outbreak detection starts with the observation of an increased number of reported cases (suspected or confirmed) of a particular disease (or potential pathogen type) in a given time, place or population group. A major challenge in outbreak detection is the definition of what constitutes an increased number of cases, or in other words, what is the expected number of cases. In the Netherlands, different methods are used to answer this question.

Signals

First and foremost, the general everyday knowledge and experience of health care workers (HCWs) is used. Most outbreaks are detected by HCWs or an expert in the field observing an unusual situation. For example, the Q-fever outbreak in the Netherlands in 2007 was detected by a general practitioner from a rural village observing an unusual increase in pneumonia cases, which was first thought to be associated with a mycoplasma pneumonia infection, but later was recognized to be the onset of a large Q-fever outbreak (17). Relevant signals received from professionals are discussed on a weekly basis by the Netherlands Early Warning Committee (NEWC), which aims to identify, as early as possible, infectious diseases causing a potential threat to Dutch public health. Threats are assessed and published as signals to experts working in the field of infectious diseases in order to raise awareness. In addition to the NEWC, more specialized early warning committees are in place to discuss signals from hospitals (SO-ZIA/AMR) and zoonosis related signals (SO-ZO)(18).

Surveillance and outbreak detection

In addition to signal detection through the NEWC, a range of surveillance systems are in place to monitor several characteristics of infectious diseases in the Netherlands. We distinguish between several types of surveillance systems, and in this report we focus on epidemiological surveillance and laboratory surveillance. The former focuses on time, place and person characteristics of the occurrence of infectious diseases, where the latter focuses on microbiological characteristics. Often these two types of surveillance can be combined. In the next section, we discuss outbreak detection methods using epidemiological and laboratory surveillance. In Box 3.2 we give an example of outbreak detection of Salmonella, using multiple surveillance systems and characteristics of infectious diseases.

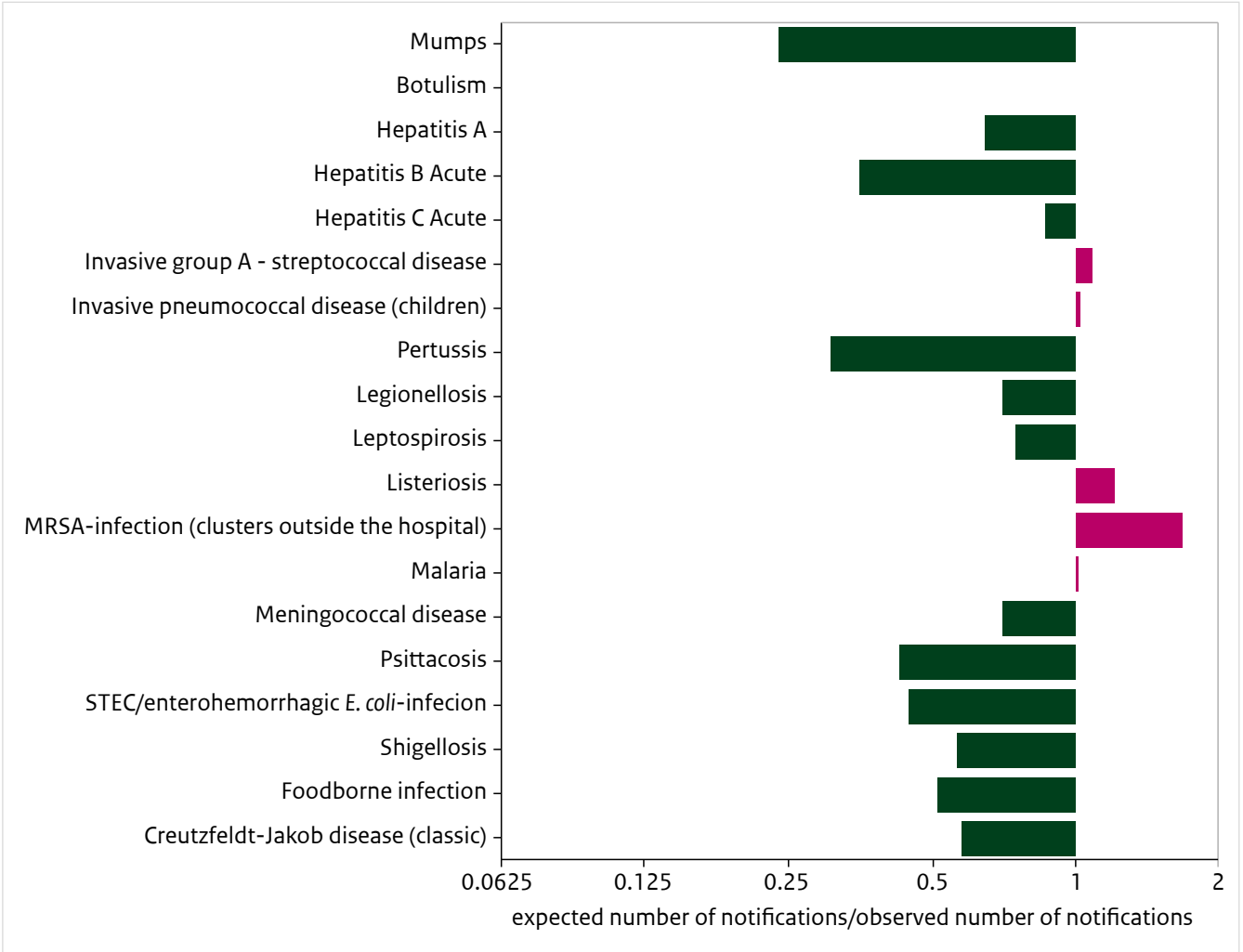
Epidemiological surveillance for outbreak detection

An important database for epidemiological surveillance and outbreak detection is the notifiable disease database (OSIRIS-AIZ). Eyeballing these surveillance data by an expert is a common method for outbreak detection, which works effectively when only a few cases of a certain disease occur. For some diseases (Ebola, MERS-CoV, polio etc.), just a single case is already 'more than expected' and hence sufficient to declare an outbreak. If diseases occur more frequently, algorithms are needed and can be applied to the data gathered during routine surveillance to detect outbreaks. The Stroup algorithm (19), for example, is applied to the notifiable disease surveillance database, and the results are visualized real-time in the 'barometer' for expert use (20) (Figure 3.3). This is a website with restricted access, as notifications which are still in the verification process are also included. In this algorithm, the number of

notifications in the past four weeks is compared to the expected value. The expected value is calculated by taking the average of the number of notifications of the same four weeks in the past five years and the four weeks before and after this period in the past five years (so the average of 15 periods of four weeks in total). The current number is considered an increase if the number is higher than the expected value plus two standard deviations. All increases are reviewed on a weekly basis by a member of the NEWC. In addition to the Stroup algorithm, other algorithms have been developed to detect outbreaks across time. A detailed overview of these can be found elsewhere (21). A limitation of using notification data for detecting outbreaks in time, is that notifications are always reported with a delay. An algorithm was developed during the influenza A/H1N1 pandemic in 2009, which predicts the current number of notifications taking into account the reporting delay ('nowcasting') (22). This algorithm was also used in the measles outbreak in 2012-2013, to get a more real-time overview of the outbreak situation.

In addition to detection of clusters in time, detection of clusters in place is an important method for detecting outbreaks. Assessing clustering in place usually starts with displaying the cases reported in a specific time period on a map. This is, for example, regularly done for Legionellosis in the Netherlands. Whether clustering is present can be assessed visually by the specific disease expert or can be assessed by applying an algorithm. A frequently used algorithm is the space-time scan statistic developed by Kulldorf (23) which is integrated in the SaTScan statistical software program (24). It can be used to detect clusters in

Figure 3.3 The 'Barometer' in week 16, 2016.



space and/or time. The algorithm scans using a window across time and/or space, and calculates the number of observed and expected cases inside each window at each location. In the Netherlands, the space-time scan statistic is not used on a routine basis for outbreak detection, as most clusters can already be detected by reviewing the map. However, in certain specific situations, the space-time statistic is applied to confirm or refute an observed clustering. For example, in 2013, an unusual increase in hepatitis B cases was observed in a specific region of the Netherlands. The scan-statistic was used to check whether significant clustering in time and space occurred, and a local cluster was found to be present among men who have sex with men (MSM) and men with an unknown route of transmission (25).

Finally, in addition to time and place characteristics of infectious diseases, personal characteristics can be reviewed to detect unusual patterns. The personal characteristics of infectious diseases (e.g. age, gender, risk group, occupation) are gathered during routine surveillance and are analyzed on a regular basis. An unexpected pattern in personal characteristics can be used to detect outbreaks, provided the characteristics are documented in the surveillance system. For age and sex, this is usually the case. For other characteristics, surveillance may need to be adapted to collect the information following external signals of an outbreak in a specific group. These signals are usually generated by alert clinicians and microbiologists. An example of outbreak detection by personal characteristics is the start of the measles outbreak in 2013 (26). In the Netherlands, several measles cases are usually notified annually, which in itself is not sufficient to define it as an outbreak. However, when a measles case occurs in an unvaccinated orthodox Protestant individual, such as in 2013, a major outbreak is much more likely, as vaccination levels among orthodox Protestants are very low.

Laboratory surveillance for outbreak detection

For an increasing number of pathogens, samples from laboratory confirmed cases are sent to a pathogen-specific reference laboratory for further typing (defined as the identification of different types of organisms within a species). The resulting data can be used in laboratory surveillance to detect outbreaks: by typing a specific pathogen, a cluster of patients with a new strain/subtype might indicate an outbreak. For example, in February 2010, the Dutch virology reference laboratory for hepatitis A-virus (HAV) detected a new strain in five patients (27). They had no travel history to HAV-endemic countries and this unusual situation led to an outbreak investigation. After thorough investigation, semi-dried tomatoes were indicated as the source of infection for this cluster of cases, however, these results could not be confirmed by food testing (28). There are many (molecular) typing methods available, and depending on the epidemiological question and the time available for analysis, they may be more or less appropriate. In order to use typing for outbreak detection, the typing method should ideally be able to distinguish all epidemiologically related cases, and should have sufficient discriminatory power to reveal person-to-person transmission (29). The typing method with the highest discriminatory power is whole genome sequencing (WGS). This does not mean that WGS is always needed. While WGS has become more affordable and therefore more used in recent years, the main challenge lies in rapidly computing and interpreting the relevant information from the large data sets WGS produces. Access to relevant data on background distribution of WGS is needed to interpret clusters, but is often lacking. Currently, WGS is rarely used in the Netherlands to aid outbreak detection, however, research is ongoing and the use of WGS in routine surveillance might be possible in the near future. Currently, a major research project has been started, with the aim of implementing WGS for tuberculosis surveillance (30).

Box 3.2 Detection of Salmonella outbreaks in the Netherlands

In the Netherlands, a three-step algorithm focused on clusters in time, place, and with a deviating age distribution is used to detect salmonella outbreaks. First, clusters in time are detected based on the Farrington algorithm (31): This algorithm compares the past four weeks with the same period (plus and minus four weeks) in the past five years (as does the Stroup algorithm) and with simple regression techniques a prospective value and tolerance limit is estimated based on historical values. The added value of the Farrington algorithm compared to the Stroup algorithm is that it accounts for trends and corrects for past outbreaks by down-weighting outliers in the regression process. This algorithm is applied to laboratory reports of salmonella subtypes (Figure 3.4).

Second, the detected time-clusters in the first step are tested for significant space clustering. This is done by calculating the median distance between randomly selected patients with salmonella infection and various cluster sizes from the historical database, and repeating this 1,000 times (bootstrapping). From these median distances the P2.5, P50 and P97.5 are calculated and presented graphically (see Figure 3.5). Finally, for all detected clusters in time, the median distance between patients in this cluster is calculated and these are also depicted in the graph. Clusters below the P2.5 threshold are considered to be clustered in space and time.
The third step is to look at the age distribution of the significant time clusters. This age-distribution is tested against the age-distribution of all type-specific historical salmonella cases using a Chi-square test. This is evaluated for time windows of different sizes. All time-clusters are flagged and reviewed by a salmonella expert; weekly about a thousand salmonella types are reviewed in this way. An overview of these three steps is shown in Figure 3.6.

Figure 3.4 Farrington algorithm applied to weekly salmonella time series.

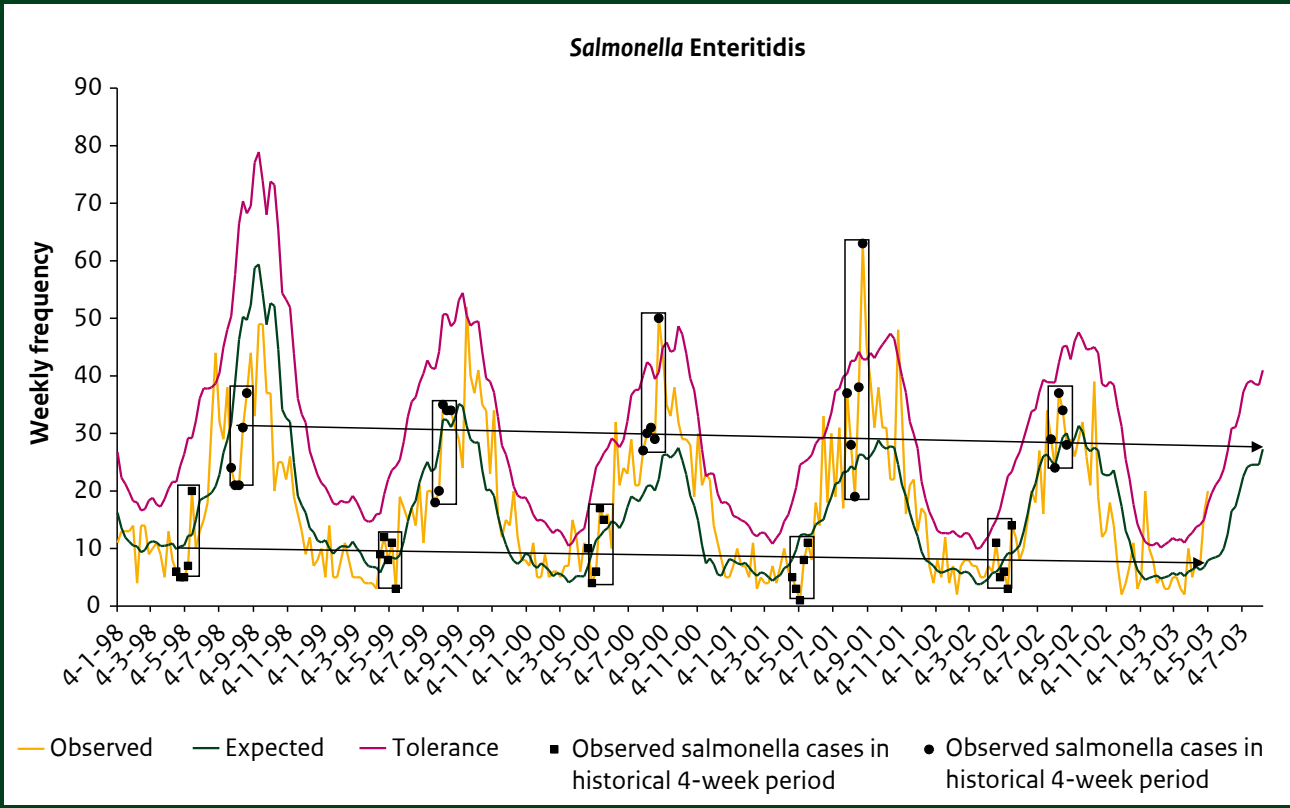


Figure 3.5 Random median distance (residence) between patients with salmonella. Empirical results after 1.000 bootstrapsamples. 274 potential outbreaks, significantly clustering in time, between 1995-2000 over 255 salmonella types.

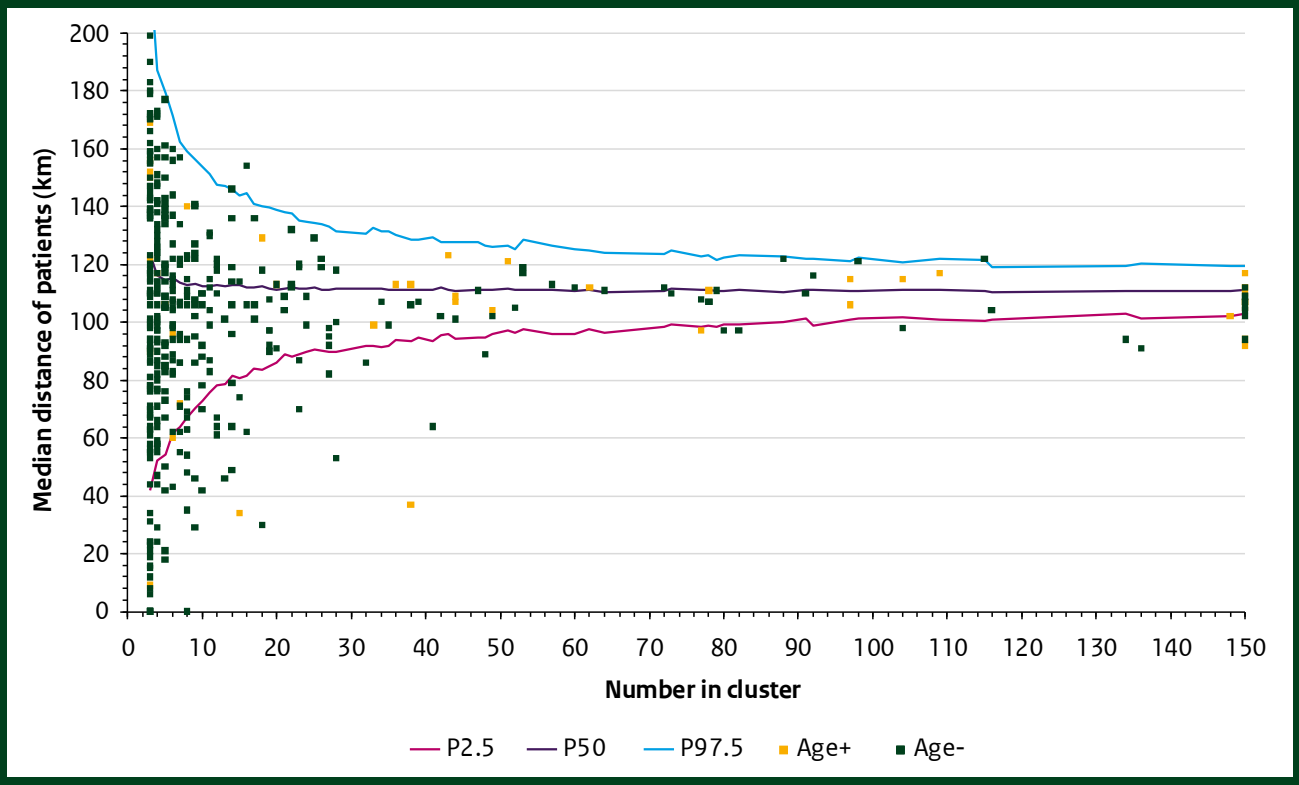
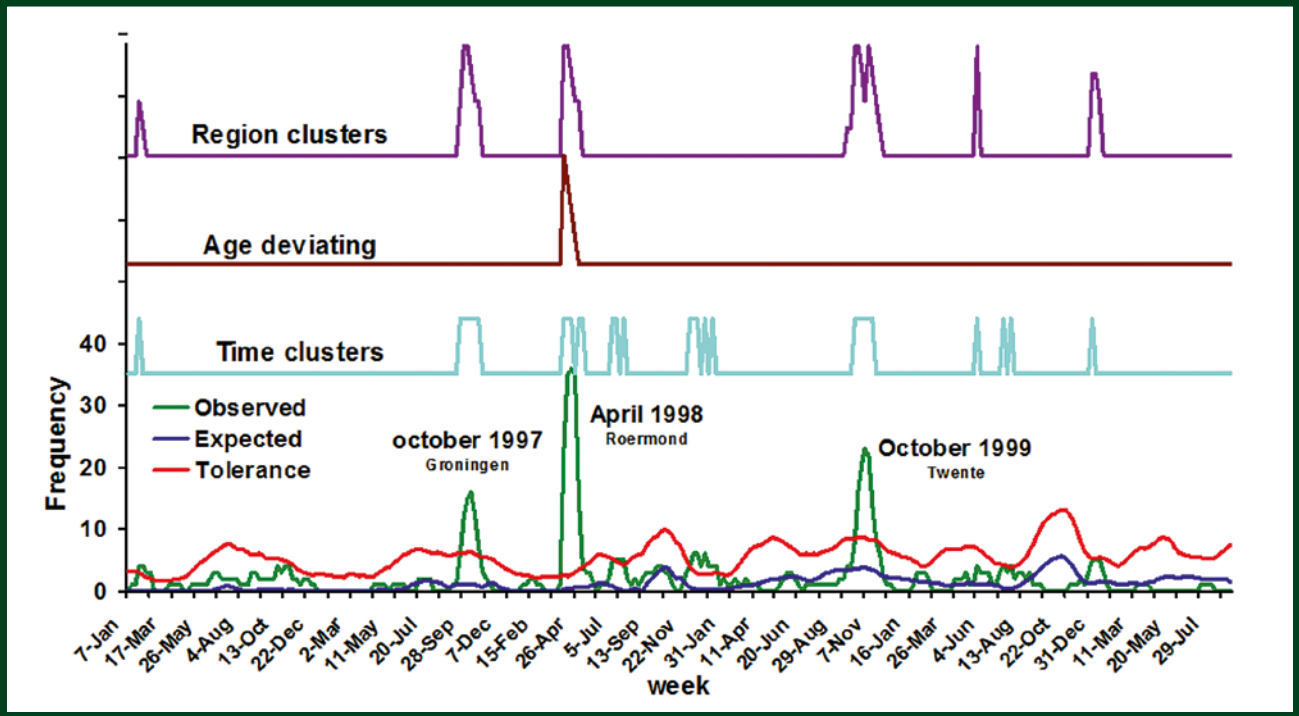


Figure 3.6 Overview of steps in outbreak detection of *Salmonella* Typhimurium Phagetype 20.



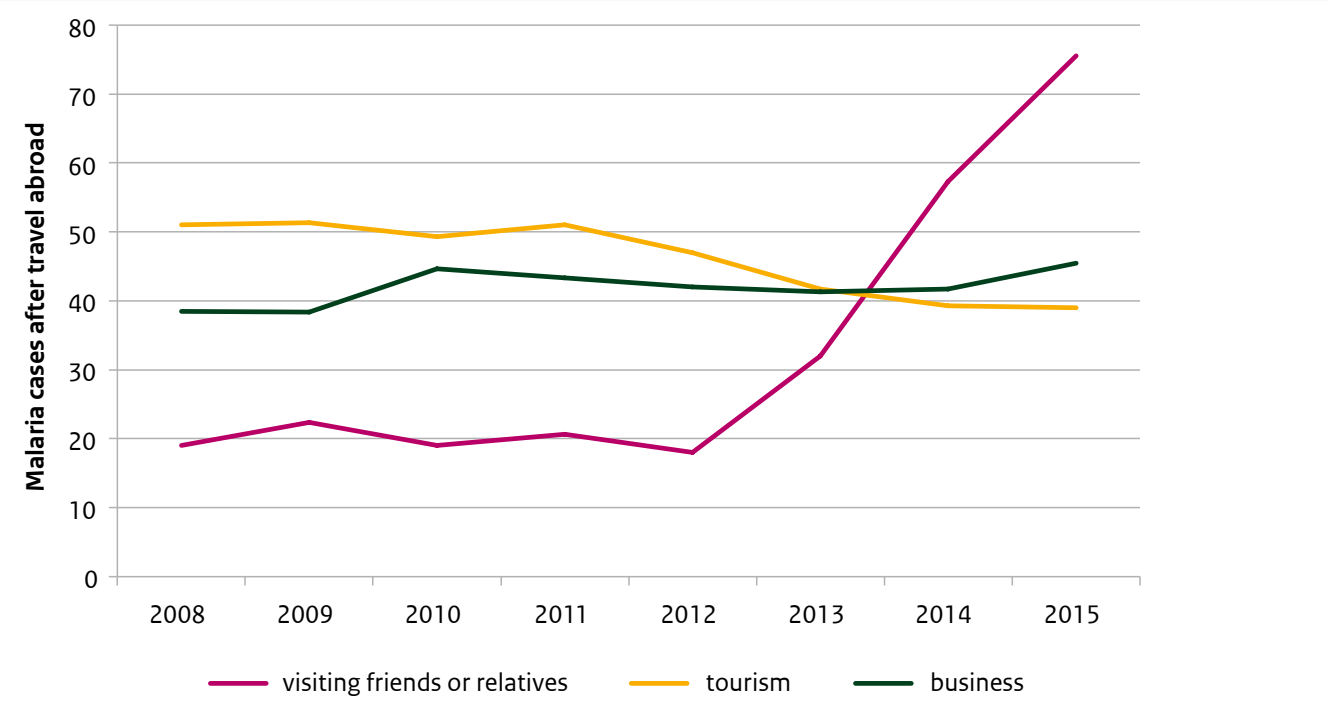
3.4 Trends

Analysis of trends is a key objective of infectious disease surveillance. Since surveillance entails the continuous collection of data, it creates a historical database. Using this data on the occurrence of disease in the past, trends can be detected. A trend is a gradual change (or lack thereof) in disease occurrence. Trends are independent of seasonal patterns; a yearly increase in influenza during the winter season is not considered a trend. When the occurrence of a disease, adjusted for seasonal patterns, changes over time, this is called a secular trend. A trend can also be specific to certain risk groups. Analysis of surveillance data for long-term trends is important, as gradual changes might otherwise go unnoticed while they may provide important information about changes in epidemiology and the need to modify control efforts.

Considering that the incidence of many infectious diseases has a seasonal pattern, statistical techniques are needed to tease out the trends from these seasonal fluctuations in surveillance data. In addition to changes in disease occurrence, changes in diagnostic requests or notification criteria can influence the number of cases registered by a surveillance system. Moreover, (media) attention for a disease can result in more people recognizing symptoms, or more doctors requesting laboratory diagnoses for this disease. In such a situation, it can be difficult to assess whether changes in disease notification reflect true changes in disease occurrence. This is especially the case when the media attention is a result of a reported or expected change in disease incidence.

In addition to trends in overall disease occurrence, epidemiologists are often interested in trends within certain age- or risk groups. Diverging trends in risk groups may even result in a stable occurrence of the disease in general, but can be very significant for public health policy. Figure 3.7 shows the occurrence of malaria in Dutch citizens who traveled abroad. While incidence in tourists and business travelers has remained stable, a sharp increase occurred in malaria in migrants after having visited friends or family in their country of origin. These trend differences show the need for tailor-made health policies or information for different risk groups: migrants visiting friends or relatives in malaria-endemic countries are less likely to comply with chemoprophylaxis advice (32).

Figure 3.7 Notified malaria cases in Dutch citizens after travel to malaria-endemic areas, 3-month moving average, 2008-2015, by reason for travel.



3.5 Seasonality

Many infectious diseases are intricately linked with seasonality. This is a result of season-specific changes in human behavior (e.g. crowding, travel) and/or in the environment (e.g. humidity, vector biology), which may favor survival and/or transmission of pathogens. The 'flu season' is probably the best-known example of seasonality in infectious disease. Influenza, but also many other pathogens causing respiratory infections, have an increased incidence during the winter. This is due to several causes, such as crowding and air humidity (33, 34). In addition to the flu season, more infectious disease seasons exist. For example, foodborne infections increase during the summer (due, for example, to inadequate meat heating on barbecues) and travel-related illnesses such as malaria and typhoid fever are mostly seen at the end of the summer holidays. In these cases, the seasonality of the disease is driven mostly by human behavior. Knowledge about seasonality can inform policy or advice. In the summer, awareness of safe food preparation is stimulated, while during the winter, health promotion includes information on cough and sneeze hygiene. In the Netherlands, every year in April, awareness is raised regarding tick bites and Lyme disease, in order to promote preventive measures in the population.

Despite the relatively predictable nature of seasonal patterns, they are also analyzed using surveillance data. After all, it is important to assess whether a disease season has shown a different timing, duration or severity than usual, or whether risk groups were differentially affected. It is also important to monitor which pathogens or strains are dominant, since this varies between seasons and can affect vaccine or treatment effectiveness. Awareness of the onset of the influenza season is important for health professionals, so public health actions can be aptly timed. Also, knowledge about the onset and characteristics of an influenza epidemic can aid health care planning, such as hospital bed availability. If an increase in disease occurrence is expected, such as at the beginning of the influenza season, it is difficult to detect an outbreak or epidemic of this disease. Still, each year an announcement is made that 'an influenza epidemic has started' at a certain point in time. This epidemic is not simply defined as the onset of increasing disease occurrence, but rather as a certain incidence among the population. For influenza in the Netherlands, the threshold for influenza epidemics is an incidence of influenza-like illness of 51 per 100,000 inhabitants, for two weeks in a row. How this threshold was defined is shown in Box 3.3. An influenza epidemic is only officially declared if there is evidence that an influenza virus is circulating in the community. A clear definition of a seasonal influenza epidemic allows analysis of differences in onset, duration and severity of seasonal epidemics. Seasonality analyses can also provide a tool for assessing to which pathogens, diseases in the population are attributable. For many infectious diseases, diagnosis of the responsible pathogen is not routine clinical practice. In addition, most pathogens are not mandatorily notifiable, and available surveillance systems may not have national coverage. When syndromic surveillance shows a seasonal pattern in clinical disease, such as pneumonia, this can be statistically related to the seasonal patterns of several pathogens found in other laboratory surveillance systems (although these can be diagnosed in other patients) to attribute this syndrome to different circulating pathogens. This method has been utilized to estimate causes of respiratory illness nationwide, despite the fact that pathogen diagnostics are not commonly employed for respiratory illness in the general population. An example and limitations of this method are presented in Box 3.4.

Seasonality is a form of periodicity. Certain infectious diseases also exhibit other types of periodicity and show epidemics recurring every few years (35, 36). Such a pattern is usually explained by a build-up period of a new 'pool of susceptibles', a non-immune population large enough to lead to a new outbreak. Therefore, this type of periodicity is mostly described for infections after which immunity is retained for a long time. However, there are more drivers of such recurring epidemics, such as population density, mobility and demography (37). Of course, vaccination coverage and possible herd immunity strongly influence the chance of disease recurrence.

Box 3.3 Influenza epidemic definition: "The Spanish method"

For both health care planning and scientific purposes, a clear definition of the onset of an influenza epidemic is needed. The threshold used in the Netherlands is based on a method developed by Tomás Vega Alonso et al. (39, 40) This method makes use of information from previous influenza seasons. As a first step, it defines the duration of the epidemic per season. To determine the number of weeks that best describes the duration of each season, the number of weeks is plotted against the percentage of all influenza cases occurring in those weeks (Figure 3.8). Naturally, the more weeks included, the more influenza cases covered. To find the optimum number of weeks describing the duration of the epidemic, the point is sought where the slope of the curve decreases most strongly. In other words, the minimum number of weeks covering the maximum number of cases is defined as the duration of the season.

After the durations have been calculated for each season, the onset of each season is defined by starting the epidemic at the optimum week number, so that the epidemic contains the maximum number of cases. When the onset is defined, the maximum number of cases in the "pre-epidemic period" is found. An average of the highest weekly number of cases in pre-epidemic periods of past influenza seasons gives a threshold that can be used to define future seasons. For the Netherlands, this threshold is 51 cases of influenza-like illness cases seen by general practitioners per 100,000 inhabitants. As the Spanish method uses historical data, the threshold can be re-calculated every year. Because the re-calculated thresholds have thus far not deviated much from 51 per 100,000 and for purposes of continuity, the current threshold has been in place since 2007.

Figure 3.8 Adapted from ref (40)

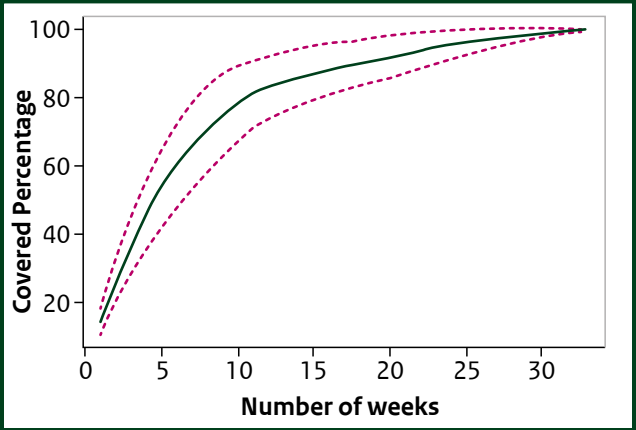
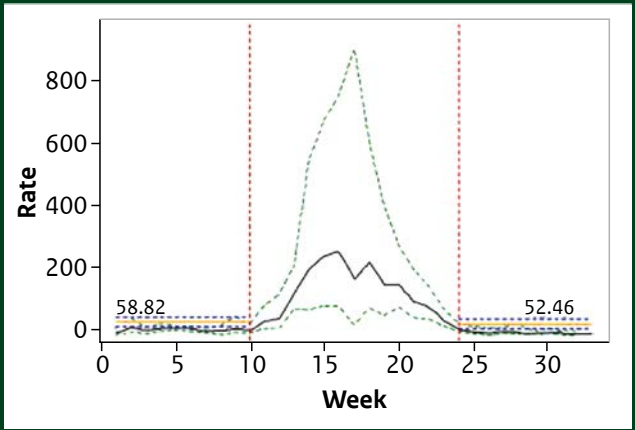


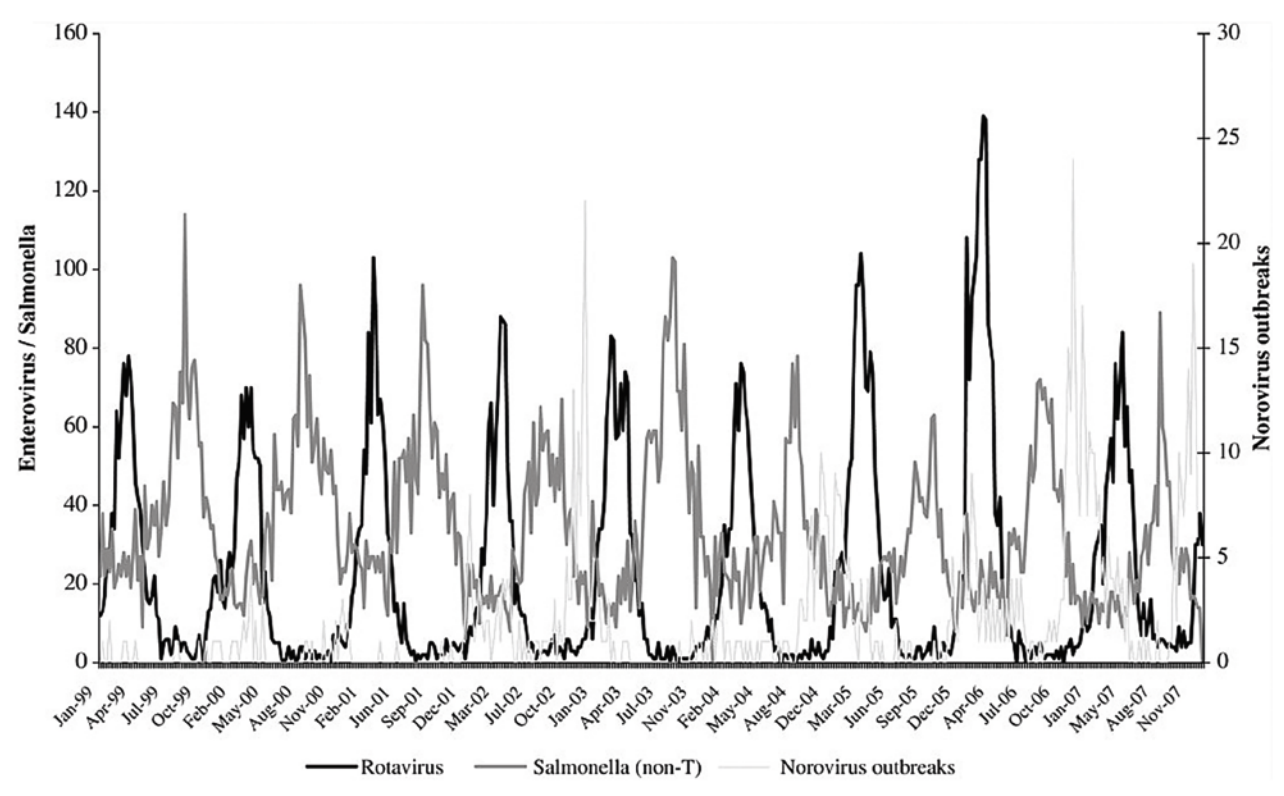
Figure 3.9 Adapted from ref (40)



Box 3.4 Attribution of mortality in elderly to respiratory pathogens

The exact cause of death is often unknown, especially in elderly persons where several factors may contribute to mortality, and underlying chronic conditions are usually reported as the cause of death. Even when it is apparent that pneumonia was the cause of death, the pathogen causing the pneumonia often remains unknown. RIVM researcher Liselotte van Asten and colleagues compared the seasonality of mortality in the elderly to seasonality of nine common pathogens. Mortality counts are available as nationwide statistics, while pathogen counts are often only available from a number of laboratories but are considered to represent pathogen circulation in the population. Correlation between the seasonal patterns allows for statistical attribution of mortality to these pathogens. Two to five viruses were estimated to explain on average 4.6% of mortality per season in elderly people, with RSV seasonality explaining almost as much mortality as influenza A. This type of model uses associations between time series, which provide an indication of the role of these pathogens but must not be confused with direct causality. Other pathogens with similar seasonality may have played a role in the disease, and many environmental and behavioral factors show similar seasonal patterns that could also contribute to disease incidence, such as humidity and crowding. In addition, the week in which laboratory detections of a pathogen take place, may not be the same week in which the supposedly affected patients die from the infection. This warrants the used time lags in the models, which may potentially obscure or interfere with associations of mortality with other variables.

Figure 3.10 Seasonality of rotavirus, salmonella and norovirus (38)



3.6 Burden of disease

In addition to knowledge about disease occurrence, surveillance data can serve as input for disease burden calculations. The burden of a disease is a combination of its occurrence and its severity: 'how much health is lost' due to this disease? Disease burden can be expressed as several different composite health measures, of which the disability-adjusted life year ('DALY') is most often used. DALYs are also used to assess cost-effectiveness of health interventions: when intervention effects are expressed as the amount of euros needed to prevent one DALY lost, many different types of interventions can be compared, even curative versus preventive. Burden of disease is also sometimes expressed as its monetary cost for society (cost of illness), or as a combination of DALYs and cost of illness. Further explanation of the DALY health measure is given in the State of Infectious Diseases 2013 and in Chapter 5 (41). The first and largest initiative to estimate disease burden worldwide was the Global Burden of Disease study (GBD), commissioned by the World Bank in the early 1990s. Since that time, the World Health Organization and the Bill and Melinda Gates Foundation have facilitated GBD updates every couple of years, and the methodology and conditions studied have steadily developed ever since (42). GBD studies use the prevalence of a certain condition, i.e. how many people are suffering at this moment, to estimate current burden. The conditions studied are very heterogeneous and can be defined by e.g. a causative pathogen (e.g. malaria), a multifactorial disease (e.g. anemia) or even injuries such as traffic accidents or violence. It has been argued that this approach is not optimal for estimating burden of infectious disease, as many conditions can be (long-term) sequelae of infections but are not attributed to pathogens in the GBD framework. Therefore, the European Centre for Disease Prevention and Control (ECDC) commissioned the development of a methodology to specifically estimate the burden of infectious disease. This project, called the Burden of Communicable Disease in Europe (BCoDE), was led by the RIVM and resulted in an incidence-based and pathogen-based methodology for DALY calculations (43). An initial goal of disease burden calculations was "to decouple epidemiological assessment from advocacy so that estimates of the mortality or disability from a condition are developed as objectively as possible" (44). However, measurement of disease burden by DALYs has limitations, and therefore the notion of using DALYs for policy prioritization has also been criticized (45). Ample debate has surrounded questions on how to establish reliable disease severity measures (disability weights), whether the application of time discounting or age weighting is appropriate, and which life expectancies to apply. DALY calculations also raise ethical issues, as lives of disabled people are valued less. In addition, critics have argued that prioritizing the most cost-effective health interventions may increase inequity among populations, when further improving the health of relatively rich and healthy people would be less expensive than improving the health of people with fewer resources (45). Furthermore, currently successful prevention strategies, such as immunization programs, drastically reduce disease burden but must continue to receive resources to keep this burden low.

Box 3.5 Disease burden models

Disease burden models can be used to predict the dynamics of disease burden under projected demographic changes, such as the ageing of the Dutch population. RIVM researcher Scott McDonald and colleagues investigated how aging and demographic change might influence the future burden of influenza and hepatitis B. While influenza disease burden is mostly associated with a very short time period after infection, hepatitis B disease burden is due to complications (sequelae) that take a long time to develop following initial infection. For both diseases, burden was predicted to increase in the future, however much less so for hepatitis B than for influenza. Patients will live with chronic sequelae of hepatitis B infection for a longer time, due to increasing life expectancy, but this rising contribution to the HBV burden will be offset by the projected decrease in the incidence of new infections. Increasing numbers of susceptible elderly people and their increased life expectancy are also expected to contribute significantly to future influenza burden. Studies like these can inform health policy makers regarding which diseases are expected to cause the most disease burden to society in future years (46).

3.7 Planning and evaluation of interventions

Intervention planning

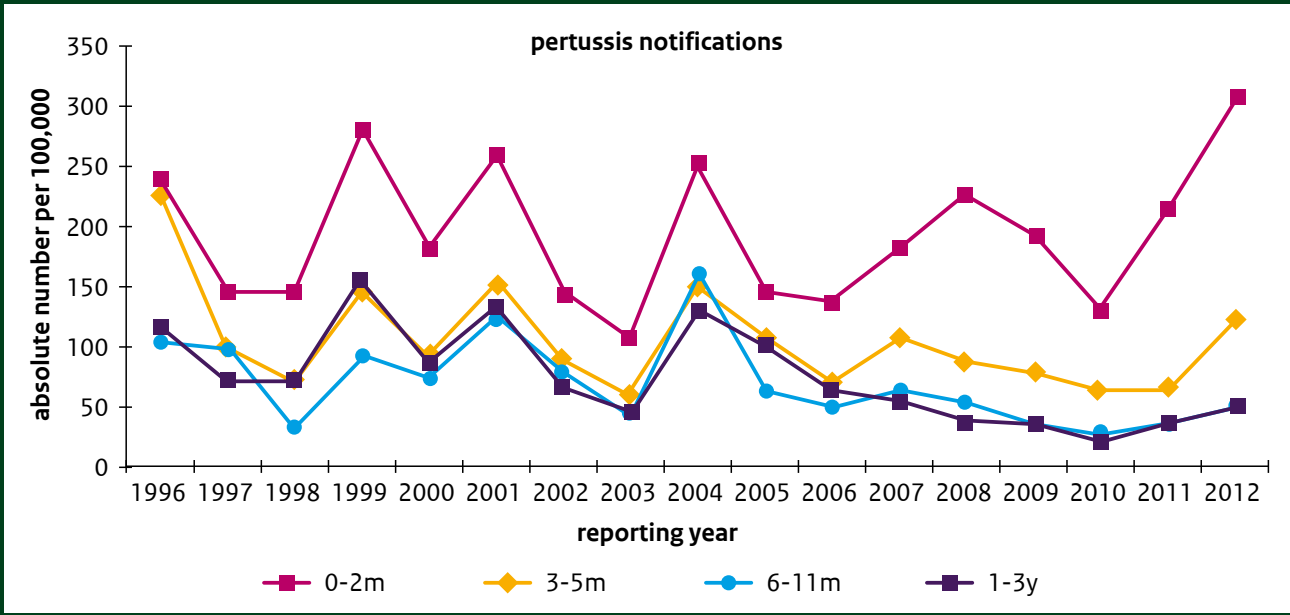
The purpose of conducting infectious disease surveillance is to assess the ongoing pattern of disease occurrence and its determinants in a population in order to be effective in investigating and controlling disease in that population. Surveillance data can contribute to the identification of where interventions are needed to prevent and control infectious diseases. The most successful example of the use of surveillance data to plan interventions is the eradication of smallpox. During the eradication program, acquiring surveillance data and planning interventions was an important and ongoing process. Weekly case reports were drawn up by health units to identify where interventions

were needed. Surveillance teams questioned families and schoolchildren about potential smallpox cases and checked if everyone was vaccinated. By identifying cases, ring vaccination could be carried out resulting in the eradication of smallpox.

The planning of interventions for infectious disease control depends on the nature of the infectious disease, the availability of intervention measures, as well as logistic, economic and political constraints (47). To plan public health interventions, it is important to assess the impact of possible interventions and the allocation of resources. With the arrival of new emerging diseases, public health bodies face questions on how to deploy limited control measures to minimize infectious disease transmission. The general problem is how to choose groups of the population that should receive priority in getting the intervention when resources are limited. Existing approaches to allocating budget to infection control either rely on detailed knowledge of transmission parameters, or on estimates of the eventual number of infections that occur in each group during the entire epidemic (48). Decisions on how to allocate resources can be made by using different types of mathematical modelling. Economic evaluations in general and cost-effectiveness analyses specifically are prominent tools for evaluating the impact of a specific intervention against a specific disease on the associated costs and effects. The role of cost-effectiveness analyses has become progressively important for decision-making related to assessing (preventive) health interventions, medical technology, and pharmaceuticals (49).

Box 3.6 Pertussis vaccination for pregnant women

Figure 3.11 Incidence of pertussis notifications per 100,000 for 0-2, 3-5 and 6-11 month-olds and 1-3 year-olds for 1996-2012 (50).



Since the 1950s, pertussis vaccination programs have been introduced worldwide. Despite constant high vaccine coverage, pertussis has resurged in many countries, including the Netherlands. In the Netherlands, pertussis notifications increased suddenly in 1996 and since then have remained at a higher level, with additional peaks every 3–4 years. Despite various changes in the pertussis vaccination schedule as implemented in the period 1996 to 2012, routine surveillance data shows an increase in overall incidence rates of notifications. The measures taken to reduce pertussis burden in the Netherlands reduced infection rates in children eligible for vaccination. However, rates in adolescents and adults steadily increased, while rates in infants not yet (fully) vaccinated remained high and showed an increase in the 2011–2012 epidemic (Figure 3.11) (50). The changes monitored in the surveillance data contributed to the Health Councils advice that vaccination against pertussis should be made available to pregnant women. Recent insights and the data indicate that vaccination of pregnant women can potentially reduce the number of cases of pertussis among infants aged five months and younger (51).

Intervention evaluation

Surveillance data are frequently used to quantify the impact of program interventions. The objective of intervention evaluation is to determine as systematically and objectively as possible the relevance, effectiveness, and impact of interventions with respect to their aims. By using the described methods to analyze surveillance data, changes in the surveillance data can be identified which might be attributed to the intervention. The challenge in intervention evaluation is assessing which part of the impact can be attributed to the intervention. One method to assess this is by implementing the intervention as a stepped wedge design. In this design, interventions are rolled-out sequentially over a number of time periods. In the end, all subjects receive the intervention, but the order in which the intervention is received is randomized. The stepped wedge design is particularly useful when it is not feasible to provide the intervention to everyone or every community at once, and for evaluating the effectiveness of interventions that have been shown to be efficacious in a more limited, research setting and that are being scaled up to the community level (52).

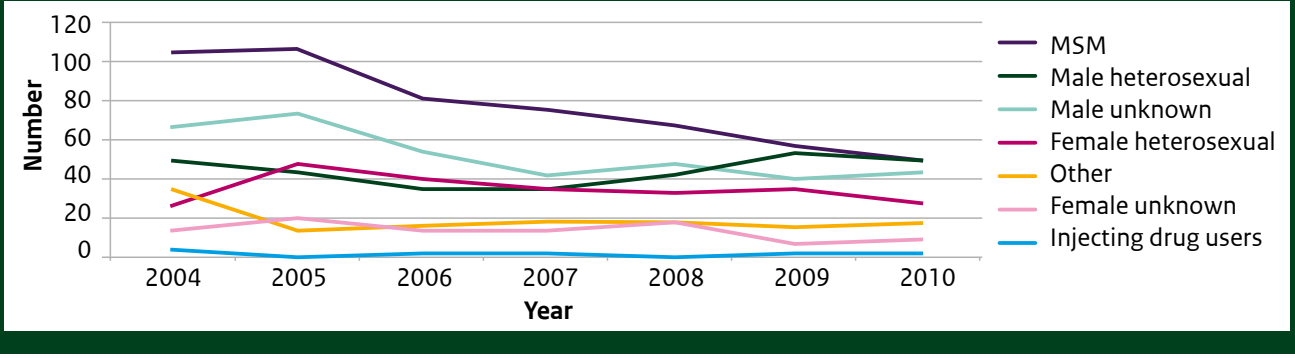
Interventions can also be evaluated by estimating the reproduction number for every case during an outbreak. For example, an outbreak of norovirus infection occurred at an international scout jamboree in the Netherlands during the summer of 2004. The Municipal Health Service instructed participants regarding enhanced hygiene measures. Using statistical methods, the reproduction number for every case during the norovirus outbreak was estimated. As the norovirus outbreak spread through the jamboree, the estimated reproduction numbers decreased over time after the implementation of enhanced hygiene measures. This demonstrated the effectiveness of enhanced hygiene measures in containing a norovirus outbreak (53).
The use of surveillance data to measure the effectiveness of interventions is prone to error, as relationships observed for groups do not necessarily hold for individuals. This is known as ecological fallacy. The ecological fallacy may arise when inferences on relationships between causes and outcomes are drawn for units defined at a lower level (such as individuals) based on data collected for units at higher level (such as groups). In other words: relationships observed for groups do not necessarily hold for individuals (54).

Box 3.7 Evaluation of vaccination programme HBV risk groups

In the Netherlands, a selective free hepatitis B virus (HBV) vaccination program was started in 2002 targeting behavioral high-risk groups (men having sex with men, drug users, commercial sex workers and heterosexuals with frequent partner changes). From 2007 onwards, heterosexuals with multiple partners were excluded from the target population as there was insufficient evidence of an increased risk in this group. Reports on acute HBV infection in the Netherlands between 2004 and 2010 were analyzed to assess the program's effectiveness in order to guide policy on HBV prevention.

The incidence of reports declined from 1.8 to 1.2 per 100,000 population between 2004 and 2010, mainly because of the declining incidence among men, from 3.1 to 1.9 per 100,000. For women, the incidence remained constant at around 0.7 per 100,000. Most of the decrease in the number of acute HBV reports could be attributed to a declining number of reports for MSM (Figure). The number of infected men with an unknown mode of transmission also declined from about 70 annually in 2004 and 2005, to about 45 annually from 2007 onwards. These results suggest that the Dutch selective vaccination programme for behavioral high-risk groups very likely reduced transmission of HBV in the Netherlands, primarily by reducing the HBV incidence among MSM (55). Universal HBV infant vaccination was added to the selective vaccination programme in 2011.

Figure 3.12 Number of cases of acute HBV infection by most probable mode of transmission and year reported in the Netherlands, 2004–2010 (N=1687) (55).



3.8 Future opportunities and challenges in infectious disease surveillance

Surveillance has developed from an early form in the 14th century to detect disease among people who were placed in quarantine as a measure to control the spread of pneumonic plague, to one of the corner stones of infectious disease prevention and control in the 20th century. This chapter has provided an overview of surveillance in the Netherlands, with a focus on methodologies and applications. In this final section, we look at the future, and discuss surveillance in relation to societal changes.

There are a number of developments in society that may necessitate adaptation of the current system of surveillance of infectious diseases. First, we face a globalizing world, in which economies and cultures are increasingly connected. In the perspective of infectious diseases, this can lead to the faster spread of microorganisms. The increased globalization of the food supply and distribution can lead to international outbreaks. Similarly, increased travel enhances the speed and range of infectious disease transmission (56). The speed at which diseases can spread globally is matched by the need for timely surveillance and detection systems, sensitive early warning, and effective dissemination of signals at national and international level. For clinicians, increased globalization leads to greater diversity in infectious diseases their patients may present with. In addition, aging and medical developments result in changes in populations at risk. A major issue is the threat of antimicrobial resistance. Surveillance systems will need to respond to these changes and to emerging infectious disease to deliver appropriate information so that populations at risk can be identified and proper control actions taken.

Moreover, the future will bring technological advances in (medical) information systems that make it easier to collect, analyze and disseminate data rapidly. Simultaneously, the field of bioinformatics is rapidly developing. We have described the associated challenges in the 2012 edition of the State of Infectious Disease report. In brief, we stated that bio-informatics is of growing importance, allowing the combination of molecular and epidemiological data. These developments open new opportunities to use these data for infectious disease research and surveillance. The combination, analysis and interpretation of these datasets ('big data') in order to gain relevant public health insights poses a challenge. Big data is a generic term for data sets (such as genomic data) that are so large or complex that traditional data processing applications are inadequate. Related to this is the push from governments, also in the Netherlands, towards transparency and data availability in the public domain (https://data.overheid.nl/). This is important and justified, as it increases the opportunities for use of the data. The main concerns with open data, however, are about privacy of individuals, companies, organizations, and even regions or countries. The limits of open data in relation to these privacy concerns have not yet been well-defined. The possibility of the combination of large amounts of data, both from (bio)informatics and from public data availability, leads to additional privacy concerns. Making optimal use of data while guaranteeing the maintenance of privacy will certainly prove challenging, which stresses the need for clear legislation. With the increasing availability of data sources, there is a continuous need to assess whether they can or should be used to optimize infectious disease control. Further work in this area is therefore warranted, in which lawyers and public health epidemiologists will need to collaborate closely.

Further, there is an increasing trend in the use of internet and social media. Data from social media platforms might be used as new tools for infectious disease surveillance. Traditional surveillance relies on patient reporting and the supply of laboratory test results, focusing on the top of the surveillance pyramid. These surveillance systems confirm outbreaks, at the earliest, within a few weeks after they begin. Social media can potentially flag incidents more timely (57). Social media systems may therefore be useful as an additional tool for early warning, although development and validation of analytical methods is still needed.

Lastly, the use of surveillance data can be greatly enhanced by exchanging and disseminating surveillance data and signals between different professions. Combining veterinary, environmental, and human surveillance data from the veterinary field are important in the context of the One Health approach. In the Netherlands, important steps have been taken in recent years, such as close collaboration between the human and zoonotic Early Warning Committees and the establishment of the Netherlands Center for One Health, in 2016.

In conclusion, high quality surveillance depends on the cooperation and collaboration of many individuals across many disciplines, including professionals in clinical medicine, infection control, microbiology, veterinary medicine, law, communication, and health economics. For the detection of outbreaks, the general, everyday knowledge and experience of health care workers is of vital importance, and therefore public health institutes need to have close ties to health care workers. Changes in society and in the epidemiology of infectious diseases require flexible and sensitive surveillance systems, and an adequate methodology to respond to these changes and to make the results of surveillance as widely used as possible within limits such as technology and privacy.

3.9 Literature

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4 Virological surveillance in the Netherlands - Virological weekly reports

4.1 Introduction

Real-time surveillance of viral infections enables the early detection of outbreaks and allows continuous monitoring of trends in these infections in the Netherlands. The insights gained form surveillance contribute to the definition, implementation and evaluation of policies to prevent viral infections, and the generation of hypotheses for further research. Several Dutch surveillance systems monitor viral infections, including the system of notifiable infectious diseases, in which symptomatic cases of disease are registered (Chapter 2). Another data source for infection surveillance are the virological weekly reports which constitute a unique voluntary system for laboratory surveillance of pathogens, mainly viruses, managed by the Dutch national institute for public health and the environment (RIVM). The virological weekly reports were established in 1989, when a number of medical microbiological laboratories registered with the Dutch Working Group of Clinical Virology (NWKV) started weekly reporting of the number of positive diagnoses of a range of pathogens. Due to this consistent weekly reporting, the data in the virological weekly reports are timely, making it a valuable system for early detection of outbreaks and unusual trends.

The data from the virological weekly reports are used for early detection of outbreaks and research. Data from a selection of the pathogens in these reports are presented in a number of annual disease reports, however until now, there was no overview of the reported data for all pathogens mentioned in the weekly reports. This chapter describes the type of data included in the virological weekly reports, the method of data collection, and the use and dissemination of the reported data. The third section of the chapter presents the annual numbers reported for all pathogens in the virological weekly reports from 2008 to 2015. A short explanation is given for any noteworthy results and observed trends. This section of the chapter constitutes a new way of data dissemination for the virological weekly reports which will be continued annually in the coming editions of the State of Infectious Diseases report.

4.2 General description of the virological weekly reports

Data: sources and collection

The virological weekly reports include 31 virus species with distinct (sub)types and serotypes, as well as 6 species of bacteria, reported on weekly by the individual laboratories in an online registration system (table 4.1). The bacteria were included in the reports because the type of diagnostic test used for these bacteria historically was performed at virological laboratories. The online database is managed and maintained by the RIVM. Up to 21 medical microbiological laboratories provide data for this virological surveillance system. These laboratories are located throughout the country and include hospital laboratories (n=13) and regional laboratories (n=8) (figure 4.1). The data in the weekly reports are based on the outcome of diagnostic tests performed by these laboratories upon request from general practitioners (GPs), clinical departments in hospitals, and outpatient clinics. Various diagnostic criteria exist for reporting a positive diagnosis. A positive diagnosis is either based on a positive culture, an antigen test, a polymerase chain reaction test (PCR), seroconversion, a significant increase in antibody titer (usually 4-fold) or substantial IgM levels. Newly diagnosed chronic infections (hepatitis B and C virus and HIV) are reported only once. To identify reinfections, an interval of at least 3 months between primary infection and reinfection is required for reporting. The numbers of positive laboratory diagnosis for each pathogen are reported aggregated by week. In 2014, the laboratories were asked to report the number of conducted tests per pathogen in addition to the reported number of positive diagnoses. This denominator data can be entered on a weekly or annual basis, and is important for interpretation of the number of positive diagnoses.

Figure 4.1 The location of laboratories reporting in the virological weekly reports (n=21).

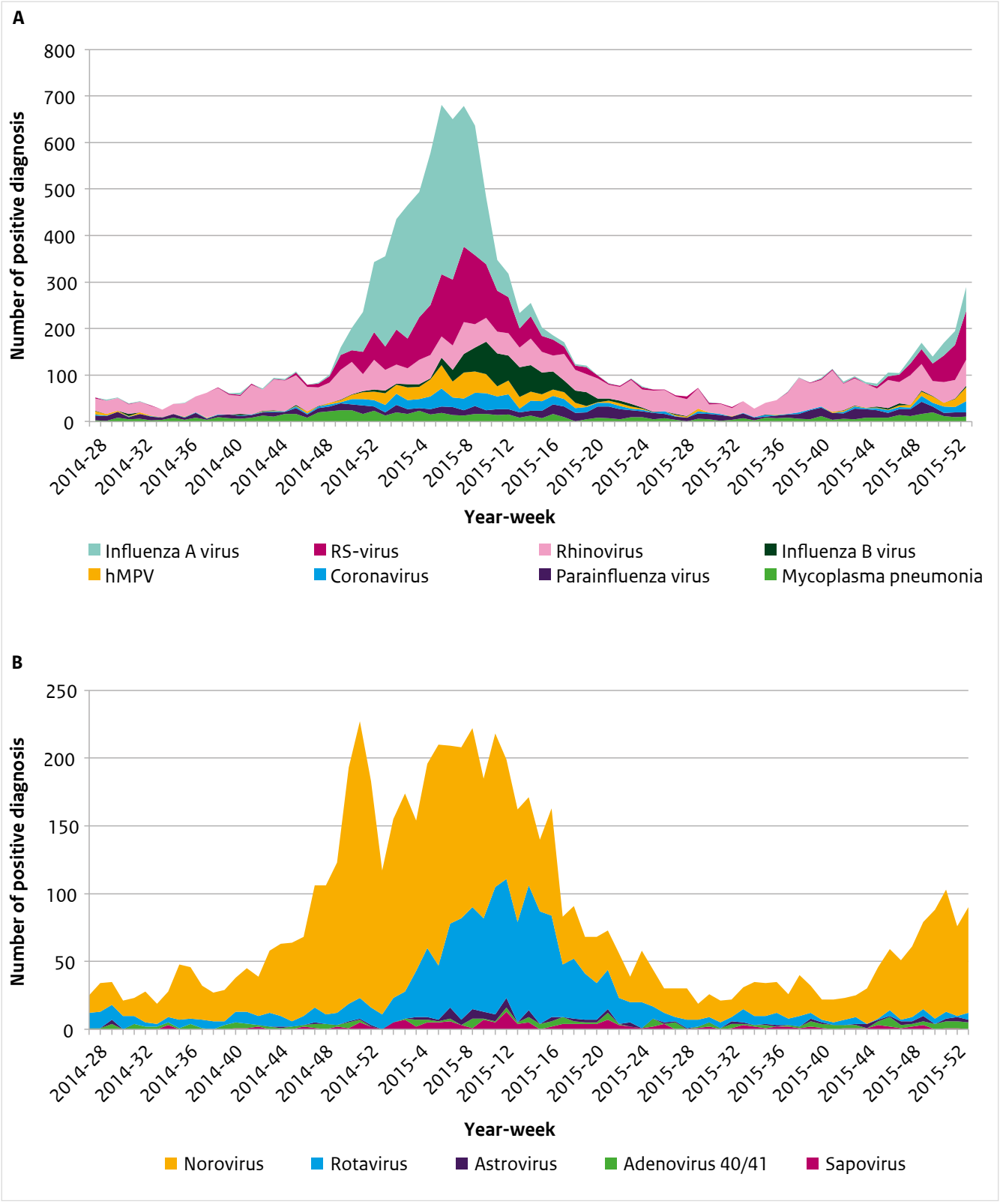
Output and data use

Approximately 40,000 positive diagnoses are reported annually in the virological weekly reports (table 4.1). One of the advantages of the virological surveillance system is the flexibility of the system regarding the list of pathogens included. For instance, in case of emerging viruses, such as a pandemic influenza virus or Zika virus, pathogens can be added to the registration system without much delay. Given that the surveillance system is voluntary, the number of reporting laboratories can differ between weeks, although most laboratories report ≥50 weeks per year (table 4.1). At the bottom of table 4.1, the total number of reports per year is shown, with an average of ~1044 reports annually.

The data in the virological weekly reports are used for different purposes by a number of disciplines in the field of public health, therefore the data are disclosed in several formats. Firstly, through reports on the RIVM website which are updated daily (http://www.rivm.nl/Onderwerpen/V/Virologische_weekstaten/Rapportages/Open_rapportages_virologische_weekstaten). In the reports, the weekly number of reported positive diagnoses for each pathogen in a particular period are displayed in tables and graphs. The open reports are freely available and contain no data that can be traced back to individual reporting laboratories. More detailed information is included in the reports that are only accessible on a restricted website for the participating laboratories and epidemiologists at the RIVM.

In addition, graphs are provided for respiratory and gastrointestinal pathogens. Figure 4.2a shows the numbers of positive diagnoses of the most frequently reported pathogens potentially causing respiratory complaints, such as Influenza or RS-virus, stacked in one graph. The figure clearly shows the seasonal distribution of respiratory pathogens, mainly for Influenza virus and RS-virus, whereas rhinovirus displays a more constant distribution over the year. Figure 4.2b shows the stacked number of pathogens potentially causing gastrointestinal complaints. Norovirus and rotavirus are the most frequently reported gastrointestinal viruses, with a seasonal rise starting in the fall for norovirus, followed by rotavirus, which peaks in February-March.

Figure 4.2 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 2014 week 27 till 2015 week 53. (hMPV= human metapneumovirus, RS-virus= respiratory syncytial virus).



In addition to the reports on the website, the data reported in the virological weekly reports are published monthly in the infectious disease bulletin (1). For some pathogens, the results are also summarized in the annual reports on respiratory infections, foodborne infections, or sexually transmitted infections (2,3,4,5). Most pathogens included in the virological surveillance system are not notifiable; in these cases, the weekly reports are the only surveillance source. An abnormal increase in a specific pathogen, potentially indicating an outbreak, or an unexpected reduction are discussed by the Netherlands Early Warning Committee (NEWC) (see Chapter 2). Sometimes, the numbers in the weekly reports lead to further research into the causes of a rise, drop or changing trend, as was the case for rotavirus (Box 4.1) and hepatitis E virus. Data from the virological surveillance system can be used for research, following approval from the NWKV.

Limitations

In 2001, the representativeness of the data in the virological weekly reports was assessed (6). A questionnaire was sent to all medical microbiological laboratories in the Netherlands (n=68). For five selected pathogens, the number of positive diagnoses, the type and number of diagnostic tests performed, and the institutions requesting the diagnostics (e.g. GPs, hospitals) were requested for a period of two years (mid 1998-mid 2000). Despite the fact that not all Dutch microbiological laboratories participate in the virological weekly reports, the coverage level appeared to be sufficient for timely detection of national trends. The virological weekly reports continue to form a valuable source for disease surveillance, primarily due to the long history of the data collection, the short reporting delay, and the fixed weekly reporting intervals. However, since the onset of the virological surveillance system, a number of limitations have appeared, which hamper accurate interpretation of the data.

Several limitations addressed in the 2001 study still apply to the current situation. The virological surveillance system lacks background information of the demographic characteristics of the patient, the professional requesting the diagnostic test, the number of tests performed, and the diagnostic testing policy. Only a few laboratories report the weekly or annual number of tests per pathogen, and the type of test most frequently used, probably because data collection and entry is time-consuming, which matches one of the conclusions of the 2001 study. Consequently, it is difficult to assess whether changes in long term trends of reported pathogens are true pathogen-related changes, or the result of alterations in diagnostic testing policy, for instance changes in restitution policy of the Government or medical assurance companies, or the introduction of new diagnostics. The number of reporting laboratories can differ from week to week due to the voluntary basis of the virological surveillance system, thereby complicating the overall interpretation of the data. Furthermore, the set of pathogens for which diagnostic tests are available have increased over time at the individual laboratories, potentially resulting in an increase in the number of diagnostic tests performed. The spread of a pathogen among certain age groups or within particular regions could be investigated if the age of those persons with a positive test result for a specific pathogen, as well as the exact catchment areas of the laboratories were known. Meanwhile, data concerning the request for the diagnostic tests, for instance a request from a GP, a clinical department in a hospital, or the intensive care unit, could give insights into disease severity, and thereby allow a global view of the impact of an infectious disease in the population.

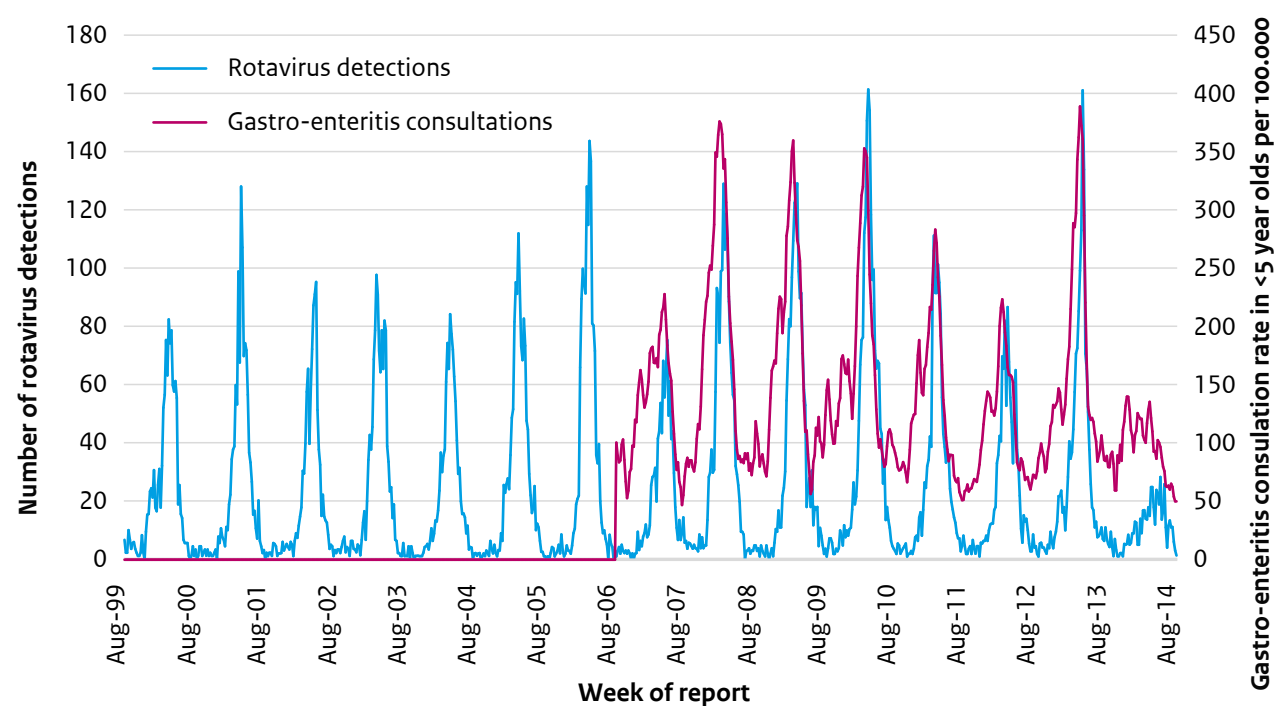
Box 4.1 Exceptionally low rotavirus incidence in the Netherlands in 2013-2014

Hahné S, Hooiveld M, Vennema H, van Ginkel A, de Melker H, Wallinga J, van Pelt W, Bruijning-Verhagen P. Exceptionally low rotavirus incidence in the Netherlands in 2013/14 in the absence of rotavirus vaccination. Euro Surveill. 2014;19(43):pii=20945.

The number of reported positive diagnoses of rotavirus was unexpectedly low in the winter of 2013-2014 (figure 4.3). All-cause gastroenteritis (GE) consultations in children aged under 5 from the Dutch sentinel general practice (GP) network as well as data in the virological weekly reports were used to assess whether rotavirus circulation was reduced. A drop of 58% in reported rotavirus diagnoses was observed in the virological weekly reports between August 2013 and July 2014, compared to August 1999 and July 2013 (adjusted for the number of reporting laboratories). Reductions of 75% and 88% were seen in February and March 2014 respectively compared to previous years. However, a peak of reported rotavirus diagnoses was observed in May. The GE consultation rate decreased by 36% in 2013-2014 compared to previous years. Due to the observed rotavirus reduction in both surveillance sources, a surveillance artefact in the virological weekly reports was excluded, and the observation probably reflected reduced rotavirus circulation. Various factors may have been the cause of the decrease, including a mild winter, a low birth rate, rotavirus vaccinations in neighboring countries, and high rotavirus incidence in the previous year.

In addition to the research by Hahné et al. (2014), a fairly normal rotavirus season was observed in the virological weekly reports in 2014-2015. Between August 2013 and July 2014, 551 positive diagnoses were reported, whereas 1383 positive diagnoses were reported in the same period in 2014-2015, which is comparable to the incidence in previous years. The incidence during winter 2015-2016 was again unusually low.

Figure 4.3 Weekly rotavirus detections[1] (August 1999-August 2014) and general practice gastroenteritis consultation rate for children under five years old (August 2006-August 2014), the Netherlands



[1] Adjusted for the weekly number of reporting laboratories by multiplying the number of rotavirus detections by the average number of reporting laboratories / the number of laboratories reporting that week.

4.3 Reported numbers of positive diagnoses in 2015

Table 4.1 shows the number of positive diagnoses reported in the virological weekly reports in 2015, as well as for the seven previous years.

Table 4.1 Number of positive laboratory diagnosis reported in the virological weekly reports, summed by year.

Pathogen	2008	2009	2010	2011	2012	2013	2014	2015
Viruses								
Adenovirus 40/41	259	229	296	185	142	141	155	126
Adenovirus non40/41	410	424	523	288	197	357	226	199
Adenovirus untyped	361	675	712	648	777	745	887	989
Astrovirus [a]	0	0	0	15	55	81	85	94
Bocavirus [a]	0	0	0	107	136	111	107	114
Coronavirus	200	192	429	288	307	376	318	573
Dengue virus	128	160	225	122	209	122	101	132
Enterovirus	932	1224	1499	1035	1212	785	1259	780
Hantavirus	17	7	17	3	10	4	47	7
Hepatitis A virus	97	96	107	63	53	38	63	49
Hepatitis B virus	1,725	1,553	1,403	1,377	1,024	676	633	691
Hepatitis C Virus	895	822	815	679	513	385	385	400
Hepatitis D Virus	15	10	13	11	7	9	12	12
Hepatitis E Virus	6	18	31	37	50	67	205	300
HIV 1	1,035	1,173	1,186	1,135	886	739	675	689
HIV 2	1	5	6	5	2	3	1	3
hMPV	205	224	419	389	298	467	385	645
HTLV	2	3	3	3	4	1	2	2
Influenza A virus	234	7,419	158	872	891	2,331	899	3,156
Influenza A(H1N1)pdm09 virus	0	4,608	70	484	0	0	0	0
Influenza B virus	203	120	63	466	64	976	47	690
Influenza C virus	1	6	3	0	0	1	0	3
Measles virus	24	7	13	8	9	212	55	8
Mumps virus	80	22	144	190	95	65	24	45
Norovirus	1,430	1,991	4,063	2,771	2,898	2,865	2,835	2,971
Parainfluenza type 1	28	208	85	114	41	138	76	149
Parainfluenza type 2	33	127	65	56	53	74	66	71
Parainfluenza type 3	138	247	232	282	238	290	217	339
Parainfluenza type 4	33	84	65	51	36	76	53	120
Parainfluenza untyped	40	107	81	102	70	54	19	28
Parechovirus	311	373	706	329	397	187	354	224
Parvovirus	233	418	221	214	216	128	175	122
Rhinovirus	899	1,994	1,906	1,987	1,780	2,045	2,189	2,383
Rotavirus	1,692	1,936	2,180	1,505	1,288	1,494	607	1,319
RS-virus	2,331	2,030	2,778	2,466	2,043	1,862	1,454	1,860
Rubella virus	16	15	17	15	15	47	27	16
Sapovirus [a]	0	0	0	9	32	59	129	139
West-Nile Virus	0	0	1	1	0	0	0	0

Table 4.1 (continued) Number of positive laboratory diagnosis reported in the virological weekly reports, summed by year.

Pathogen	2008	2009	2010	2011	2012	2013	2014	2015
Bacteria								
Chlamydia psittaci	43	30	29	37	23	23	16	18
Chlamydia pneumoniae	30	64	35	43	60	27	20	31
Chlamydia trachomatis	15,152	16,486	18,454	19,108	21,234	20,900	24,057	24,504
Chlamydia untyped	16	5	10	3	5	9	8	28
Coxiella burnetii	210	786	417	136	83	89	130	124
Mycoplasma pneumoniae	458	414	541	917	775	324	435	524
Rickettsiae	30	36	10	23	14	7	12	17
Total virological weekly reports annually	1030	1096	1087	1082	1038	982	988	1049
Annual number of laboratories which reported ≥50 weeks	19	20	21	20	18	16	15	19

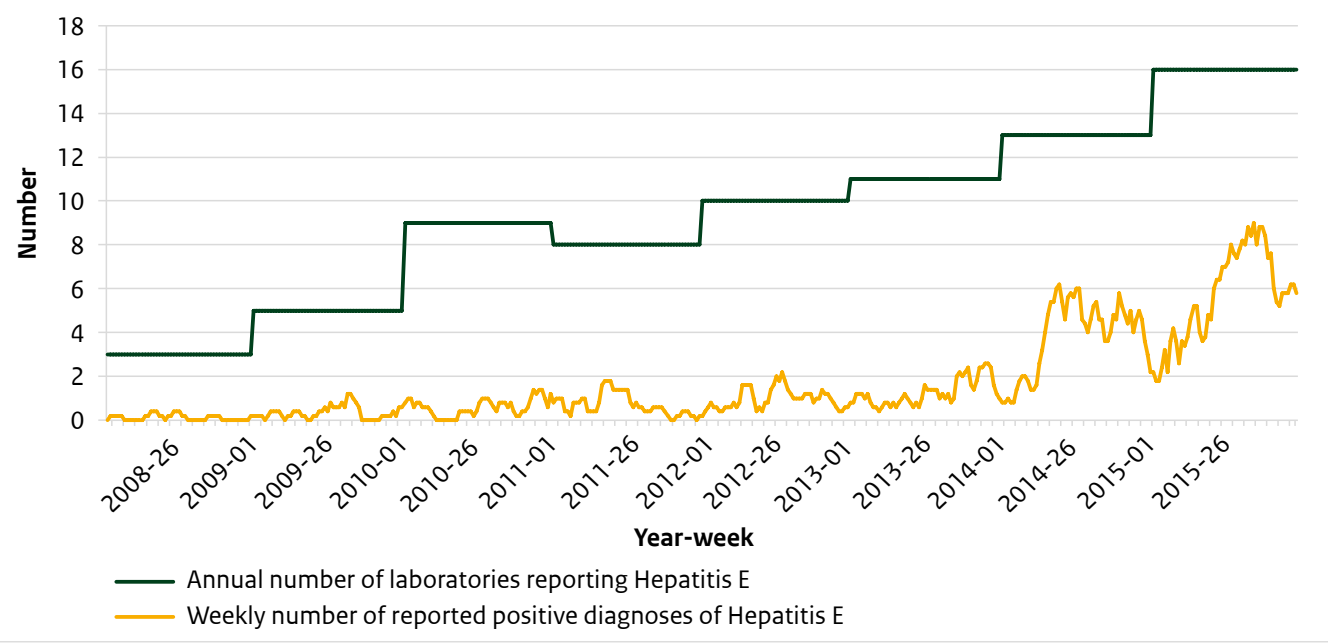
a. Included in the virological weekly reports since 2011

4.4 Signals based on data from the virological weekly reports in 2015

Hepatitis E

Since 2014, the virological weekly reports have shown a rise in positive diagnoses of hepatitis E-virus (HEV) (figure 4.4). However, the number of laboratories reporting HEV diagnoses for at least 1 week increased from 3 in 2008 to 16 in 2015 (figure 4.4). Hence it is likely that the observed increase can partly be attributed to improved diagnostics, potentially influenced by an increased focus on HEV. However, the weekly number of reported positive HEV diagnoses by laboratory also increased. In addition, studies among blood donors show an increase in HEV-IgG seroprevalence in donors aged under 21 between 2000 and 2011 (7). This could indicate a true increase in HEV-infections. In addition, in 1 in 1000 blood donors, HEV-RNA was identified in blood. In May 2015, the RIVM started a prospective case-control study assessing the risk factors for acquiring acute HEV-infection.

Figure 4.4 Annual number of laboratories reporting Hepatitis E and the weekly number of reported positive diagnoses of Hepatitis E with a 5-week moving average.



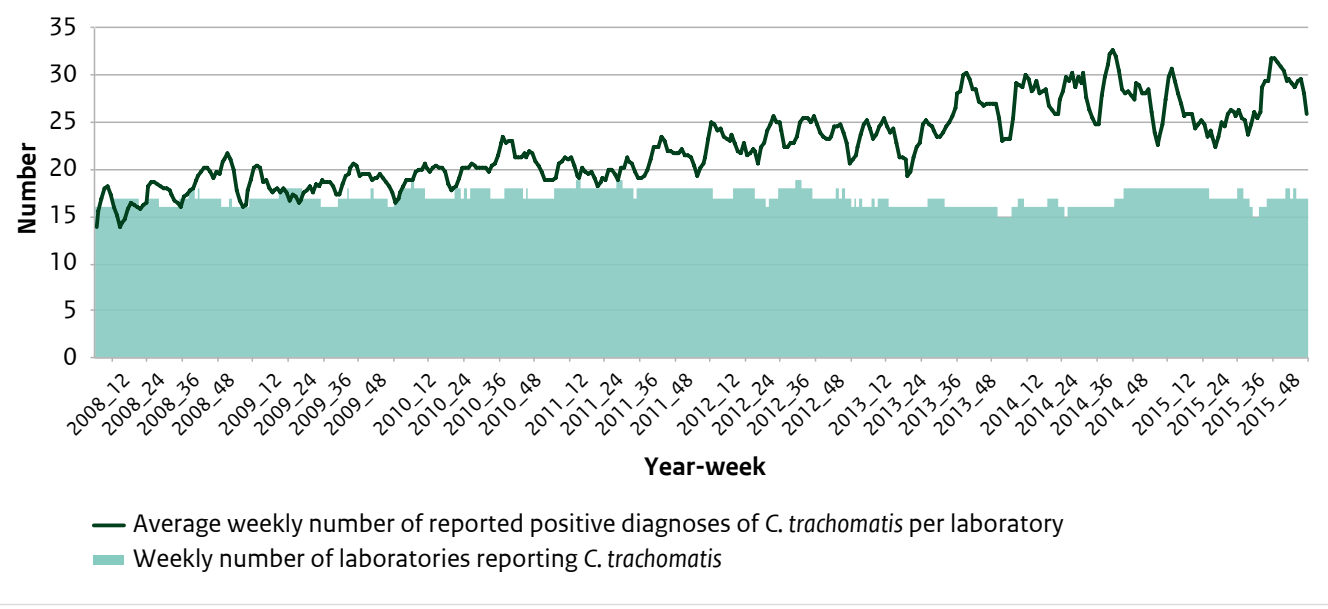
Chlamydia trachomatis

One of the remarkable trends in the virological weekly reports has been the steady increase in reported *Chlamydia trachomatis* (table 4.1). The number of reported positive diagnoses increased from 15,152 in 2008 to 24,504 in 2015. The overall number of laboratories participating in the surveillance system did not increase in this period, whereas the average weekly number of laboratories reporting *C. trachomatis* fluctuated from 16.2 in 2013 to 18 in 2011. However, the average weekly number of reported positive diagnoses of *C. trachomatis* per laboratory markedly increased from 17.5 in 2008 to 26.7 in 2015 (figure 4.4). Whether this trend indicates a true increase of *C. trachomatis* in the population or is the result of increased diagnostics or catchment areas of laboratories cannot be assessed from the data in the virological weekly reports. It is likely that it relates to increased numbers of tests requested, due to a higher awareness in the population and among physicians. Some (n=11) of the laboratories participating in the virological weekly reports perform diagnostic tests for detection of sexually transmitted infections (STI) for specific STI clinics. These clinics offer testing free of charge to specific high-risk groups. The number of Chlamydia diagnoses in the STI clinics doubled from 2008 to 2015 (from 9,403 to 17,753). The number of tests increased by more than 50% in the same period (from 87,572 in 2008 to 135,809 in 2015). GP surveillance data show no increase in Chlamydia reporting rates (4). In other countries in Europe, Chlamydia diagnostic rates clearly correlate to testing rates and the implementation of Chlamydia control through opportunistic screening policies (8).

Respiratory pathogens

In 2015, high numbers of positive Influenza A virus diagnoses were reported in the weekly reports (table 4.1). The majority of these Influenza A diagnoses were reported in the beginning of 2015 (figure 4.2a), corresponding with the exceptionally long duration of the Influenza season in winter 2014-2015 (2). In most laboratories, respiratory panels are available for molecular determination of respiratory pathogens. In these panels, testing is performed on the most frequent causal agents of respiratory infections, such as influenza virus, RS-virus, coronavirus and rhinovirus, using RT-PCR. The relatively high numbers of reported respiratory viruses such as coronavirus and human metapneumovirus (hMPV) in 2015, can probably partly be attributed to an increase in conducted respiratory panel-diagnostics due to the intense Influenza season in 2014-2015. A stable increasing trend was observed in the reported rhinovirus diagnoses. The annual number of laboratories reporting rhinovirus diagnoses varied slightly, ranging from 14-18 (average 16). Hence, the increased number of reported positive diagnoses, probably reflects a change in the number of performed diagnostics. In the respiratory season 2011-2012, a lower number of reported positive diagnoses of human respiratory syncytial virus (RS-virus) was observed. The exact reason for this decline is unclear, however it is likely that changed testing practices as a result of modifications in diagnostic policy played a role.

Figure 4.5 Weekly number of laboratories reporting *C. trachomatis* and the average weekly number of reported positive diagnoses of *C. trachomatis* per laboratory, with a 5-week moving average.



4.5 Concluding remarks

In the past decades, the virological weekly reports have been used as a source for surveillance and research of infections in the Netherlands. The data provide insight in trends of viruses, in the annual start of the respiratory season, and in the occurrence of gastrointestinal pathogens. However, surveillance of trends and outbreaks based on data from the virological weekly reports is virtually restricted to a time perspective; demographics, disease severity, and geographic spread of a disease cannot be inferred from this data due to a lack of background information about the positive diagnoses, like residence and requesting institutions. Fifteen years ago, the data in the virological surveillance system appeared to be sufficiently representative for the Netherlands regarding timely reflection of national trends. Currently, a reassessment of the virological weekly reports addressing the limitations concerning the missing background information may lead to improved data interpretation. Furthermore, optimal collaboration between the laboratories and the RIVM, with a minor work load for the laboratories, is likely to ensure the future of the virological weekly reports as a valuable system for the surveillance of infectious diseases. In 2015, noteworthy increases were observed for some pathogens in the virological weekly reports, including several respiratory viruses as well as HEV. Data in the virological reports can be triangulated with other sources of infectious disease surveillance, hence improving the quality of the virological surveillance system to detect changes in the circulation of pathogens among the Dutch population.

4.6 Literature

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5 Burden of infectious diseases in the Netherlands, 2012-2014

5.1 Introduction

Estimates of the burden of infectious diseases can be used to compare health impact between different infectious diseases in the Dutch population and to follow up trends over time. The burden of a disease is a combination of incidence, duration and severity. Disease burden is expressed here in disability-adjusted life years (DALY), which indicates the number of healthy life years lost due to a disease. DALY is a sum of years of life lost due to mortality (YLL) and years lived with disability due to morbidity (YLD) (1). The YLD is constructed by multiplying the duration of a disease by its disability weight; a measure of severity ranging between 0 (complete health) and 1 (death). The burden of infectious diseases in the Netherlands was estimated using a pathogen- and incidence-based approach (1). This means that all health loss due to an infection is attributed to the event of infection and (future) long-term sequelae of infection are included in the burden assigned to the year of infection. The DALY estimates presented in this chapter can be interpreted as the disease burden that is and will be suffered due to the average annual infections that occurred in the years 2012-2014, or the disease burden that theoretically could have been avoided by preventing infections in those years. We present an update of previous infectious disease burden estimates and include new estimates for psittacosis and Lyme borreliosis (2). The methods are described in the Appendix.

5.2 Results

Table 5.1 shows the average annual YLL, YLD, DALY and number of new infections in 2012-2014 in the Netherlands by disease category. Additionally, the DALY per 100 acute cases indicates the severity of the disease at the individual patient level. In Figure 5.1, infectious diseases are ranked by the average disease burden caused by the average annual incident cases in 2012-2014. The DALY estimates are divided into YLL and YLD. Influenza has the highest estimated disease burden, followed by invasive pneumococcal disease and chlamydia. While the estimated DALY attributed to influenza is very similar to the estimate for 2007-2011, it is based on a higher incidence, most notably in older age categories. Due to the reduced estimate of duration of uncomplicated influenza episodes from two weeks to five days (Table 5.1, A.1), this resulted in lower YLD and higher YLL estimates. Other notable differences compared to the 2007-2011 estimates are a much lower burden of Q fever (91 versus 2143) due to reduced incidence, and higher burden estimates resulting from the increased incidence of rubella and measles (due to the 2013-2014 measles outbreak). For norovirus, the estimated incidence was higher, due to an increased incidence of all-cause gastroenteritis hospitalizations in the Netherlands (3). Table 5.1 presents the total number of DALYs for Lyme borreliosis, of which 6% is attributed to erythema migrans, 8% to disseminated Lyme borreliosis and 86% to persisting symptoms. This reflects the very substantial disease burden due to Lyme-related persisting symptoms (4).

Figure 5.1 Average estimated annual disease burden in DALY, split by YLL and YLD, caused by infectious diseases in the Netherlands, 2012-2014. Red error bars indicate 95% uncertainty intervals.

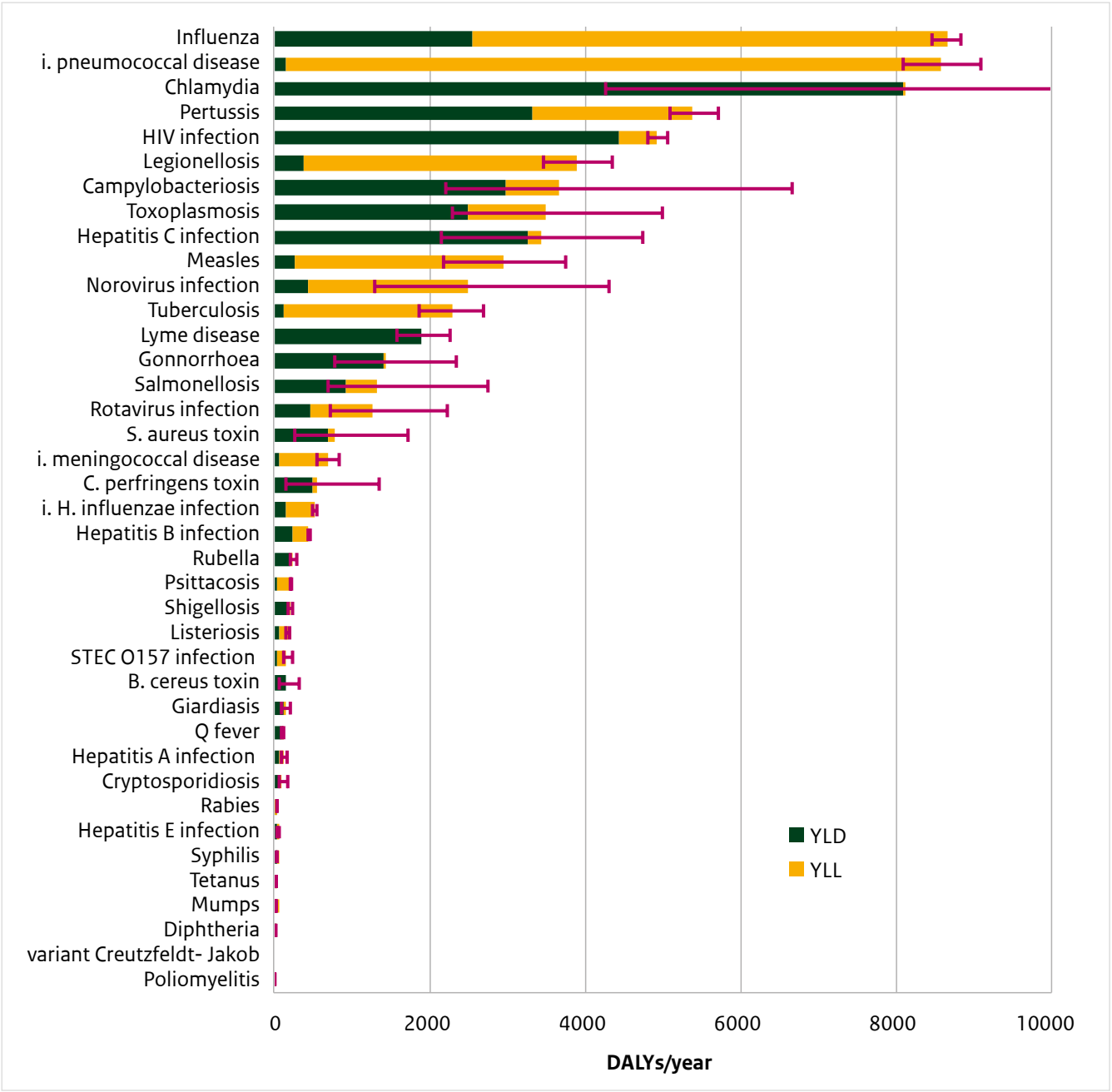


Figure 5.2 Nationwide average annual DALY caused by infection events per sex and age category, for respiratory diseases, sexually transmitted infections (STI) and vaccine preventable diseases (VPD), 2012-2014.

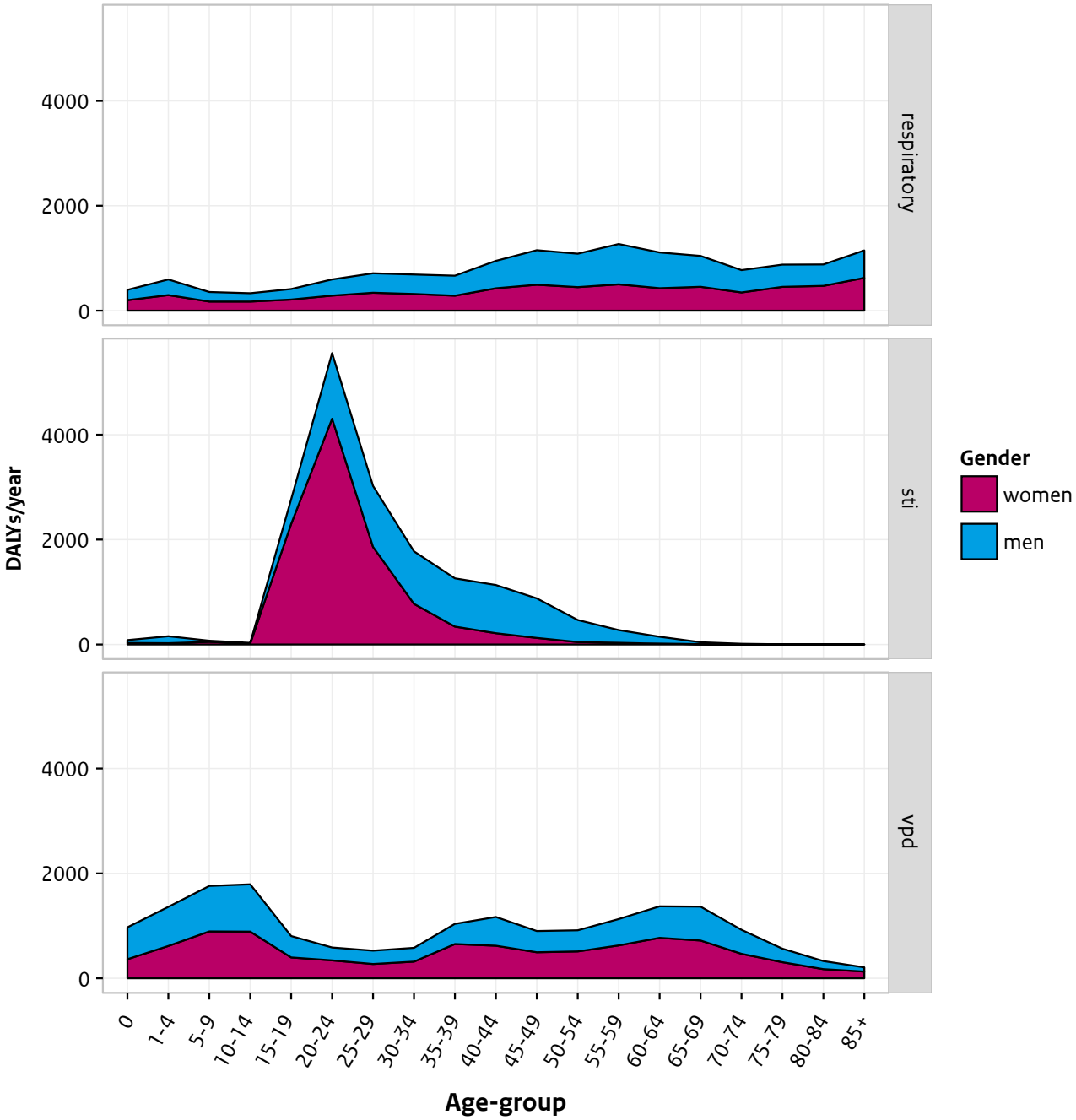
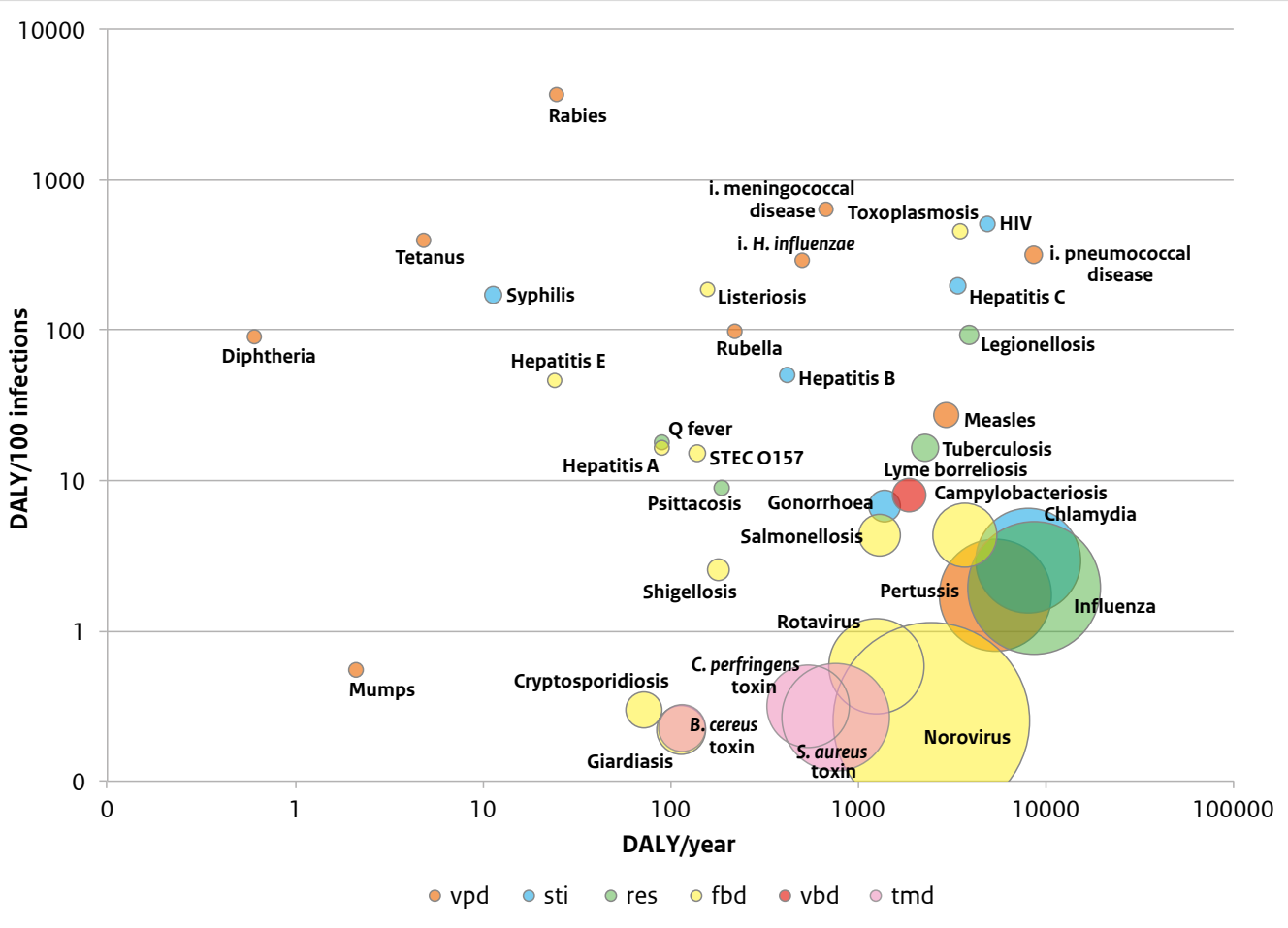


Figure 5.2 shows the disease burden by sex and age category (at the moment of infection) for respiratory diseases, sexually transmitted infections (STI), and vaccine preventable diseases (VPD). In Figure 5.2, the burden associated with an infection is fully assigned to the age when the infection event occurred. This is most visible in the STI panels showing the high DALY estimate for young women, which is mostly due to tubal infertility resulting from chlamydia. While in the model this burden is assumed equally severe every year from infection until menopausal age, Figure 5.2 shows this cumulative lifetime burden as a peak at the age of initial infection. Figure 5.2 further shows a slow but steady increase in national respiratory disease burden with age, while vaccine preventable diseases caused the highest disease burden in school-age children (mainly due to pertussis and the measles outbreak of 2013-2014) and in adults (mainly caused by invasive pneumococcal disease).

An overview of estimated DALY/year versus DALY/100 cases for all included infectious diseases is found in Figure 5.3. While the DALY/year estimate shows the disease burden at the national level, the DALY/100 cases is indicative of individual burden for the patient. While diseases such as influenza, norovirus infection, pertussis and chlamydia cause a high burden at the national level because of their high incidence, they are relatively mild at the patient level compared to the more severe and less incident rabies, invasive meningococcal disease, or HIV infection.

Figure 5.3 Ranking of infectious diseases by estimated annual burden at population (DALY/year) and individual level (DALY/100 infections) in 2012-2014. The area of the bubble is proportional to the estimated annual number of infections, with 5000 added to each bubble for visibility reasons. Colors represent disease categories: vpd: vaccine preventable diseases; sti: sexually transmitted infections; res: respiratory diseases; fbd: foodborne diseases; vbd: vector-borne disease; tmd: (foodborne) toxin-mediated disease. Please note the logarithmic scale of both axes.



5.3 Discussion

We present estimates of disease burden caused by infection events in the years 2012-2014. Since our initial estimates in the State of Infectious Diseases 2013, we have further improved the model parameters and have added burden estimates for Lyme borreliosis and psittacosis. Burden estimates for toxin-mediated diseases caused by *Staphylococcus aureus*, *Bacillus cereus* and *Clostridium perfringens* were not included in the 2013 State of Infectious Diseases overview as these are not true infection events, but have been reported on previously (3).

Notable changes were made in the model parameters for chlamydia and gonorrhea. Transition probabilities from pelvic inflammatory disease (PID) to ectopic pregnancy and tubal infertility were, in the chlamydia model, previously based on estimates of these sequelae after chlamydia infection rather than following PID (5). In the gonorrhea model, these probabilities were set higher based on other studies, but did not include a measure of uncertainty (2). In both models, transition factors from PID to tubal infertility and ectopic pregnancy including a range of uncertainty are now based on data from Weström et al and are in concordance with other published estimates (6-8). Still, much uncertainty remains surrounding the burden of chlamydia and gonorrhea infections. Asymptomatic infections of these STI are common and are at risk for disease sequelae. While this is included in the disease models, incidence of asymptomatic infection is difficult to estimate. Some cases will be diagnosed despite being asymptomatic, for example after being warned by a partner, but the relative proportion of this group is unknown. Moreover, the current disease models do not include an asymptomatic PID state, even though it has been suggested that more than 50% of chlamydia-associated PID do not cause any symptoms but can still lead to further sequelae such as tubal infertility (5). On the other hand, tubal infertility, which accounts for around 80% of both chlamydia and gonorrhea female burden estimates, has been given a high disability weight (0.18). In a more recently published disability weight system, secondary infertility has a much lower disability weight of 0.007 (9). The burden of tubal infertility is assigned to women only and is assumed to last until menopause. The reality of the experienced burden resulting from infertility is probably much more complex and very heterogeneous.

It is important to note that substantial uncertainty surrounds the current estimates. This is partly represented by the uncertainty intervals, however, not all parameters and incidence estimates that were used as input included a measure of precision. Often, no data were available to estimate the amount of uncertainty surrounding a parameter, in which case a point estimate was used. This will have led to an underestimation of the width of uncertainty intervals.

The method used to estimate Lyme borreliosis burden uses disability weights derived from questionnaires among patients rather than the general population (4). This reduces comparability across diseases. Moreover, the disability weights used in the other models are derived from different sources and further standardization would benefit comparability of disease burden estimates. Further limitations of the models and methodology have been thoroughly discussed elsewhere (1, 2).

The current disease burden estimates should be viewed within the context of currently implemented control strategies and may be used for prioritization of additional interventions. While we have extended the disease burden estimations with two new disease models (psittacosis and Lyme borreliosis), the overview presented here is still far from complete. For many infectious diseases, no disease burden models are available yet. For example, substantial disease burden is expected to be caused by infections by streptococcus, cytomegalovirus and respiratory syncytial virus. In the near future, all disease models will be reviewed again for the Dutch situation with experts. The continuous development of both new and existing disease models, in addition to implementing more uniform disease modeling and disability weighting, is essential to produce more complete, comparable and valid disease burden estimates in the future.

Table 5.1 Estimated average annual disease burden in YLD, YLL, DALY, DALY per 100 acute infections (with 95% uncertainty intervals) and estimated annual number of acute cases in 2012-2014 in the Netherlands, by disease category in order of highest to lowest DALY/year.

Disease	YLD/ year	YLL/ year	DALY/ year	DALY/ 100 infections[a]	Annual acute infections[b]
Foodborne diseases					
Campylobacteriosis	2970 (920-6688)	693 (435-1023)	3662 (2188-6662)	4.3 (2.5-8.1)	99,516
Toxoplasmosis	2479 (1091-4609)	1007 (570-1736)	3485 (2274-4983)	456 (38-575)	775
Norovirus infection	424 (269-647)	2055 (881-3859)	2479 (1284-4295)	0.3 (0.1-0.4)	980,618
Salmonellosis	903 (229-2445)	389 (339-442)	1291 (678-2740)	4.3 (2.3-10.2)	39,293
Rotavirus infection	435 (334-556)	820 (271-1777)	1255 (688-2210)	0.6 (0.3-1.0)	226,471
S. aureus toxin	670 (210-1548)	94 (2-388)	764 (249-1716)	0.3 (0.1-0.5)	290,268
C. perfringens toxin	477 (116-1230)	61 (1-256)	538 (138-1341)	0.3 (0.1-0.6)	168,729
Shigellosis	149 (121-184)	30 (24-37)	179 (146-219)	2.6 (2.5-2.7)	6974
Listeriosis	51 (30-74)	108 (108-108)	159 (142-178)	189 (169-211)	84
STEC O157 infection	23 (13-37)	115 (67-211)	138 (90-219)	15 (1-63)	2,118
B. cereus toxin	115 (31-310)	0 (0-0)	115 (31-310)	0.2 (0.1-0.4)	51,227
Giardiasis	93 (49-160)	20 (1-81)	113 (59-198)	0.2 (0.1-0.4)	55,780
Hepatitis A infection	33 (22-51)	58 (35-95)	91 (59-145)	17 (13-21)	548
Cryptosporidiosis	49 (28-80)	23 (0-102)	72 (35-153)	0.3 (0.1-0.7)	28,076
Hepatitis E infection	4 (2-6)	20 (7-43)	24 (10-48)	46 (22-83)	52
variant Creutzfeldt-Jakob disease	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0
Respiratory diseases					
Influenza	2521 (2464-2574)	6133 (5999-6258)	8653 (8466-8832)	2.0 (2.0-2.0)	444,162
Legionellosis	370 (334-407)	3504 (3115-3944)	3874 (3463-4339)	93 (86-100)	4,165
Tuberculosis	104 (101-109)	2158 (1742-2583)	2262 (1848-2689)	17 (14-20)	13,575
Psittacosis	9.8 (9.2-10.5)	178 (164-192)	187 (173-202)	9.0 (8.5-9.5)	833
Q fever	68 (60-77)	22 (20-25)	91 (80-102)	18 (16-20)	499
Sexually transmitted diseases					
Chlamydia	8093 (4224-14180)	33 (21-50)	8126 (4248-14221)	3.0 (1.6-5.2)	274,765
HIV infection	4434 (4312-4561)	484 (452-516)	4918 (4790-5051)	504 (491-517)	976
Hepatitis C infection	3249 (1983-4527)	170 (91-258)	3419 (2143-4730)	197 (123-272)	1,737
Gonorrhea	1386 (757-2320)	5.5 (3.6-8.2)	1392 (762-2326)	6.8 (3.7-11.4)	20,474
Hepatitis B infection	204 (203-205)	219 (199-238)	423 (402-443)	50 (48-52)	846
Syphilis	5.6 (5.1-6.1)	5.7 (5.0-6.5)	11 (10-13)	174 (174-174)	2,321

Table 5.1 (continued) Estimated average annual disease burden in YLD, YLL, DALY, DALY per 100 acute infections (with 95% uncertainty intervals) and estimated annual number of acute cases in 2012-2014 in the Netherlands, by disease category in order of highest to lowest DALY/year.

Disease	YLD/ year	YLL/ year	DALY/ year	DALY/ 100 infections[a]	Annual acute infections[b]
Vector-borne disease					
Lyme borreliosis	1885 (1554-2246)	0 (0-0)	1885 (1554-2246)	8.0 (6.6-9.6)	23,495
Vaccine-preventable diseases					
Invasive pneumococcal disease	136 (134-138)	8436 (7943-8954)	8571 (8078-9092)	317 (298-335)	2,706
Pertussis	3309 (3174-3446)	2068 (1866-2304)	5378 (5080-5705)	1.7 (1.6-1.8)	315,101
Measles	256 (226-287)	2692 (1923-3489)	2948 (2169-3749)	27 (20-34)	10,771
Invasive meningococcal disease	49 (39-60)	621 (496-762)	670 (537-821)	643 (581-701)	104
Invasive *H. influenzae* infection	117 (107-128)	385 (361-409)	502 (475-529)	292 (277-307)	172
Rubella	190 (152-232)	31 (26-38)	222 (178-270)	97 (78-119)	227
Rabies	0.02 (0.02-0.03)	25 (25-25)	25 (25-25)	3729 (3729-3729)	<1
Tetanus	0.03 (0.02-0.03)	4.8 (4.2-5.4)	4.8 (4.3-5.4)	402 (379-426)	1
Mumps	1.9 (1.9-2)	0.2 (0.1-0.2)	2.1 (2.0-2.2)	0.5 (0.5-0.6)	386
Diphtheria	0.01 (0.01-0.01)	0.6 (0.5-0.7)	0.6 (0.5-0.7)	90 (72-108)	<1
Poliomyelitis	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0

a: for pathogens of which asymptomatic acute infections can lead to disease burden from sequelae, the estimated annual DALY were divided by the sum of both symptomatic and asymptomatic (or latent) acute infections per year.

b: this number includes asymptomatic (or latent) infections for hepatitis B and C, Q fever, chlamydia, gonorrhea and tuberculosis. For HIV, we assumed all infected cases to come into care and to be registered by the surveillance system eventually.

5.4 Literature

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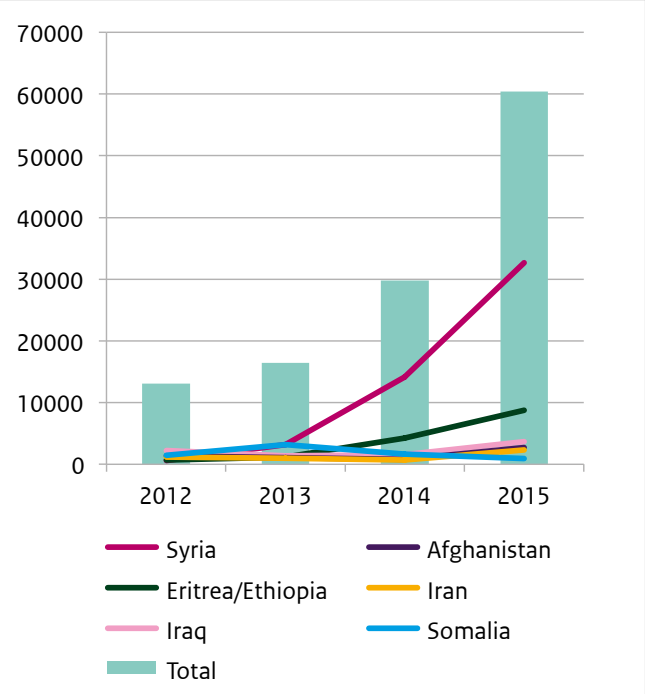
6 Notifiable infectious diseases in asylum seekers in the Netherlands, 2015

6.1 Introduction

In 2015, the influx of refugees into Europe more than tripled, with over a million refugees arriving in 2015, compared to 280,000 in 2014. Among the forces driving people to flee from their country are the conflicts in Syria, Iraq and Afghanistan, accounting for approximately 80% of the refugees. Poverty, human rights abuses, and deteriorating security are also prompting people to set out from countries such as Eritrea, Somalia, Morocco, Iran and Pakistan. This increasing influx also reached the Netherlands. In 2015, the number of asylum applications in the Netherlands was twice as high compared to the previous year (Figure 6.1). The increase in the Netherlands is mainly attributable to the increase of Syrian asylum seekers.

Since 2012, notifiable infectious diseases among refugees in the Netherlands have been monitored using Osiris, the Dutch notifiable infectious diseases database. Data on notifiable infectious diseases are collected by the municipal health services. The monitoring of tuberculosis in asylum seekers using Osiris started in 2014.

Figure 6.1 Influx of asylum seekers in the Netherlands 2012-2015 (1, 2).



6.2 Overview of notifiable infectious diseases

In this chapter, we provide an overview of notifiable infectious diseases reported in asylum seekers in the Netherlands. Table 6.1 shows the number of notifications of infectious diseases reported in asylum seekers living in asylum centers in the Netherlands by year of disease onset in the period 2012-2015. When interpreting the number of notifications, the increase in the number of asylum seekers arriving in the Netherlands has to be taken into account.
In this section, we go further into detail on the most frequently reported infectious diseases in asylum seekers: tuberculosis, chronic hepatitis B and malaria.
The surveillance of notifiable infectious diseases in asylum seekers is based on disease notifications of asylum seekers living in asylum centers and collective reception centers of the Central Agency for the Reception of Asylum Seekers (COA). Infectious diseases data on asylum seekers not living in COA-centers (e.g. Municipal emergency shelters) and refugees with a residence permit living in the community (including family reunification) cannot be identified as such from the surveillance system.

In this chapter, we have used the occupancy at COA to calculate the prevalence of a disease. For the occupancy per year, we calculated the mean of the occupancy on the first of each month from January of the given year up until January of the year after.

Table 6.1 Number of notifications of notifiable infectious diseases in asylum seekers by year of disease onset and as percentage of total notifications in the Netherlands, 2012-2015.*

Group**		2012*** (%)	2013 (%)	2014 (%)	2015 (%)
Group A[1]		0	0	0	0
Group B1[2]	Tuberculosis[5]	n.a.	n.a.	79 (9.2)	106 (11.8)
Group B2[3]	Hepatitis A	0	2 (< 1.0)	2 (1.9)	9 (11.4)
	Hepatitis B Acute	1 (< 1.0)	3 (2.1)	2 (1.4)	1 (< 1.0)
	Hepatitis B Chronic	61 (4.6)	69 (6.1)	91 (8.5)	106 (10.6)
	Invasive group A streptococcal disease	0	0	2 (1.3)	1 (< 1.0)
	Measles	0	1 (< 1.0)	0	1 (14.3)
	Paratyphi C	0	0	0	1 (25.0)
	Pertussis	49 (< 1.0)	8 (< 1.0)	19 (< 1.0)	8 (< 1.0)
	STEC/enterohemorragic *E.coli* infection	2 (< 1.0)	0	1 (< 1.0)	1 (< 1.0)
	Shigellosis	0	0	3 (< 1.0)	4 (< 1.0)
	Typhoid fever	0	0	0	2 (11.8)
Group C[4]	Brucellosis	0	0	0	1 (11.1)
	Hantavirus infection	0	0	1 (2.7)	0
	Invasive pneumococcal disease (in children 5 years or younger)	0	0	0	1 (2.3)
	Legionellosis	0	0	0	1 (< 1.0)
	Malaria	4 (2.0)	6 (4.2)	106 (37.2)	126 (36.3)
	Meningococcal disease	0	0	1 (1.2)	0
	Mumps	0	0	0	1 (1.1)
	Psittacosis	0	0	1 (2.4)	0

* The Table was sourced from the Dutch notifiable infectious diseases database 'Osiris' on 02 May 2016. 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 was 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 depending on the legal measures that may be imposed.

*** It was not until 2012 that the question 'if a person is living in an asylum center' was added to Osiris. Therefore, it could be that notifications in 2012 are an underreporting of the actual number of disease notifications in asylum seekers in 2012.

1 0 cases for MERS-CoV, polio, SARS, smallpox and viral hemorrhagic 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, Creutzfeldt-Jakob disease –variant, dengue, invasive *Haemopilus influenzae* 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 'if the patient is living in an asylum center' was added to the tuberculosis questionnaire. N.a.: not available

Tuberculosis

In 2015, 106 cases of tuberculosis (TB) in asylum seekers were notified, accounting for 11.8% of all TB notifications in the Netherlands. This is a slight increase compared to 2014, when 79 cases of TB were notified, accounting for 9.2% of all TB notifications in the Netherlands (Table 6.1). The largest group accounting for TB cases in asylum seekers originated from Eritrea/Ethiopia with 68 cases in 2015 and 45 cases in 2014 (Table 6.2). In the last two years, most asylum-seekers originated from Syria and among them TB was relatively uncommon. The total number of TB notifications per 100 asylum seekers staying at COA in 2014 and 2015 was 0.4. In 2015, the number of TB notifications per 100 asylum seekers from Eritrea/Ethiopia (1.3) and Somalia (0.8) decreased compared to 2014 (Table 6.2). In 2015, TB was only reported in asylum seekers in the age groups 5-17 and 18-50. The total number of TB notifications per 100 asylum seekers staying at COA in the age groups 5-17 and 18-50 decreased slightly compared to 2014, to 0.3 and 0.4 respectively (Table 6.3). In 2014, 13 of 79 (16%) asylum seekers with TB living in asylum centers in the Netherlands were diagnosed with infectious pulmonary TB. In 2015, more asylum seekers with infectious pulmonary TB were reported: 26 of 106 (25%). Between 2010-2015 the proportion of infectious pulmonary TB in the total number of TB patients in the Netherlands varied between 23% and 26%.

Asylum seekers are screened for TB within a week of arrival in the Netherlands. The TB-screening of asylum-seekers from countries with a TB incidence of less than 50 per 100,000 populations during the period 2011-2015 was evaluated and stopped in 2015. This was based on an advice by the Netherlands Tuberculosis Control Policy Committee to the Ministry of Health, following the low yield in these populations. These include asylum seekers coming from Syria. In the Netherlands, asylum-seekers and immigrants from countries with an estimated World Health Organization-incidence of more than 200 per 100,000 populations and from specified other high-risk countries, such as Eritrea, are invited for a six monthly follow-up CXR screening for a period of two years (3).

Table 6.2 Tuberculosis notifications in asylum seekers by country of birth and occupancy at COA by country of origin, 2014-2015.

Country of birth	2014			2015		
	Notifications	Occupancy COA	Notifications per 100 persons	Notifications	Occupancy COA	Notifications per 100 persons
Eritrea/ Ethiopia	45	2,957	1.5	68	5,205	1.3
Syria	2	5,398	0.0	9	12,861	0.1
Afghanistan	0	1,321	0.0	7	1,399	0.5
Somalia	14	1,568	0.9	7	853	0.8
Other	18	8,308	0.2	15	9,680	0.2
Total	79	19,552	0.4	106	29,998	0.4

Table 6.3 Tuberculosis notifications in asylum seekers age distribution by occupancy at COA, 2014-2015.

Age groups	2014			2015		
	Notifications	Occupancy COA	Notifications per 100 persons	Notifications	Occupancy COA	Notifications per 100 persons
0-4	1	1,821	0.1	0	2,337	0.0
5-17	15	4,115	0.4	21	6,037	0.3
18-50	63	12,530	0.5	85	20,132	0.4
50+	0	1,087	0.0	0	1,492	0.0
Total	79	19,552	0.4	106	29,998	0.4

Chronic hepatitis B

In 2015, 106 chronic hepatitis B virus (HBV) infection cases in asylum seekers were notified, accounting for 10.6% of all notified chronic HBV infection cases in the Netherlands. This is an increase compared to 2014, when 91 chronic HBV infection cases in asylum seekers were notified, accounting for 8.5% of all cases (Table 6.1).

Over the last two years, most notified chronic HBV cases originated from Syria and Eritrea (Table 6.4). 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 in 2015 was 0.5. This is comparable to the years prior to that. The number of notifications per 100 asylum seekers from Sierra Leone has decreased over the past few years from 2.9 per 100 asylum seekers in 2012 to 0.8 in 2015. In 2015, a slight increase was observed in chronic HBV notifications in asylum seekers from Eritrea/Ethiopia (0.5) and Somalia (0.5) compared to 2014 (Table 6.4).

In 2015 and 2014, the number of chronic HBV notifications per 100 asylum seekers was highest in the age group 18-50 (Table 6.5). In 2015 and 2014, the number of notifications of chronic HBV per 100 asylum seekers in the age group 5-17 was 0.1 and 0.2 respectively. Compared to 2013, this is a substantial decrease given the number of notifications per 100 asylum seekers in the age group 5-17 was 0.5.

Asylum seekers in the Netherlands are not systematically screened for chronic HBV, however general practitioners from the Asylum Seekers Health Centers occasionally offer tests for chronic HBV. Pregnant women are screened for chronic HBV through antenatal screening, which is in place throughout the Netherlands. 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 the increasing influx of refugees from higher prevalence countries is not associated with an increasing transmission of HBV within the Dutch population. In addition, to assess the risk of vaccine preventable disease among asylum seekers, the RIVM initiated a seroprevalence study in 2016.

Table 6.4 Chronic hepatitis B notifications in asylum seekers by country of birth and occupancy at COA by country of origin, 2012-2015.

Country of birth	2012			2013			2014			2015		
	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	6	517	1.2	7	1,089	0.6	14	5,398	0.3	26	12,861	0.2
Eritrea/ Ethiopia	2	498	0.4	6	721	0.8	11	2,957	0.4	24	5,205	0.5
Somalia	6	1,764	0.3	11	1,840	0.6	3	1,568	0.2	4	853	0.5
Sierra Leone	7	242	2.9	6	250	2,4	3	277	1.1	2	257	0.8
Afghanistan	6	2,244	0.3	3	1,868	0.2	3	1,321	0.2	5	1,399	0.4
Unknown/ Other	34	9,124	0.4	36	8,937	0.4	57	8,031	0.7	45	9,423	0.5
Total	61	14,389	0.4	69	14,705	0.5	91	19,552	0.5	106	29,998	0.4

Table 6.5 Chronic hepatitis B notifications in asylum seekers age distribution by occupancy at COA, 2012-2015.

Age groups	2012			2013			2014			2015		
	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	1,560	0.0	0	1,593	0.0	1	1,821	0.1	0	2,337	0.0
5-17	13	2, 816	0.5	18	3,281	0.5	7	4,115	0.2	5	6,037	0.1
18-50	46	9,071	0.5	50	8,910	0.6	75	12,530	0.6	98	20,132	0.5
50+	2	942	0.2	1	921	0.1	8	1,087	0.7	3	1,492	0.2
Total	61	14,389	0.4	69	14,705	0.5	91	19,552	0.5	106	29,998	0.4

Malaria

Over the last 2 years an increase in malaria cases has been observed in the Netherlands. The increase is largely explained by the increase of malaria cases in asylum seekers. In 2015, 126 malaria cases in asylum seekers were notified, accounting for 36.3% of all malaria cases in the Netherlands. In 2014, 106 malaria cases in asylum seekers were notified, accounting for 37.2% of all malaria cases in the Netherlands (Table 6.1). In the years prior to that, only a few malaria cases were reported in asylum seekers. In 2014 and 2015, over 90% of asylum seekers with malaria were born in Eritrea or Ethiopia (Table 6.6). The total number of malaria notifications per 100 asylum seekers staying at COA slightly decreased from 0.5 in 2014 to 0.4 in 2015. This decrease was also observed in the notifications per 100 asylum seekers from Eritrea/Ethiopia, from 3.2 in 2014 to 2.3 in 2015 (Table 6.6). In 2015, the number of malaria notifications per 100 asylum seekers was highest in the age groups 5-17 and 18-50 (Table 6.7). This is comparable to previous years. In 2015, a small decrease in malaria notifications in the age groups 5-17 and 18-50 was observed compared to 2014, to 0.6 and 0.4 malaria notifications per 100 asylum seekers.

The parasite mostly responsible for the malaria cases in asylum seekers was *Plasmodium vivax*. Characteristic for *P. vivax* is its ability to relapse weeks to months after initial infection. In Dutch resident travelers (including work related travel), *P. falciparum* is the parasite that most often causes malaria (Figure 6.2).

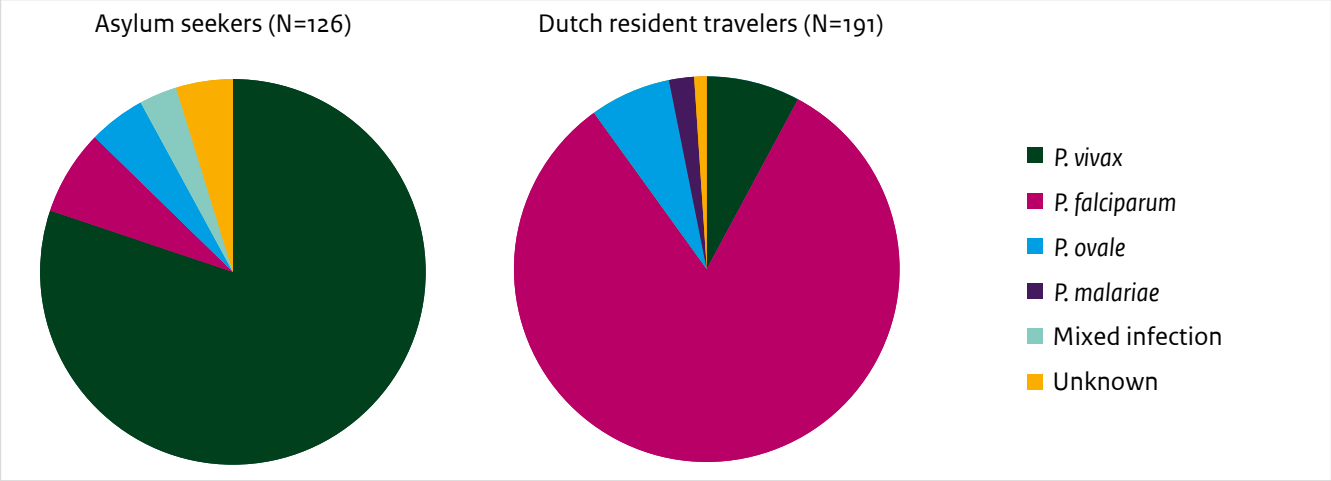
Table 6.6 Malaria notifications in asylum seekers by country of birth and occupancy at COA by country of origin, 2012-2015.

Country of birth	2012			2013			2014			2015		
	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	1	498	0.2	4	721	0.6	96	2,957	3.2	118	5,205	2.3
Unknown/ Other	3	13,891	0.0	2	13,984	0.0	10	16,595	0.1	8	24,793	0.0
Total	4	14,389	0.0	6	14,705	0.0	106	19,552	0.5	126	29,998	0.4

Table 6.7 Malaria notifications in asylum seekers age distribution by occupancy at COA, 2012-2015.

Age groups	2012			2013			2014			2015		
	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	1,560	0.0	0	1,593	0.0	0	1,821	0.0	0	2,337	0.0
5-17	0	2, 816	0.0	0	3,281	0.0	39	4,115	0.9	36	6,037	0.6
18-50	4	9,071	0.0	6	8,910	0.1	67	12,530	0.5	89	20,132	0.4
50+	0	942	0.0	0	921	0.0	0	1,087	0.0	1	1,492	0.1
Total	4	14,389	0.0	6	14,705	0.0	106	19,552	0.5	126	29,998	0.4

Figure 6.2 *Plasmodium* spp. in asylum seekers and Dutch resident travelers, 2015.



6.3 Concluding remarks

The influx of asylum seekers into the Netherlands doubled in 2015 compared to 2014. The most frequently reported notifiable infectious diseases in asylum seekers in the Netherlands were tuberculosis, chronic hepatitis B and malaria. There is no risk of malaria transmission, as the vector is not present in the Netherlands. There is no evidence of significant transmission of TB and chronic HBV to the Dutch population. ECDC assessed the risk for EU/EEA countries of infectious disease outbreaks as a consequence of the current influx of asylum seekers as being extremely low (4).
Even though the large influx in asylum seekers is mainly attributed to the increase of Syrian asylum seekers, most infectious diseases reported in asylum seekers are from people originating in the Horn of Africa. The prevalence of infectious diseases varied according to the country of origin, as well as to the countries visited en route and conditions there.
In addition to notifiable infections, there are some indications that the burden of other infections, e.g. scabies, is increased among asylum seekers. The RIVM-CIb in collaboration with NIVEL and others therefore initiated a pilot primary care syndromic surveillance project for infectious diseases among asylum seekers.

6.4 Literature

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Appendix: Methods to calculate disease burden

Disease burden was calculated using the methods described in the State of Infectious Diseases in the Netherlands 2013 (1), with the exception of HIV, for which the burden was calculated using Burden of Communicable Disease in Europe (BCoDE) version 1.1 (2). Disease models for HIV, chlamydia, gonorrhea and influenza were thoroughly reviewed again with disease experts. Model parameters and multiplication factors were set as described before (1), with a few modifications which are shown in Table A.1. Averages of population age distributions for 2012-2014 were calculated (3). Life expectancy table West level 26 was applied (1).

A new model was built for psittacosis (Figure A.1). Three types of symptomatic infection were defined: nonspecific febrile illness, pneumonia and invasive illness. Proportions of these among all clinical presentations were estimated using random effects meta-analysis for proportions, based on three published studies (4-6). Apart from mortality, no long-term sequelae were included. The multiplication factor used on the notified cases of psittacosis was 35.58 (with a Pert distribution between 24.51 and 46.64), based on a meta-analysis estimating the proportion of community-acquired pneumonia hospitalizations (CAP) caused by *C. psittaci*, applied to national incidence of CAP in hospitals. These calculations and underlying assumptions are further described elsewhere (7).

A separate method was used to calculate Lyme borreliosis disease burden; the method is described by Van den Wijngaard et al (8). Incidence was re-measured in 2014 and used as input for the model (9). As no incidence estimates are available for 2012 and 2013, only the 2014 burden was estimated for Lyme borreliosis. The models developed by Havelaar et al were applied for campylobacteriosis, cryptosporidiosis, giardiasis, hepatitis A infection, listeriosis, norovirus infection, salmonellosis, toxoplasmosis, and STEC O157 infection, as well as disease mediated by toxins of *S. aureus*, *B. cereus* and *C. perfringens* (1, 10). These models also use an incidence-based and pathogen-based approach, but incorporate incidence of e.g. hospitalizations in addition to overall incidence of infection.

Figure A.1 Outcome tree for the psittacosis disease model.

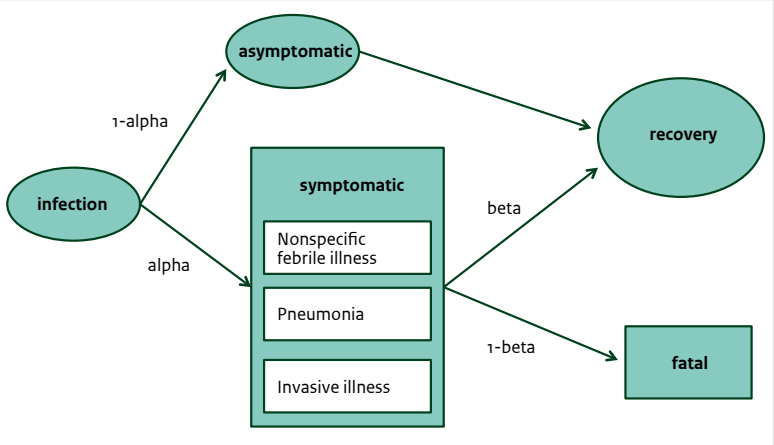

Table A.1 Disease model parameter changes since the DALY estimates published in the State of Infectious Diseases in The Netherlands, 2013.

Disease model	Parameter change from those in State of Infectious Disease 2013	Reason
Syphilis	Multiplication factor UE set to 1.1	Incidence estimation now extended to GP practices and congenital cases. The sex-specific proportion of syphilis positive samples with titer >1:8 in two large regional laboratories was used to estimate amount of infectious syphilis among GP diagnoses.
Chlamydia	Transition probability PID to ectopic pregnancy to Pert(0.075,0.091,0.11)	Based on Weström et al 1992, proportion of ectopic pregnancies after PID with 95% confidence interval (6)
Chlamydia	Transition probability PID to tubal infertility to Pert(0.006, 0.0796,0.214)	Based on Weström et al 1992, weighted average of tubal infertility after one mild, moderate or severe PID episode (6, 10, 11)
Gonorrhea	Transition probability PID to ectopic pregnancy to Pert(0.075,0.091,0.11)	Based on Weström et al 1992, proportion of ectopic pregnancies after PID with 95% confidence interval (6)
Gonorrhea	Transition probability PID to tubal infertility to Pert(0.006, 0.0796,0.214)	Based on Weström et al 1992, weighted average of tubal infertility after one mild, moderate or severe PID episode (6)
Measles	Multiplication factor UE set to Pert(8.44, 11.21,15.02)	Based on meta-analysis of published and unpublished data (12)
Rubella	Multiplication factor UE set to Pert(8.44, 11.21,15.02)	Measles used as proxy (12)
Mumps	Multiplication factor UE set to Pert(1.55, 1.79, 2.13)	Based on meta-analysis of published data (12)
Pertussis	Multiplication factor UE: Pert(23,41,66) (<1y) Pert(17,25,34) (1-4 y) Pert(16,26,39) (5-9 y) Pert(6,10,15) (10-19 y) Pert(37,47,59) (20-59 y) Pert(49,69,96) (60+ y)	Based on evidence synthesis approach (13)
Influenza	Duration uncomplicated acute illness set to 0.014 years	Uncomplicated acute influenza is estimated to last 5 days (14)

UE: underestimation

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