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State of Infectious Diseases *in the Netherlands, 2013*

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Colophon

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Publiekssamenvatting

Staat van Infectieziekten in Nederland, 2013

De uitbraak van mazelen in 2013 was de meest in het oog springende infectieziekte van dat jaar. Dit blijkt uit de Staat van Infectieziekten in Nederland 2013, die inzicht geeft in ontwikkelingen van infectieziekten bij de Nederlandse bevolking. Daarnaast worden de ontwikkelingen in het buitenland beschreven die voor Nederland relevant zijn. Met deze jaarlijkse uitgave informeert het RIVM beleidsmakers van het ministerie van Volksgezondheid, Welzijn en Sport (VWS).

Elk jaar komt in de Staat van Infectieziekten een thema aan bod; dit jaar is dat de hoeveelheid jaren in goede gezondheid die verloren gaan (ziektelast) door infectieziekten. Sommige infectieziekten, zoals maag-darminfecties, komen erg vaak voor maar veroorzaken over het algemeen geen ernstige klachten. Andere daarentegen, 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).

Voor 32 infectieziekten is de ziektelast in Nederland tussen 2007 en 2011 geschat. De gemiddelde jaarlijkse ziektelast voor de totale Nederlandse bevolking was het hoogst voor ernstige pneumokokkenziekte (9444 DALY's per jaar) en griep (8670 DALY's per jaar), die respectievelijk 16 en 15 procent van de totale ziektelast van alle 32 infectieziekten vertegenwoordigen. Na polio en difterie (0 gevallen in de onderzochte periode), werd de laagste ziektelast geschat voor rodehond op 0,14 DALY's per jaar. De ziektelast voor deze ziekten is zo laag dankzij het Rijksvaccinatieprogramma. De ziektelast per individu varieerde van 0,2 DALY's per honderd infecties voor giardiasis (diarree die wordt veroorzaakt door een parasiet), tot 5081 en 3581 DALY's per honderd infecties voor respectievelijk hondsdolheid en een variant van de ziekte van Creutzfeldt-Jakob.
Voor alle ziektelaststudies geldt dat de resultaten afhankelijk zijn van de modelparameters en aannames, en van de beschikbaarheid van accurate gegevens over de mate waarin de ziekten voorkomen. Toch kunnen deze schattingen informatief zijn voor beleidsmakers binnen de gezondheidszorg om prioriteiten te kunnen aanbrengen in preventieve en andere maatregelen.

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

Abstract

State of Infectious Diseases in the Netherlands, 2013

The measles outbreak in 2013 was the most striking infectious disease of that year. This is demonstrated in the State of Infectious Diseases in the Netherlands 2013, which provides insight into infectious disease trends in the Dutch population. Developments in other countries that are relevant for the Netherlands are also described. This annual RIVM publication informs policy-makers from the Ministry of Health, Welfare and Sport (VWS).

Every year the State of Infectious Diseases publishes reports on a particular theme. This year's topic concerns the estimation of disease burden: how many years of healthy life are lost due to infectious diseases? Some infectious diseases, such as gastrointestinal infections, occur frequently in the population, but do not generally give rise to serious complaints. In contrast, other diseases, for example tetanus, occur rarely but may lead to a high risk of death. A summary measure of population health that combines the morbidity and premature mortality attributable to a disease in a single quantity is the Disability Adjusted Life Year (DALY). For 32 infectious diseases, we estimated the disease burden in the Netherlands between 2007 and2011. The highest average annual burden for the total Netherlands population was estimated for invasive pneumococcal disease (9444 DALYs per year) and influenza (8670 DALYs per year), which represented 16 and 15 percent, respectively, of the total burden of all 32 diseases considered. After poliomyelitis and diphtheria (no cases in the period investigated), the lowest burden was estimated for rubella, at 0.14 DALYs per year. The extremely low burden for these diseases is due to the National Immunisation Programme. The disease burden per individual varied from 0.2 DALYs per 100 infections for giardiasis (diarrhea that is caused by a parasite), to 5081 and 3581 DALYs per 100 infections for rabies and variant Creutzfeldt-Jakob disease, respectively. As with all burden of disease studies, results depend on disease model parameters and assumptions, and on the availability of accurate data on the incidence of infection. Nevertheless, estimates of disease burden can be informative for public health policy-makers regarding the prioritisation of preventive and other measures.

Keywords: state of infectious diseases, infectious diseases, disease burden, DALY, notifiable diseases

Contents

1 Introduction

This is the ninth edition of the report on State of Infectious Diseases in the Netherlands. This annual publication is written to inform policy makers at the Ministry of Health, Welfare and Sports (VWS) and 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 2013. This chapter includes the table with annual numbers of notified diseases in the Netherlands.

One particular topic is highlighted each year. This year the focus is on the burden of infectious disease in the Netherlands. In this report, we present the first comprehensive national burden of disease estimates, for 32 infectious diseases in the period 2007-2011. We computed the disability-adjusted life years (DALY) measure, which combines the burden due to both morbidity and premature mortality associated with all short and long-term consequences of infection. The highest average annual burden was observed for invasive pneumococcal disease (9444 DALYs/year) and influenza (8670 DALYs/year), which represents 16% and 15%, of the total burden of all 32 diseases considered, respectively. Results depend on disease model parameters and assumptions, and on the availability of accurate data on the incidence of infection, which usually must be estimated using imperfect surveillance data. Estimates of disease burden van be informative for public health policy decisions regarding the prioritisation of interventions and preventive measures.

2 The state of Infectious Diseases in the Netherlands, 2013

2.1 Introduction

In this chapter, we provide an overview of key infectious diseases events in 2013 previously reported in the weekly reports written by the Dutch early warning committee (http://signaleringsoverleg.infectieziekten.eu/). These include both national and international events. Table 2.1 shows the number of notifications of all notifiable infectious diseases in the Netherlands by year of disease onset in the period 2006-2013. In section 2.2 to 2.5 we describe the most important events concerning mandatory notifiable diseases under the Dutch Public Health Act (1). Section 2.6 deals with notable occurrences regarding non-notifiable infectious diseases for the Netherlands, including events in the rest of the world. We have included information from the year 2014, in case an outbreak or unusual event started in 2013 and continued into 2014. We have not included information about outbreaks or events that started in 2014.

2.2 Group A-diseases

Polio

In 2013, 416 patients with poliomyelitis were reported to the World Health Organization (WHO) globally (www.polioeradication.org). This number is higher than in 2012 with 223 reported cases, but an enormous decrease since 1998 (350.000 cases), the year the World Health Assembly resolved to eradicate the disease. Of the 416 patient in 2013, 160 (38 %) were reported from the last 3 countries were poliomyelitis is endemic (Nigeria 53 patients, Pakistan 93 patients, and Afghanistan 14 patients). The other patients were

Table 2.1 Number of notifications of notifiable infectious diseases in the Netherlands by year of disease onset, 2006-2013[1].

Group*	Infectious disease	2006	2007	2008	2009	2010	2011	2012	2013
Group A	Smallpox	0	0	0	0	0	0	0	0
	Polio	0	0	0	0	0	0	0	0
	Severe Acute Respiratory Syndrome (SARS)	0	0	0	0	0	0	0	0
	Middle East Respiratory Syndrome (MERS)								0[b]
	Viral haemorrhagic fever	0	0	1	0	0	0	0	0
Group B1	Human infection with zoonotic influenza virus			0[a]	0	0	0	0	0
	Diphtheria	0	0	0	0	0	1	1	0
	Plague	0	0	0	0	0	0	0	0
	Rabies	0	1	0	0	0	0	0	1
	Tuberculosis	1030	999	1013	1158	1068	1004	957	848
Group B2	Typhoid fever	20	25	27	27	24	20	17	25
	Cholera	3	3	5	4	0	3	3	0
	Hepatitis A	276	161	185	180	261	116	124	109
	Hepatitis B Acute	244	224	225	215	196	155	174	140
	Hepatitis B Chronic	1499	1570	1591	1772	1570	1544	1322	1127
	Hepatitis C Acute	25	41	28	39	30	72	53	64
	Pertussis	4381	7743	8135	6350	3691	7044	13859	3474
	Measles	1	10	109	15	15	51	19	2650
	Paratyphi A	20	11	9	17	19	14	25	22
	Paratyphi B	14	21	26	16	16	27	18	15
	Paratyphi C	0	2	1	3	0	1	3	2
	Rubella	5	1	2	7	0	3	1	57
	STEC/enterohemorragic *E.coli* infection	42	111	154	279	397	647	903	844
	Shigellosis	242	406	438	413	533	584	750	469
	Invasive group A streptococcal disease			28[a]	255	211	186	178	201
	Clusters of foodborne infection**	95	97	85	39	48	42	47	34

Table 2.1 (continued) Number of notifications of notifiable infectious diseases in the Netherlands by year of disease onset, 2006-2013[1].

Group*	Infectious disease	2006	2007	2008	2009	2010	2011	2012	2013
Group C	Anthrax	0	0	0	0	0	0	0	0
	Mumps			7[a]	80	563	609	397	204
	Botulism	1	1	7	0	0	0	2	0
	Brucellosis	7	6	5	3	6	1	3	5
	Creutzfeldt-Jakob disease	22	15	15	20	27	27	28	23
	Creutzfeldt-Jakob disease - Variant	0	0	1	0	0	0	0	0
	Yellow fever	0	0	0	0	0	0	0	0
	Invasive *Haemophilus influenzae* type b infection			0[a]	16	31	20	22	18
	Hantavirus infection			2[a]	7	19	7	23	4
	Legionellosis	440	325	339	256	473	315	308	306
	Leptospirosis	27	42	29	22	29	29	44	27
	Listeriosis			8[a]	56	69	86	70	74
	Malaria	241	229	221	234	245	242	199	164
	Meningococcal disease	177	184	155	158	143	99	106	108
	MRSA-infection (clusters outside hospitals)			4[a]	16	13	6	2	10
	Invasive pneumococcal disease (in children age 5 years or younger)			5[a]	42	57	48	53	28
	Psittacosis	67	53	79	81	73	70	44	53
	Q fever	13	195	1003	2424	411	77	63	20
	Tetanus			0[a]	1	2	5	2	1
	Trichinosis	0	0	1	1	0	1	0	0
	West Nile virus infection			0[a]	0	1	1	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 Diseases' reports. The Table was sourced from the Dutch notifiable infectious diseases database 'Osiris' on April 29 2014. 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.

reported from Cameroon (4), Syrian Arab Republic (35), Ethiopia (9), Somalia (194) and Kenya (5).
In addition, since February 2013, wild polio virus type 1 has been detected in sewage samples from different sampling sites in southern and central Israel. In addition, positive environmental samples have also been collected from the West Bank and Gaza. These findings indicate widespread wild polio virus circulation in this region without identified clinical cases. As Israel is a popular destination for European Union travellers and vice versa, there is a risk of import cases of polio and outbreaks (particularly within groups with a low vaccination coverage) in European countries (http://www.ecdc.europa.eu/en/publications/Publications/Communicable-disease-threats-report-21-sep-2013.pdf).
In addition, since October 2013 cases due to wild poliovirus type 1 were confirmed in the Syrian Arab Republic. Cases were from different parts of the country, indicating widespread circulation of the virus. Wild poliovirus was last reported in Syria in 1999. Most of the cases were very young (below two years of age), and were unvaccinated or partly vaccinated due to the war situation in the country. WHO estimated that immunisation rates in the Syrian Arab Republic declined from 91% in 2010 to 68% in 2012. With the arrival of many refugees from Syria into the Netherlands, there is a small risk of importation of poliovirus. Although the Dutch population is generally well protected against polio, introduction of poliovirus in the Dutch orthodox protestant community could result in an epidemic. In the Netherlands, the last poliomyelitis epidemic occurred in 1992-1993 when 71 polio patients were notified who were unvaccinated because of religious beliefs (2).
In May 2014 the WHO declared polio a public health emergency of international concern. The WHO Director-General determined that the spread of wild poliovirus to 3 countries – during what is normally the low-transmission season – was an 'extraordinary event' and a public health risk to other countries, and that a coordinated international response was essential to prevent exacerbation during the high-transmission season (http://www.who.int/mediacentre/news/statements/2014/polio-20140505/en/). Currently 10 countries have active wild poliovirus outbreaks that could spread to other countries through the movement of people. From January to April 2014 – that is the low-transmission season for polio – the virus was transmitted to 3 countries: in central Asia (from Pakistan to Afghanistan), in the Middle East (from Syrian Arab Republic to Iraq) and in Central Africa (from Cameroon to Equatorial Guinea).

MERS-coronavirus

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). From September 2012 to May 9 2014, WHO had been informed of a total of 536 laboratory-confirmed cases of infection with MERS-CoV, including 145 deaths, globally (http://www.who.int/csr/disease/coronavirus_infections/MERS_CoV_Update_09_May_2014.pdf?ua=1). All cases have been directly or indirectly linked, through travel or residency, to 4 countries in the Middle East: Saudi Arabia, Qatar, Jordan, and the United Arab Emirates. This includes cases reported from Germany, the United Kingdom, France, Italy and Tunisia. In May 2014 2 Dutch patients were diagnosed with MERS-CoV infection. These patients had visited Saudi Arabia (4).
There has been person-to-person transmission on a small scale amongst people who had close contact with cases, for example by sharing a household or work place, or by caring for a patient in a health care setting. Coronaviruses belong to a large family of viruses causing a range of illnesses in humans, from the common cold to severe acute respiratory syndrome (SARS). Coronaviruses also cause a range of diseases in animals. Research found a high prevalence of antibodies against MERS-CoV in camels from different countries, suggesting that these animals are a potential reservoir (5, 6). A role for bats as reservoir has also been suggested (7).

2.3 Group B1-diseases

Tuberculosis

In 2013, there were 848 notifications of tuberculosis in the Netherlands, of which 469 were of pulmonary tuberculosis (http://www.rivm.nl/dsresource?objectid=rivmp:241606&type=org&disposition=inline). Of the pulmonary tuberculosis patients, 141 had smear positive tuberculosis, the most infectious type of tuberculosis. The number of notified tuberculosis patients has decreased since 2002 and the decrease continued into 2013. The incidence rate in 2013 was 5.1 per 100,000 inhabitants. Nearly three quarters (74%) of tuberculosis diagnoses in 2013 originated from people born abroad. Of these patients, the largest group (24%) was born in Somalia. In 2013, there were 17 notifications of multidrug-resistant (MDR)-tuberculosis cases. There have not been any notifications of cases with extreme drug-resistant (XDR)-tuberculosis since 2009, in which year 3 cases

were notified. In 2012, the percentage of patients who successfully completed their treatment was on average 85%.

Rabies

In 2013, a Dutch citizen died from rabies. He had been bitten by a dog on a compound in Port-au-Prince, Haiti on 6 May 2013 (http://www.promed-mail.org/direct.php?id=1791201). He had not been vaccinated against rabies before the incident. On 20 June 2013, after his return to the Netherlands, he was admitted to a hospital, with suspected rabies. Presence of rabies virus (genotype 1) was confirmed in skin biopsies of the neck, in liquor and saliva. In the Netherlands, 4 people have been notified with this disease: in 1962, 1996, 2008 and in 2013.

Human infection with zoonotic influenza virus

On 31 March 2013, Chinese authorities reported the identification of a novel reassortant influenza A/H7N9 virus isolated from 3 unlinked fatal human cases of severe respiratory disease in eastern China, 2 in Shanghai and 1 in Anhui province. This was the first time human infections with avian influenza virus A/H7N9 have been identified (8). This event marked the identification of fatal human infections caused by a low pathogenicity virus of avian origin. Since then, human cases have continued to be reported from China. As of 18 February 2014, there were 354 laboratory-confirmed cases of A/H7N9 reported in China (with a case–fatality rate of 32%). In addition, the virus has been detected in 1 asymptomatic case in Beijing. Since the beginning of 2014, there has been a notable increase in the number of human cases, which may indicate a growing wild or domestic bird reservoir, an increase in the number of exposed individuals, enhanced transmissibility of the virus, a seasonal transmission pattern or a combination of these factors. The continued and increasing transmission of a novel reassortant avian influenza virus capable of causing severe disease in humans in one of the most densely populated areas in the world remains a cause for concern due to the pandemic potential. However, the most likely current scenario for China is that these outbreaks remain zoonotic in which the virus is transmitted sporadically to humans in close contact with the animal reservoir, similar to the influenza A/H5N1 situation. Influenza A/H5N1 has been circulating in poultry in China for almost two decades, causing occasional human cases (654 globally, of which 46 cases in China). In early 2014, a case most probably infected in Beijing was detected by and reported from Canada. Three human cases of influenza A/H10N8 virus have been reported in Jiangxi province in China (9). The first human case was reported by the Chinese authorities on 17 December 2013, in a 73-year-old female with multiple underlying medical conditions, who was admitted to hospital on 30 November 2013, and died on 6 December 2013. According to local authorities, the patient had visited a local live-poultry market. Since then 2 more cases have been detected, of which 1 has died. In May 2013, a human case of influenza A/H6N1 was detected in Taiwan (10). While likely human-to-human transmission of A/H7N9 and A/H5N1 in clusters of reported cases has been documented in a few instances, there is no indication of sustained human-to-human transmission.

2.4 Group B2-diseases

Hepatitis A

From January 2013, 1,444 cases of hepatitis A virus (HAV) infection have been reported by 12 European countries as potentially linked to the same ongoing HAV infection outbreak (http://ecdc.europa.eu/en/publications/Publications/ROA-Hepatitis%20A%20virus-Italy%20Ireland%20Netherlands%20Norway%20France%20Germany%20Sweden%20United%20Kingdom%20-%20final.pdf). Although the outbreak was first associated with travellers to Italy, 8 other countries (France, Germany, Ireland, Norway, the Netherlands, Sweden, United Kingdom and Finland) have reported cases with no travel history in the 2 months before the onset of their disease. In the Netherlands, 15 cases have been reported with the outbreak strain. Epidemiological investigations and trace back activities in different countries did not pin point a clear hot spot, but suggested frozen berries as the vehicle of a common, continuous source in Europe. However, other hypotheses such as cross contamination in a food production environment or that the outbreak strain was already widespread but had gone undetected, cannot be excluded. The current outbreak in several European countries poses a risk of secondary transmission through infected individuals.

Measles

In 2013, a large measles outbreak occurred in the Dutch orthodox protestant community in the Netherlands. The outbreak started in May 2013 and continued on until February 2014 (11). The first 2 measles cases in this outbreak were reported from an orthodox Protestant school in the Province of South Holland on 27 May 2013. As of 26 February 2014, there were 2,640 reported cases, including 182 hospitalisations and 1 death. Most cases were

orthodox Protestants (91%) and unvaccinated (95%). Cases who acquired infection in the Netherlands have been reported by 24 Municipal Health Services (Figures 2.1 / 2.2). The case with the earliest date of onset of rash in this outbreak had not travelled abroad and the initial source of infection remains unknown.

A unique outbreak control intervention was implemented: a personal invitation for measles-mumps-rubella (MMR) vaccination was sent to parents of all children aged 6–14 months living in municipalities with an MMR vaccination coverage below 90% as the main risk group for developing measles complications. This age group is at relatively high risk since most mothers are currently vaccinated against measles, which leads to lower levels of maternal antibodies than natural infection. In addition, all unvaccinated individuals aged 14 months up to 19 years were invited for catch-up vaccination through the media. National recommendations to reduce the risk of measles in healthcare workers were finalised in the beginning of the outbreak. These suggest that healthcare workers born after 1965 should actively check their vaccination or measles infection status and complete their MMR vaccination schedule if needed. Healthcare workers born before 1965 and those vaccinated twice are considered immune. All hospitals in the Netherlands have been approached and encouraged to comply with these recommendations. The effects of the control measures will be evaluated.

A single dose of monovalent measles vaccine was included in the Dutch national immunisation programme in 1976 for children aged 14 months. Since 1987, vaccination against measles, mumps and rubella in a two-dose schedule has been available to children, at 14 months and nine years of age. Vaccination coverage is generally high in the Netherlands. In 2012, the MMR coverage was 96% for the first dose and 93% for the second dose (birth cohorts 2010 and 2002, respectively). However, vaccination uptake is low in some specific groups, for religious reasons (orthodox Protestantism), anthroposophic reasons, and in those with a critical attitude towards vaccination. While the latter 2 groups are scattered across the Netherlands, orthodox Protestants are a close-knit community of 250,000 persons, mostly living in an area that stretches from the south-west to the north-east of the country, the so-called Bible belt. Vaccination coverage in general among orthodox Protestants was assessed in 2006-2008 to be about 60%.

Rubella

In May 2013 a rubella outbreak occurred at an orthodox Protestant school in the province of South Holland. In total 54 cases were reported, mainly children aged between 4 and 11 years. Most cases were unvaccinated because of religious beliefs. In 2013 a large measles outbreak occurred in the same community (see Measles). Three other rubella cases were in adults, all whom had a link to Poland where a large rubella outbreak was ongoing.

2.5 Other relevant events related to non-notifiable infectious diseases

Tularaemia

In 2013 and 2014 4 human cases were diagnosed with tularaemia (see Figure 2.3). The first case of indigenous tularaemia in the Netherlands since 1953 was detected in 2011 (12). In 1953 8 family members were infected after eating an infected hare. Tularaemia is a zoonotic infection caused by *Francisella tularensis*. Tularaemia naturally occurs in rabbits, hares and in rodents, especially voles, vole rats and muskrats. Transmission to humans has been reported by direct contact with infected animals, arthropod bite, inhalation of contaminated dust and ingestion of contaminated food or water. The clinical presentation depends on the mode of transmission. From 2011, diseased or dead hares presented at the Dutch Wildlife Health Centre for research on cause of death, are routinely tested on tularaemia. In 2013 en 2014 3 hares tested positive for tularaemia. Tularaemia is an endemic disease in wildlife in many European countries, including Belgium and Germany.

Chikungunya in the Carribean

On 6 December 2013, two laboratory-confirmed cases of chikungunya without a travel history were reported on the French part of the Caribbean island of Saint Martin, signalling the start of the first documented outbreak of chikungunya in the Americas. Between 6 December 2013 and 27 March 2014 the virus spread to several Caribbean islands, including Sint-Maarten and over 17,000 suspected and confirmed cases were reported (13). Further spread and establishment of the disease in the Americas is likely, given the immunologically naïve population, the high number of people travelling between the affected and non-affected areas and the widespread occurrence of efficient vectors. Chikungunya is a mosquito-borne viral disease caused by an alphavirus from the Togaviridae family. The virus is transmitted by the bite of *Aedes* mos-

Figure 2.1 Reported measles cases by week of onset of exanthema and Municipal Health Service region, the Netherlands, 1 May 2013 – 26 February 2014 (n=2,640).

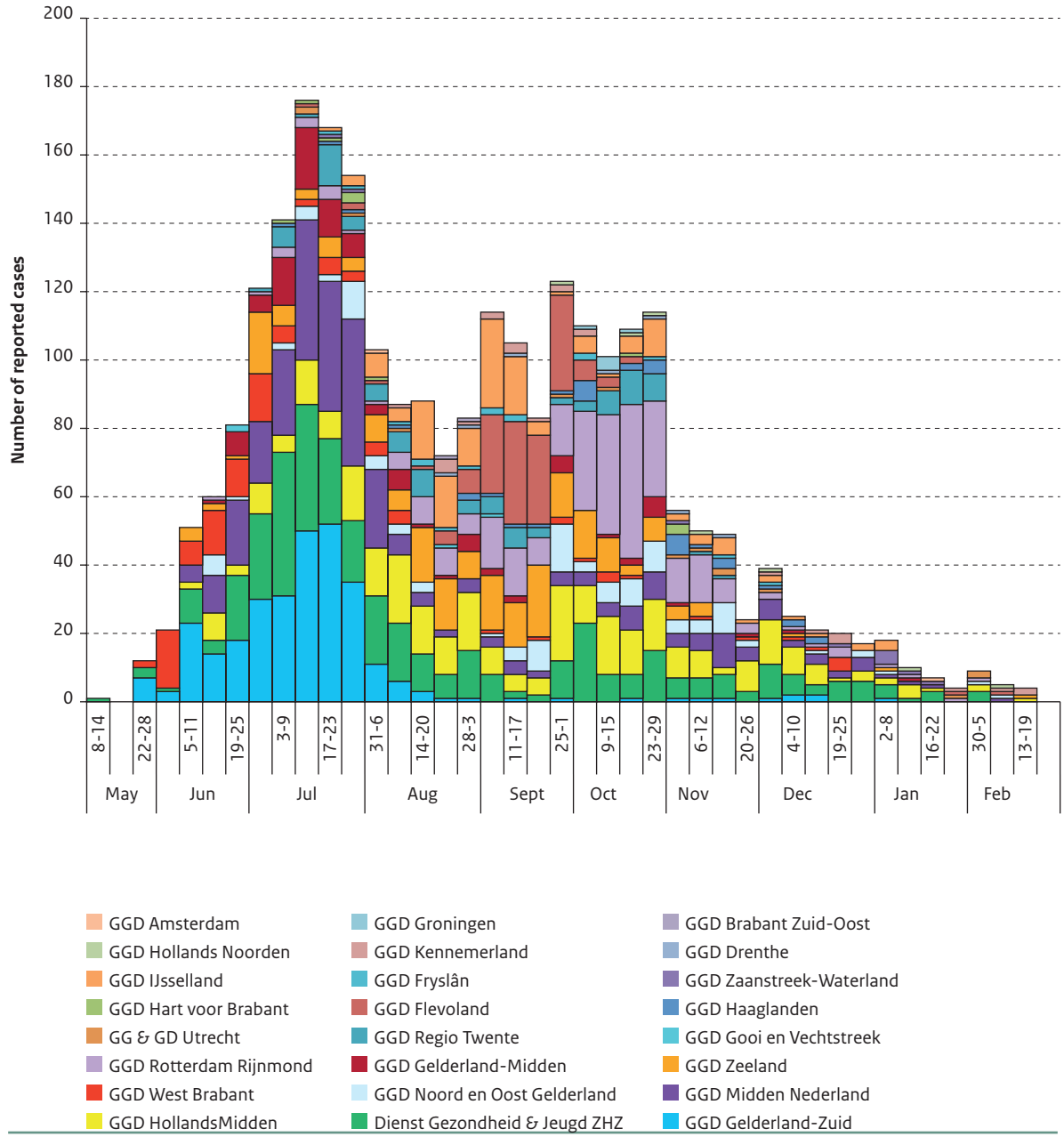


Figure 2.2 Reported measles cases by municipality, the Netherlands, 1 May 2013 – 26 February 2014 (n=2,640).

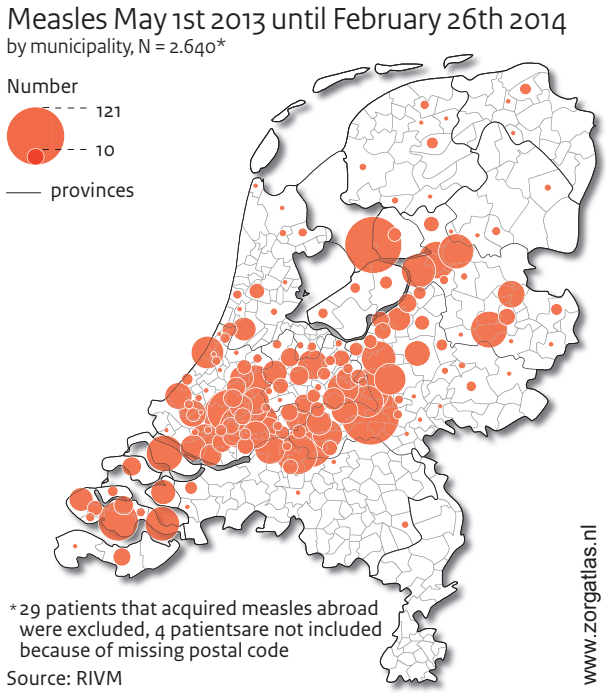
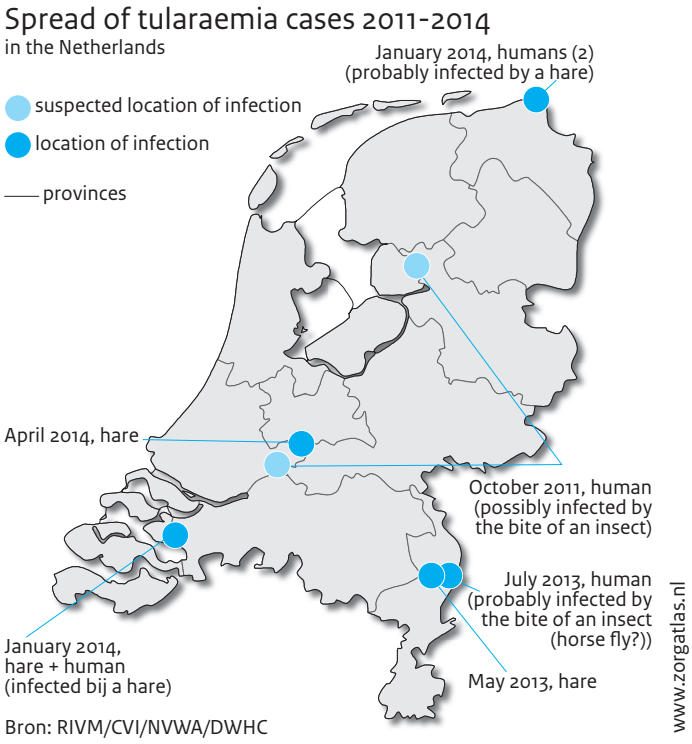


Figure 2.3 Geographical spread of tularaemia cases in the Netherlands, 2011-2014.



quitoes, primarily *Aedes aegypti* and *Aedes albopictus*. The typical clinical signs of the disease are fever and severe arthralgia, which may persist for weeks, months or years after the acute phase of the infection. General complications include myocarditis, hepatitis, ocular and neurological disorders. The detection and diagnosis of the disease can be challenging especially in settings where dengue is endemic, because the similarities in symptoms between the diseases.
Up to the year 2005, Chikungunya was endemic in parts of Africa, Southeast Asia and on the Indian subcontinent only. From 2005 to 2006, large chikungunya outbreaks were reported from Comoros, Mauritius, Mayotte, Réunion and various Indian states. Autochthonous transmission in continental Europe was first reported from Emilia-Romagna, Italy, in August 2007 with more than 200 confirmed cases and subsequently in France in 2010 with 2 confirmed cases (14, 15). In both areas the vector *Aedes albopictus* has been established. In 2014 Chikungunya became a notifiable disease in the Dutch Carribean.

2.6 Literature

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3 Disease burden of infectious diseases in the Netherlands

Key points

- The first comprehensive national burden of disease estimates, for 32 infectious diseases in the period 2007-2011, are presented for the Netherlands.
- The disability-adjusted life years (DALY) measure was computed, which combines the burden due to both morbidity and premature mortality associated with all short and long-term consequences of infection.
- The highest average annual burden is observed for invasive pneumococcal disease (9444 DALYs/year) and influenza (8670 DALYs/year), which represents 16% and 15% of the total burden of all 32 diseases, respectively.
- Results depend on disease model parameters and assumptions, and on the availability of accurate data on the incidence of infection, which is usually estimated using imperfect surveillance data.
- For public health policy decisions regarding the prioritisation of interventions and preventive measures, estimates of disease burden can be informative.

3.1 Introduction

Accurate estimates of the current and future burden of specific infectious diseases, and information regarding the ranked estimated burden among a number of infectious diseases, can support national public health policy and priority setting within the field of infectious disease epidemiology. Infectious diseases and their short- and long-term consequences (i.e., complications, sequelae) are quite heterogeneous in terms of severity and the risk of mortality. Infections with certain pathogens are common but with relatively mild health consequences, whereas others may be associated with a high mortality rate, but occur only rarely. Consequently, it is difficult to compare the burden of different diseases based solely on incidence or mortality rates. To enable such comparisons, a number of composite measures of health have been developed that combine morbidity and mortality (1).

In particular, the burden of disease methodology, as developed jointly by the World Bank, Harvard School of Public Health, and the World Health Organization (WHO) for the Global Burden of Diseases, Injuries, and Risk Factors study (GBD), is a suitable approach as it facilitates setting priorities among infectious diseases and comparing their relative disease burden (2-4). Commissioned by the WHO, Murray and Lopez performed a first study of the global burden of disease (4), in which they estimated the global disease burden for a wide range of diseases, including mental illness, chronic conditions, (consequences of) accidents, and infectious diseases. To compare the impact of these diseases in terms of quality of life and their effect on life expectancy, they developed a composite measure: the disability-adjusted life year (DALY) (see section 3.2.1). The idea behind this approach is that the impact of a particular disease can be divided into the number of years of life lost (i.e., premature mortality) and the number of years lived at less than full health (i.e., morbidity). The result is a single measurement unit that quantifies the years of healthy life lost due to a certain disease or infection. The DALY has since been widely applied for estimating disease burden at national, regional, and global levels (4-8).

In practice, the DALY computation is not as straightforward as desired. The relevant data are not always available, and a number of often critical choices and assumptions need to be made (9). Symptomatic as well as asymptomatic infections may lead to long-term chronic sequelae, which may not always be recognised as being originally caused by an infection. For many infectious diseases the possible relationships with later chronic sequelae are not clearly established or quantified. Therefore, criteria are needed to decide if the strength of evidence is sufficient for attributing (part of the) disease burden of those sequelae to an infectious cause, an essential requirement for the GBD 2010 project (10). Attributing long-term sequelae to infection with a specific pathogen may also require adding disease burden that occurs over long time periods (e.g., the time between acute hepatitis B infection and death may span decades) (9).

Our adopted methodology is consistent with the methodology developed for a pilot study in which the burden was estimated for seven infectious diseases in 23 European countries (11) and for a preliminary report of the estimated infectious disease burden within the Netherlands (12). In the current report, the first comprehensive burden estimates for 32 infectious diseases in the Dutch context are presented. This set of diseases comprises infectious diseases that are currently responsible for, or are able to cause, significant burden. In the coming years, we intend to further develop and refine the methods and aim to produce annual estimates.

3.2 Methodology

Several fundamental methodological decisions are required for burden of disease estimation. We decided to take the pathogen as a starting point (in contrast to an outcome-based approach), and to work with incidence data (see section 3.2.1.3). The preference for the latter was to use, if available, statutory notification data to which a correction factor is applied to account for the under-reporting and under-ascertainment inherent in notification data (see section 3.2.1.4 and Appendix 2). For non-notifiable diseases, we located the best alternative data source(s) to determine incidence; for instance, from laboratory surveillance and sentinel general practice /primary health care surveillance systems (see Appendix 1).

Outcome trees, which describe the various health outcomes and how they are related within a disease's natural history, transition probabilities between health outcomes, disability weights and durations, and various other parameters, assumptions and decisions were adopted from the expert-reviewed disease models developed as part of the Burden of Communicable Diseases in Europe (BCoDE) project and disease models developed by Havelaar et al. (13) (see online appendix www.rivm.nl/bibliotheek/rapporten/appendix150205001.pdf and sections 3.2.1.5-3.2.1.7).

The following sections describe the computation of the disability-adjusted life year (DALY) measure, the choices, assumptions, and parameters that are required when calculating disease burden, and which aspects of these assumptions are important for infectious diseases in particular.

3.2.1 DALY

The DALY is the simple sum of two components:

1. premature mortality, quantified as the number of years of life lost (Years of Life Lost = YLL), and
2. morbidity, the number of years lived with that health outcome (Years Lived with Disability = YLD). The DALY for a pathogen is therefore the sum of the YLL and YLD associated with all health outcomes specified within the natural history of infection by that pathogen.

$$DALY = YLL + YLD$$

3.2.1.1 YLL

Premature mortality associated with a health outcome is expressed in terms of the number of years of life lost (YLL). YLL is calculated as the number of deaths (d_i) multiplied by the remaining life expectancy (e_i) at the age of death, summed over all *n* fatal health outcomes of the disease, in a given population and time period. Typically, d_i is estimated from the case-fatality rate associated with a particular health outcome. The remaining life expectancy, e_i, is age- and sex-specific (see Table 3.1), and case-fatality rates can also be specified as dependent on age and/or sex.

$$YLL = \sum_{i=1}^{n} d_i \times e_i$$

3.2.1.2 YLD

YLD is calculated for each health outcome by multiplying the number of incident cases (I_i) by the disability weight (DW_i) - a measure of the severity of the health outcome/disabling condition - and by the duration (D_i) of the health outcome. For example, if a health outcome has a disability weight of 0.25, this implies that a year living with this condition is similar to 75% of the value of a healthy life-year (or the loss of a quarter of a year due to ill health). All parameters can be specified by age and/or sex. The YLD for a disease is the sum of the YLD associated with all *n* health outcomes comprising the natural history for that disease, in a given population and time period.

$$YLD = \sum_{i=1}^{n} I_i \times DW_i \times D_i$$

3.2.1.3 Pathogen-based / incidence-based approach

We adopted the *pathogen* as the starting point for the disease burden calculation. This is opposed to the approach where one starts with a certain health outcome, such as cancer, and then assigns the burden of specific cancers to pathogens and other causes. When the pathogen is taken as a starting point, the focus of burden calculation is on all health outcomes that can be causally attributed to that specific pathogen. These outcomes may include various categories of disease; for example, health outcomes associated with *Salmonella* spp. infection include diarrhoea, Irritable Bowel Syndrome (IBS), and reactive arthritis. This approach gives justice to the potential long-term sequelae of infectious diseases, and permits a better understanding of the health benefits associated with the prevention of infections. The main disadvantage of the pathogen-based approach is a greater risk of double counting, with consequent over-estimation of the total disease burden.

As opposed to working with *prevalence* data, we calculate burden based on *incidence* data. In this way, all new cases of a particular disease are counted, and the burden associated with all health outcomes (including those that might occur in future years) that are attributable to the initial infection is included, and is assigned to the year of initial infection. Working with incidence data can lead to a better understanding of the possible future health gains from prevention initiatives that decrease the risk of transmission, and consequently reduce the incidence of infection. However, the incidence approach does not take into account the burden of disease among patients who have contracted a (chronic) infectious disease in the past, and still suffer from the health consequences (e.g., HIV and hepatitis B infection).

3.2.1.4 Under-estimation of incidence

It is important to establish whether the incidence data used for disease burden estimates adequately reflect the actual situation, or additional adjustment for under-ascertainment and/or under-reporting is needed (14, 15). *Under-ascertainment* refers to the extent to which incidence is under-estimated because there are cases in the community that do not get in contact with health services, such as their general practitioner. They may have no contact because infection is asymptomatic, or because they suffer from mild illness only. *Under-reporting* refers to those infected individuals who do contact health services, but whose disease status is incorrectly diagnosed or classified, or fails to be reported to the organisation responsible for surveillance.

Adjustment for both under-ascertainment and under-reporting can be done in a single step or in two steps, depending on the disease-specific data available. Appropriate multiplication factors (MFs) - with uncertainty intervals if available - were derived by disease surveillance specialists. These multiplication factors were based either on published studies or from analyses of relevant datasets, or on some combination of the two (see Appendix 2). Additionally, for a number of diseases (see Table 3.2), correction of the reported case numbers for the coverage of the surveillance system needed to be applied because the sentinel laboratory surveillance systems used do not cover the whole Dutch population.

3.2.1.5 Life expectancy, disability weights and durations

Life expectancy values are required for the calculation of YLL as well as YLD (i.e., for long-term sequelae that persist until death). Remaining life expectancy for those persons who die from an infectious disease or its complications was derived from standard life tables, as the age of these individuals was either known or could be approximated. In the GBD study, a standard life table (West Level 26) was adopted, with a life expectancy at birth of 82 years for women and 80 years for men (2, 16). This life table was selected because it contains the highest reported national life expectancy (82 years for Japanese women). We have chosen to use the West Level 26 as well (see Table 3.1).

Table 3.1 Life expectancy (*e*) of males and females by age group (*a*) (17).

	Standard *e*(*a*) West Level 26	
Age group	Males	Females
0	79.94	82.43
1-4	77.77	80.28
5-9	72.89	75.47
10-14	67.91	70.51
15-19	62.93	65.55
20-24	57.95	60.63
25-29	52.99	55.72
30-34	48.04	50.83
35-39	43.10	45.96
40-44	38.20	41.13
45-49	33.38	36.36
50-54	28.66	31.68
55-59	24.07	27.10
60-64	19.65	22.64
65-69	15.54	18.32
70-74	11.87	14.24
75-79	8.81	10.59
80-84	6.34	7.56
85+	3.54	4.25

The YLD for a given health outcome is weighted for the severity of illness using disability weights. A disability weight can range from 0 (perfect health) to 1 (death) and is typically based on the preferences of a panel that rates the relative undesirability of hypothetical health outcomes. These panels can include patients, medical experts, and lay people from the general population. The current research adopted the set of disability weights compiled for the BCoDE project, which were developed using a mix of Person-Trade-Off and more novel techniques (18), similar to the methods used by the GBD (4) and other disease burden assessments (19).

Disability durations for each health outcome, required for the calculation of YLD, were also adopted from the BCoDE project. These values were based on literature review and/or expert opinion.

3.2.1.6 Outcome trees

For all pathogens investigated, an 'outcome tree' was prepared in order to represent the natural history of disease, linking incident cases to all associated health outcomes, including sequelae and death. Outcome trees provide a structural representation of disease progression by ordering all relevant health outcomes associated with the pathogen along a time-line (see Figure 3.1), where the chance of developing a subsequent health outcome is quantified by a transition probability. The starting point is usually acute symptomatic infection (8, 9, 14). The health outcome 'asymptomatic infection' does not contribute to the disease burden, but may lead to symptomatic cases or sequelae later in life (e.g., hepatitis B infection). Dividing a single health outcome into multiple 'health states' (in terms of severity) was necessary for several pathogens, in order to better represent the burden when a particular health outcome is associated with differing degrees of disability, and possibly leads to different sequelae or to death, with transition probabilities that depend on severity. Pathogen outcome trees developed as part of the BCoDE project, which have been reviewed by disease specialists at the European Centre for Disease Prevention and Control (ECDC) and the National Institute for Public Health and the Environment (RIVM), were adopted (see online Appendix, www.rivm.nl/bibliotheek/rapporten/appendix150205001.pdf). For a number of diseases, default BCoDE values for certain parameters were modified to better reflect the Dutch context (see online Appendix, www.rivm.nl/bibliotheek/rapporten/appendix150205001.pdf).

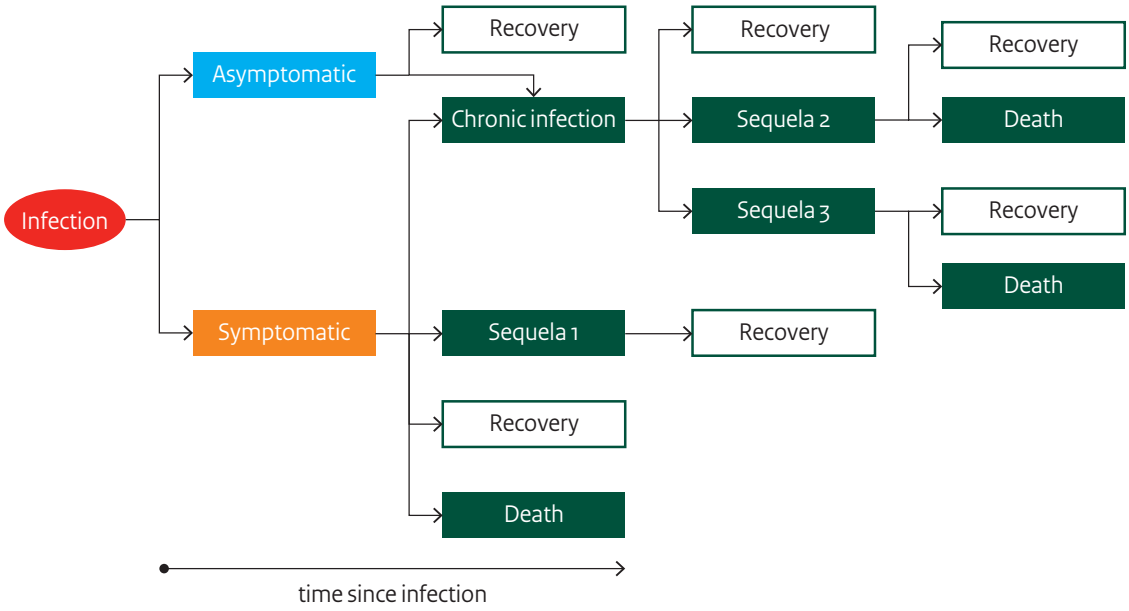
For two of the set of 11 foodborne diseases investigated, we estimated the burden for the period 2007-2011 based on the BCoDE approach; for the other nine we used the disease models developed by Havelaar et al. (13, 20). These researchers have considerable experience in burden estimation for foodborne diseases, and apply a sophisticated methodology that is designed specifically for foodborne diseases in the Netherlands.

3.2.1.7 Other decisions

Incidence data for most pathogens were stratified by sex and by 5-year age-group, except for the first two and last age-groups (<1 years, 1-4 years, 85+ years). However, for most foodborne diseases (other than shigellosis, listeriosis, toxoplasmosis, hepatitis A infection, and variant Creutzfeldt-Jakob disease), six different age-groups were used: <1 years, 1-4 years, 5-11 years, 12-17 years, 18-64 years and 65+ years. For listeriosis and hepatitis A infection, incidence was based on active surveillance with known age of cases. Congenital toxoplasmosis by definition occurs only in newborns (<1 year age-group), and acquired toxoplasmosis occurs predominantly in the age group 18–64 years. Incidence data for most diseases were adjusted using pathogen-specific multiplication factors to account for under-estimation of the number of cases by notification or other surveillance sources. The incidence of disease due to food-related pathogens (except for shigellosis and variant Creutzfeldt-Jakob disease) was based on several national cohort studies (13), rather than notification data adjusted by multiplication factors. For details regarding statutory notification and the various surveillance systems involved, see Appendix 1. For a number of pathogens, there was sufficient information to specify age- and/or sex-dependent MFs. For others, a single MF – either a point estimate or a range, depending on the information available – was applied for both sexes and all age-groups. Multiplication factors were chosen to either adjust in one step (under-estimation), or in two steps (under-reporting and under-ascertainment) (see Appendix 2).

In contrast to the majority of chronic diseases, the incidence of a given infectious disease may fluctuate greatly from year to year. These fluctuations may be due to infection attack rates that vary across seasons (e.g., as observed for influenza), or because of build-up of a pool of susceptibles over years (e.g., measles in the Netherlands). As a result, the estimated disease burden for a given year may not be representative of the 'typical' burden associated with the pathogen. As a partial solution to this issue, we estimated the annual incidence as the mean incidence over a five-year period (2007-2011) whenever possible. However, in the presence of an increasing or decreasing temporal trend, taking the mean incidence may lead to under- or

Figure 3.1 An outcome tree linking infection to all associated health outcomes. The outcome tree displays how individuals progress through various disease stages from acute infection through sequelae and death. The process is quantified by attaching probabilities to the arrows depicting transitions, and durations to the various health outcomes (9).



over-estimation, respectively, of the disease burden. For diseases exhibiting outbreak years (e.g., measles, pertussis, rubella, influenza, and Q fever), we discuss the magnitude of the impact of an outbreak year on our estimates.

Because data on the transition probability parameters and multiplication factors are often based on small samples or are limited in other ways, uncertainty in these values was modelled by specifying a probability distribution for the uncertainty and employing appropriate sampling techniques (see section 3.2.2 below).

Finally, adjustments such as age-weighting and discounting (2) can be integrated within the DALY framework. We chose not to implement either of these extensions, in agreement with GBD 2010 methods (10).

3.2.2 Software for burden estimation

For this report, we used version 0.94 of the BCoDE software toolkit (21) to estimate the burden for 23 diseases (i.e. excluding campylobacteriosis, cryptosporidiosis, giardiasis, hepatitis A infection, listeriosis, norovirus infection, salmonellosis, toxoplasmosis, and infection with STEC O157; see section 3.2.1.6). As the BCoDE toolkit implements the incidence- and pathogen-based approach (see section 3.2.1.3), all health outcomes including and subsequent to acute infection are taken into account in the burden computation. Uncertainty intervals around mean DALYs and other outputs were estimated using Monte-Carlo sampling methods; a total of 5000 iterations were run per disease model. Specifically, for multiplication factors specified as distributions (Uniform or PERT; the latter is a special case of the Beta distribution specified by three parameters: a minimum, most likely, and maximum value), the mean and 95% uncertainty interval were computed from the output distribution. In case of a constant multiplication factor, uncertainty around the point estimate value (no. cases x MF) was simulated as a Gamma distribution with shape parameter equal to the point estimate, and with scale parameter set to 1 (20).

3.3 Estimated annual disease burden in the Netherlands, 2007-2011

The total number of reported cases per year, the selected multiplication factors, and the estimated annual incident cases and deaths over the period 2007-2011 for all 32 diseases are provided in Table 3.2. Table 3.3 gives a comprehensive overview of the national burden estimates for each of the 32 diseases investigated, reporting several measures (YLD/year, YLL/year, DALYs/year, DALYs per 100 cases). Mean

Table 3.2 Total number of new cases in the years 2007-2011, multiplication factors (MFs) chosen to adjust for under-estimation, and the estimated annual number of new cases and deaths (averaged over the period 2007-2011 and adjusted for under-estimation), per disease.

Disease	Total number of new cases					MF(s) chosen (see Appendix 2)	Estimated annual number 2007-2011	
	2007	2008	2009	2010	2011		Infections	Deaths
Sexually transmitted infections								
Chlamydia (a)	35658	35658	35658	35658	35658	UR: 1.111	181481	0.002
Gonorrhoea *	1830	1969	2426	2815	3578	UE: 2.53	9195	0.03
Hepatitis B infection	227	219	208	197	159	UA: 1.33 UR: Uniform(1.20,1.22)	1124	14
Hepatitis C infection	44	45	52	47	68	UE: Uniform(1, 5.12)*29/30 + Pert(0, 47, 464.4)*1/30 (d)	1233	8
HIV infection (b)	1194	1246	1134	1093	855	UE: 1	1922	115
Syphilis *	660	793	711	696	545	UE: 4.21	5761	0.4
Vaccine-preventable diseases								
Diphtheria	0	0	0	0	0	n.a.	0	0
Invasive *H. influenzae* infection *	115	108	129	143	139	UE: Uniform(1.05,1.20)	143	11
Invasive meningococcal disease *	186	159	157	137	99	UE: 1.05	155	16
Invasive pneumococcal disease (e)	2648	2328	2408	2252	2496	UE: Uniform(1.05,1.20)	2729	410
Measles	10	109	15	15	50	UE: Uniform(11.11,14.93)	518	2
Mumps *	n.a.	n.a.	32	424	642	UA: 1.84 UR: 1	673	0.005
Pertussis *	7374	8745	6461	3733	5450	UE: 21.9 (0-9 yrs); 25.0 (>9 yrs)	155480	29
Poliomyelitis	0	0	0	0	0	-	0	0
Rabies	0	1	0	0	0	UE: 1	0.2	0.2
Rubella	1	2	7	0	1	UE: Uniform(11.11,14.93)	29	0.002
Tetanus	n.a.	n.a.	1	1	6	UE: Uniform(1.0,1.41)	3	0.3
Foodborne diseases								
Campylobacteriosis (c,e)	6731	6431	7256	8294	8547	See Havelaar et al. (13, 20)	95420	39
Cryptosporidiosis (c,f)	184	184	184	184	184	See Havelaar et al. (13, 20)	28100	2
Giardiasis (c,g)	2331	2142	1982	1821	1658	See Havelaar et al. (13, 20)	78960	2
Hepatitis A infection (c)	168	183	176	262	125	See Havelaar et al. (13, 20)	894	3
Listeriosis (c) - perinatal - acquired	66 6 60	52 1 51	79 3 76	77 4 73	88 9 79	See Havelaar et al. (13, 20)	72 5 68	5 1 4
Norovirus infection (c)	n.a.	n.a.	n.a.	n.a.	n.a.	See Havelaar et al. (13, 20)	655100	60
Salmonellosis (c,e)	1968	2576	1921	2291	2029	See Havelaar et al. (13, 20)	38820	40

Table 3.2 (continued) Total number of new cases in the years 2007-2011, multiplication factors (MFs) chosen to adjust for under-estimation, and the estimated annual number of new cases and deaths (averaged over the period 2007-2011 and adjusted for under-estimation), per disease.

Disease	Total number of new cases					MF(s) chosen (see Appendix 2)	Estimated annual number 2007-2011	
	2007	2008	2009	2010	2011		Infections	Deaths
Shigellosis (h)	389	438	411	522	577	UE: PERT(1.2,11.6,49.6)	7561	1
Toxoplasmosis (c) - congenital - acquired	n.a.	n.a.	n.a.	n.a.	n.a.	See Havelaar et al. (13, 20)	795 371 424	13 13 0
vCreutzfeldt-Jakob disease	0	0	1	0	0	UE: 1	0.2	0.2
Infection with STEC O157 (c)	83	45	57	51	65	See Havelaar et al. (13, 20)	2128	4
Respiratory diseases								
Influenza **	39028	73455	135170	18390	92887	UA: Uniform(4.12,5.13) UR: 1	331995	432
Legionellosis	322	337	252	467	312	UA: 1 UR: PERT(9.95,11.03,24.14)	4407	176
Q fever	168	1000	2354	504	81	UE: PERT(0.75,1.575,3.25) (0-14 yrs) PERT(2.4,5.04,10.4) (15+ yrs)	11271	18
Tuberculosis *	999	1013	1158	1068	1003	UA: 1 UR: Uniform(1.08,1.16)	16295	60

UE = under-estimation, UA = under-ascertainment, UR = under-reporting.

Notes: * Cases with unknown age and/or sex were imputed using the univariate method.

** Because the sex distribution of cases was unknown, we applied the sex distribution of the total population.

(a) Reported cases are assumed same for each year; representing the total of cases at centres for sexually-transmitted infections (2010) and cases at sentinel general practitioners (averaged over 2008-2011).

(b) Estimated annual number of cases also reflects adjustment for reporting delay.

(c) For these foodborne diseases, a different estimation method was used, see Havelaar et al., 2012 (13, 20).

(d) MF is a weighted sum derived from the estimated incidence of HCV among HIV-positive and HIV-negative MSM, weighted for the proportion of notified cases represented by the two respective groups. Note that the estimated annual incidence is quite uncertain (95% CI: 855-1662); this is due to the wide MF distribution specified for HIV-negative MSM, itself attributable to the wide uncertainty range in the incidence rate estimated for this group. This MF was only applied to males aged 20-69 years; for all other age groups and females, MF was set to 1.

(e) Corrected for coverage of the sentinel surveillance system: 25% coverage for invasive pneumococcal disease, 52% coverage for campylobacteriosis, and 64% coverage for salmonellosis.

(f) Calculated from the reported incidence rate for 2007; a constant incidence from 2007 onwards was assumed.

(g) Calculated from a linear regression model fitted to the reported incidence rate between 2001-2007.

(h) Total notified cases for 2011 includes 161 cases that were not culture-confirmed and perhaps should have not been included; this was due to the sudden popularity of PCR testing and culture-confirmation in 2011-12. Culture-confirmation has been legally required since 2013.

Table 3.3 Estimated annual burden in the period 2007-2011 for new cases of sexually-transmitted infections, vaccine-preventable diseases, foodborne diseases, and respiratory diseases in this period: mean (with 95% uncertainty intervals) YLD/year, YLL/year, DALYs/year, and DALYs/100 cases.

Disease	YLD/year	YLL/year	DALYs/year	DALYs/100 cases
Sexually transmitted infections				
Chlamydia	3551 (1470-7327)	0.1 (0.1-0.2)	3551 (1470-7328)	2.0 (0.8-4.0)
Gonorrhoea	1269 (666-2320)	2.0 (1.3-3.1)	1271 (668-2323)	14 (7-25)
Hepatitis B infection	268 (267-270)	241 (212-269)	509 (480-538)	157 (148-165)
Hepatitis C infection	2209 (1536-3026)	65 (45-95)	2274 (1600-3085)	749 (672-834)
HIV infection	3811 (3461-4175)	3176 (2889-3476)	6987 (6374-7622)	618 (564-675)
Syphilis	13 (9-17)	14 (10-18)	26 (20-35)	0.5 (0.3-0.6)
Vaccine-preventable diseases				
Diphtheria	0	0	0	n.a.
Invasive *H. influenzae* infection	103 (93-112)	337 (316-358)	439 (415-464)	308 (292-325)
Invasive meningococcal disease	77 (64-91)	988 (823-1159)	1065 (889-1250)	686 (638-733)
Invasive pneumoococcal disease	148 (146-150)	9296 (8767-9811)	9444 (8911-9961)	346 (327-365)
Measles	12 (11-13)	119 (91-145)	130 (103-157)	25 (20-30)
Mumps	3.4 (3.1-3.6)	0.3 (0.2-0.4)	3.7 (3.4-4.0)	0.5 (0.5-0.6)
Pertussis	1633 (1625-1641)	1602 (1593-1610)	3235 (3219-3251)	2.1 (2.1-2.1)
Poliomyelitis	0	0	0	n.a.
Rabies	0.01 (0.01-0.01)	10 (10-10)	10 (10-10)	5081 (5081-5081)
Rubella	0.04 (0.03-0.04)	0.10 (0.08-0.12)	0.14 (0.12-0.16)	0.5 (0.4-0.5)
Tetanus	0.07 (0.07-0.08)	4.3 (3.9-4.7)	4.4 (4.0-4.8)	137 (132-143)
Foodborne diseases				
Campylobacteriosis *	2780 (864-6274)	534 (333-809)	3314 (1286-6872)	3.5 (2.4-7.4)
Cryptosporidiosis *	53 (30-83)	22 (0.4-99)	75 (38-155)	0.3 (0.1-0.7)
Giardiasis *	121 (65-206)	29 (0.7-117)	150 (78-263)	0.2 (0.1-0.4)
Hepatitis A infection *	53 (37-83)	95 (57-158)	148 (96-237)	17 (13-21)

Table 3.3 (continued) Estimated annual burden in the period 2007-2011 for new cases of sexually-transmitted infections, vaccine-preventable diseases, foodborne diseases, and respiratory diseases in this period: mean (with 95% uncertainty intervals) YLD/year, YLL/year, DALYs/year, and DALYs/100 cases.

Disease	YLD/year	YLL/year	DALYs/year	DALYs/100 cases
Listeriosis *	50 (29-73)	109 (109-109)	158 (137-182)	219 (195-246)
- perinatal	33 (17-51)	81	114 (98-132)	2482 (2128-2862)
- acquired	17 (12-22)	27	44 (39-50)	65 (59-73)
Norovirus infection *	318 (209-470)	1329 (588-2461)	1647 (900-2783)	0.3 (0.1-0.4)
Salmonellosis *	913 (238-2456)	462 (402-526)	1375 (671-2877)	3.5 (2.3-10.9)
Shigellosis	163 (131-198)	33 (26-40)	196 (158-236)	2.6 (2.5-2.7)
Toxoplasmosis *	2534 (1114-4725)	1059 (600-1825)	3593 (1715-6601)	452 (383-583)
- congenital	1192 (485-2449)	1059 (681-1906)	2251 (1088-4322)	607 (450-942)
- acquired	1342 (630-2276)	0	1342 (627-2279)	317 (317-317)
vCreutzfeldt-Jakob disease	0.2 (0.1-0.3)	7.0 (6.8-7.1)	7.2 (7.1-7.2)	3581 (3540-3611)
Infection with STEC O157 *	23 (13-37)	115 (67-212)	138 (80-250)	6.5 (1.5-65)
Respiratory diseases				
Influenza	4090 (3993-4187)	4580 (4474-4687)	8670 (8468-8874)	2.6 (2.6-2.6)
Legionellosis	391 (351-435)	3892 (3447-4389)	4283 (3819-4805)	97 (90-105)
Q fever	1568 (1386-1755)	574 (508-642)	2143 (1897-2395)	48 (47-49)
Tuberculosis	126 (121-130)	2615 (2117-3138)	2741 (2241-3264)	233 (191-278)

* Burden estimated using the methods of Havelaar et al. (13, 20).

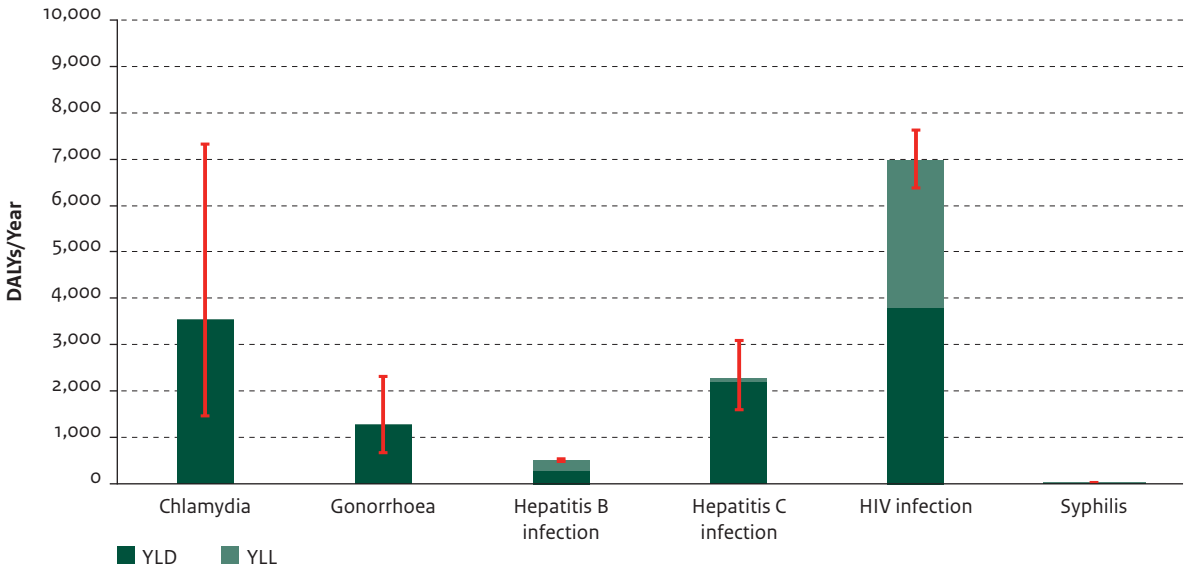
estimates with 95% uncertainty intervals are provided. In the following sections, we present the results for these 32 diseases grouped into four mutually exclusive disease categories: sexually-transmitted infections, vaccine-preventable diseases, foodborne diseases, and respiratory diseases.

3.3.1 Sexually-transmitted infections

Figure 3.2 shows the estimated average annual burden (in DALYs/year) in the period 2007-2011 for *new* cases of the six STI, with the YLD and YLL components shown separately, and uncertainty around the mean DALYs/year value indicated. The greatest disease burden within this disease group was estimated for HIV infection (6987 DALYs/year; largely driven by high mortality: 115 estimated deaths per year and 3176 YLL/year; note that HAART was not taken into account), followed by chlamydia (3551 DALYs/year), hepatitis C infection (2274 DALYs/year), and gonorrhoea (1271 DALYs/year). Please refer to Table 3.3 for the associated 95% uncertainty intervals.

The relationship between individual-level burden (DALYs/100 cases) and population-level burden (DALYs/year) is depicted in Figure 3.6. Syphilis has a relatively low burden at both the population and the individual levels. The other sexually-transmitted infections included have a relatively high population-level burden, but for chlamydia and gonorrhoea the burden at individual level is limited compared with HIV, hepatitis B and hepatitis C infection.

Figure 3.2 Estimated annual burden in the period 2007-2011 for new cases of sexually-transmitted infections in this period, with the YLD and YLL components shown separately.



Note 1: red lines indicate 95% uncertainty intervals.

Note 2: vaccination is available for hepatitis B infection only (in the Netherlands behavioural high-risk groups have been vaccinated since 2002, universal childhood vaccination has been introduced in 2011).

3.3.2 Vaccine-preventable diseases

The estimated average annual burden of the 11 vaccine-preventable diseases for *new* cases in the period 2007-2011 is depicted in Figure 3.3 For diphtheria and poliomyelitis, there was zero estimated disease burden because there were no cases reported in this period. For mumps, rabies, rubella, and tetanus, the disease burden was estimated to be very low (≤ 10 DALYs/year). Within this disease group, the highest burden was estimated for invasive pneumococcal disease (9444 DALYs/year; reflecting the large impact of mortality: 410 estimated deaths per year and 9296 YLL/year), followed by pertussis (3235 DALYs/year), and invasive meningococcal disease (1065 DALYs/year). The burden of pertussis and invasive meningococcal disease was localised in children; 48% and 72% of the total DALYs for these two diseases were in those aged <15 years.

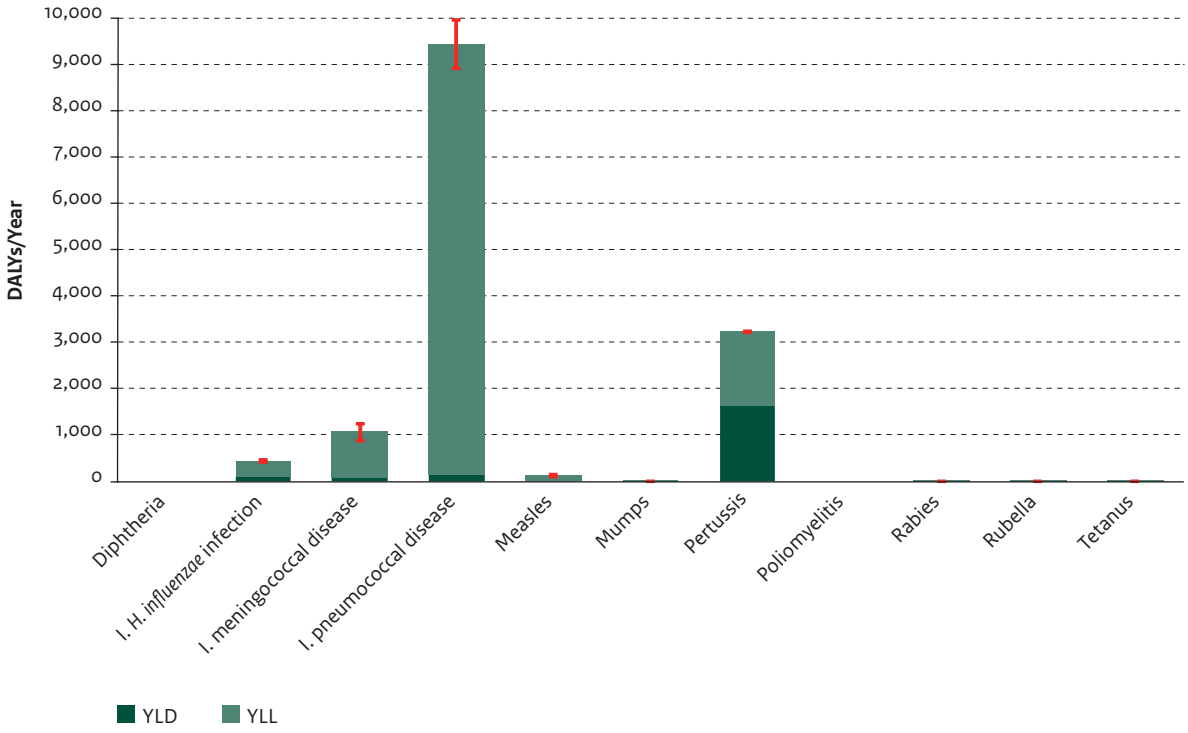
Of the four vaccine-preventable diseases with the lowest estimated burden at the population level (rubella, mumps, rabies and tetanus), the burden at the individual level for the former two diseases is low in comparison to the latter two diseases (Figure 3.7). Note that in this period there were no reported cases of *congenital* rubella syndrome (CRS), which has a high individual level burden. Among the vaccine-preventable diseases with a high estimated disease burden at the population level, the individual-level burden is also quite high (with the exception of pertussis).

3.3.3 Foodborne diseases

Figure 3.4 shows the estimated average annual burden in the period 2007-2011 for *new* cases of the 11 foodborne diseases considered. The greatest burden within this disease group was estimated for toxoplasmosis (3593 DALYs/year), campylobacteriosis (3314 DALYs/year), norovirus infection (1647 DALYs/year), and salmonellosis (1375 DALYs/year). For most foodborne diseases, the YLL component is relatively small.

The relationship between estimated burden at the individual level and the population-level burden is shown in Figure 3.8. For most foodborne diseases, the disease burden at the individual level is low. Among the diseases with a high burden at the individual level (i.e., variant Creutzfeldt-Jakob disease, toxoplasmosis, and listeriosis), the disease burden at the population level is comparatively limited (with the exception of toxoplasmosis).

Figure 3.3 Estimated annual burden in the period 2007-2011 for new cases of vaccine-preventable diseases in this period, with the YLD and YLL components shown separately.



Note 1: red lines indicate 95% uncertainty intervals.

Note 2: for the three invasive diseases there was only a vaccine available against certain serotypes in the period 2007-2011: *Haemophilus influenzae* serotype **b (Hib)**, meningococcal **C** and pneumococcal serotype **4, 6B, 9V, 14, 18C, 19F, 23F**.

3.3.4 Respiratory diseases

The estimated average annual disease burden in the period 2007-2011 for *new* cases of the four respiratory diseases is provided in Figure 3.5. Within this disease group, the greatest disease burden was estimated for influenza (8670 DALYs/year) and legionellosis (4283 DALYs/year). This was due to a high mortality for both diseases (432 (4580 DALYs/year) and 176 (3892 DALYs/year) estimated deaths per year, respectively). Mortality and YLL from influenza were disproportionally high in the elderly, with 23% of the total DALYs in those aged 75+ years. In contrast, 69% of the total burden of legionellosis was seen in the age group 45-69 years.

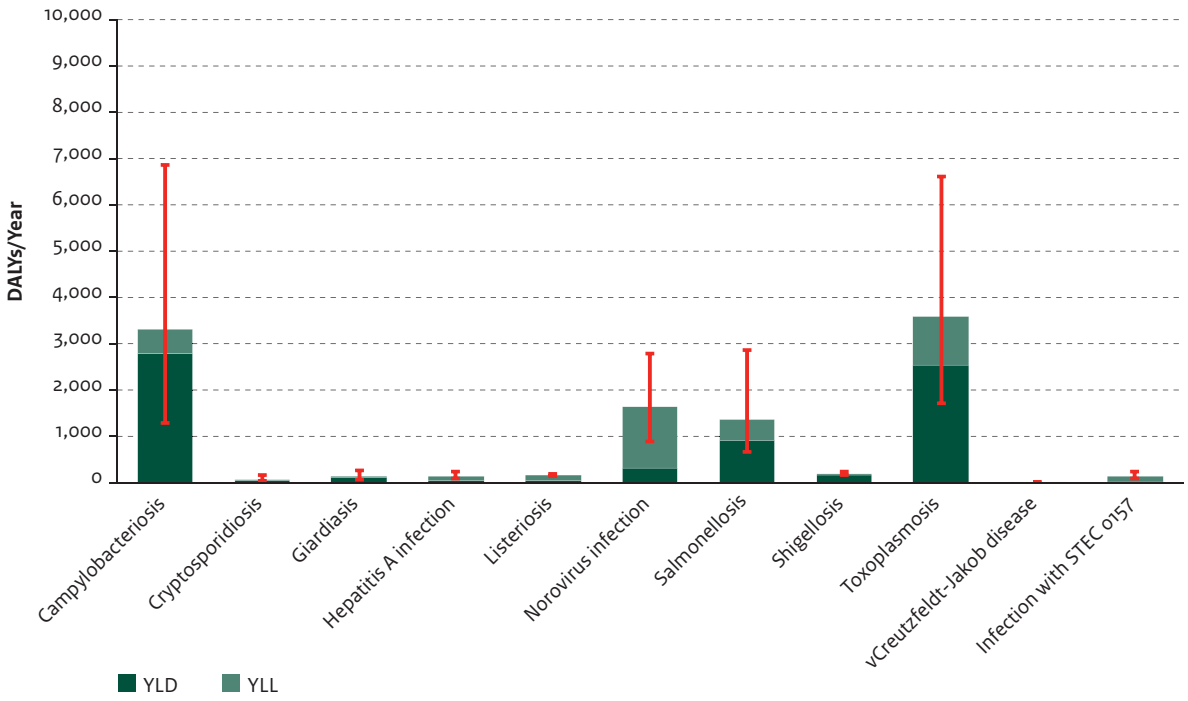
For all RD, the disease burden at the population level is considerably larger than that at the individual level (Figure 3.9); the individual-level burden for influenza in particular is relatively small (2.6 DALYs/100 cases).

3.4 Discussion

3.4.1 General discussion

This study is the first extensive investigation into the burden of infectious diseases in the Netherlands. We have compiled disease burden estimates for 32 diverse infectious diseases - using a common pathogen- and incidence-based approach - in a single report. For foodborne diseases, there is a long history of disease burden estimation (13). A diverse selection of infectious diseases, including several investigated here, were included in a previous comprehensive Dutch burden of disease study, but a different methodology was used (22, 23). Preliminary estimates for a number of the diseases have already been presented in a previous issue of the State of Infectious Diseases in the Netherlands, in 2010 (12). However, these preliminary estimates are not comparable with the current estimates, because the parameters of most disease models have been modified since then. We note that comparability will also be an issue for future burden estimates, as

Figure 3.4 Estimated annual burden in the period 2007-2011 for new cases of foodborne diseases in this period, with the YLD and YLL components shown separately.



Note 1: red lines indicate 95% uncertainty intervals.

Note 2: vaccination is available for hepatitis A infection only (only advised for certain groups in the Netherlands).

improvements to the methodology are a natural consequence of scientific progress, and disease models are continually being refined.

The estimated disease burden varied greatly across a set of pathogens that possess very different patterns of incidence and associated health outcomes. At the population level, invasive pneumococcal disease accounted for the highest annual burden, with an estimated 9444 DALYs/year, followed by influenza, at 8670 DALYs/year. At the individual level (i.e., as captured by the number of DALYs per 100 cases measure), rabies and variant Creutzfeldt-Jakob diseases had the highest burden, with 5081 and 3581 DALYs/100 cases respectively (but these diseases, together with diphtheria and poliomyelitis, occur with a very low incidence).

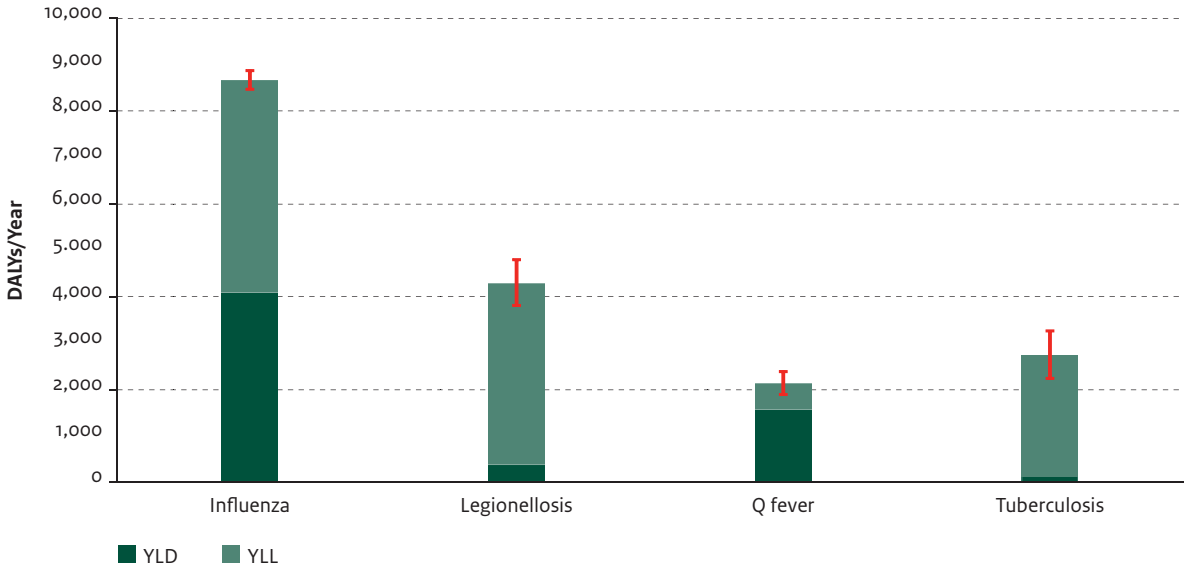
3.4.2 Discussion by disease group

3.4.2.1 Sexually-transmitted infections

For most STI, the estimated disease burden was relatively high, which is attributable to either a severe natural history (e.g., HIV, hepatitis B, and hepatitis C infection), or a high incidence (e.g., chlamydia and gonorrhoea). Because most sexually-transmitted infections are not notifiable, it was a challenge to get good estimates of the national incidence. Furthermore, most surveillance systems for sexually-transmitted infections focus on specific high-risk groups visiting clinics for sexually-transmitted infections. Therefore, estimating the degree of under-ascertainment for these diseases is also extremely difficult.

The current disease burden estimates only reflect the burden of *new* cases that occurred in the period 2007-2011. This means that, for diseases with chronic manifestations (e.g., hepatitis B, hepatitis C, and HIV infection), our estimation method did not take into account chronic cases that had been infected prior to this period. The relatively low disease burden of hepatitis B infection in the Netherlands is likely due to vaccination of high-risk groups, for example men who have sex with men (MSM), drug users, commercial sex workers, and heterosexuals who change partners frequently. This selective vaccination programme, begun in 2002, has been shown to reduce the incidence of acute hepatitis B infection, chiefly by preventing hepatitis

Figure 3.5 Estimated annual burden in the period 2007-2011 for new cases of respiratory diseases in this period, with the YLD and YLL components shown separately.



Note 1: red lines indicate 95% uncertainty intervals.

Note 2: vaccination is available for influenza and tuberculosis (in the Netherlands influenza vaccination is offered to high-risk groups and people aged 60 or older; the BCG (Bacillus Calmette-Guérin) vaccine against tuberculosis is only advised for certain groups).

B infections in MSM (24). Additionally, children at high risk (i.e., children with at least one parent born in a hepatitis B endemic country, and children whose mother tested positive for HBsAg) have been vaccinated against hepatitis B within the National Immunisation Programme (NIP) since 2003. Universal hepatitis B vaccination was introduced to the Dutch NIP in 2011; this is expected to affect future disease burden estimates. An explanation for the relatively high YLL estimated for hepatitis B as compared with hepatitis C infection is the difference in the age distributions of notified cases: hepatitis C cases tend to be somewhat older and therefore have a lower risk of progressing to severe sequelae before the end of their natural lifetime.

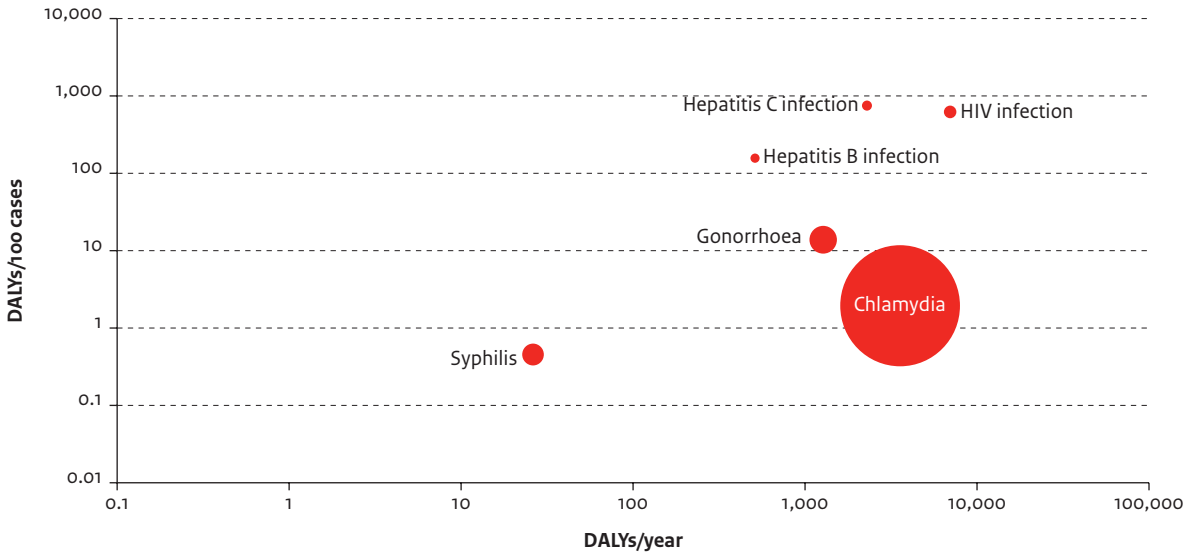
For HIV infection we used the estimated proportion of undiagnosed HIV infections (25) as a proxy for the proportion of asymptomatic HIV infections. This may have resulted in over-estimation of the number of symptomatic infections, and therefore the disease burden, because the undiagnosed proportion is based on living infected persons only. Symptomatic persons were more likely to die in the pre-HAART era compared with the post-HAART eras. We note that burden was based on a natural history model excluding the effects of HAART; a much reduced burden would be expected if the positive impact of treatment on mortality is taken into account. Nevertheless, for a severe disease such as HIV infection - with almost two thousand estimated new cases annually - inclusion in the list of notifiable diseases should perhaps be reconsidered. For HIV, and especially hepatitis C infection, treatment options have recently changed, or will change in the near future, which will lead to improved prognosis and a consequent reduction in burden.

The estimated relatively high disease burden of chlamydia is striking. Chlamydia was the most frequently diagnosed bacterial sexually-transmitted infection in 2012, and the positivity rate has increased in recent years, especially in the younger age groups (26). Unfortunately, the Chlamydia Screening Implementation (CSI), a large scale trial offering annual screening to more than 300,000 young people in Amsterdam, Rotterdam and South-Limburg showed that population based chlamydia screening in the Netherlands is unlikely to be cost effective (27).

3.4.2.2 Vaccine-preventable diseases

Universal vaccination in the Netherlands against diphtheria, pertussis, tetanus and poliomyelitis began in the 1950s with the introduction of the NIP, and was followed by vaccination against rubella (in

Figure 3.6 Ranking of sexually-transmitted infections by estimated burden at population (DALYs/year) and individual level (DALYs/100 cases) in the period 2007-2011.
The area of each bubble is proportional to the average number of estimated annual cases.



Note 1: both axes are on a logarithmic scale.

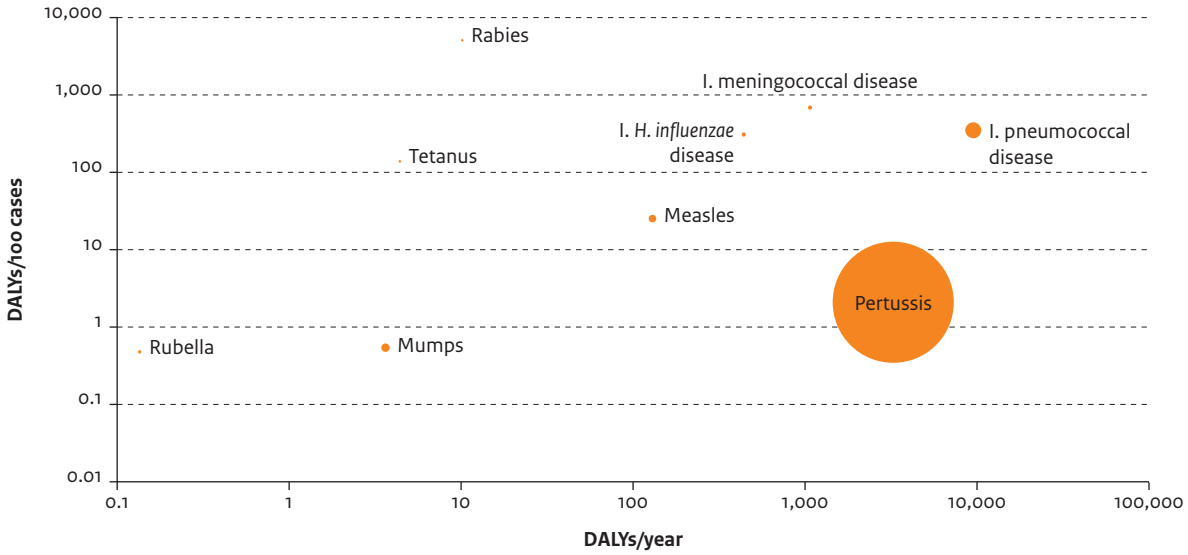
Note 2: vaccination is available for hepatitis B infection only (in the Netherlands behavioural high-risk groups have been vaccinated since 2002, universal childhood vaccination has been introduced in 2011).

1974), measles (1976), mumps (1987), and *Haemophilus influenzae* type b (1993). More recently, the NIP was expanded with vaccination against meningococcal C disease (2002), pneumococcal disease (2006), human papilloma virus (2009), and hepatitis B infection (2011). The estimated disease burden for most of the vaccine-preventable diseases is relatively low, testimony to the effectiveness of the NIP (28-30) which has achieved a high coverage (31). It is vital to maintain this attained level of coverage in the future to prevent resurgence of those vaccine-preventable diseases that are currently under control. The current burden estimates for vaccine-preventable diseases are consistent with the general perception that pertussis is not yet under control, and that vaccination against invasive bacterial disease (*H. influenzae*, meningococcal, and in particular pneumococcal infection) only protects against certain serotypes.

In 2012, which was an epidemic year for pertussis, the estimated disease burden was more than twice as high (6842 DALYs and 63 deaths) than the estimated annual burden in the period 2007-2011 (3235 DALYs/year and 29 deaths). Although the number of officially reported pertussis deaths (2 in the period 2007-2011 (32)) might be under-estimated to some extent, especially among older people, an annual average of 29 pertussis deaths during 2007-2011 and 63 deaths during 2012 is probably unrealistic for the Dutch situation. In comparison: in England 18 of 46 estimated pertussis deaths were officially reported and 9 annual pertussis deaths were estimated in total (33). Therefore, it is likely that we have somewhat over-estimated the disease burden of pertussis.

As mentioned before, current vaccines do not cover all *H. influenzae*, meningococcal and pneumococcal serotypes; however, our results illustrate the effectiveness of the NIP because the vaccine-preventable serotypes are under control. In the period 2007-2011, 30% of the burden of invasive *H. influenzae* disease was caused by serotype b (*Hib*), only 4% of the burden of invasive meningococcal disease was due to Men C (86% was caused by Men B, for which vaccination is not included in the NIP), and 25% of the burden of invasive pneumococcal disease was caused by a serotype covered by the 7-valent pneumococcal vaccine (PCV7) that was used until 2011. For invasive pneumococcal disease, for which vaccination was introduced in the NIP in 2006, this proportion decreased from 40% in 2007 to 15% in 2011. However, although pneumococcal conjugate vaccination decreases the occurrence of vaccine-type invasive pneumococcal disease, non-vaccine type invasive pneumococcal disease may increase

Figure 3.7 Ranking of vaccine-preventable diseases by estimated burden at population (DALYs/year) and individual level (DALYs/100 cases) in the period 2007-2011; diphtheria and poliomyelitis could not be included because there were no cases reported in this period.
The area of each bubble is proportional to the average number of estimated annual cases (50 cases were added to each bubble for visibility reasons).



Note 1: both axes are on a logarithmic scale.

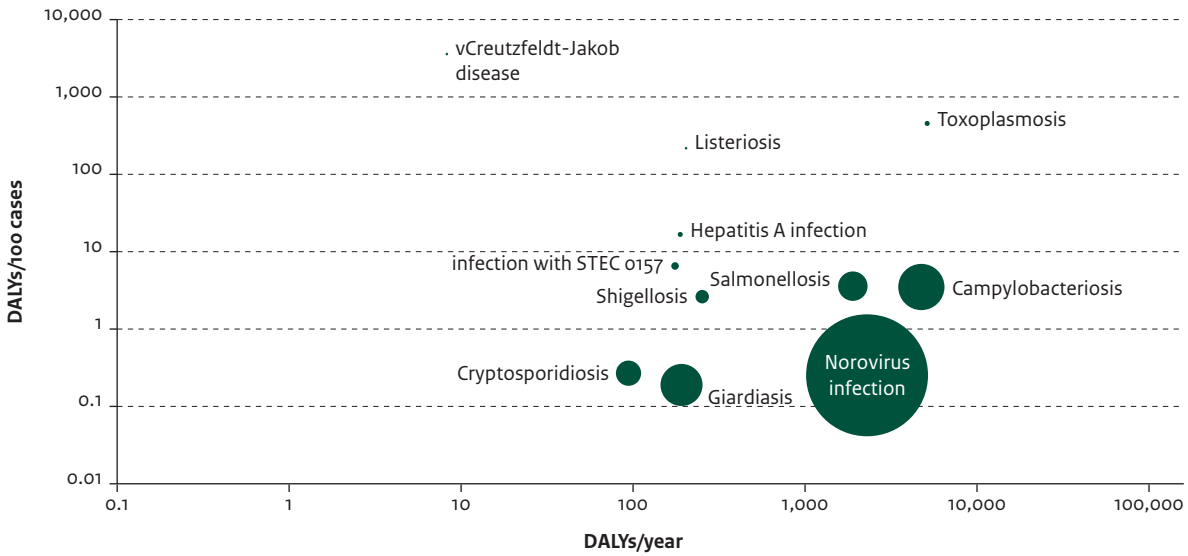
Note 2: for the three invasive diseases there was only a vaccine available against certain serotypes in the period 2007-2011: *Haemophilus influenzae* serotype **b (Hib)**, meningococcal **C** and pneumococcal serotype **4, 6B, 9V, 14, 18C, 19F, 23F**.

due to serotype replacement, thereby reducing the overall benefit of vaccination (34).

Invasive pneumococcal disease occurs more frequently among the elderly. Due to the ageing of the population - it is predicted that more than a quarter of the Dutch population will be aged 65 or over in 2060 (35) - the disease burden for (invasive) pneumococcal disease is expected to increase in the coming years. Vaccination of the elderly against pneumococcal disease might mitigate this increase. A randomised placebo-controlled trial with approximately 85,000 participants (CAPITA study) showed that PCV13 significantly decreased vaccine-type community-acquired pneumonia (CAP) by 46% in adults of 65 years or older, and vaccine-type invasive pneumococcal disease was significantly reduced by 75% (36). The actual disease burden for pneumococcal disease is even higher than presented, because we computed the burden for the *invasive* form of pneumococcal disease only; the burden of otitis media and pneumonia attributable to non-invasive pneumococcal infection was not included. Non-invasive forms of *H. influenzae* and meningococcal infection were also excluded, meaning that comparison of the disease burden with other vaccine-preventable diseases or with infections from other disease groups should take this restriction to invasive forms into account. Mortality, and thus burden, associated with invasive pneumococcal disease might have been over-estimated, because Dutch data indicates a mortality risk of 12% (34), whereas the mortality risk in the disease model was set to 10-20%.

For the vaccine-preventable diseases the disease burden per year can fluctuate enormously due to outbreaks that occur mainly among members of orthodox religious communities, who do not participate in vaccination programmes (37-40). The estimated disease burden due to measles in the epidemic year 2013 was, at 9319 DALYs, 139 times higher than the annual burden in the inter-epidemic period 2001-2012 (67 DALYs/year). The total estimated disease burden for the poliomyelitis outbreak in 1992/1993 was 442 DALYs (71 reported cases), whereas there were no cases and thus no burden in the period 2007-2011. The rubella outbreak in 2004/2005 had a total estimated disease burden of 8449 DALYs (415 reported cases), compared with <1 DALY/year in the period 2007-2011; 99.7% of this estimated burden could be attributed to CRS.

Figure 3.8 Ranking of foodborne diseases by estimated burden at population (DALYs/year) and individual level (DALYs/100 cases) in the period 2007-2011.
The area of each bubble is proportional to the average number of estimated annual cases (200 cases were added to each bubble for visibility reasons).



Note 1: both axes are on a logarithmic scale.

Note 2: vaccination is available for hepatitis A infection only (only advised for certain groups in the Netherlands).

Prevention of CRS was the principal motivation for introducing rubella vaccination. For mumps, the estimated disease burden was quite low despite the relatively high number of reported cases in the period 2007-2011. Even in the epidemic year 2011, the estimated disease burden for mumps remained low (6 DALYs), due to the fact that the risk of severe disease and mortality is relatively low.

3.4.2.3 Foodborne diseases

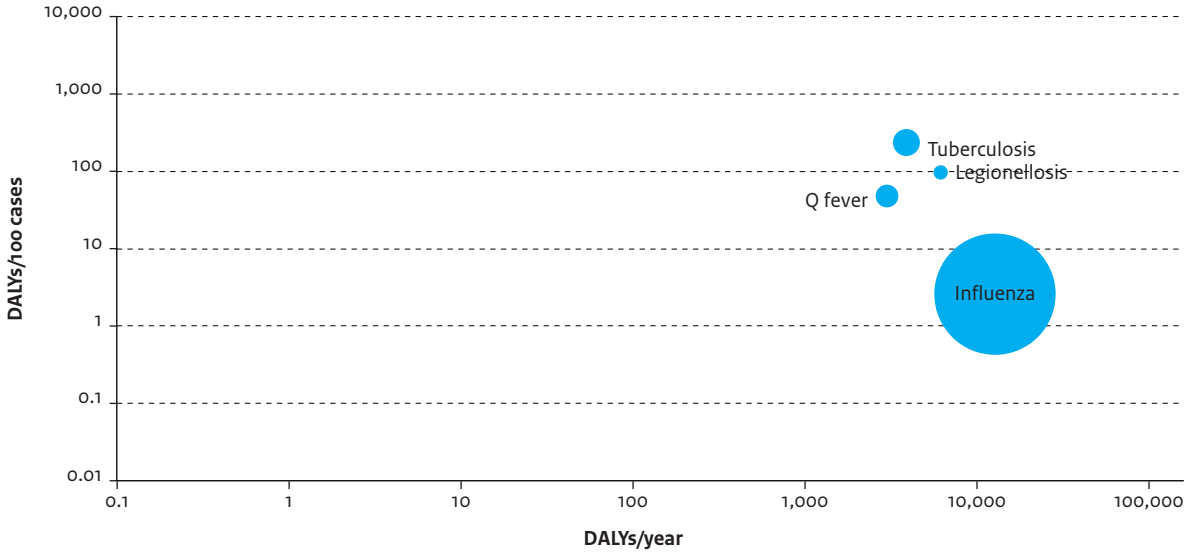
Of the foodborne diseases, the highest annual burden within the period 2007–2011 was estimated for toxoplasmosis, campylobacteriosis, norovirus infection, and salmonellosis (3593, 3314, 1647, and 1375 DALYs/year, respectively). The observed high population-level burden (as measured by DALYs/year) of the aforementioned four diseases is mainly driven by the large number of persons infected. The burden estimates for these four diseases, although based on the average incidence over a 5-year period, are comparable to previously published estimates for the year 2009 only: 3620, 3250, 1480, and 1270 DALYs for toxoplasmosis, campylobacteriosis, norovirus infection, and salmonellosis respectively (13). The mean estimated individual-level burden for foodborne diseases other than variant Creutzfeldt-Jakob disease, toxoplasmosis, and listeriosis is very low (≤17 DALYs/100 cases).

In the burden estimation approach developed by Havelaar et al. (13) (which we applied to all foodborne diseases except variant Creutzfeldt-Jakob disease and shigellosis), transition probabilities for the severity of disease were integral to the burden calculation for several foodborne diseases; for others, separate incidence estimates were made for cases in the general population, cases visiting their general practitioner, and hospitalised patients. The latter method makes use of available national cohort studies for a number of health outcomes (incidence derived from population-wide studies, general practitioner visits, hospital admissions), which are attributed to different pathogens through laboratory examination of faecal specimens. The two approaches are equivalent if the transition probabilities are derived from the same national data sources.

3.4.2.4 Respiratory diseases

The estimated disease burden for most of the respiratory diseases is relatively high, reflecting simultaneously the large impact of mortality and the large number of incident cases (e.g., influenza). Despite recommended vaccination against influenza for high-risk groups and people aged 60 or older, this disease is associated with significant disease burden.

Figure 3.9 Ranking of respiratory diseases by estimated burden at population (DALYs/year) and individual level (DALYs/100 cases) in the period 2007-2011.
The area of each bubble is proportional to the average number of estimated annual cases.



Note 1: both axes are on a logarithmic scale.

Note 2: vaccination is available for influenza and tuberculosis (in the Netherlands influenza vaccination is offered to high-risk groups and people aged 60 or older; the BCG (Bacillus Calmette-Guérin) vaccine against tuberculosis is only advised for certain groups).

As for many vaccine-preventable diseases, incidence and thus the disease burden of influenza and Q fever can fluctuate enormously per year. The burden of Q fever in 2009 (the year with the most incident cases due to an outbreak that started in 2007) was estimated at 6162 DALYs; this can be compared with the estimated annual burden of 2143 DALYs/year in the period 2007-2011. For influenza, 2009 (the year of the H1N1 pandemic) was also the year with the most reported cases within this period. The estimated disease burden for 2009 was almost twice as high (16,378 DALYs) as the estimated average annual burden for the period 2007-2011 (8670 DALYs/year). Note that the H1N1 pandemic year incidence was included when calculating the annual average incidence for the period 2007-2011.

The estimated disease burden for legionellosis is considerable; this could be due to several factors. Firstly, the large legionellosis burden may be attributable to over-estimated incidence, due to the relatively high multiplication factor derived from a combination of Dutch data and a German study on community-acquired and hospitalised pneumonia patients (41). The proportion of legionellosis among pneumonia cases reported in the literature can vary substantially (41-43), and because pneumonia occurs frequently in the population, the proportion assumed can have a significant effect on the estimated incidence of legionellosis. Furthermore, legionellosis often has a more severe course than other respiratory diseases (e.g., Q fever), and is therefore likely to be notified earlier.

Secondly, the Dutch surveillance system is considered to be of high quality (44, 45), and the number of reported cases of legionellosis in the Netherlands is relatively high compared with other countries (46). Routine use of the *Legionella pneumophila* urinary antigen test has become standard of care in patients with severe CAP in many Dutch hospitals (47).

Thirdly, in the period 2007-2011, 40% of the reported legionellosis cases (range 32% in 2010 to 46% in 2007) were travel-related and thus were likely to have been acquired abroad. In this period, 43% of the estimated disease burden comprised travel-related legionellosis, which cannot be prevented through the implementation of national control measures. However, the Netherlands actively participates in the European Legionnaires' Disease Surveillance Network (ELDSNet), which aims to prevent and control such travel-associated cases. The increase of legionellosis in 2010, the year with the lowest proportion (32%) of travel-related legionellosis cases within our study period, may have

been related to weather conditions (i.e., the unusually hot summer of 2010, which was followed by extensive rainfall) or to environmental factors (46, 48, 49). This exceptional year 2010 had a marked effect on the annual disease burden estimate; the burden in 2010 was 5863 DALYs compared with 4283 DALYs/year for the total period 2007-2011.

There are several limitations to the estimated burden of tuberculosis. Firstly, migration patterns have considerable influence on tuberculosis incidence. In recent years, the proportion of patients with extrapulmonary tuberculosis (which can differ in clinical severity from pulmonary tuberculosis) has increased (50), and is notably higher than in other European countries (51). This is due to an increased number of imported cases among asylum seekers originating from Somalia (50). Such recent changes in clinical severity are not captured by the disability weights used in the current tuberculosis disease model. Secondly, we note a risk of double counting of active tuberculosis cases. The number of active tuberculosis cases that develop from latent infection is determined by the disease model, by first back-calculating the total number of infections from the number of reported cases. However, reported cases actually represent a mixture of active tuberculosis cases following both primary and latent infection, and therefore some active tuberculosis cases following latent infection may effectively be 'counted twice'. Finally, the transition probability by which patients progress to active tuberculosis following primary infection (specified as the range 5-10%) is expected to be lower for the Netherlands compared with other countries due to the practice of screening and preventive treatment of latently infected tuberculosis contacts and of other high risk groups. Through preventive treatment, the risk of developing active tuberculosis can be reduced by 60-90% (52).

3.4.3 General limitations

Several disease-specific limitations have already been mentioned in the disease group-specific sections above. One important additional remark is that we have set disease model parameters in collaboration with experts to ensure the plausibility of the estimated disease burden. This may have introduced bias, because diseases for which preliminary burden calculations were high received more attention and provoked more discussion regarding model parameters compared with diseases with a low estimated burden. Researchers conducting disease burden studies in the future are therefore advised to strengthen consistency checking among disease models.

Secondly, burden estimates are limited by the accuracy and comprehensiveness of the pathogen outcome trees specified. By linking all health consequences causally to the initial infectious event (i.e., acute infection), the total estimated health burden associated with the pathogen is dependent on the correctness of the model. On the one hand, if the outcome tree omits a relevant health outcome, or the transitional probability of developing a certain sequela is too low, then the disease burden would be under-estimated. On the other hand, if for some health outcomes the specified transition probabilities and/or disability weights are too high, the disease burden could be over-estimated. Model parameters are sometimes very uncertain and can change over time, thus continuous updating of the disease models will be necessary. In addition, most parameters (i.e., case-fatality rates, transition probabilities of progressing to severe sequelae) were derived from studies among reported cases, and so applying the same parameters also to non-reported cases may not always be correct.

For almost all of the diseases investigated, adjustment for under-ascertainment/reporting of notified cases was carried out via age- and sex-independent multiplication factors, because there was insufficient data to specify stratified multiplication factors. As a consequence, sex- and/or age-groups with relatively more notified severe cases may be over-represented, and groups with fewer notified severe cases may be under-represented (8). Such bias would have greater consequences for those diseases with long natural histories. Furthermore, multiplication factors specific to the Dutch situation were not always available, and were therefore necessarily based on international studies. In addition, multiplication factors may have been derived from very specific situations (e.g., during an outbreak year), and may not be applicable to the period 2007-2011.

Fourthly, co-morbidity with chronic disease or co-infection with other pathogens was not considered. Various methods for adjusting disability weights to capture the severity of simultaneous health outcomes, and for adjustment of YLL in the case of fatal comorbidity have been explored, but have not yet reached a satisfactory level of development to permit straightforward incorporation in the current methodology.

Variability in annual incidence over time was not incorporated, since we calculated the mean inciden-

ce over the period 2007-2011. Averaging incidence across years does not affect the uncertainty regarding the number of incident cases – and hence the disease burden – for an 'average' year; however, it does conceal potentially interesting variation, such as outbreaks. For several diseases with periodic variation in incidence (e.g., measles, pertussis), we have discussed the differences in estimated burden between outbreak years and other years (see section 3.4.2.2 for vaccine-preventable diseases and section 3.4.2.4 for respiratory diseases).

Finally, the current national disease burden estimates were derived under the 'steady-state' assumption; i.e., both the transmission and pathogenicity of infections and the size and age-structure of the susceptible population were considered static. Demographic change, due to population ageing and changing migration patterns, diminishing natural immunity to certain infectious agents, and new interventions would be expected to influence the projected future disease burden of most, if not all, pathogens (53, 54). Therefore, caution must be exercised when extrapolating the estimated burden derived from the average number of cases over the recent period 2007-2011 to future years.

3.5 Conclusions

This report presents the estimated national disease burden for 32 diseases based on the estimated annual incidence in the period 2007-2011. The estimates depend on the parameters and assumptions inherent in the disease models, and also on the incidence in this specific time frame. Therefore, the results represent a first attempt to assess the burden of infectious diseases in the Netherlands. It is important to develop the disease models further and to describe trends in disease burden over time; the latter may be a more relevant research goal for some investigators than the comparison of diseases with each other, as even a standardised burden estimate may not capture all the essential information for assessing public health impact. The current approach to burden estimation may be useful for other diseases within the four disease groups considered in this report (e.g., human papilloma virus infection, infection with *Helicobacter pylori*), and for other disease groups, such as vector-borne diseases (e.g., Lyme disease (55)).

Disease burden methodology provides a new perspective on infectious disease surveillance data; it avoids the devotion of excessive attention to rare infections with dramatic outcomes and the neglect of common disorders. In general, the disease burden also reflects the balance between threats and the effectiveness of preventive strategies, such as vaccination. A low estimated burden for those diseases included in the NIP stresses the need for the continued support of these strategies, whereas a high burden for diseases covered by the NIP suggests that additional preventive measures may be needed. For prioritising interventions and preventive measures, estimates of trends in disease burden are undoubtedly informative and may reflect the overall impact of control efforts. Together with other factors such as the availability of preventive strategies, costs, and public perception, they can be useful in defining public health policy.

3.6 Call for feedback

As this report represents the first comprehensive attempt to assess the burden of infectious diseases in the Netherlands, we very much welcome input to guide further development of the methodology. Please send your suggestions regarding model parameters, assumptions, and any other remarks to Paul Bijkerk (paul.bijkerk@rivm.nl).

Online appendix

See separate file 'appendix150205001.pdf. www.rivm.nl/bibliotheek/rapporten/appendix150205001.pdf

3.7 Literature

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3.8 Appendix 1: surveillance data

General surveillance

Notification of infectious diseases started in the Netherlands in 1865. These notification data, registered nowadays in OSIRIS, are an important source of information on the occurrence of infectious diseases in the Netherlands. In December 2008, a new law ("Wet Publieke Gezondheid") was passed, which meant that physicians, laboratories and heads of institutions are required to report 42 notifiable infectious diseases to the Public Health Services (see Table A.1 below) (56). However, for several diseases there is under-ascertainment, under-reporting and delay in reporting (57). Because of this under-estimation, it is important to consider the use of multiplication factors in burden of disease calculations. Note that several diseases (e.g., mumps) only became notifiable at the end of 2008, but our burden calculations were carried out for the period 2007-2011.

Disease-specific surveillance

Chlamydia, gonorrhoea, syphilis: national surveillance at clinics for sexually-transmitted infections (STI) and STI surveillance in general practice
The national STI surveillance system is organised into eight regions. In each region there is one STI clinic responsible for the coordination of STI surveillance. A total of 26 STI clinics provide low-threshold STI/HIV testing and care, free of charge, targeted at high-risk groups. Currently, people who satisfy one or more of the following criteria are considered to be at high risk of STI acquisition: (1) report STI-related symptoms; (2) notified or referred for STI testing; (3) are aged below 25 years; (4) MSM; (5) are involved in commercial sex work; (6) originate from an HIV/STI endemic area; (7) report three or more sexual partners in the previous six months; and (8) report a partner from a high-risk group. Attendees are mandatorily tested for chlamydia, gonorrhoea and syphilis and there is an opt-out policy for HIV testing. All consultations and corresponding diagnoses are reported online to RIVM for surveillance purposes. This process is facilitated by a web-based application (SOAP) (26).

Data from general practitioners, who perform the bulk of STI consultations, are extrapolated from the Netherlands Information Network of General Practice (LINH). This sentinel surveillance network covers approximately 2.5% of the total Dutch population. Ailments and illnesses are recorded using the International Classification of Primary Care (ICPC) (26).

The number of cases with congenital syphilis was based on immunoglobulin M (IgM) diagnostics offered by RIVM for neonates and young infants (< 1 year) who are suspected of being infected with congenital syphilis (26).

HIV infection: national registration of patients at HIV treatment centres
HIV-infected individuals are registered at 26 recognised HIV treatment centres and are entered in an anonymous HIV/AIDS reporting system for patients entering care. These data are collected by Stichting HIV Monitoring (the Dutch HIV monitoring foundation) (26).

Invasive *H. influenzae* disease and invasive pneumococcal disease: Netherlands Reference Laboratory for Bacterial Meningitis (NRBM)
The Netherlands Reference Laboratory for Bacterial Meningitis (NRBM) is a collaboration between RIVM and the Academic Medical Centre of Amsterdam (AMC). All microbiological laboratories throughout the Netherlands send, on a voluntary basis, *H. Influenzae* isolates from blood and cerebrospinal fluid (CSF) to the NRBM for further typing. Nine sentinel laboratories throughout the country, covering approximately 25% of the Dutch population, are asked to send all *S. pneumoniae* isolates from blood and CSF to the NRBM for further typing (58).

Campylobacteriosis, cryptosporidiosis, giardiasis, norovirus infection, salmonellosis, toxoplasmosis: SENSOR study, sentinel laboratory surveillance, and PIENTER study
Data from the SENSOR study (59) were used to estimate the incidence of gastroenteritis in the Dutch population. Data were updated to reflect the period 2007-2011, based on trends in laboratory surveillance data. The Dutch laboratory surveillance network for gastroenteric pathogens consists of 15 out of the 16 regional public health laboratories serving mainly general practices but also hospitals. For each patient, a standardised form is completed and sent to RIVM. This surveillance network has a 52.7% regular coverage and 61.8% effective coverage of the Dutch population. Coverage is based on the number of stools screened, which is used as a proxy for the number of consulting gastroenteritis cases. The coverage of the surveillance network differs by pathogen (60). Norovirus infection is not included in case-based laboratory surveillance and therefore trends in hospitalisation data for viral gastroenteritis

Table A.1 Diseases that have been notifiable since 2008 (56).

Disease	Year of introduction of mandatory notification
Group A*	
Smallpox	2004
Polio†	1923
Severe acute respiratory syndrome (SARS)	2003
Group B1*	
Avian influenza	2008
Diphtheria†	1872
Plague	1897
Rabies†	1928
Tuberculosis†	1980
Viral haemorrhagic fever	1977
Group B2*	
Typhoid fever	1872
Cholera	1872
Hepatitis A†	1950
Hepatitis B†	1950
Hepatitis C†	1998
Invasive group A streptococcal disease	2008
Pertussis†	1975
Measles†	1975
Paratyphus A, B and C	1928
Rubella†	1950
Shigellosis†	1873
Shiga toxin-producing *E. coli* / enterohemorrhagic *E. coli* infection†	1999
Foodborne infections	1975
Group C*	
Anthrax	1975
Mumps†	2008
Botulism	1984
Brucellosis	1928
Yellow fever	1928
Hantavirus infection	2008
Invasive *Haemophilus influenzae* type b disease†	2008
Invasive pneumococcal disease (for children)†	2008
Legionnaires' disease†	1987
Leptospirosis	1928
Listeriosis†	2008
Malaria	1940
Meningococcal disease†	1905
MRSA-infection, clusters of	2008
Psittacosis	1940
Q fever†	1975
Tetanus†	2008
Trichinosis	1975
West Nile fever	2008
Creutzfeldt-Jakob disease†	2002

* Diseases in category A have to be reported directly by telephone following a laboratory-confirmed diagnosis. Diseases in the categories B1, B2 and C must be reported within 24 hours or one working day after laboratory confirmation. In each of the latter three categories, various intervention measures can be enforced to prevent spreading of the disease.
† Diseases included in this chapter.

was used. For toxoplasmosis the annual incidence was estimated based on seroprevalence data from the Pienter study (61).

Listeriosis: enhanced surveillance

From 2005 to December 2008, a voluntary surveillance system for *Listeria monocytogenes* was in place in the Netherlands, in which all public health laboratories were requested to report positive cultures of *L. monocytogenes* to the local public health authorities. Laboratories were also asked to continue sending isolates from patients with meningitis or sepsis to the Dutch Reference Laboratory for Bacterial Meningitis (RBM). As part of the surveillance procedure, RBM forwards all isolates to RIVM. Isolates from patients with other symptoms can be sent directly to RIVM for serotyping and PFGE. Patients were interviewed by health authorities regarding their medical history, illness and exposure to possible risk factors in the 30 days before the date of illness onset. In December 2008, listeriosis became a mandatory notifiable disease. The voluntary questionnaire was replaced by a notification questionnaire; the voluntary system for the submission of isolates remained unchanged.

Influenza: Dutch Sentinel General Practice Network

Within the Sentinel General Practice Network of the Netherlands Institute for Health Services Research (NIVEL), general practitioners submit reports on a weekly (or annual) basis on the occurrence of diseases, events and treatments that are not covered by routine registration. The network covers approximately 0.8% of the total Dutch population, and is representative with regard to age, sex, region and degree of urbanisation. For influenza-like-illness (ILI), the following definition is used: an illness with an acute onset (prodromal stage of ≤4 days), fever (defined as a rise in rectal temperature to at least 38 °C), and at least one of the following symptoms: cough, rhinitis, sore throat, frontal headache, retrosternal pain, and myalgia (62). Swabs from a subset of ILI patients are taken for virological analysis to determine the true influenza positivity rate.

Tuberculosis: Netherlands Tuberculosis Register (NTR)

The Netherlands Tuberculosis Register held by KNCV Tuberculosefonds/RIVM contains all registered tuberculosis patients who have been treated or diagnosed in the Netherlands. The NTR is an anonymous, current database in which relevant information on the occurrence of tuberculosis in the Netherlands and the results of treatment are recorded. It involves all forms of tuberculosis; i.e., both pulmonary and extrapulmonary tuberculosis (50).

3.9 Appendix 2: rationale for multiplication factors

Table A.2 Rationale for multiplication factors.

Disease	MF(s) chosen	Explanation
Sexually transmitted infections		
Chlamydia	UA: 1 UR: 1.111	We assumed 10% under-reporting because some people get tested in other settings (gynaecologist, directly at laboratory, self-test?).
Gonorrhoea	UE: 2.53	MF is based on absolute numbers from SOAP and LINH.
Hepatitis B infection	UA: 1.33 UR: Uniform(1.20,1.22)	For under-ascertainment, we assume that 75% of all symptomatic cases is reported; this is based on England and Wales data from 1992-1996 (63). For under-reporting, the lower bound was derived from a 1996 audit, and the upper bound was taken from Swaan et al.'s (unpub.) study of reporting completeness (weighted mean of 83.1%) by 13 Zuid-Holland laboratories, 2005-2010.
Hepatitis C infection	UE: Uniform(1, 5.12)*29/30 + PERT(0, 47, 464.4)*1/30	MFs were calculated for MSM only, and it was assumed that there is no under-estimation for non-MSM risk groups. MF is a weighted sum derived from the estimated incidences of HCV among HIV-positive and HIV-negative MSM, weighted for the proportion of notified cases represented by the two respective groups. Note that the estimated annual incidence is quite uncertain (95% CI: 855-1662); this is due to the wide MF distribution specified for HIV-negative MSM, itself attributable to the wide uncertainty range in the incidence rate estimated for this group. This MF was only applied to males aged 20-69 years; for all other age groups and females, MF was set to 1.
HIV infection	UE: 1	No MF is available to estimate actual incidence from diagnoses. Because it takes about two years for the HIV diagnosis register to become complete, we corrected for reporting delay (to estimate completeness as of 2012, the number of diagnoses in 2011 was multiplied by 11% and the number of diagnoses in 2010 was multiplied by 3%).
Syphilis	UE: 4.21	MF based on absolute numbers from SOAP and LINH.
Vaccine-preventable diseases		
Diphtheria	not applicable	not applicable
Invasive *H. influenzae* infection	UE: Uniform(1.05,1.20)	Approximately 83-95% of isolates are sent to the Netherlands Reference Laboratory for Bacterial Meningitis and this leads to an MF of 1.05 to 1.20.
Invasive meningococcal disease	UE: 1.05	Meningococcal disease is a notifiable disease and notifications are cross-checked with data of the Netherlands Reference Laboratory for Bacterial Meningitis. Therefore coverage will be very high, around 95%. This leads to an MF of 1.05.
Invasive pneumococcal disease	UE: Uniform(1.05,1.20)	Approximately 83-95% of isolates are sent to the Netherlands Reference Laboratory for Bacterial Meningitis; this leads to an MF of 1.05 to 1.20.

Table A.2 (continued) Rationale for multiplication factors.

Disease	MF(s) chosen	Explanation
Measles	UE: Uniform(11.11,14.93)	According to Van Isterdael et al. (2004) (64) 9% of all measles cases were reported (MF=11.11). Wallinga et al. (2003) (65) estimated that 6.7% of all infections were reported (MF=14.93). Both estimates are based on the 1999/2000 measles outbreak in the Netherlands.
Mumps	UA: 1.84 UR: 1	Under-ascertainment MF based on Greenland et al. (2010) (66). No data on under-reporting was available; we applied MF=1.
Pertussis	UE: 21.9 (0-9 yrs); 25 (>9 yrs)	MFs are based on Pienter-2 data (67), corrected for the proportion symptomatic, separately for children 0-9 years and for persons >9 years.
Poliomyelitis	UE: 1	Because there were 0 cases in the period 2007-2011, this MF was only applied to calculate the disease burden of the poliomyelitis outbreak in 1992/1993. Because of the severity of the disease, we assumed that all cases are identified.
Rabies	UE: 1	Because of the severity of the disease we assumed that all cases are identified.
Rubella	UE: Uniform(11.11,14.93)	No information available. We therefore used the MF for measles as a proxy (the clinical picture is probably less clear compared with measles, except for congenital rubella syndrome).
Tetanus	UE: Uniform(1.0,1.41)	Range of 1 to 1.41 was based on expert opinion that the MF would be close to 1.0 (set as lower bound), and a Danish study suggesting 1.41 (upper bound) (68).
Foodborne diseases		
Campylobacteriosis, Cryptosporidiosis, Giardiasis, Hepatitis A infection, Listeriosis, Norovirus infection, Salmonellosis, Toxoplasmosis, Infection with STEC O157		For these foodborne diseases, an estimation method developed by Havelaar et al. was used that is specific for the Dutch situation (13, 20).
Shigellosis	UE: PERT(1.2,11.6,49.6)	As a proxy, an MF calculated for salmonellosis (based on the proportion of (a) the number of estimated salmonellosis cases in 2009 (13) and (b) the mean number of reported salmonellosis cases in 2007-2011) was used.
vCreutzfeldt-Jakob disease	UE: 1	No correction due to the 100% fatality of the disease. Cases may be missed, especially elderly patients, if symptoms are attributed to a different cause.

Table A.2 (continued) Rationale for multiplication factors.

Disease	MF(s) chosen	Explanation
Respiratory diseases		
Influenza	UA: Uniform(4.12,5.13) UR: 1	MF for under-ascertainment is based on the estimated proportion of people who go to the general practitioner when they have ILI symptoms (source: "Grote Griepmeting"). MF ranged from 4.12 to 5.13 in the period 2007-2011 (2007: 4.43, 2008: 4.12, 2009: 4.19, 2010: 5.13 and 2011: 4.42).
Legionellosis	UA: 1 UR: PERT(9.95,11.03,24.14)	Based on Dutch notification data, the estimated number of pneumonia cases in the Netherlands (69, 70), and the expected proportion with diagnosis legionellosis (41-43).
Q fever	UE: PERT(0.75,1.575,3.25) (0-14 yrs) PERT(2.4,5.04,10.4) (15+ yrs)	Van der Hoek et al. (2012) (71) showed that in the highest incidence areas of the Netherlands in 2009, one notification represented 12.6 infections (95% CI: 6-26) (either symptomatic or asymptomatic). In the international literature, a symptomatic percentage of 12.5% (0-14 years) and 40% (15 years or older) is applied. Therefore, we estimate that one notification represents 1.6 (0-14 years) or 5 symptomatic cases (15+ years).
Tuberculosis	UA: 1 UR: Uniform(1.08,1.16)	Based on Van Hest et al. (2007) (72): 1.08 (record-linkage study) to 1.16 (capture-recapture analysis).

UE = under-estimation, UA = under-ascertainment, UR = under-reporting.

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Erratum for report 150205001/2014: State of Infectious Diseases in the Netherlands, 2013

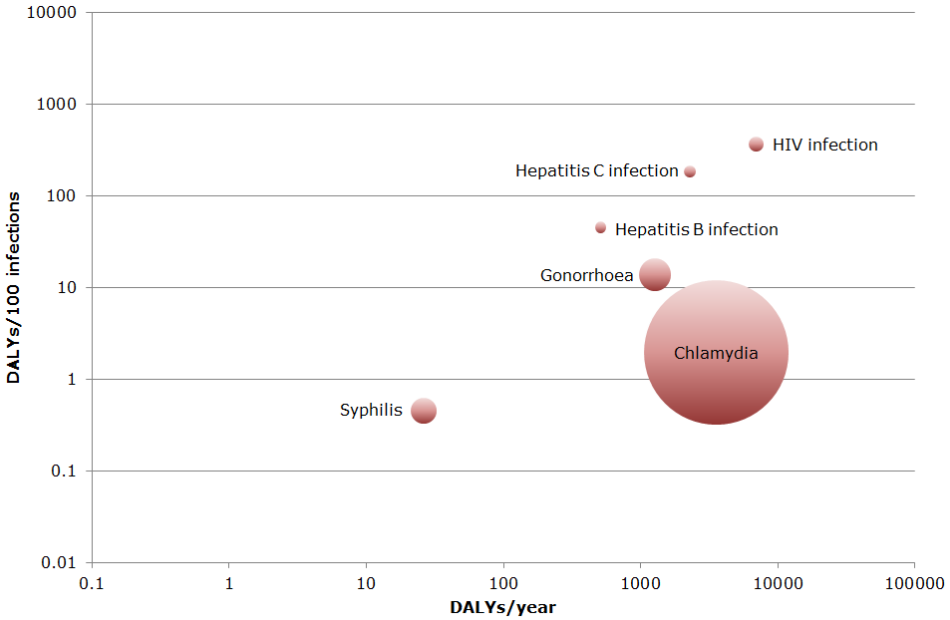
In the report "**State of Infectious Diseases in the Netherlands, 2013**", the disease burden at individual level (DALYs per 100 cases) was not calculated consistently. For most diseases, it was calculated as the number of DALYs per 100 infections, but for some exceptions the burden was calculated as the number of DALYs per 100 symptomatic cases. These exceptions were hepatitis B infection, hepatitis C infection, HIV infection, Q fever, and tuberculosis. Below we present Table 3.3 and Figures 3.6/3.9 for which the disease burden at individual level was calculated as the number of DALYs per 100 infections for all diseases.

Table 3.3 Estimated annual individual level burden in the period 2007-2011 for new cases of sexually-transmitted infections, vaccine-preventable diseases, foodborne diseases, and respiratory diseases in this period: mean (with 95% uncertainty intervals).

Disease	DALYs/ 100 infections
Sexually-transmitted infections	
Chlamydia	2.0 (0.8-4.0)
Gonorrhoea	14 (7-25)
Hepatitis B infection*	45 (43-48)
Hepatitis C infection*	184 (130-250)
HIV infection*	363 (332-396)
Syphilis	0.5 (0.3-0.6)
Vaccine-preventable diseases	
Diphtheria	n.a.
I. *H. influenzae* infection	308 (292-325)
I. meningococcal disease	686 (638-733)
I. pneumoococcal disease	346 (327-365)
Measles	25 (20-30)
Mumps	0.5 (0.5-0.6)
Pertussis	2.1 (2.1-2.1)
Poliomyelitis	n.a.
Rabies	5081 (5081-5081)
Rubella	0.5 (0.4-0.5)
Tetanus	137 (132-143)
Foodborne diseases	
Campylobacteriosis	3.5 (2.4-7.4)
Cryptosporidiosis	0.3 (0.1-0.7)
Giardiasis	0.2 (0.1-0.4)
Hepatitis A infection	17 (13-21)
Listeriosis	219 (195-246)
- perinatal	2482 (2128-2862)
- acquired	65 (59-73)
Norovirus infection	0.3 (0.1-0.4)
Salmonellosis	3.5 (2.3-10.9)
Shigellosis	2.6 (2.5-2.7)
Toxoplasmosis	452 (383-583)
- congenital	607 (450-942)
- acquired	317 (317-317)
vCreutzfeldt-Jakob disease	3581 (3540-3611)
Infection with STEC O157	6.5 (1.5-65)
Respiratory diseases	
Influenza	2.6 (2.6-2.6)
Legionellosis	97 (90-105)
Q fever*	19 (17-21)
Tuberculosis*	17 (14-20)

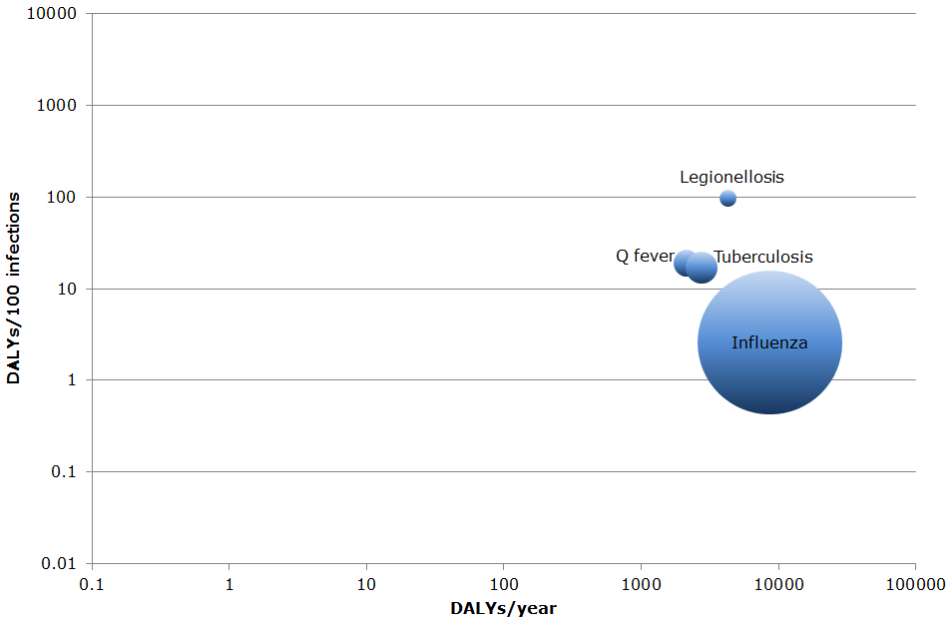
* In the original report, the burden at individual level for these diseases was presented per 100 symptomatic cases instead of per 100 infections.

Figure 3.6 Ranking of sexually-transmitted infections by estimated burden at population (DALYs/year) and individual level (DALYs/100 infections) in the period 2007-2011. The area of each bubble is proportional to the average number of estimated annual cases.



Note 1: both axes are on a logarithmic scale.
Note 2: vaccination is available for hepatitis B infection only (in the Netherlands behavioural high-risk groups have been vaccinated since 2002, universal childhood vaccination has been introduced in 2011).

Figure 3.9 Ranking of respiratory diseases by estimated burden at population (DALYs/year) and individual level (DALYs/100 infections) in the period 2007-2011. The area of each bubble is proportional to the average number of estimated annual cases.



Note 1: both axes are on a logarithmic scale.
Note 2: vaccination is available for influenza and tuberculosis (in the Netherlands influenza vaccination is offered to high-risk groups and people aged 60 or older; the BCG (Bacillus Calmette-Guérin) vaccine against tuberculosis is only advised for certain groups).

Voor akkoord, 28-07-2015

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