Annual report Surveillance of influenza and other respiratory infections in the Netherlands: *winter 2017/2018*

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Colophon

Synopsis

Surveillance of influenza and other respiratory infections: Winter 2017/2018

Influenza
In the winter of 2017/2018 the influenza epidemic lasted 18 weeks. This is longer than the average over the last 20 years (nine weeks). Between October 2017 and May 2018, an estimated 900,000 people had symptomatic influenza and 340,000 people consulted their general practitioner with influenza-like symptoms. Hospitals were also temporarily overstretched as many patients had to be admitted due to complications of flu (usually pneumonia); this number is estimated to have been over 16,000. Also, during the epidemic, 9,500 more people died than would normally be the case in the influenza season (October to May). Throughout the entire epidemic, people mostly became ill due to an influenza type B virus of the Yamagata lineage. This is the first time that an influenza type B virus has been dominant right from the start of the epidemic.

Influenza vaccine effectiveness
In the current season, vaccination prevented 44% of the vaccinated people from getting the influenza B virus. This is despite the fact that the Yamagata lineage of influenza virus type B was not included in the vaccine. Apparently, the other B virus in the vaccine provided a reasonable level of cross-protection. The long duration of the flu epidemic can therefore not be explained by a low effectiveness of the vaccine.

The effectiveness of the vaccine can differ greatly from season to season. This is because the composition of the vaccine is decided upon six months in advance and is determined based on the viruses that dominated in the previous season all over the world. However, influenza viruses can change and when the influenza season breaks out in the Netherlands other viruses may dominate. This is why it is not possible to predict exactly which viruses will be dominant.

Notifiable respiratory infections
Some respiratory infections have to be notified to the Public Health Services in order to prevent any further spread. In 2017, there was a striking increase in the number of notifications of legionella; at 561 this was the highest number ever reported. The number of reports of tuberculosis dropped to 787. The number of reports of Q fever (23) and psittacosis (52) remained stable. Q fever, psittacosis and legionella generally manifest themselves in the form of pneumonia. The number of reported cases is an underestimation of the real number as these diseases are normally not tested for when people have pneumonia.

Key words: respiratory infections, flu, influenza, RS virus, pneumonia, legionella, Parrot fever, psittacosis, Q fever, tuberculosis.

Publiekssamenvatting

Surveillance van griep en andere luchtweginfecties: winter 2017/2018

Griep

In de winter van 2017/2018 duurde de griepepidemie 18 weken. Dat is langer dan het gemiddelde van de afgelopen 20 jaar (negen weken). In totaal zijn tussen oktober 2017 en mei 2018 ongeveer 900.000 mensen ziek geworden door het griepvirus. Naar schatting bezochten 340.000 mensen de huisarts met griepachtige klachten. Daarnaast waren ziekenhuizen tijdelijk overbelast door de vele patiënten die vanwege complicaties van griep (meestal longontsteking) moesten worden opgenomen; naar schatting ruim 16.000. Ook zijn er tijdens de epidemie 9.500 meer mensen overleden dan gebruikelijk is in het griepseizoen (oktober tot mei). Tijdens de gehele epidemie zijn mensen vooral ziek geworden van het type B (Yamagata-lijn) griepvirus. Het is niet eerder voorgekomen dat een type B-griepvirus vanaf het begin van de epidemie overheerst.

Effectiviteit griepvaccin

In het onderzochte seizoen heeft het vaccin bij 44 procent van de mensen die zich tegen de griep hebben laten vaccineren, voorkomen dat ze griepvirus B kregen. De Yamagata-lijn van griepvirus type B zat niet in het vaccin van het afgelopen seizoen. De redelijke bescherming die het vaccin bood komt doordat er wel een ander type B in zat. De lange duur van de griepepidemie kan dan ook niet verklaard worden door de lage effectiviteit van het vaccin. De effectiviteit van het vaccin kan per seizoen sterk verschillen. Dat komt omdat de samenstelling van het griepvaccin een half jaar van tevoren wordt bepaald op basis van de virussen die het seizoen ervoor in de wereld heersten. Griepvirussen kunnen echter veranderen of andere virussen kunnen overheersen tegen de tijd dat het griepseizoen in Nederland aanbreekt. Daardoor kan van tevoren nooit precies worden voorspeld welke virussen zullen overheersen.

Meldingsplichtige luchtweginfecties

Sommige luchtweginfecties moeten bij de GGD worden gemeld om te voorkomen dat ze zich verder verspreiden. Opvallend in 2017 was de toename van het aantal meldingen van legionella naar 561, het hoogste aantal ooit gerapporteerd. Het aantal gemelde gevallen van tuberculose (787) is gedaald. Het aantal meldingen van Q-koorts (23) en psittacose (52) bleef stabiel. Q-koorts, psittacose en legionella ziekten uiten zich meestal in de vorm van longontstekingen. Het aantal gemelde gevallen is een onderschatting van het werkelijke aantal, omdat vaak niet op deze ziekten wordt getest als mensen een longontsteking hebben.

Kernwoorden: luchtweginfecties, griep, influenza, RS-virus, longontsteking, pneumonie, legionella, papegaaienziekte, psittacose, Q-koorts, tuberculose

Influenza like-illness surveillance at a glance

Figure 1 Percentage of specimens from patients with influenza-like illness positive for influenza virus, RSV, rhinovirus or enterovirus, taken by sentinel GPs, and ILI incidence with epidemic threshold during the 2017/2018 respiratory season (week 40 of 2017 through week 20 of 2018), displayed by week of sampling (Source: Nivel Primary Care Database; RIVM).
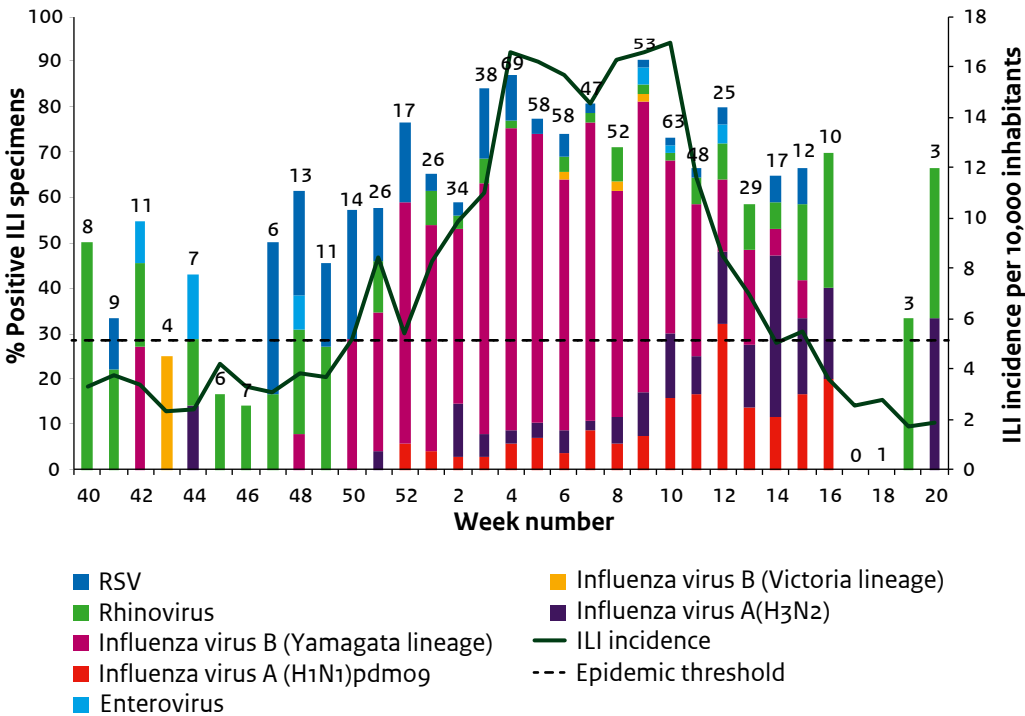
Footnote: ILI = influenza-like illness; GP = general practitioner; RSV = respiratory syncytial virus
The numbers above the bars are the total number of tested specimens.

Contents

Chapter 1
Introduction

1.1   Aim and focus of this report

This report describes the current trends and epidemiology of various respiratory infectious diseases and pathogens in the Netherlands. This is an annual report that is meant for policymakers, epidemiologists, microbiologists, staff of public health services and others working or interested in the field of respiratory infectious diseases. The national surveillance of respiratory infectious diseases considered in this report is the responsibility of the Department for Respiratory Infections (RES) at the Centre for Infectious Diseases, Epidemiology and Surveillance (EPI), a part of the Centre for Infectious Disease Control (CIb) of the National Institute for Public Health and the Environment (RIVM) in the Netherlands, in collaboration with other partners within and outside RIVM.

Chapter 2 describes the different syndromic surveillance systems used: influenza-like illness (ILI), acute respiratory infections (ARI), pneumonia, severe acute respiratory infections (SARI) and mortality. The term 'influenza-like illness' is based on the notion that this clinical syndrome may be caused by influenza virus, but also by a range of other pathogens. The causative pathogen remains unknown in the majority of patients with respiratory infections, because most infections are not laboratory-confirmed but based on clinical diagnosis only. This surveillance is important because of the high burden of disease in terms of patient numbers, mortality and the impact on the health care system. The surveillance of ILI, ARI and pneumonia is currently mainly based on the registration of consultations by general practitioners (GPs) participating in Nivel Primary Care Database (in Dutch: Nivel Zorgregistraties eerste lijn). Elderly care physicians provide data within the context of the national sentinel surveillance network for infectious diseases in nursing homes (SNIV). Laboratory-confirmed influenza in these two networks is assessed by the National Influenza Centre (NIC), location RIVM (at the Centre for Infectious Disease Research, Diagnostics and Laboratory Surveillance (IDS) of CIb). Laboratory-confirmed influenza cases reported by hospital and peripheral laboratories are monitored at NIC, location Erasmus Medical Centre. As real-time, cause-specific data on deaths are not available, mortality surveillance is based on all-cause mortality, using weekly data from Statistics Netherlands (CBS). Chapters 3 and 4 show the surveillance data for

influenza virus infection and respiratory syncytial virus (RSV) infection. Since the respiratory syndromes as well as influenza virus and RS-virus infections show winter seasonality, data in the Chapters 2-4 are reported for the 2017/2018 respiratory season, i.e. week 40 of 2017 through week 20 of 2018.

Chapter 5 provides results of the surveillance of the notifiable respiratory infectious diseases legionellosis, psittacosis, Q fever, tuberculosis, animal influenza virus infections and MERS-CoV infections for the 2017 calendar year. Special emphasis in the present edition of the report is given to legionellosis. Q fever and psittacosis will be described in greater detail in the report 'State of Zoonotic Diseases 2017' (manuscript in preparation). More details on tuberculosis will be described in the next surveillance report on tuberculosis, 'Tuberculose in Nederland, 2017' that will be published in December 2018. Other notifiable respiratory diseases that are targeted by the National Immunization Programme, such as pertussis and invasive pneumococcal disease, are described in the annual RIVM publication 'The National Immunization Programme in the Netherlands' and are not reported here.

Chapter 6 describes diagnoses of respiratory infections reported in the virological laboratory surveillance for the 2017 calendar year. Chapter 7 provides an update on the burden of disease from five respiratory diseases: influenza, legionellosis, tuberculosis, Q fever and psittacosis. In Chapter 8, the main findings of this report are discussed and put into perspective. Finally, Chapter 9 describes the data sources and methods used for surveillance of the different diseases or pathogens.

1.2   Collaborations: national and international

For the surveillance of respiratory infectious diseases, the CIb collaborates with many partners: Nivel (Netherlands institute for health services research), including the network of sentinel general practices; the surveillance network in nursing homes (SNIV); the National Influenza Centre (NIC), location Erasmus MC; KNCV Tuberculosis Foundation; the Regional Public Health Laboratory Kennemerland, Haarlem (national reference laboratory for legionellosis); and Statistics Netherlands (CBS). The collaboration with the Public Health Services (in Dutch: GGD) is the basis for the surveillance of notifiable infectious diseases. For zoonoses (psittacosis and Q fever), collaboration with the Netherlands Food and Consumer Product Safety Authority (NVWA) is in place and for psittacosis with the Zuyderland Medical Centre in Sittard. The laboratories that report the data for the virological laboratory surveillance are all members of the Working Group for Clinical Virology of the Dutch Society for Medical Microbiology (NVMM). SARI surveillance was implemented on a pilot basis during the 2015/2016 season in two hospitals: the Jeroen Bosch hospital and Leiden University Medical Centre (LUMC). In 2017, University Medical Centre Utrecht (UMC Utrecht) was added as a third study site.

A part of the data in this report is also reported internationally. The notifiable infectious diseases legionellosis, Q fever and tuberculosis are reported annually to the European Centre for Disease Prevention and Control (ECDC). Travel-related legionellosis is reported daily to the European Legionnaires Disease Surveillance Network (ELDSNet) of the ECDC. Moreover, the RIVM (CIb/IDS and CIb/EPI) participates together with Nivel and Erasmus MC in the European Influenza Surveillance Network (EISN) of ECDC. The Dutch data are reported weekly in the joint ECDC/WHO regional office for Europe FluNews Europe Bulletin, and in FluNet and FLuID of the WHO (World Health Organization) headquarters in Geneva. All-cause mortality is reported weekly to EuroMoMo, a European consortium that weekly publishes the mortality data of 19 European countries. For the purpose of estimating vaccine effectiveness at a European level, RIVM and Nivel participate in the European I-MOVE (influenza monitoring vaccine effectiveness) network.

Chapter 2
Syndrome surveillance

2.1   Acute respiratory infections (ARI) and influenza-like illness (ILI)

Authors: Marit de Lange, Gé Donker, Adam Meijer, Mariëtte Hooiveld
Contributors: Daphne Reukers, Anne Teirlinck, Linda Verhoef, Paul Bergervoet

2.1.1   Key points
- In the 2017/2018 winter season, the influenza epidemic lasted 18 weeks (week 50 of 2017 through week 15 of 2018). This is the second longest epidemic in the last five seasons, only the 2014/2015 influenza epidemic lasted longer (21 weeks).
- Similarly, the number of patients with ILI and ARI that were reported by GPs in 2017/2018 was only exceeded in the 2014/2015 season.
- The peaks of ILI incidence and ARI consultations reported by GPs were earlier in this season for children in the age group 0-4 years, compared to the older age groups.
- In the last five seasons, the 2017/2018 peaks of ILI incidence and ARI consultations reported by GPs among the elderly (65 years or older) and ILI incidence in nursing home residents were the latest.

2.1.2   Background
Acute respiratory infections (ARI) and the subgroup of influenza-like illness (ILI) are clinical diagnoses that can be caused by a range of viruses and bacteria. However, the case definition for ILI is more specific for influenza virus infection, which is defined according to the 'Pel criteria' (Pel 1965): sudden onset of symptoms, fever ≥ 38°C and at least one of the symptoms cough, rhinorrhoea, sore throat, frontal headache, retrosternal pain, or myalgia. ILI surveillance performed by sentinel general practitioners (GPs) of the Nivel Primary Care Database is the basis of the influenza surveillance in the Netherlands. Since 1992, it combines the clinical syndrome ILI and the sampling of a subset of the ILI patients by taking a combined nose swab and throat swab, to determine the main causes of ILI and whether the epidemic curve of ILI is a true reflection of influenza virus circulation. Based on these data, the influenza epidemic is declared when the ILI incidence is higher than 5.1/10,000 inhabitants for two consecutive weeks in combination with the detection of influenza virus in the specimens of patients with

ILI. ARI surveillance is a complementary surveillance system, which is also performed by GPs participating in the Nivel Primary Care Database. It has a broader respiratory case definition: acute upper respiratory infection, acute/chronic sinusitis, acute laryngitis/tracheitis, acute bronchitis/bronchiolitis or influenza (and therefore includes the ILI case definition). Besides, a larger number of GPs performs the ARI surveillance and it does not have a laboratory diagnosis component. A third system for ILI/ARI surveillance is the surveillance of ILI in nursing homes (SNIV). Nursing home residents are a vulnerable group for influenza virus related complications but are not captured in the GP surveillance because they receive primary care and secondary care from elderly care physicians. Similar to the GP sentinel surveillance, a subset of ILI patients is swabbed to determine the cause of ILI.

2.1.3 Epidemiological situation, season 2017/2018

Acute respiratory infections (ARI)
The peak of patients that consulted a GP participating in Nivel Primary Care Database for ARI was seen in week 8 of 2018 (48 per 10,000 inhabitants). The peak of the weekly ARI numbers in the 2017-2018 season was comparable with the highest peak in the four previous seasons, which was in the 2014/2015 season. Next, the second highest cumulative seasonal number of ARI consultations were reported by GPs compared to the four previous seasons, only the 2014/2015 season had a higher number. The weekly number of ARI consultations was highest in young children in the age group 0-4 years, followed by the elderly (65 years or older), which is in line with the four previous seasons. The weekly number of ARI consultations in the youngest age group peaked early in the season (week 50 2017), while the peaks in other age groups were seen later in the season (from week 4 through 10 of 2018), with the latest peak for people aged 65 years and older. Among the elderly (65 years or older), the peak of ARI consultations reported by GPs was late this season compared to the four previous seasons.

Influenza-like illness (ILI)
The influenza epidemic lasted 18 weeks, from week 50 of 2017 through week 15 of 2018. This is the second longest epidemic in the last five seasons, only the 2014/2015 influenza epidemic lasted longer (21 weeks) and that was the longest epidemic since the start of the registration in 1970. The weekly ILI incidence of 2017/2018 season showed two peaks: 16.6 per 10,000 inhabitants in week 4, and 17.0 per 10,000 inhabitants in week 10. Both peaks were higher than the peaks reported in the previous four seasons. Similarly, the cumulative ILI incidence (weeks 40 through 20) in the 2017/2018 season was with 247/10,000 the second highest in the last five seasons, only the 2014/2015 season had a higher number (265 per 10,000 inhabitants). The GP-attended ILI incidence was highest among young children in the age group 0-4 years, followed by the elderly (65 years or older), which is in line with the four previous seasons. The ILI incidence among young children peaked twice in week 51 2017 and in week 4 2018, while it peaked much later in the elderly (in week 10 2018). The peak in ILI incidence among nursing home residents was relatively high. However, the cumulative ILI incidence was within the range of the previous four seasons. Also in this population of older people, the ILI incidence peaked later in the season (week 9 2018) compared to the previous four seasons.

2.1.4   Discussion

The influenza epidemic lasted long in the 2017/2018 season. On the other hand, among nursing home residents it was an average season. In this season, the peaks of ILI incidence and ARI consultations reported by GPs were found earlier for young children (0-4 years), compared to the community dwelling elderly, which is comparable with three of the four previous seasons. The first peak in ILI incidence and the ARI peak in the young children might be explained by the contribution of other viruses than influenza virus, especially RS virus (see Chapter 4). The second peak in ILI incidence in the young children (0-4 years) is probably more explained by influenza virus circulation (Chapter 3). Among elderly patients (65 years or older) both at the GP and in nursing homes, the peaks of ILI incidence and ARI consultations were late this season compared to the four previous seasons, which might be explained by the late circulation of influenza type A(H3N2) causing relatively high ILI morbidity in the elderly (see Chapter 3) (Freitas and Donalisio 2017, Paules and Subbarao 2017).

2.1.5   Figures

GP consultations for ARI

Figure 2.1 Seasonal cumulative number of patients consulting a GP because of ARI within the respiratory season (week 40 trough week 20) and outside the respiratory season (week 21 through week 39) of 2013/2014 - 2017/2018 (Source: Nivel Primary Care Database).
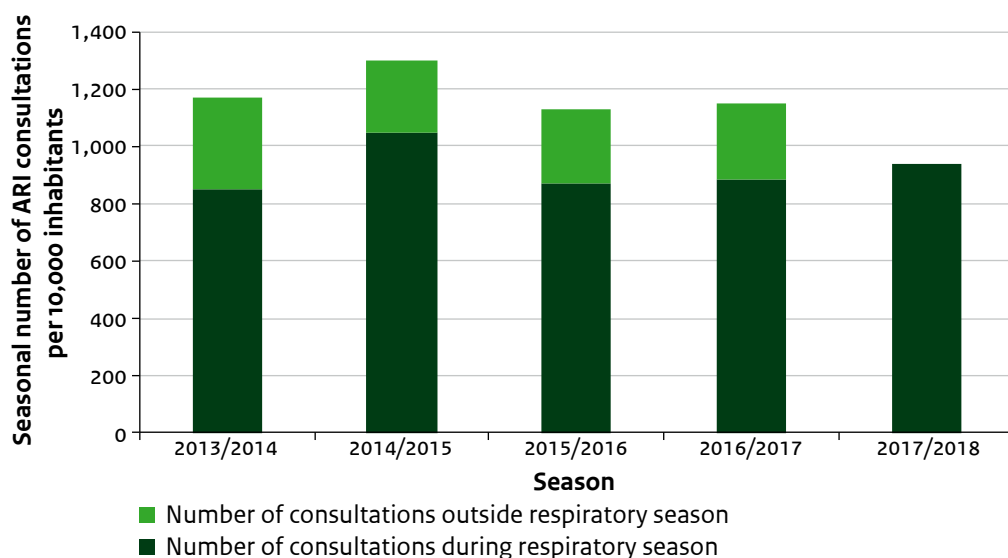
Footnote: ARI = acute respiratory infections (including influenza-like illness); GP = general practitioner.
For the 2017/2018 season, numbers for outside the respiratory season were not yet available.

Figure 2.2 Weekly number of patients consulting a GP because of ARI per 10,000 inhabitants in the respiratory season (week 40 through week 20) of 2017/2018 and the trend lines for seasons 2013/2014 - 2017/2018 (Source: Nivel Primary Care Database).
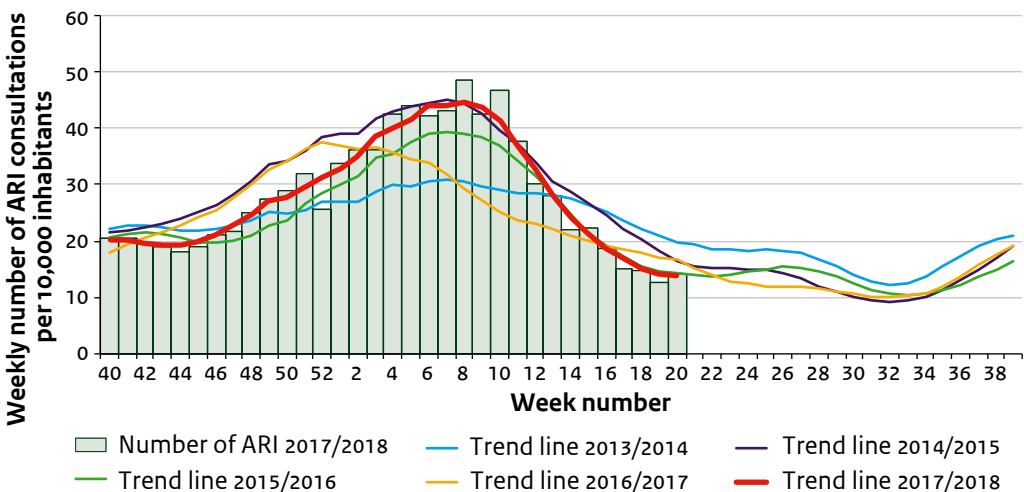
Footnote: Trend lines indicate a 5-weeks moving average. ARI = acute respiratory infection, including influenza-like illness; GP = general practitioner.

Figure 2.3 Seasonal cumulative number of patients consulting a GP because of ARI in the respiratory seasons (weeks 40 through 20) of 2013/2014 through 2017/2018 per 10,000 inhabitants by age group (Source: Nivel Primary Care Database).

Footnote: ARI = acute respiratory infection, including influenza-like illness; GP = general practitioner.

Figure 2.4 Weekly number of patients consulting a GP because of ARI per 10,000 inhabitants in 2017/2018 (through week 20 of 2018) by age group (Source: Nivel Primary Care Database).
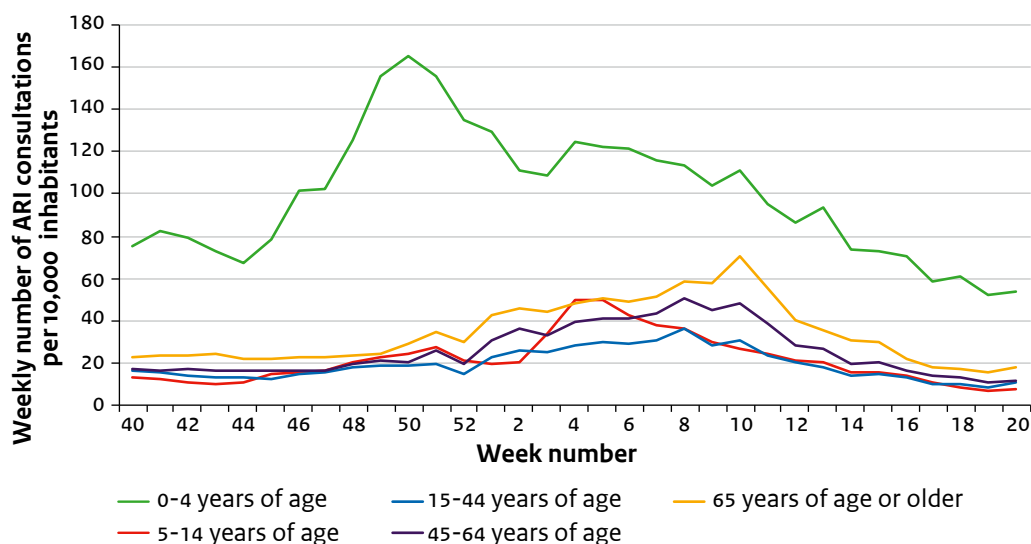
Footnote: ARI = acute respiratory infection, including influenza-like illness; GP = general practitioner.

ILI incidence: sentinel GP practices

Figure 2.5 Seasonal ILI incidence within the respiratory season (week 40 trough week 20) and outside the respiratory season (week 21 through week 39) of 2013/2014 - 2017/2018 (Source: Nivel Primary Care Database).
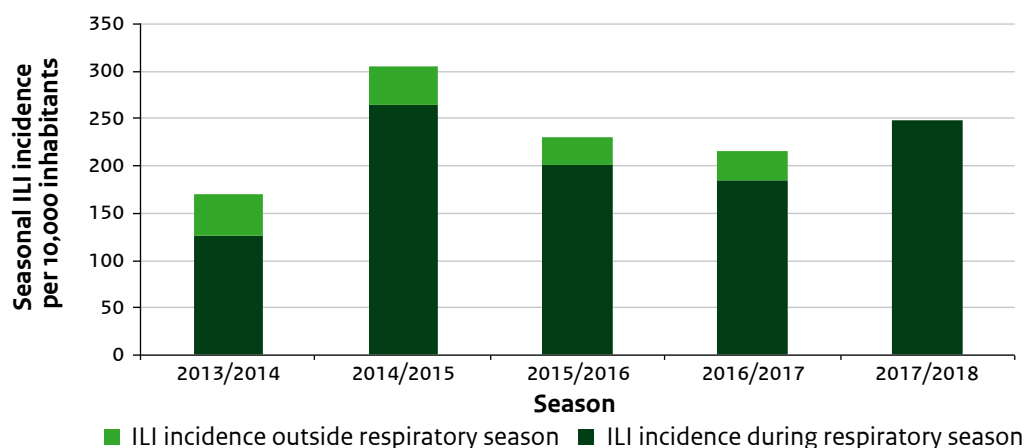
Footnote: ILI = influenza-like illness.
For the 2017/2018 season, numbers for outside the respiratory season were not yet available.

Figure 2.6 Weekly ILI incidence during the seasons 2013/2014 - 2017/2018 (through week 20 of 2018) (Source: Nivel Primary Care Database).
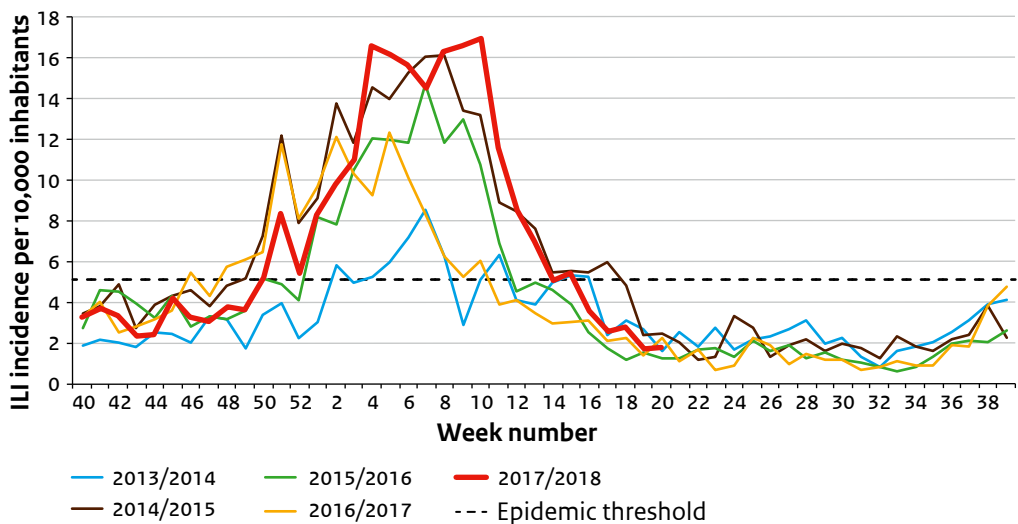
Footnote: ILI = influenza-like illness.

Figure 2.7 Seasonal ILI incidence in the respiratory seasons 2013/2014 - 2017/2018 per 10,000 inhabitants by age group (Source: Nivel Primary Care Database).
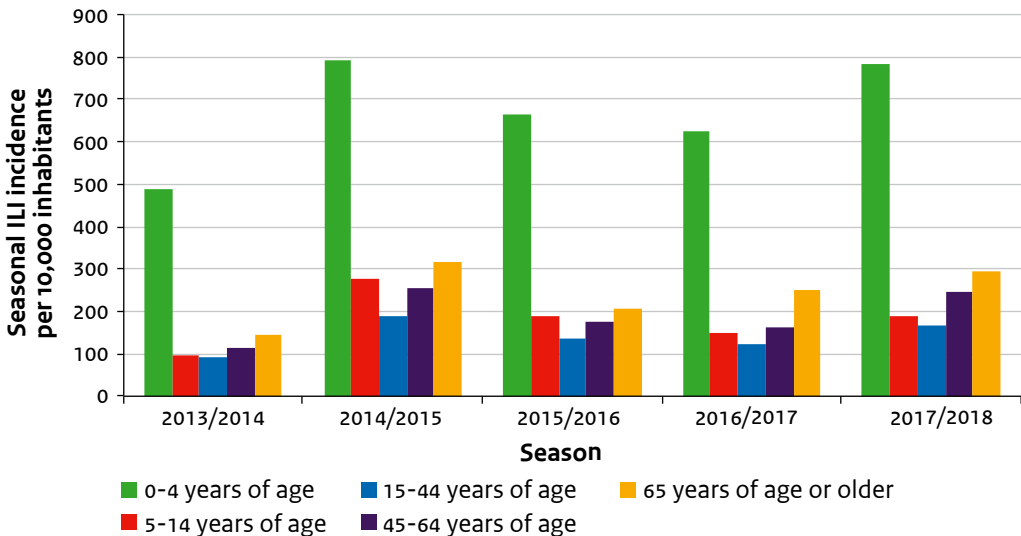
Footnote: ILI = influenza-like illness.

Figure 2.8 Weekly ILI incidence per 10,000 inhabitants in respiratory season 2017/2018 by age group (Source: Nivel Primary Care Database).
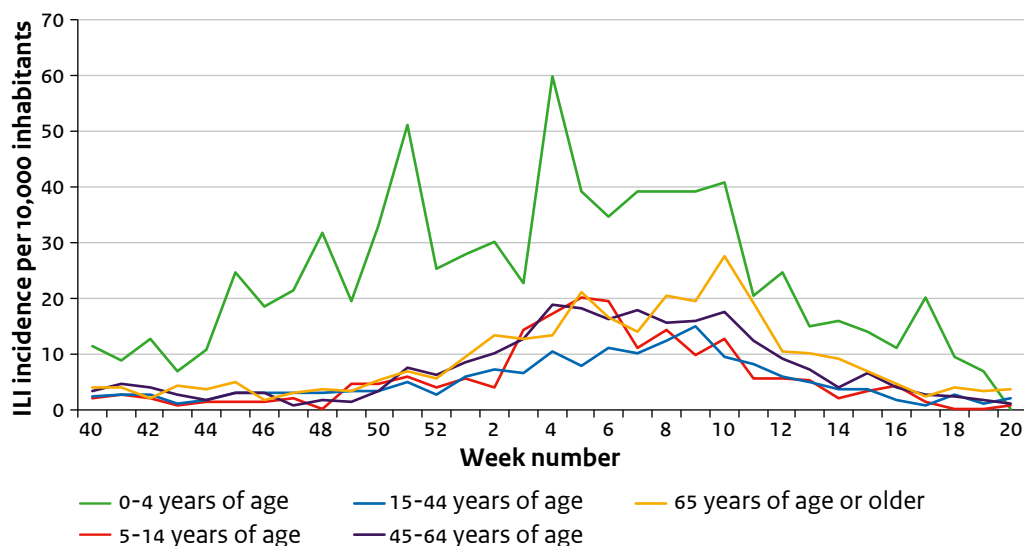
Footnote: ILI = influenza-like illness.

ILI incidence: in nursing homes

Figure 2.9 Seasonal ILI incidence in SNIV nursing homes per 10,000 residents within the respiratory season (week 40 trough week 20) and outside the respiratory season (week 21 through week 39) of 2013/2014 - 2017/2018 (Source: SNIV, RIVM).

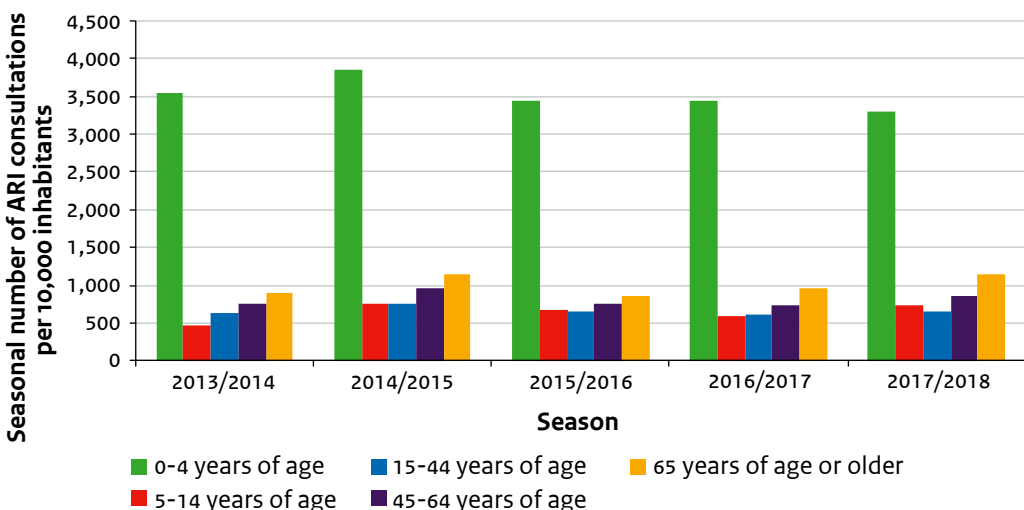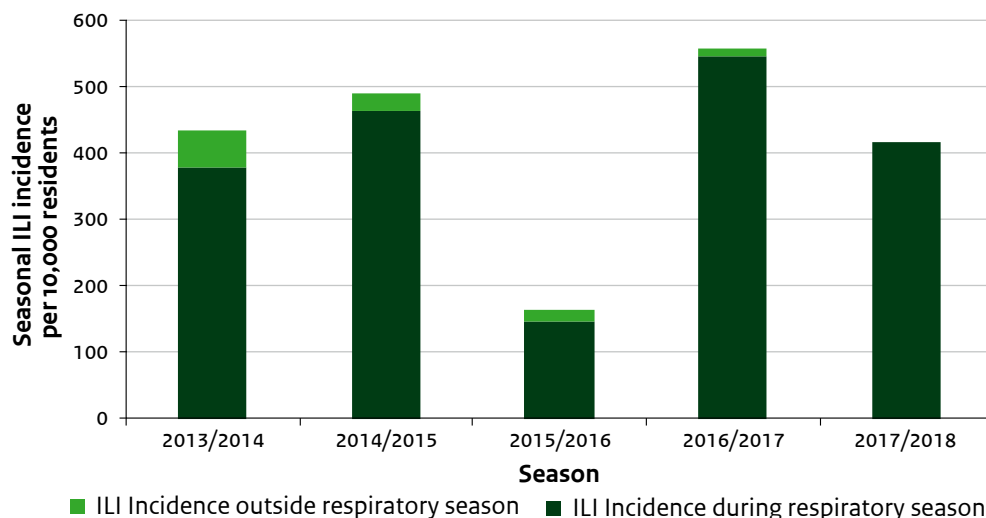**Footnote:** ILI = influenza-like illness.
For the 2017/2018 season, numbers for outside the respiratory season were not yet available.

Figure 2.10 Weekly ILI incidence in SNIV nursing homes per 10,000 residents in the 2017/2018 respiratory season (week 40 of 2016 through week 20 of 2018) and trend lines for the seasons 2013/2014-2017/2018 (Source: SNIV, RIVM).
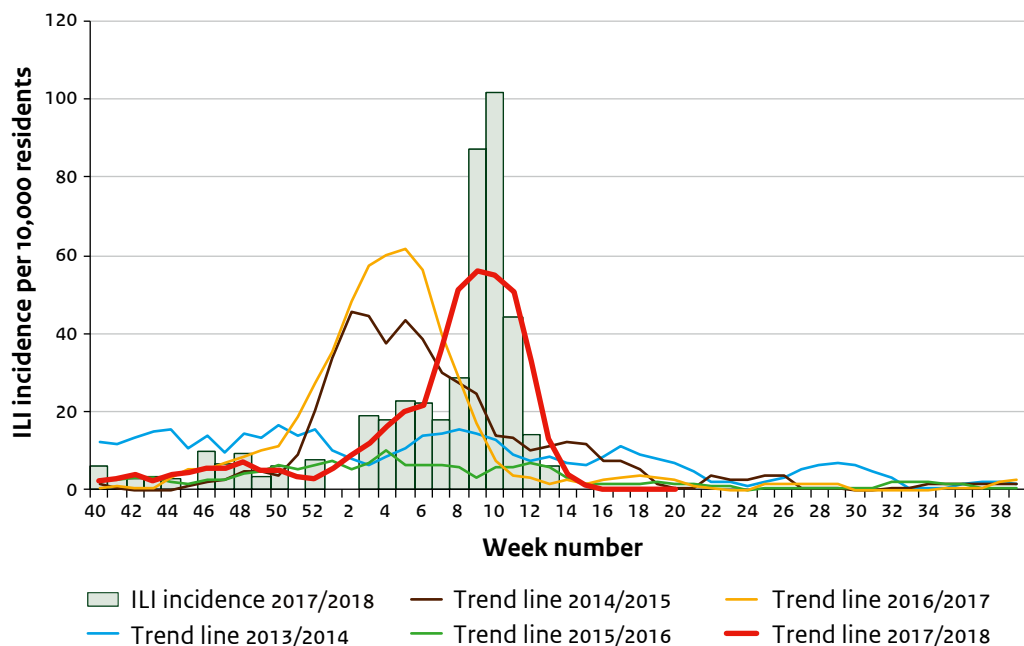
Footnote: Trend lines are based on 5-week moving averages. No epidemic threshold for this data has been calculated.
ILI = influenza-like illness
SNIV = national sentinel surveillance network for infectious diseases in nursing homes.

2.2   Community-acquired pneumonia (CAP) in primary care

Authors: Rianne van Gageldonk-Lafeber, Mariëtte Hooiveld
Contributor: Linda Verhoef

2.2.1   Key points
- The overall seasonal cumulative pneumonia estimate (week 40 through week 20) of general practitioner (GP) consultations for 2017/2018 was 155 per 10,000 inhabitants (range 2013/2014-2016/2017: 115-161 per 10,000 inhabitants).
- The peak in weekly pneumonia GP consultations (9 per 10,000 inhabitants) was observed in week 10 of 2018 (range 2013/2014-2016/2017: 4-7 per 10,000 and week 1 – week 9).
- The cumulative number of GP consultations for pneumonia in 2017/2018 (week 40 through week 20) in the age group 0-4 years was the lowest compared to the previous four seasons (136 per 10,000 inhabitants; range: 178-216 per 10,000 inhabitants).
- In contrast, the cumulative weekly number of GP consultations for inhabitants aged 65 or older was the highest compared to the previous four seasons (446 per 10,000 inhabitants; range: 321-388 per 10,000 inhabitants).
- The overall seasonal cumulative incidence (week 40 trough week 20) of pneumonia in SNIV nursing homes for 2017/2018 was 1,231 per 10,000 residents, lower than in the previous four seasons (range : 1,250-1,731 per 10,000 residents).

2.2.2   Background
Pneumonia is a common clinical disorder of the lower respiratory tract with high morbidity and mortality, especially in the elderly. Typical symptoms include cough, chest pain, fever and difficulty breathing.
Many studies in the Netherlands and other countries show that *Streptococcus pneumoniae* is the predominant aetiological agent of community-acquired pneumonia (CAP), but CAP can be caused by many other microorganisms, mainly bacteria and viruses (Verheij, Hopstaken et al. 2011, van Gageldonk-Lafeber, Wever et al. 2013). In daily clinical care, a general practitioner (GP) diagnosis of CAP is based on clinical criteria, often without confirming the presence of a new infiltrate on a chest X-ray and without laboratory-confirmed diagnosis (Verheij, Hopstaken et al. 2011). Also in hospital settings, causative pathogens remain unknown in the majority of CAP patients, since microbiological tests are not routinely used and are usually limited to blood and sputum cultures for bacterial causes. Antibiotic treatment is therefore generally empirical, guided by the clinical condition of the patient.
The pneumonia surveillance in this report includes both the registration of pneumonia by GPs (Nivel Primary Care Database) and the registration of incidence of pneumonia in nursing homes (SNIV).

2.2.3   Discussion
As in 2014/2015, the long influenza epidemic in 2017/2018 resulted in high numbers of patients consulting their GP with pneumonia. The overall peak in weekly pneumonia GP consultations in 2017/2018 coincided with the peak of influenza-like illness (week 10 2018) and was higher than reported in the four previous seasons.

The high number of pneumonia consultations and the late peak are attributable to the oldest age groups. In children in the age group 0-4 years the number of pneumonia consultations was remarkably low and peaked already in week 49 2017. This difference between age groups might be caused by variation in causative agents of pneumonia. Nevertheless, since laboratory diagnostics are not included in the pneumonia surveillance, it is unclear to what extent pneumonia is associated with the circulation of RSV, influenza virus and other pathogens. Despite the prolonged influenza epidemic in 2017/2018, the cumulative incidence (week 40 through week 20) of pneumonia in SNIV nursing home residents was relatively low, while the peak in the weekly incidence for pneumonia was within the range of peak incidences in the four previous seasons. This coincided with the peaks in weekly pneumonia and influenza-like illness GP consultations in 2017/2018.

In the current season the incidence of pneumonia patients in nursing homes is about 3 times higher than it is in patients aged 65 years or older in general practice. The difference between both surveillance systems can largely be explained by the fact that the nursing home surveillance covers more frail elderly compared to the community dwelling elderly included in the GP surveillance.

2.2.4 Figures

GP consultations because of pneumonia

Figure 2.11 Seasonal cumulative number of patients consulting their GP for pneumonia per 10,000 inhabitants within the respiratory season (week 40 through week 20) and outside the respiratory season (week 21 through week 39) of 2013/2014 - 2017/2018 (Source: Nivel Primary Care Database
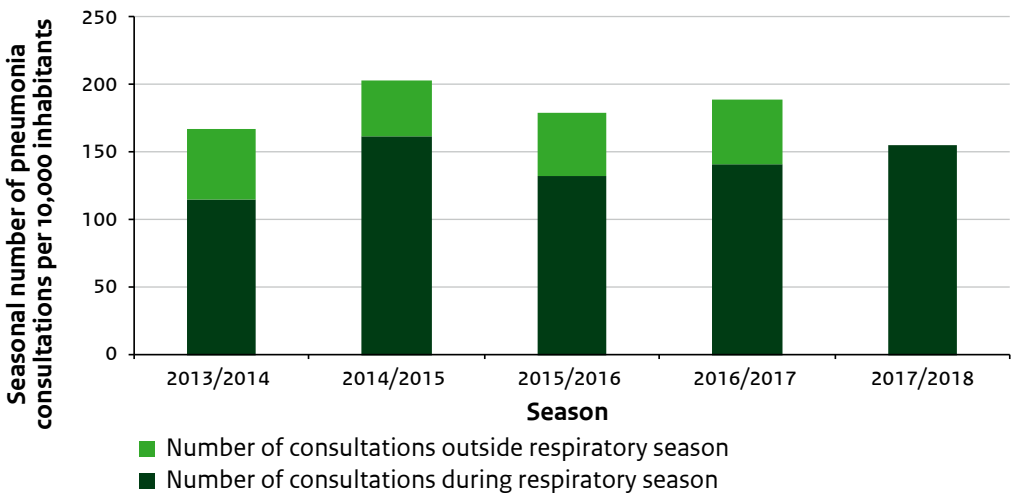
Footnote: for the 2017/2018 season, numbers for outside the respiratory season were not yet available.

Figure 2.12 Weekly number of patients consulting their GP for pneumonia per 10,000 inhabitants in 2017/2018 (through week 20) and the trend lines for 2013/2014 - 2017/2018 (2017/2018: through week 20). Trend lines are based on a 5-week moving average (Source: Nivel Primary Care Database).
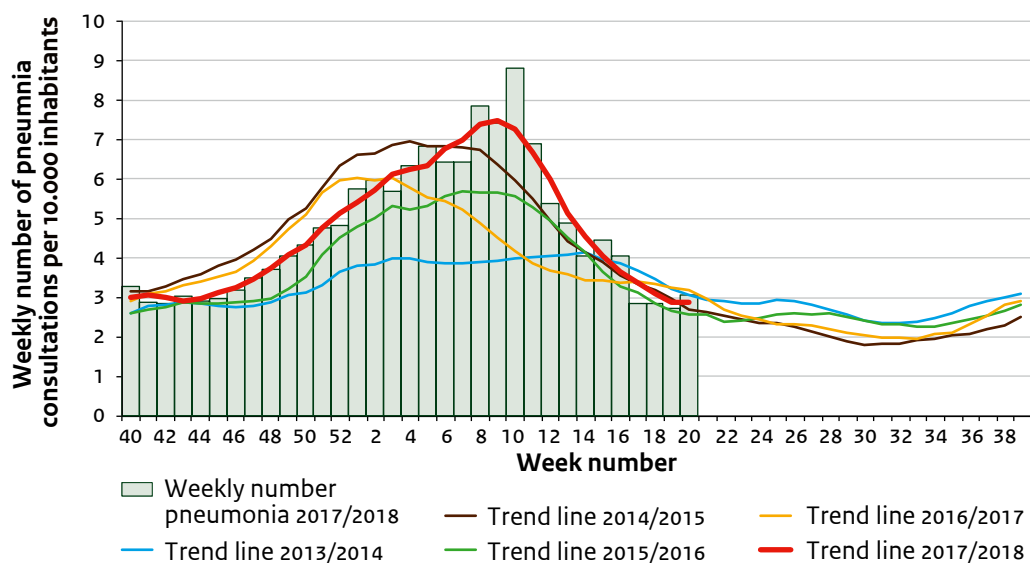
Figure 2.13 Seasonal cumulative number of GP consultations for pneumonia per 10,000 inhabitants by age group in the respiratory seasons 2013/2014 – 2017/2018 (week 40 through week 20) (Source: Nivel Primary Care Database).
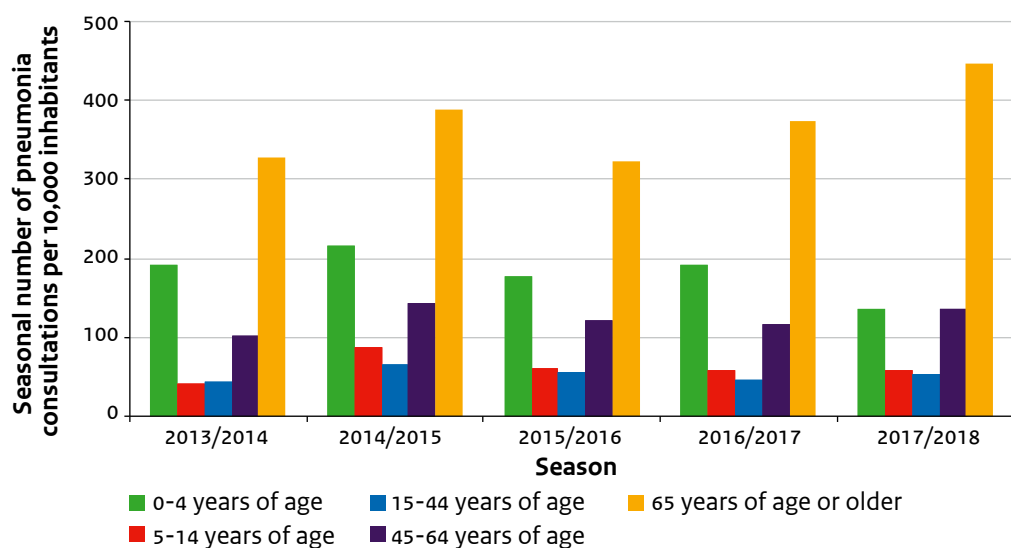
Incidence of pneumonia (nursing homes)

Figure 2.14 Seasonal pneumonia incidence in SNIV nursing homes per 10,000 residents within the respiratory season (week 40 trough week 20) and outside the respiratory season (week 21 through week 39) of 2013/2014 - 2017/2018 (Source: SNIV, RIVM).

■ Pneumonia incidence outside respiratory season
■ Pneumonia incidence during respiratory season
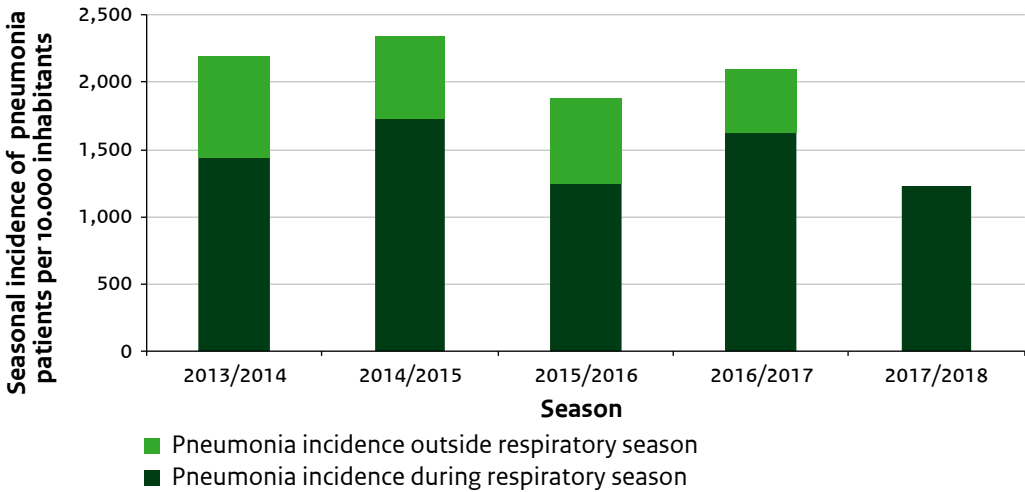
Footnote: for the 2017/2018 season, numbers for outside the respiratory season were not yet available.

Figure 2.15 Weekly incidence of pneumonia patients in SNIV nursing homes per 10,000 residents in 2017/2018 and trend lines for the seasons 2013/2014 – 2017/2018 (through week 20). Trend lines are based on a 5-week moving average (Source: SNIV, RIVM).

☐ Weekly incidence pneumonia 2017/2018
— Trend line 2013/2014
— Trend line 2014/2015
— Trend line 2015/2016
— Trend line 2016/2017
— Trend line 2017/2018
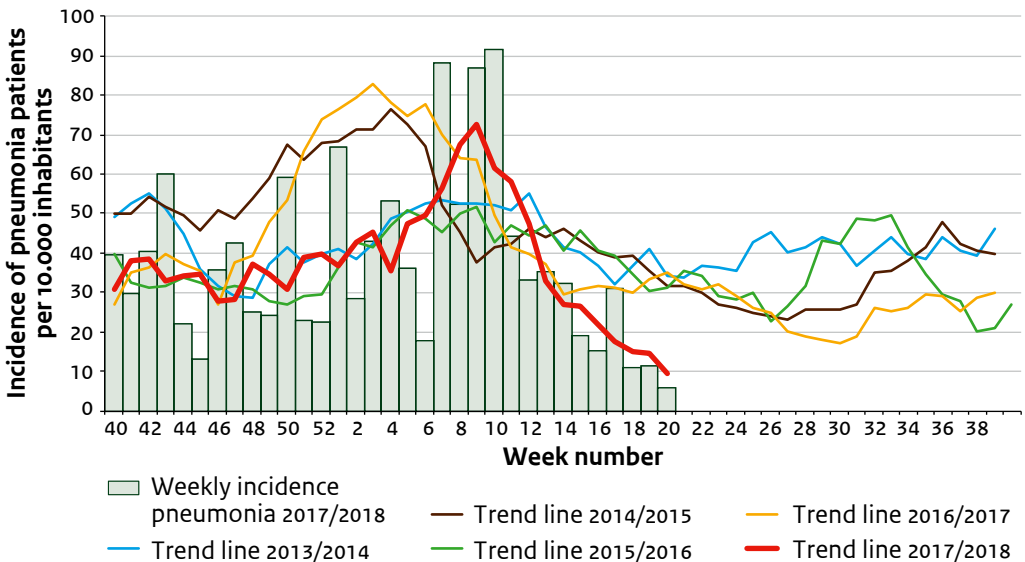
2.3 Severe acute respiratory infections (SARI)

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2.3.1 Key points
- At Jeroen Bosch Hospital (JBZ), the overall seasonal cumulative SARI incidence was 33 per 10,000 inhabitants during the influenza season 2017/2018. The peak incidence (2 per 10,000 inhabitants) was reached in week 10 of 2018.
- At Leiden University Medical Centre (LUMC), the seasonal cumulative SARI incidence was 42 per 10,000 inhabitants during the 2017/2018 season. In week 52 of 2017, the SARI incidence peaked with 2 cases per 10,000 inhabitants.
- SARI surveillance still has insufficient data for describing historical trends and might not be representative for the entire country.

2.3.2 Background
Severe acute respiratory infections (SARI) are clinical syndromes of respiratory infections requiring hospitalisation. A sudden increase in the number of SARI patients may pose a significant burden for hospitals in managing bed and staff capacity. Because SARI surveillance has been the missing link in the existing respiratory infections surveillance systems in the Netherlands, a pilot study started in Leiden University Medical Centre (LUMC) and Jeroen Bosch Hospital (JBZ) in 2015. In 2017, University Medical Centre Utrecht (UMC Utrecht) was added as a third study site. In LUMC, a passive syndromic SARI surveillance is operative, while in JBZ and UMC Utrecht an active surveillance based on laboratory confirmed outcome is implemented. See Chapter 9.3 for the methodological details.

2.3.3 Epidemiological situation, season 2017/2018

Leiden University Medical Centre
In the Leiden-The Hague region, an automated real-time tool for detection of clusters of infectious diseases, based on financial DBC/DOT codes, is operational (ICARES). The seasonal cumulative SARI incidence was 42 per 10,000 inhabitants during the 2017/2018 season (week 40 of 2017 through week 20 of 2018), which is lower compared to the two previous seasons: 2015/2016 (45 per 10,000 inhabitants) and 2016/2017 (46 per 10,000 inhabitants). The percentage of SARI patients admitted to the intensive care unit (ICU) was 8% (61/770). In week 52 of 2017, the SARI incidence peaked with 2 cases per 10,000 inhabitants. Most SARI patients were aged 60 years and older (297/770; 39%), followed by children in the age group 0-4 years (261/770; 34%). Vaccination history is not registered in the ICARES system.

Jeroen Bosch Hospital
During the 2017/2018 season (week 40 of 2017 through week 20 of 2018) the seasonal cumulative SARI incidence was 33 per 10,000 inhabitants. This is higher compared to the two previous seasons: 2015/2016 (29 per 10,000 inhabitants) and 2016/2017 (16 per 10,000 inhabitants). This cumulative incidence was retrospectively based on a selection of financial

DBC/DOT codes related to the clinical syndrome SARI. The peak in weekly SARI incidence (2 cases per 10,000 inhabitants) was reached in week 10 of 2018. In 427 of the 1016 patients (42%) more detailed information was available, because these patients were included in the pilot study. Most of these SARI patients were aged 60 years or older (357/427; 84%) and 8% (32/427) was admitted to the ICU. A high percentage of these SARI patients had an indication for influenza vaccination based on current guidelines (399/427; 93%)(Vrieze, van Haaren et al. 2017). The percentage of SARI patients who received an influenza vaccination (67%) was comparable to the previous two seasons: 2015/2016 (64%) and 2016/2017 (69%). See chapter 3 for data on influenza virus infections in JBZ.

University Medical Centre Utrecht
A total number of 140 SARI patients were included in the SARI surveillance pilot study (week 40 of 2017 trough week 20 of 2018). In week 11 of 2018, the number of included SARI patients (n=16) peaked. Only adult SARI patients, aged 18 years and older, were included in the SARI surveillance in UMC Utrecht. Most adult SARI patients were aged 60 years or older (96/140; 69%). A majority of the included SARI patients had an indication for influenza vaccination (135/140; 96%). Of the 140 SARI patients, 80 (57%) received an influenza vaccination in the season 2017/2018.

2.3.4 Discussion
During the 2017/2018 season, SARI incidence could be calculated for the first time, which is an important improvement of SARI surveillance compared to the previous two seasons. Based on the seasonal cumulative incidence, the 2017/2018 respiratory season was a more severe SARI season compared to season 2016/2017 at JBZ. The trend of influenza-like illness (ILI) in primary care was reflected in the SARI surveillance data of JBZ. However, at LUMC, the seasonal cumulative incidence was lower than in the previous two seasons. This might have to do with the more restricted DBC/DOT code set that was used in LUMC in the context of the ICARES programme compared to JBZ. Similar to 2015/2016 and 2016/2017, most SARI patients were aged 60 years and older, followed by children in the age group 0-4 years. SARI surveillance still has insufficient data for describing historical trends and might not be representative for the entire country. To obtain a more robust SARI surveillance programme, data from UMC Utrecht will be added.

On request of JBZ, the aim of the SARI surveillance pilot study changed from a research study to a quality of care management strategy in February 2017. The quality of care of SARI patients is evaluated based on quality indicators, such as diagnostics (requested respiratory diagnostics according to hospital protocol: yes/no), infection control measures (droplet isolation for influenza patients: yes/no), and treatment (antibiotic and antiviral treatment according to hospital protocol: yes/no). This change to a quality of care management strategy of SARI patients, led to a more robust SARI surveillance system in the 2017/2018 season. Multiple factors were responsible for this, such as improved reporting of SARI cases, including microbiological test results, and better population coverage. At JBZ, this was made possible by more efficient screening and inclusion method by research nurses because of absence of patient informed consent procedures; the implementation of point-of-care-test leading to a

threefold increase of the number of tested SARI patients for influenza virus and RSV; and broader coverage of participating medical departments and study sites in SARI surveillance. Long-term future goals for SARI surveillance include developing a semi-automated SARI surveillance system to decrease the administrative burden and gain more sustainability.

2.3.5 Figures

Figure 2.16 SARI incidence during influenza season 2015/2016 through 2017/2018 (week 40 through week 20), in the Leiden region based on DBC/DOT codes
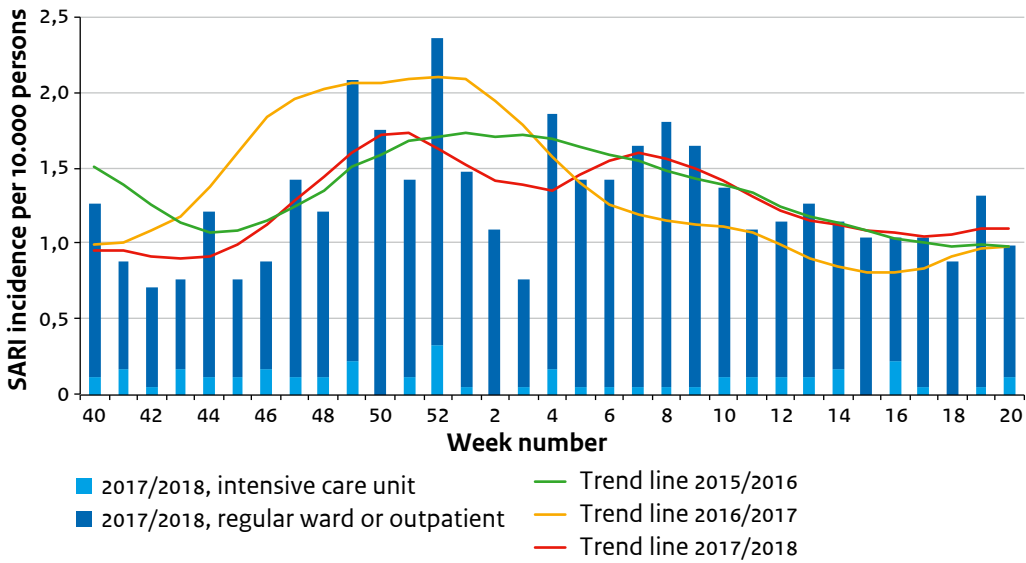
Footnote: SARI=severe acute respiratory infection

Figure 2.17 Age distribution of patients with SARI per age category in the 2015/2016 through 2017/2018 respiratory season (week 40 through week 20) in the Leiden region reported by ICARES
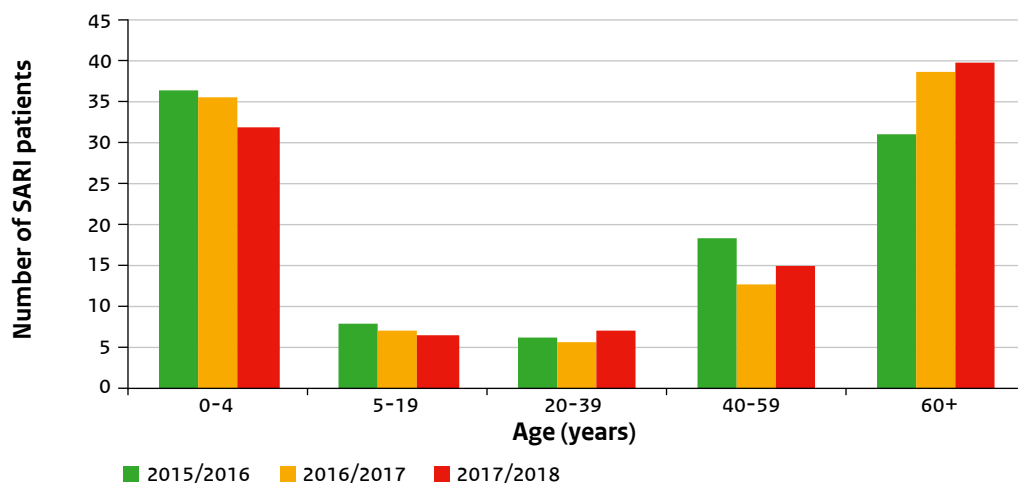
Footnote: SARI=severe acute respiratory infection

Figure 2.18 SARI incidence at the Jeroen Bosch Hospital during influenza season 2017/2018, 2016/2017 and 2015/2016
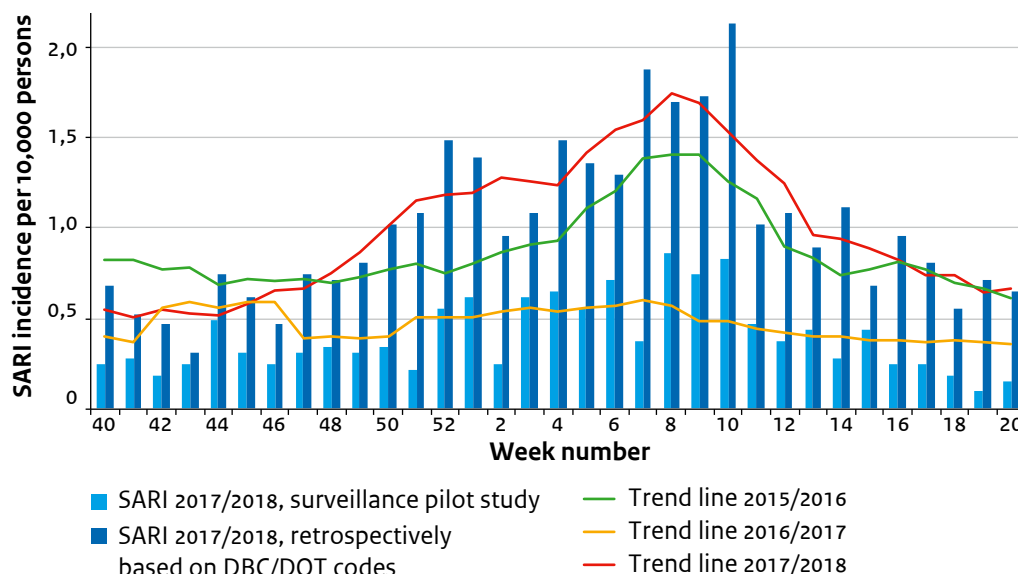
Footnote: SARI=severe acute respiratory infection

Figure 2.19 Number of SARI patients included in the SARI surveillance study at University Medical Centre Utrecht during influenza season 2017/2018
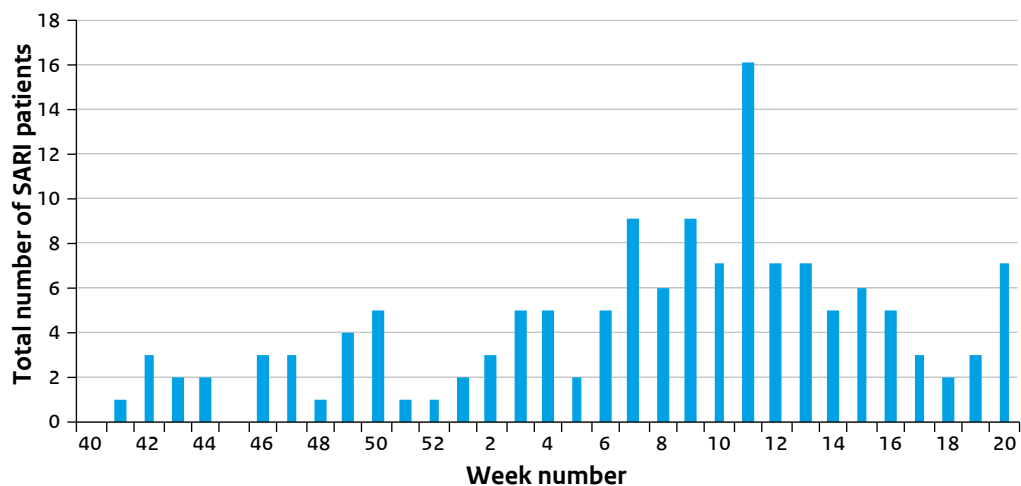
Footnote: SARI=severe acute respiratory infection

2.4 Weekly mortality monitoring

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2.4.1 Key Points

- Increased mortality started 1 week later than the influenza epidemic and ended one week before the end of the influenza epidemic (week 51 of 2017 to week 14 of 2018, with a dip in week 52). In parts of week 9 and 10 there was also a concurrent cold snap.
- Mortality peaked in week 10 with 4,049 deaths, which is the highest number since the start of the monitoring in 2009 and includes an excess of 1,189 deaths (an average of 2,773 deaths occurred weekly in the Netherlands over the past 5 years, 2013-2017).
- Cumulative excess mortality was the highest recorded since the start of the monitoring (2009): during the 18 weeks of the 2017/2018 influenza epidemic an estimated 9,444 excess deaths were reported (range: 0 to 8,582 excess deaths in the previous four epidemics).
- Cumulative excess mortality was even higher than during the 2014/2015 influenza epidemic, which was the longest recorded epidemic in the Netherlands (21 weeks with 8,582 excess deaths).
- Excess mortality was estimated at 8,885 during the total respiratory season (week 40 of 2017 through week 20 of 2018, a total of 33 weeks).
- Excess mortality was mostly observed in persons 75 years and older, but also occurred to a lesser extent in 55-64 and 65-74 year olds.

2.4.2 Background

The Dutch weekly mortality monitoring system was initiated in August 2009, during the influenza A(H1N1)pdm09 pandemic. It is a collaboration between the RIVM Centre for Infectious Disease Control (RIVM CIb) and Statistics Netherlands (CBS). The system monitors the number of deaths reported nationwide (population size of 17.1 million in 2017) from all causes, as information on cause of death is not available in real-time.

Each week, the death notification data is checked for the presence of any excess mortality (i.e. mortality levels above a pre-defined threshold) in deaths reported within 1, 2, and 3 weeks (coverage 44%, 97% and 99% respectively). Excess mortality gives an indication of the impact of any expected and unexpected events that potentially affect population health. Examples of expected events are heat waves, cold snaps, and seasonal influenza epidemics, for which the morbidity and mortality burden varies due to variations in the circulation of influenza (sub)types.

2.4.3 Epidemiological situation, season 2017/2018

In the 2017/2018 winter-season, all-cause mortality was significantly increased during 15 weeks of the 18-week influenza epidemic (week 51-2017 through 14 of 2018 with a dip in week 52) (based on deaths reported within 3 weeks). Cumulative excess mortality was estimated at 9,444 deaths occurring during the 18 weeks of the 2017/2018 influenza epidemic, which is the highest since the monitoring was initiated in 2009. It was even higher than during the longest 21-week influenza epidemic of 2014/2015 (with estimated 8,582 deaths).

The highest number of deaths (4,049 of which 1,189 were excess deaths) was observed in week 10 of 2018 (based on deaths reported within 2 weeks). This partially coincided with a cold snap that occurred in week 9 and 10: for seven consecutive days a maximum temperature of 1°C or less was measured from February 25th to March 3rd (-5 °C to 1°C).

During the influenza epidemic the highest excess mortality was observed in persons 75 years and older (7,633 excess deaths), but excess was also observed in 55-64 year olds (353 excess deaths) and 65-74 year olds (1,089 excess deaths) (based on deaths reported within 3 weeks).

Excess Mortality in Europe

The Netherlands participates in weekly mortality monitoring at a European level in the EuroMOMO collaboration [www.EuroMOMO.eu] (Vestergaard, Nielsen et al. 2017). The majority of 24 participating European countries have had a marked excess in all-cause mortality, the start of which varied by country between early December 2017 to early February. In week 48 2017, the pooled excess all-cause mortality of the 24 participating countries rose sharply in the age groups 15-64 years and 65 years or older. The excess mortality peaked in the beginning of 2018, but a second lower peak occurred in February-March 2018. The influenza season in Europe was dominated by the influenza B virus of the Yamagata lineage and Europe experienced a cold snap at the end of February/beginning of March (report in preparation).

2.4.4 Discussion

In terms of number of excess deaths during the influenza epidemic (weeks 50 2017 – 15 2018), the 2017/2018 season in the Netherlands was more severe than any in the past 8 years (since the start of the mortality monitoring). Cumulated excess deaths were even higher than in the 2014/2015 season, which was the longest recorded epidemic in the Netherlands with 21-weeks and with an estimated 8,582 excess deaths vs 9,444 excess deaths in the current season. However, when comparing the total respiratory season (weeks 40 through 20), both seasons were more comparable (8,885 vs 9,199) excess deaths. The number of excess deaths during the total respiratory season (31 weeks) are lower than during the epidemic (18 weeks), because the overall mortality decreased below the threshold in the weeks after the epidemic, which could be (in part) due to a harvesting effect.

The influenza epidemic often coincides with increased mortality. It is assumed that influenza plays a role in the increased mortality observed during wintertime in the Northern Hemisphere (Mølbak, Espenhain et al. 2015). Other typical winter pathogens can also play a role in increased seasonal mortality, such as RS-virus and norovirus (van Asten, van den Wijngaard et al. 2012). Cold temperatures may also play a role in increased mortality. There was a 7-day cold snap during the influenza epidemic in week 9 and 10 (end of February/beginning of May). This coincided with the highest mortality peak observed in the past 10 years, which was in week 10 with 1,189 excess deaths.

Estimates of influenza-attributable deaths have been made using statistical models. Although estimates vary hugely between seasons due to influenza virus strain variability, an average of 1,400 - 2700 deaths per year for the Netherlands were estimated to be attributable to influenza A and B infections based on data from 1999-2009 (van Asten, van den Wijngaard et al. 2012, van den Wijngaard, Asten et al. 2012). Updates of these estimates for more recent years are required to see if influenza-attributable mortality is increasing in recent years.

Weekly mortality monitoring is performed using unspecified mortality data. Using cause-specific death reports to estimate the impact of influenza circulation on weekly mortality is not an option because: 1) deaths registered as influenza deaths reflect only a small part of the mortality attributable to influenza, because laboratory diagnosis is usually not performed, 2) in the elderly, underlying chronic conditions are often recorded as the cause of death on the death certificate, even if influenza infection might have played an additional role and, 3) crude mortality data is available in a much more timely fashion than death-cause-specific data, the latter being available per quarter rather than per week in the Netherlands.

Figure 2.20 Weekly number of deaths from 2010 to 2018 (through week 20 of 2018) by date of death (notified within three weeks from date of death).
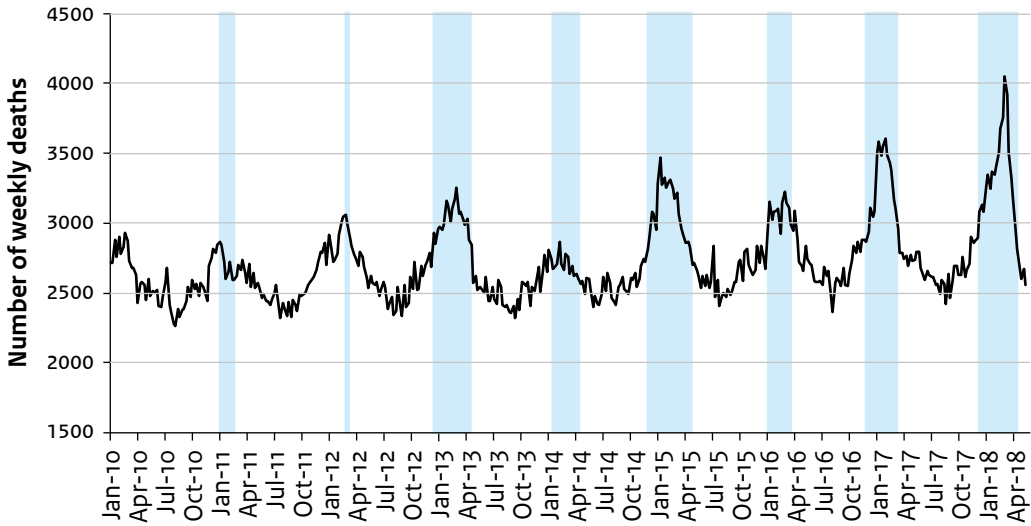
Footnote: Black line: deaths notified within three weeks. Blue shading: influenza epidemic weeks.

Figure 2.21 Observed and expected ('baseline') weekly number of deaths
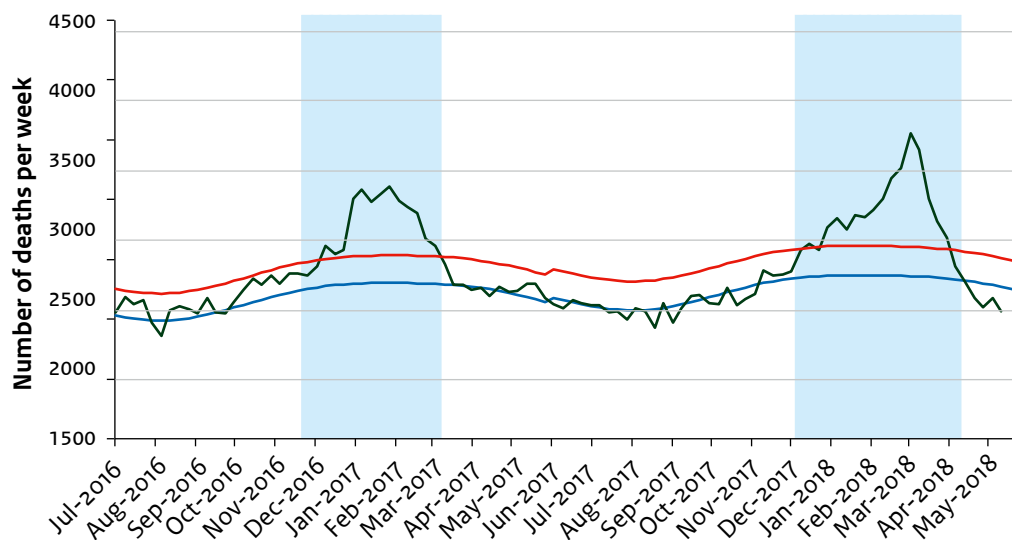
Footnote: Data from July 2016 to May 2018 with the influenza epidemic weeks depicted by blue shading.
Black line: number of deaths per week (reported within three weeks).
Blue line: expected number of deaths (calculated using historical data in which extremes were excluded).
Red line: prediction limit.

Chapter 3
Influenza

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3.1 Key points

- In the 2017/2018 winter season, the influenza epidemic lasted 18 weeks.
- Type B (Yamagata lineage) was the predominant influenza virus detected during most of the epidemic, while influenza virus types A(H3N2) and A(H1N1)pdm09 predominated during the last weeks of the epidemic.
- An influenza virus type B (Yamagata lineage) strain was not included in the 2017/2018 trivalent vaccine, which was used in the Netherlands.
- The number of influenza virus type B diagnoses was higher than in the ten preceding seasons in the virological laboratory surveillance.
- In the 2017/2018 respiratory season 5,440 (95% uncertainty interval (UI): 4,760-6,230) per 100,000 inhabitants had symptoms of an influenza virus infection, which was higher than in the four previous seasons. Symptomatic influenza incidence in respiratory season 2017/2018 was highest for the age group 0-4 years, corresponding to an estimated 90,300 cases, compared with an estimated 542,000 cases among the working age (15-64 years) inhabitants.
- Except for one A(H1N1)pdm09 virus, all 744 viruses tested for antiviral susceptibility were sensitive for neuraminidase inhibitors.
- In the Netherlands, the vaccine effectiveness (VE) against laboratory confirmed influenza virus type B (Yamagata lineage) infection was estimated at 44% [95% confidence interval (CI): 11% to 65%] overall. For people younger than 60 years, the VE against this virus type was 39% (95% CI: -31% to 72%), and for people 60 years and older 56% (95% CI: 11 to 78%).
- Preliminary end-of-season estimates of the European I-MOVE study, in which the Netherlands participates, shows a lower influenza VE of 23% [95% CI: 8% – 36%] for patients at the primary care level against influenza type B (Yamagata lineage) and 32% [95% CI: 18% - 44%] at the secondary care level against any influenza type B.

3.2   Background

Influenza is an acute respiratory infection caused by influenza viruses. Most patients recover quickly, although an influenza virus infection can cause severe illness especially in the elderly and in patients with an underlying medical condition.
Human influenza viruses cause yearly epidemics, mostly in winter. Most influenza virus infections in humans are caused by the influenza virus types A and B. Influenza type A viruses are divided into subtypes, based on proteins on the surface of the virus: hemagglutinin (HA) and neuraminidase (NA). Many different combinations of HA and NA proteins are possible, for example H1N1 and H3N2, the subtypes currently causing epidemics. Influenza type B viruses are divided into genetic lineages based on their gene coding for the HA. Currently, circulating influenza B viruses belong to the lineage B/Yamagata/16/88 or B/Victoria/2/87. Both type A and B influenza viruses are constantly mutating, possibly resulting in small phenotypic changes that are called antigenic drift and might escape existing or vaccine induced immunity.

3.3   Epidemiological situation, season 2017/2018

In the 2017/2018 season, there was an influenza epidemic from week 50 of 2017 through week 15 of 2018. More information about influenza-like illness (ILI) incidence measured by sentinel general practitioner (GP) surveillance can be found in Chapter 2.1. During almost the entire epidemic, influenza virus B (Yamagata lineage) predominated in sampled ILI and other acute respiratory infections (ARI) patients from GP sentinel surveillance. In the virological laboratory surveillance, the number of influenza virus type B diagnoses was higher than in ten preceding seasons. In the last weeks of the epidemic, influenza virus type A was predominant, with subtypes A(H1N1)pdm09 and A(H3N2) detected in equal proportions. In the ILI incidence two peaks were notable; the first peak in week 4 of 2018 was largely caused by influenza virus type B infections in sampled ILI patients, and the second peak in week 10 by the emergence of influenza type A detections on top of the declining influenza type B detections. In the weeks outside the epidemic period (week 40-49 of 2017, and week 16-20 of 2018), the percentage influenza virus positive ILI specimens in the GP sentinel surveillance ranged from 0% 40%. During the epidemic, the percentage influenza virus positive ILI specimens ranged from 29% - 83%. In routine GP ILI and other ARI virologic surveillance a seasonal reassortant A(H1N2) influenza virus was detected in a single sample from a 3-year old ILI patient without indication of further transmission, which harboured two genome segments (HA and NS) from seasonal A(H1N1)pdm09 and the other six genome segments from seasonal A(H3N2) virus (Meijer, Swaan et al. 2018).

The dominating virus of the 2017/2018 season, type B (Yamagata lineage), was not included in the 2017/2018 trivalent influenza vaccine (TIV). However, the vaccine effectiveness (VE) against this virus detected by sentinel GP surveillance was moderate with 44% (95% confidence interval (CI): 11% - 65%) in Dutch estimates for all ages, and 23% [95% CI: 8% - 36%] in preliminary end-of-season European estimates, to which the Netherlands also contributed data. Two distinct genetic groups of A(H3N2) viruses were observed by sequencing of the HA. Similar to previous seasons, antigenic characterisation of A(H3N2) viruses was difficult due to lack of hemagglutination and virus neutralisation assays had to be used instead. Limited virus neutralisation data showed, despite the genetic diversification, a good to moderate antigenic match with the vaccine strain. Genetically, all sequenced A(H1N1)pdm09 viruses belonged to the same genetic HA group with little diversification. As a consequence, the circulating A(H1N1) pdm09 influenza viruses were antigenically indistinguishable from the vaccine virus. Although type B (Victoria-lineage) was only detected sporadically, all sequenced B (Victoria-lineage) viruses contained a deletion in the HA that resulted in these viruses being antigenically different from the vaccine virus. The B (Yamagata-lineage) viruses showed little genetic diversification of the HA and good to moderate antigenic match with the vaccine strain included in quadrivalent influenza vaccine (QIV) used elsewhere.

Influenza incidence estimated using statistical modelling can be used to compare the intensity of symptomatic influenza virus infection in the total population between seasons. This incidence estimate combines medically-attended ILI incidence, the estimated non-medically attended ILI incidence, and the percentage specimens positive for influenza virus (McDonald, Presanis et al. 2014). During the 2017/2018 season, an estimated 5440 (95% uncertainty interval (UI): 4760-6230) per 100,000 inhabitants had ILI symptoms caused by an influenza virus infection, which was higher than in the four previous seasons. The estimated symptomatic influenza incidence in the 2017/2018 respiratory season was highest in children in the age group 0-4 years (10,410 per 100,000 inhabitants of 0-4 years (95% UI 5910-18,990)). This corresponds to an estimated 90,300 children of 0-4 years; for comparison an estimated 542,000 persons of working age (15-64 years) had symptomatic influenza in the 2017/18 season. In all age groups, estimated symptomatic influenza incidence was higher than in all previous four seasons.

In the 2017/2018 season there was considerable media attention about hospitals overwhelmed by patients with influenza virus infections. Unfortunately, we only have information from a few hospitals that participate in a severe acute respiratory infection (SARI) pilot study and not on a national level. This SARI surveillance pilot study started its third season at the Jeroen Bosch Hospital (JBZ) and Leiden University Medical Centre (LUMC), while University Medical Centre Utrecht (UMC Utrecht) joined late 2017. During the influenza season 2017/2018, 304 respiratory specimens of 427 SARI patients in JBZ were tested for influenza virus (71%). In 130 of 304 respiratory specimens, influenza virus was detected (43%), of which 31% type A and 69% type B. The median age of SARI patients with a positive influenza virus test was 73 years (SD 16, range 0-96). Influenza B (Yamagata-lineage) was the dominant strain detected at the JBZ (30% of all influenza virus tests).

3.4 Discussion

During the 18-week epidemic in the 2017/2018 season, influenza virus B (Yamagata-lineage) was predominant; however, this virus was not included in the trivalent influenza vaccine used for the 2017/2018 season in the Netherlands. Despite this lineage mismatch, the influenza vaccine effectiveness (VE) was moderate against this B lineage. A possible explanation for the moderate VE is cross protection by antibodies induced by influenza virus type B (Victoria lineage) which was included in the 2017/2018 trivalent vaccine [http://www.who.int/influenza/ vaccines/virus/recommendations/201709_qanda_recommendation.pdf]. Because of the good match between the circulating A(H1N1)pdm09 viruses and the A(H1N1)pdm09 vaccine strain A/ Michigan/45/2015-like virus, this strain has again been selected by the WHO for the trivalent vaccine for the 2018/2019 season in the northern hemisphere [http://www.who.int/influenza/ vaccines/virus/recommendations/2018_19_north/en/]. The B component in the 2017/2018 trivalent vaccine remains a B (Victoria-lineage) component, but will be updated to a B/ Colorado/06/2017-like virus, because of the emergence of the deletion variants of B (Victoria-lineage) viruses and antigenic drift between these circulating viruses and the 2017/2018 vaccine strain. As a third component, an A(H3N2) A/Singapore/INFIMH-16-0019/2016-like virus was selected for the 2018/2019 vaccine. This is a change compared to the 2017/2018 season and the updated vaccine strain shows a higher degree of affinity with the circulating A(H3N2) viruses. In the WHO vaccine recommendations, the composition of the QIV is now mentioned first. In this QIV, a B (Victoria-lineage) as well as a B (Yamagata-lineage) virus are included. The B (Yamagata-lineage) vaccine strain B/Phuket/3073/2013-like for 2018/2019 season is the same as included in the 2017/2018 QIV.

The low number of specimens that is generally available from sentinel GP surveillance results in broad confidence intervals in VE analyses, especially in age-stratified analyses. To overcome this problem, the Netherlands has participated in the I-MOVE (<65 years) and I-MOVE+ (≥65 years) studies since the 2015/2016 season, and contributes data to a pooled VE analysis. The European point estimate is somewhat lower than Dutch estimate for the predominating influenza virus type B (Yamagata- lineage) in the 2017/2018 season; however, the 95% confidence intervals are overlapping. Influenza VE remains suboptimal and is lower overall than the effectiveness of many childhood vaccinations. This can partly be explained by the unpredictability of which influenza virus type and subtype or lineage will dominate in the coming season and what the antigenic properties will be. Circulating influenza viruses evolve over time and therefore can antigenically deviate from the selected vaccine viruses and vaccine of which the production has started half a year before the vaccination campaign starts (Meijer, Timmermans et al. 2017).

More SARI patients were included in the SARI surveillance pilot study in 2017/2018 than in the preceding two influenza seasons. The quality-of-care management strategy of SARI patients, in effect from February 2017 in the JBZ hospital (see Chapter 2.3), has improved SARI surveillance through more efficient screening and inclusion of SARI patients. A higher percentage of SARI patients had been tested for influenza virus by their treating physicians at the JBZ during the 2017/2018 influenza season. This was largely due to implementation of a point-of-care test for influenza at the Emergency Department. This is a PCR-based point-of-care-test for influenza virus types A and B and RSV, with a turnaround time of 20 minutes. In addition, a separate ward for influenza virus-positive patients was established to facilitate cohort isolation.

3.5 Tables and figures

Virus surveillance

Table 3.1 Characteristics of influenza-like illness (ILI) and other acute respiratory infection (ARI) patients, who are sampled in the Nivel GP sentinel surveillance in the 2017/2018 season (through week 20 of 2018) (Source: NIC location RIVM).

Characteristics	ILI patients n/N (%)	Other ARI patients n/N (%)
Male gender	331/785 (42)	203/451 (45)
Vaccinated against influenza	154/783 (20)	122/450 (27)
If yes, brand was Influvac If yes, brand was Vaxigrip	119/152 (78) 33/152 (22)	108/120 (90) 12/120 (10)
Belongs to target group for vaccination	267/784 (34)	211/451 (47)
Lung disease (e.g. asthma, COPD)	98/267 (37)	94/211 (45)
Immune deficiency due to treatment (e.g. chemotherapy and radiotherapy)	13/267 (5)	7/211 (3)
Immune deficiency due to disease (e.g. HIV)	4/267 (2)	6/211 (3)
Cardiac disease (myocardial infarction, angina pectoris, arrhythmias, valvular heart disease, heart failure)	37/267 (14)	42/211 (20)
Diabetes mellitus	43/267 (16)	32/211 (15)
Obesitas	112/775 (14)	51/442 (12)

Characteristics	ILI patients n/N (%)	Other ARI patients n/N (%)
Smoking:		
Yes or stopped < 1 year	86/760 (11)	56/429 (13)
No, stopped > 1 year	91/760 (12)	55/429 (13)
Never	583/760 (77)	318/429 (74)
Women:		
Pregnant	6/454 (1)	2/248 (1)
People ≥65 years and older:		
Needs assistance with showering	4/120 (3)	3/117 (3)
Needs assistance with walking	3/120 (2)	2/117 (2)
Delay in sampling, in days[a]	3 (2-5)	4 (3-7)

[a] Number of days between the first day of illness and the day of sampling (median, 1st, and 3rd quartile)

Footnote: ILI =influenza-like illness; ARI = acute respiratory tract infection; GP = general practitioner; n = the number in the corresponding group; N = total number of patients, for whom the information was available. Please note that for the virological surveillance, the ARI patients do not include the ILI patients, hence the notation 'other ARI'.

Figure 3.1 Age distribution of ILI and other ARI patients, sampled by Nivel sentinel GPs, and the ILI cumulative seasonal incidence per age category in the 2017/2018 respiratory season (week 40 of 2017 through week 20 of 2018) (Source: Nivel Primary Care Database, NIC location RIVM).
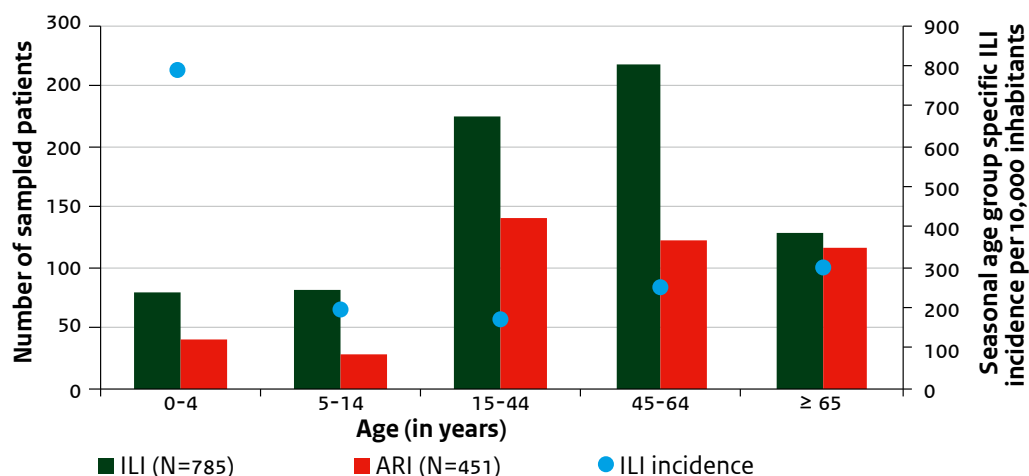
Footnote: ILI = influenza-like illness; ARI = other acute respiratory tract infections, GP = general practitioner. Please note that for the virological surveillance, the ARI patients do not include the ILI patients, hence the notation 'other ARI'.

Figure 3.2 Number and proportion of detected influenza viruses among ILI and other ARI patients, who were sampled in the Nivel GP sentinel surveillance in the 2017/2018 respiratory season (through week 20 of 2018) (Source: NIC location RIVM).
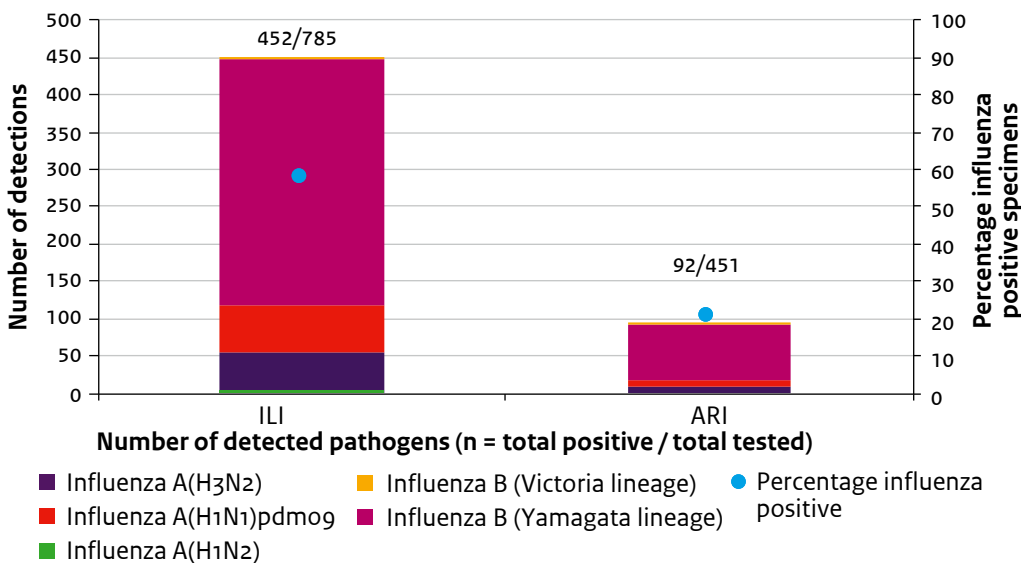
Footnote: ILI =influenza-like illness; ARI = other acute respiratory tract infection.
Please note that for the virological surveillance, the ARI patients do not include the ILI patients, hence other ARI.

Figure 3.3 Percentage of ILI specimens taken by sentinel GPs positive for influenza virus, and ILI incidence with epidemic threshold during the 2017/2018 respiratory season (week 40 of 2017 through week 20 of 2018), displayed by week of sampling (Source: Nivel Primary Care Database, NIC location RIVM).
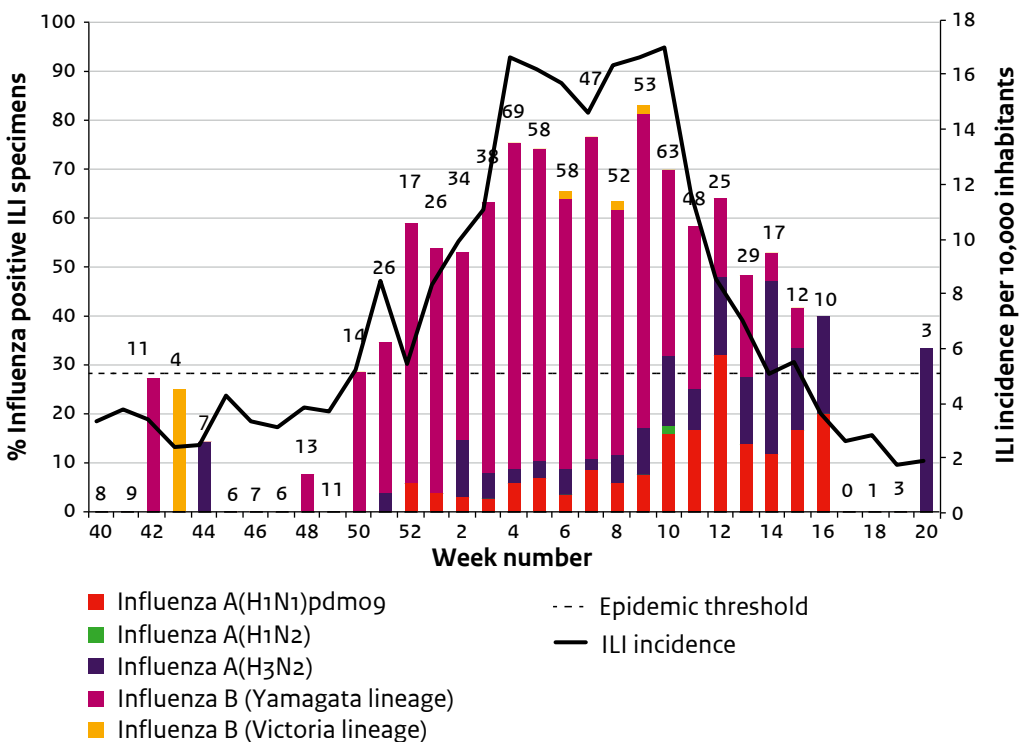
Footnote: ILI = influenza-like illness; GP = general practitioner
The numbers above the bars are the total number of tested specimens.

Figure 3.4 Percentage of influenza virus positive specimens among ILI (graph A) and other ARI (graph B) patients per age group, taken by sentinel GPs, during the epidemic weeks (week 50 of 2017 through 15 of 2018) of the 2017/2018 season (Source: NIC location RIVM).
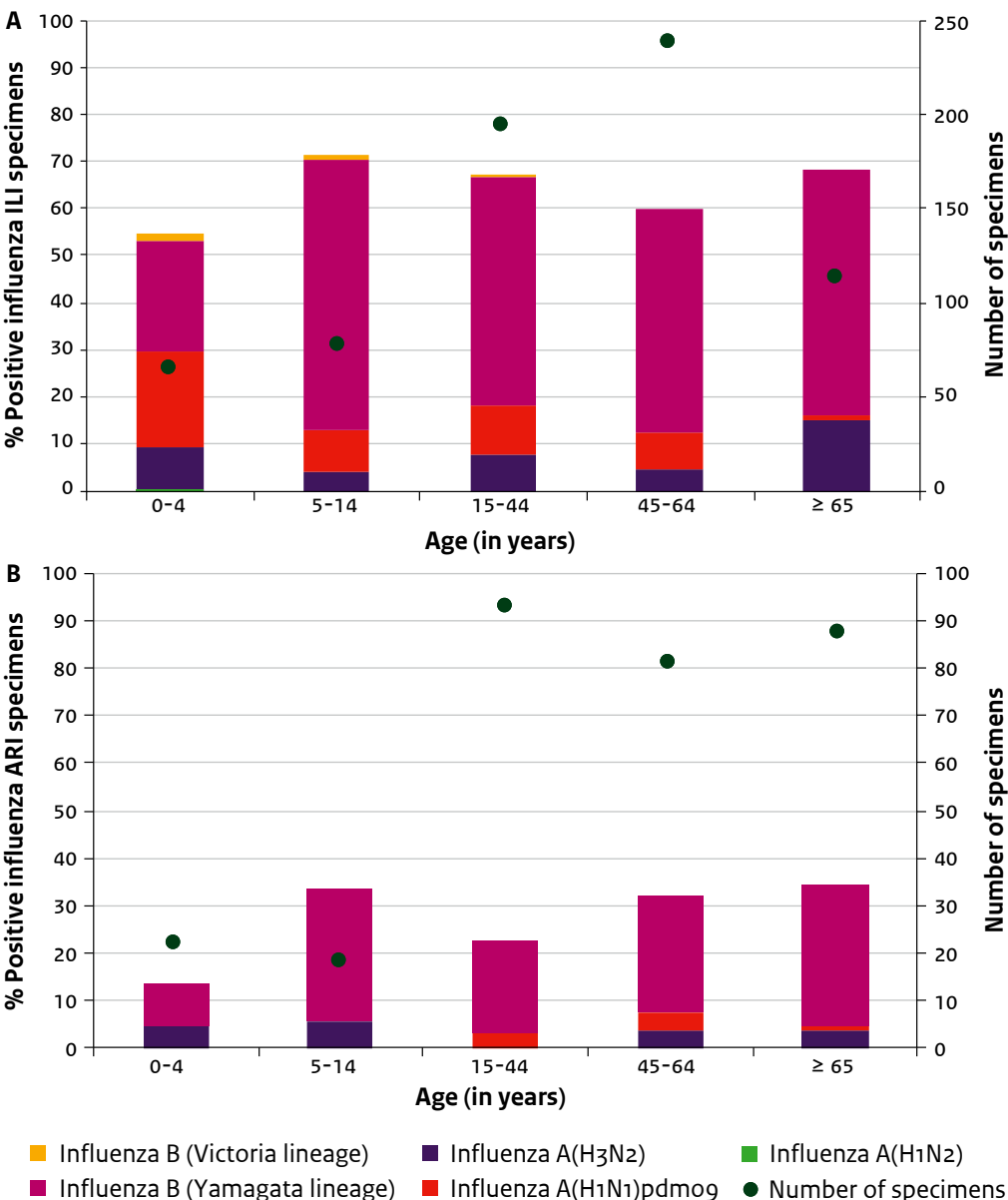
Footnote: ARI = acute respiratory tract infection, ILI = influenza-like illness
Please note that for the virological surveillance, the ARI patients do not include the ILI patients, hence other ARI.

Figure 3.5 Subtyping of influenza viruses submitted by Dutch laboratories to the NIC location Erasmus MC during the 2017/2018 season, displayed by week of specimen collection, excluding specimens taken for sentinel GP surveillance and the SNIV nursing home surveillance (Source: NIC location Erasmus MC).
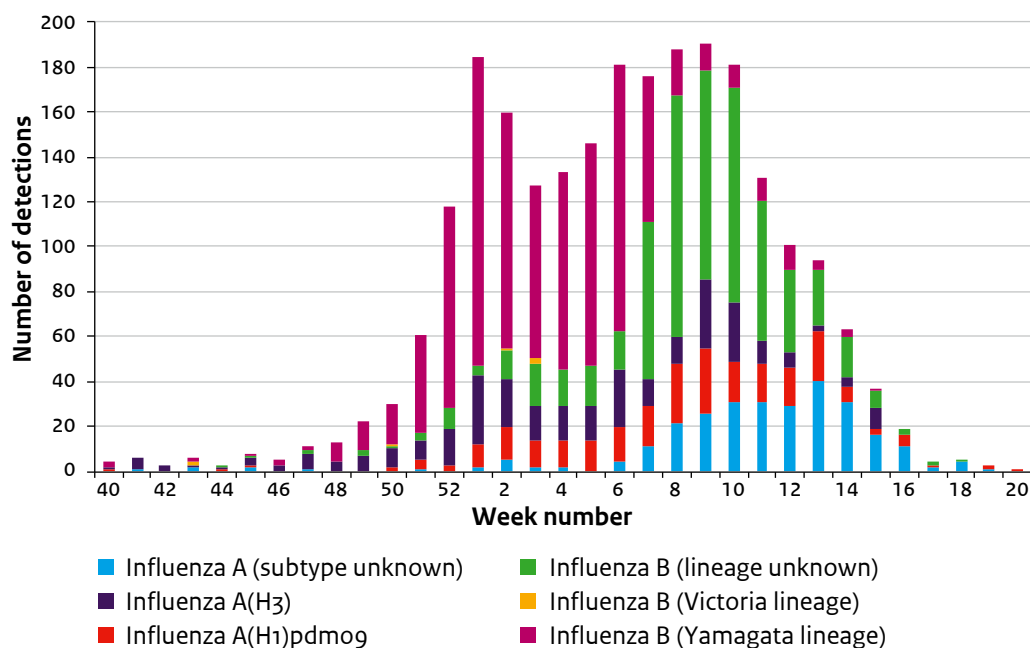
Footnote: GP = general practitioner.

Note: Since the beginning of 2018, the laboratories have been asked to send only a representative set of influenza virus positive samples per week (5-6 specimens) to the Erasmus MC. Therefore, the trend in the samples received by Erasmus MC is no longer a reflection of the course of the epidemic. The peak seen between weeks 3 and 16 is driven by one diagnostic laboratory that submitted all influenza virus positive specimens. The graph only shows what viruses were submitted to the Erasmus MC for further characterization. In addition, since week 7 2018, the Erasmus MC has decided not to subtype all submitted viruses anymore, due to the large numbers received viruses. The laboratory in the region where the A(H1N2) reassortant virus was detected has been asked to send all influenza viruses type A to the Erasmus MC that were detected in the month preceding confirmation of the A(H1N2) case 18 March 2018.

Figure 3.6 Subtyping of influenza viruses submitted by Dutch laboratories to the NIC location Erasmus MC during the 2017/2018 season, displayed by week of specimen collection, excluding specimens taken for sentinel GP surveillance and the SNIV nursing home surveillance, per age group (Source: NIC location Erasmus MC).
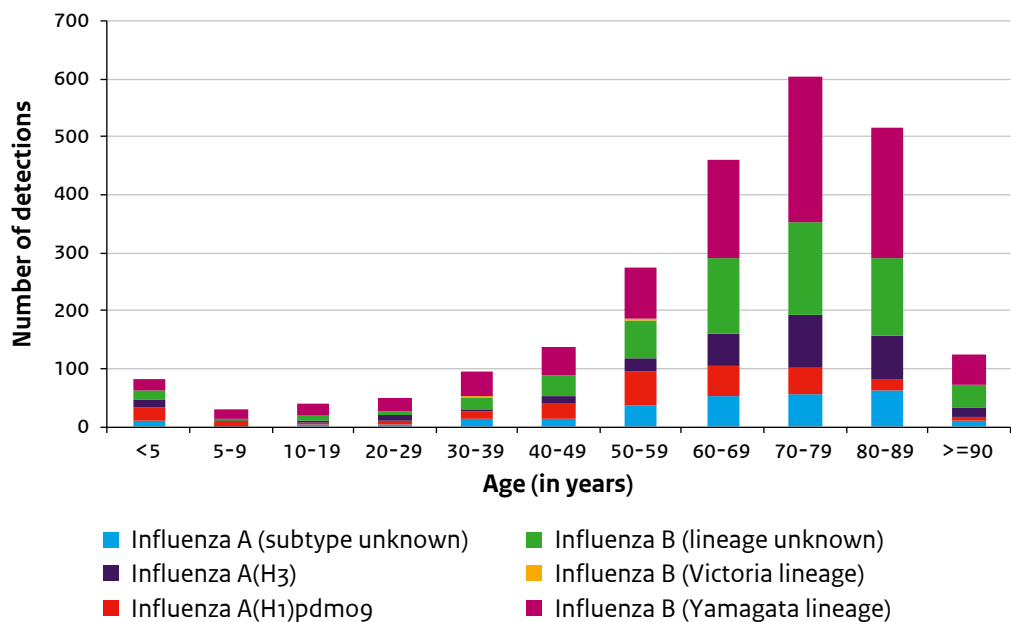
Footnote: GP = general practitioner.
Note: Since the beginning of 2018, the laboratories have been asked to send only a representative set of influenza virus positive samples per week (5-6 specimens) to the Erasmus MC which might have influenced the number submitted per age group.

Table 3.2 Genetic characterisation of influenza viruses, week 40 of 2017 through week 13 of 2018 (Source: NIC location RIVM, NIC location Erasmus MC; status by 2 May 2018)

Virus (sub)type	Clade	Antigenic match with 2017/2018 vaccine strains[a]	Source	
			Sentinel GP[b]	Virology labs[c]
A(H1N1)pdm09 (n=39)	6B.1	Good	35	4
A(H3N2) (n=50)	3C.2a2	Good to moderate[d]	24	4
	3C.2a1b + 135T	Good to moderate[d]	12	3
	3C.2a1b + 135N	Good to moderate[d]	1	0
	3C.2a3	Good to moderate[d]	0	2
B-Yamagata (n=126)	3	Absent[f]	124	2
B-Victoria (n=3)	1A subgroup with 162-163 amino acid deletion[g]	Bad	2	1

Footnote: GP = general practitioner

[a] Composition 2017/2018 vaccine: an A/Michigan/45/2015 (H1N1)pdm09-like virus; an A/Hong Kong/4801/2014 (H3N2)-like virus; and a B/Brisbane/60/2008-like (Victoria lineage) virus. Antigenic match based on a limited number of Dutch viruses analysed and the WHO CC, London, interim report. (https://www.crick.ac.uk/media/409431/crick_feb2018_report_for_the_web.pdf).

[b] Source NIC location RIVM.

[c] Source NIC location Erasmus MC.

[d] Clade 3C.2a viruses and its subclades match antigenic moderately with the egg-grown vaccine strain A/HongKong/4801/2014, but match well with the cell-grown vaccine strain and the egg-grown A/Singapore/INFIMH-16-0019/2016 vaccine virus recommended for the 2018/2019 season. Egg-grown viruses are used for vaccine production.

[f] A B-Yamagata lineage virus was not included in the trivalent influenza vaccines used in the Dutch National Influenza Prevention Programme (NPG) in the 2017/2018 season.

[g] In the 2016/2017 Northern Hemisphere and 2017 Southern Hemisphere season, variants of the Victoria lineage of influenza type B viruses emerged with 2 (position 162-163) or 3 (position 162-164) amino acid deletions in the haemagglutinin resulting in antigenic drift and mismatch with the current vaccine strain B/Brisbane/60/2008-like (Victoria lineage) virus.

Figure 3.7 Phylogenetic analysis of the haemagglutinin gene of A(H3N2) influenza viruses sequenced directly from clinical specimens collected week 40 of 2017 through week 13 of 2018 (Source: NIC location RIVM, NIC location Erasmus MC; status by 2 May 2018).
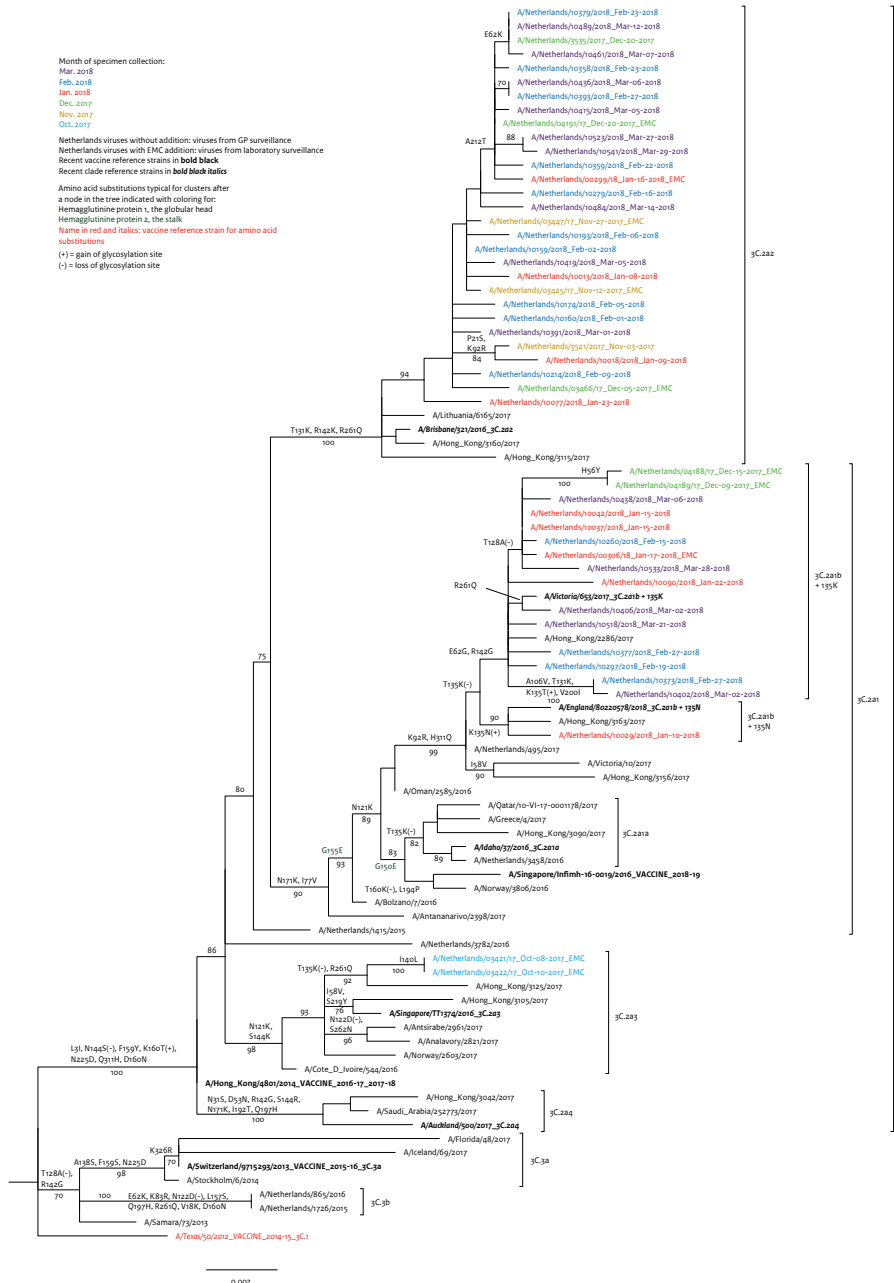
Table 3.3 Influenza virus diagnostics of SARI patients; comparison influenza season 2015/2016, 2016/2017 and 2017/2018 at the Jeroen Bosch Hospital

Total	Influenza season[a] 2015/2016[b] N=138	Influenza season[a] 2016/2017 N=175	Influenza season[a] 2017/2018 N=427
	N (%)	N (%)	N (%)
Influenza test performed	90 (65)	101 (58)	304 (71)
Influenza virus positive	32 (36)	38 (38)	130 (43)
Type A and B	0	0	2
Type A	24 (75)	38 (100)	42 (31)
H3N2[c]	0 (0)	32 (84)	18 (43)
H1N1pdm09[c]	17 (71)	0 (0)	10 (24)
Missing[d]	7 (29)	6 (16)	14 (33)
Type B	8 (25)	0 (0)	90 (69)
Yamagata[c]	0 (0)	0 (0)	67 (74)
Victoria[c]	4 (50)	0 (0)	0 (0)
Missing[d]	4 (50)	0 (0)	23 (26)
Influenza virus negative	58 (64)	74 (42)	174 (57)

Footnote: SARI = severe acute respiratory infection; N = Number of SARI patients.

[a] Influenza season = week 40 through week 20 the following year.
[b] Influenza season 2015/2016 is limited from week 42 of 2015 through week 20 of 2016.
[c] Influenza virus A subtype and B lineage determined at NIC location RIVM.
[d] Missing, because SARI surveillance pilot study is dependent on routinely collected, residual respiratory material.

Symptomatic influenza incidence estimation

Figure 3.8 Estimated symptomatic influenza (SI) incidence per 100,000 inhabitants during the respiratory season (week 40 through week 20 the next year), outside the respiratory season (week 21 through week 39) and for the total respiratory year (week 40 through week 39 the next year) , for the seasons 2013/2014 through 2017/2018 (Source: Nivel Primary Care Database, NIC location RIVM, Influenzanet).
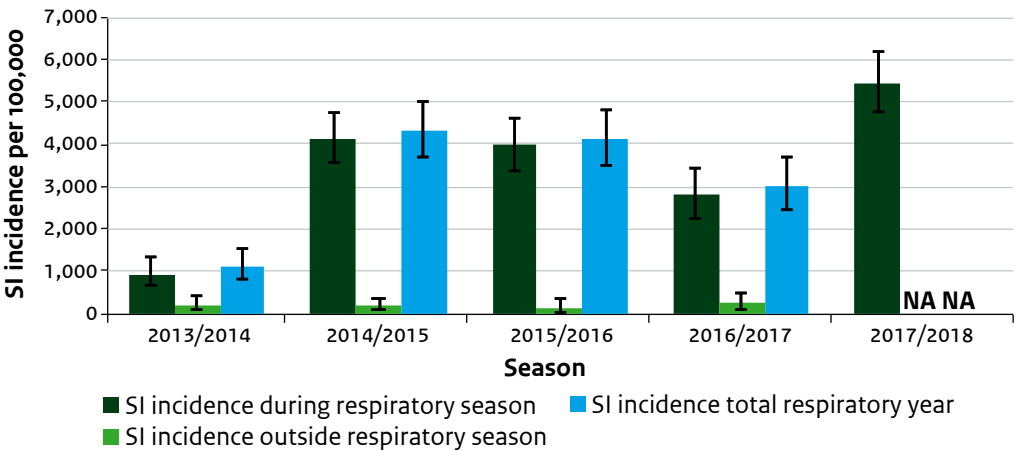
Footnote: NA= not applicable.
Error bars represent 95% uncertainty intervals (UI). For the 2017/2018 season, no numbers for outside the respiratory season were yet available.

Figure 3.9 Estimated symptomatic influenza (SI) incidence per 100,000 inhabitants by subtype for the respiratory seasons (week 40 through week 20) 2013/2014 through 2017/2018 (Source: Nivel Primary Care Database, NIC location RIVM, Influenzanet).
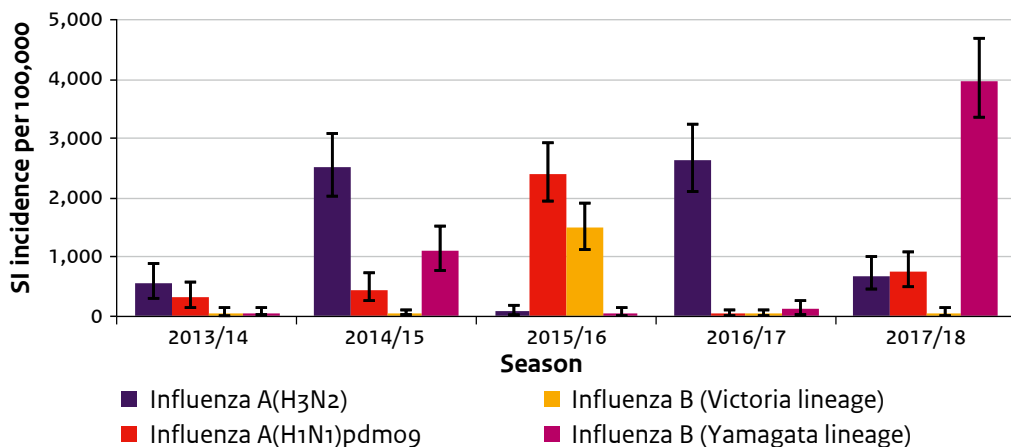
Footnote: Error bars represent 95% uncertainty intervals (UI).

Figure 3.10 Estimated symptomatic influenza (SI) incidence per 100,000 inhabitants by age group for the respiratory seasons (week 40 through week 20) 2013/2014 through 2017/2018 (Source: Nivel Primary Care Database, NIC location RIVM, Influenzanet).
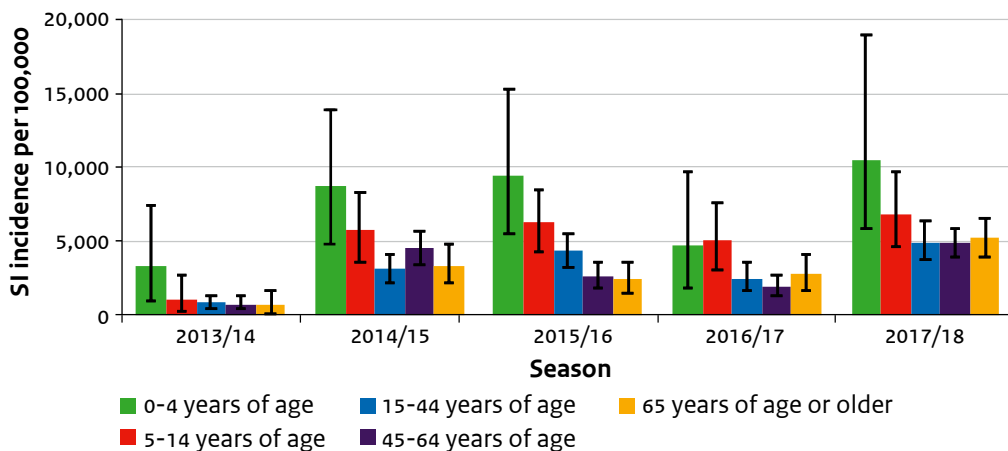
Footnote: Error bars represent 95% uncertainty intervals (UI).

Influenza diagnostics in virological laboratories

Figure 3.11 Weekly number of influenza virus type A and B diagnoses, reported by the virological laboratory surveillance in the period week 1 of 2008 through week 20 of 2018 (Source: Virological laboratory surveillance, RIVM).
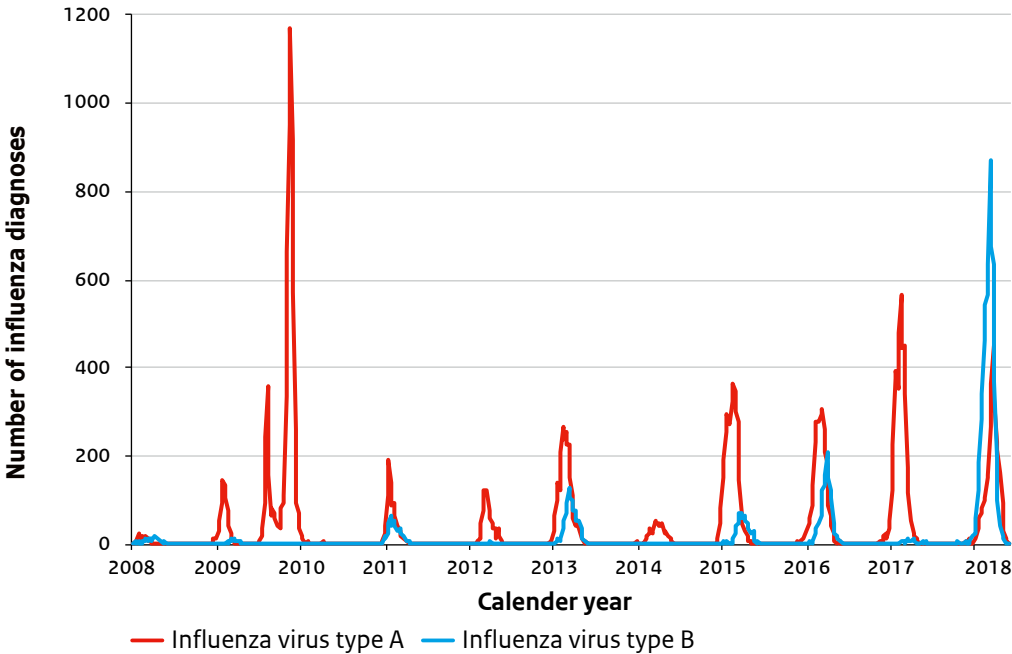
Figure 3.12 Weekly number of influenza virus type A and B diagnoses reported in the virological laboratory surveillance, for the period week 40 of 2017 through week 20 of 2018 (Source: Virological laboratory surveillance, RIVM).
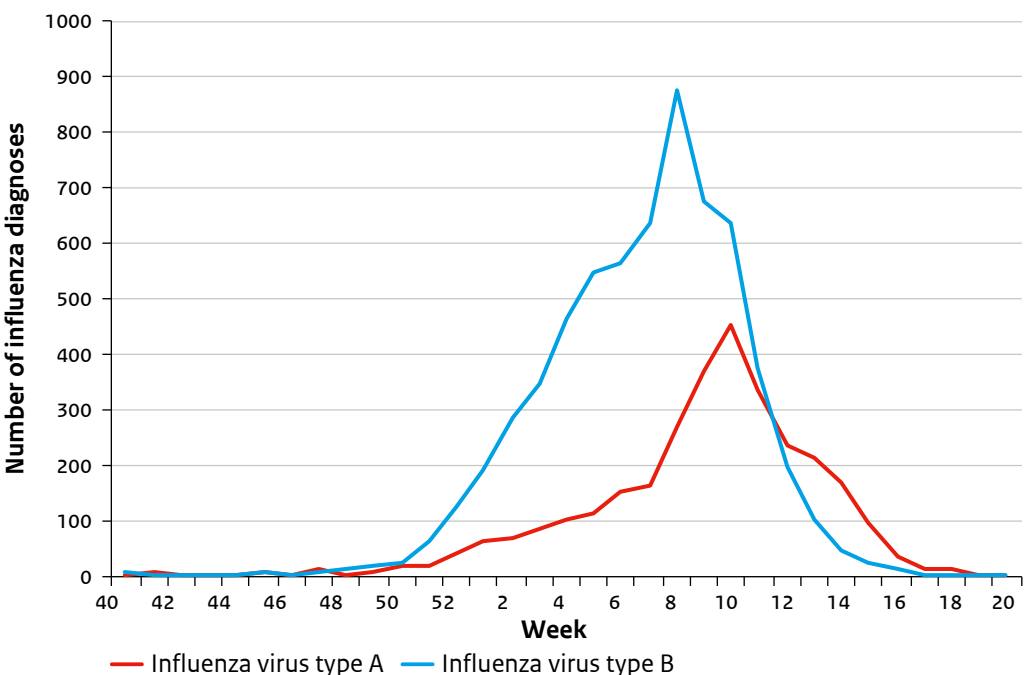
Antiviral resistance

Table 3.4 Reduced inhibition of influenza viruses by neuraminidase inhibitors and M2 ion-channel blockers, 2015/2016 – 2017/2018 (Source: NIC location RIVM, NIC location Erasmus MC)[a]

Antiviral Influenza virus (sub)type	Viruses with reduced inhibition by season		
	2015/2016 n/N (%)	2016/2017 n/N (%)	2017/2018 n/N (%)[b]
Neuraminidase inhibitor			
A(H1N1)pdm09	1/1191 (<1)[c]	2/11 (18)[d]	1/233 (1)[e]
A(H3N2)	0/44 (0)	0/911 (0)	0/355 (0)
B	1/69 (1.5)[f]	0/14 (0)	0/156 (0)
M2 ion-channel blocker			
A(H1N1)pdm09	73/73 (100)	2/2 (100)	1/1 (100)
A(H3N2)	4/4 (100)	56/56 (100)	1/1 (100)

[a] Combined results obtained with phenotypic (virus isolates) and genotypic (clinical specimens) assays. Season defined as week 40 of the first year to week 39 of the following year.

[b] Preliminary data week 40/2017 through week 18/2018; status by 4 May 2018.

[c] One virus with highly reduced inhibition by oseltamivir due to mixture 275H/Y amino acid substitution in the neuraminidase. No patient characteristics or antiviral exposure data available.

[d] Two viruses from one patient taken 10 days apart with both highly reduced inhibition by oseltamivir due to a H275Y amino acid substitution. The patient was treated with oseltamivir prior to specimen collection.

[e] One virus with highly reduced inhibition by oseltamivir due to mixture 275H/Y amino acid substitution in the neuraminidase. No patient characteristics or antiviral exposure data available.

[f] One virus with highly reduced inhibition by zanamivir and reduced inhibition by oseltamivir due to an E105K amino acid substitution in the neuraminidase. However, highly likely induced by virus isolation as in the clinical specimen this amino acid substitution was not detectable. The patient was not treated with antivirals prior to specimen collection.

Influenza vaccine effectiveness

Figure 3.13 Influenza vaccine effectiveness in the 2017/2018 season in the Netherlands, measured in GP sentinel surveillance, against laboratory confirmed influenza type B (Yamagata-lineage) virus infection (Source: Nivel Primary Care Database, NIC location RIVM).
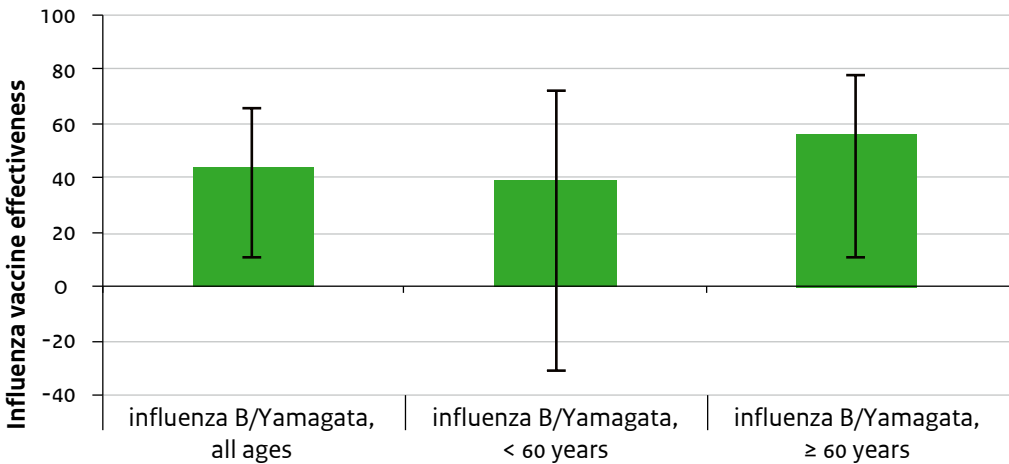
Footnote: GP = general practitioner. Error bars represent 95% confidence intervals (CI).

Table 3.5 Estimation of vaccine effectiveness (VE) against laboratory confirmed influenza for all ages, based on influenza virus positive and influenza virus negative ILI and other ARI patients (test negative design), which were collected for the Dutch sentinel GP surveillance in the 2017/2018 season (Source: Nivel Primary Care Database, NIC location RIVM).

	Adjustment / stratification	Cases			Controls			Adjusted VE	95% CI
		All	Vaccinated	%	All	Vaccinated	%		
All ages	All A subtypes/ B lineages [a]	491	104	21	431	113	26	42	11 to 63
	B/Yamagata [a]	367	79	22	420	110	26	44	11 to 65
<60 years	All A subtypes/ B lineages [b]	360	30	8	325	36	11	34	-32 to 67
	B/Yamagata [b]	264	20	8	317	35	11	39	-31 to 72
>=60 years	All A subtypes/ B lineages	127	71	56	104	75	72	72	16 to 91
	B/Yamagata [b]	103	59	57	103	75	73	56	11 to 78

Footnote: VE= vaccine effectiveness, ILI = influenza-like illness, ARI = other acute respiratory tract infection, GP = general practitioner.
Please note that for the virological surveillance, the ARI patients do not include the ILI patients, hence other ARI.
[a] Adjusted by age, comorbidity.
[b] Adjusted by age, comorbidity, period.
[c] Adjusted by age, comorbidity, period, smoking.

Figure 3.14 Influenza vaccine effectiveness in the 2017/2018 season in Europe, measured in, I-MOVE/I-MOVE+ multicentre case control studies, against laboratory confirmed influenza virus type B, per age group (Source: I-MOVE/I-MOVE+ study).
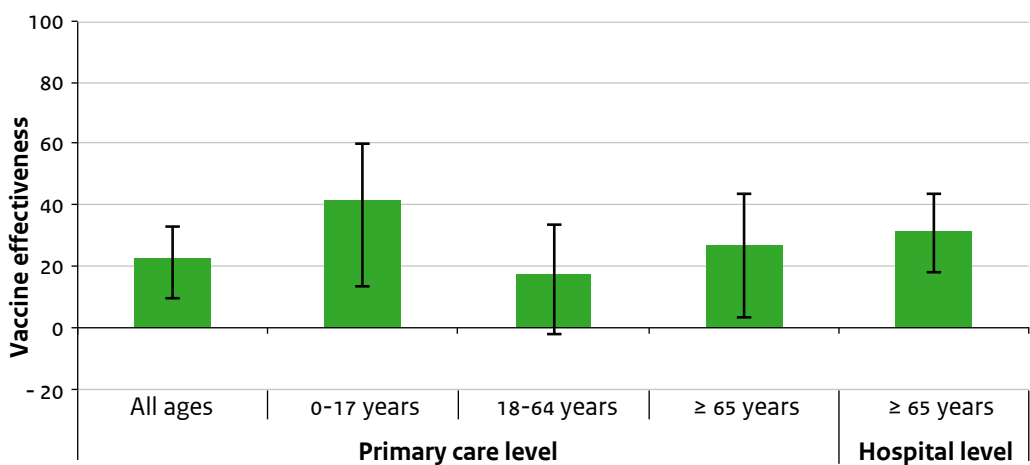
Footnote: All results are from preliminary end-of-season data. Error bars represent 95% confidence intervals (CI).

Chapter 4
RS-Virus

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4.1   Keypoints

- The RSV season, defined as the consecutive number of weeks with at least 20 positive RSV diagnoses reported by the virological laboratory surveillance, started in week 46 of 2017 and lasted 21 weeks.
- During the respiratory season, the number of RSV diagnoses in the virological laboratory surveillance (n=192) peaked in week 1 of 2018 and the cumulative number of RSV diagnoses (n=2006) was similar to the previous season (2016/2017), but higher than the three seasons before that.
- A total of 75 RS-viruses were detected in 1236 combined nose swabs and throat swabs taken from ILI and other ARI patients, collected by sentinel GPs in the 2017/2018 respiratory season.
- The overall percentage of RSV positive specimens taken by the GPs was highest in children in the age group 0-1 years: 24% in ILI patients and 27% in other ARI patients. Which is much higher compared to the percentage of RSV positive specimens in the age group 65 years or older: 3% in ILI patients and 6% in other ARI patients.

4.2   Background

Respiratory Syncytial Virus (RSV) causes respiratory infection and is commonly contracted by children (Hall, Weinberg et al. 2009),mostly in the winter season in temperate countries. During their first two years of life, most children are infected with this virus and re-infections later in life are very common. Especially in risk groups, such as newborns and preterms, infection can lead to severe illness, hospitalisation and even death (Nair, Nokes et al. 2010, Diez-Domingo, Perez-Yarza et al. 2014). Studies suggest that RSV is also a common cause for respiratory infections in the elderly (Falsey, Hennessey et al. 2005, Fleming, Taylor et al. 2015) causing outbreaks in elderly care facilities (Meijer, Overduin et al. 2013). RSV is subdivided in RSV-A and RSV-B, mainly based on the variation in the attachment protein, the G-protein. These two types may circulate simultaneously in the population. Currently, no vaccine for RSV is available, but 60 vaccine candidates are in the pipeline. Most vaccine candidates that are currently in phase 2 and phase 3 clinical trials are based on the fusion protein (F-protein) [https://www.path.org/publications/files/CVIA_RSV_snapshot_fs.pdf].

4.3   Epidemiological situation, season 2017/2018

The RSV season is defined as the period with at least 20 RSV-diagnoses per week reported by the virological laboratory surveillance. The RSV season lasted 21 weeks from week 46 of 2017 through week 14 of 2018. The total number of positive RSV diagnoses reported by 18 Dutch virological laboratories participating in the virological laboratory surveillance in 2017/2018 (n=2006; through week 20 of 2018) was similar to the previous season (2016/2017), but higher than the three seasons before that. The number of RSV-diagnoses peaked in week 1 of 2018 (n=192).
In addition to the virological laboratory surveillance, RSV test results are also available from the nose/throat swabs taken by sentinel GPs from ILI and other ARI patients in the context of influenza surveillance. The ARI patients do not include the ILI patients, therefore the notation 'other ARI'. In the 2017/2018 season (week 40 through week 20), 75 of 1,236 ILI and other ARI patients were tested RSV positive (6%). Among the 76 RS-viruses detected (one patient had an infection with both RSV-A and B), 14 were RSV-A (18%) and 62 were RSV-B (82%).

4.4　Discussion

Both data sources used for RSV surveillance have limitations. The virological laboratory surveillance provides real-time data on absolute number of RSV diagnoses, but a denominator, age and clinical background information is lacking. Such background information is available for ILI and ARI patients that are swabbed by sentinel GP's. However, GPs are instructed to focus primarily on sampling ILI patients, while the vast majority of RSV cases would likely fit the 'other ARI' case definition.

The need for a clear case definition for RSV possibly differentially targeted at very young children, children and adults because of differences in presentation, and better estimates of incidence and burden of RSV has been emphasised in the previous (2016/2017) annual report. RIVM plays an important role in European initiatives on RSV and works closely together with ECDC and other public health institutes, specifically SSI (Denmark) in order to strengthen international collaboration on RSV surveillance. Furthermore, RIVM is partner in the RESCEU project [http://resc-eu.org/], which aims to explore the burden (clinical, economic and social) from RSV. The aim is to create a sound epidemiological and virological baseline, before the introduction of a vaccine, to identify appropriate target groups for vaccination.

4.5 Tables and figures

Figure 4.1 Percentage of RSV-positive specimens from ILI and other ARI patients, taken by sentinel GPs during the seasons 2013/2014 – 2017/2018 (week 40 2017 through week 20 of 2018) (Source: Nivel Primary Care Database, RIVM).
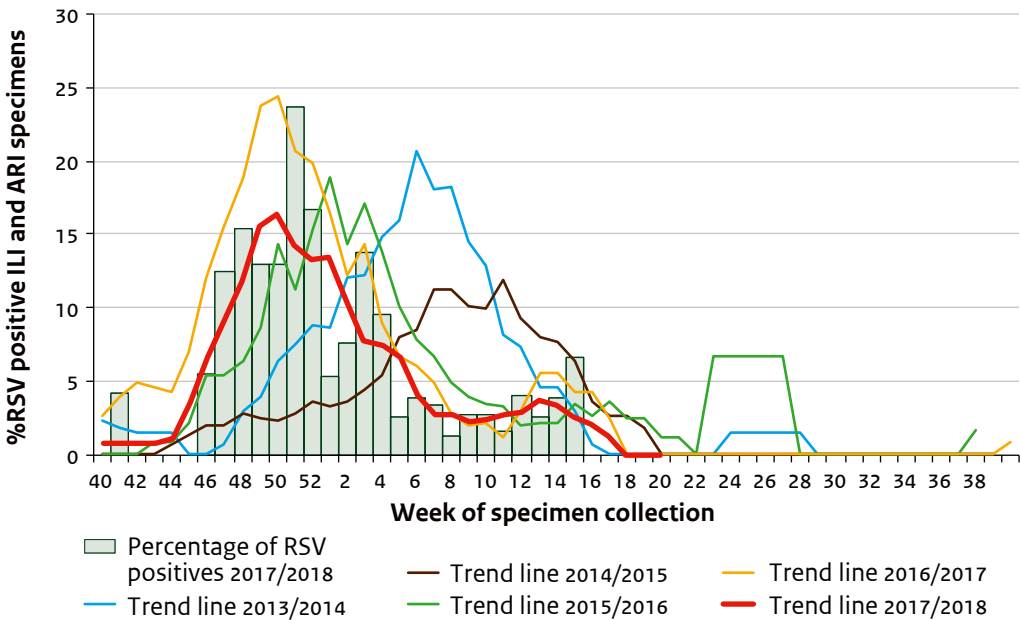
Footnote: Trend lines indicate a 5-weeks moving average. ILI= influenza-like illness; ARI = acute respiratory infection

Figure 4.2 Percentage of positive ILI and other ARI specimens, taken by sentinel GPs, and number of RSV diagnoses as reported by the virological laboratory surveillance, during the 2017/2018 respiratory season (week 40 of 2017 through week 20 of 2018), displayed by week of sampling (Source: RIVM, virological laboratory surveillance).
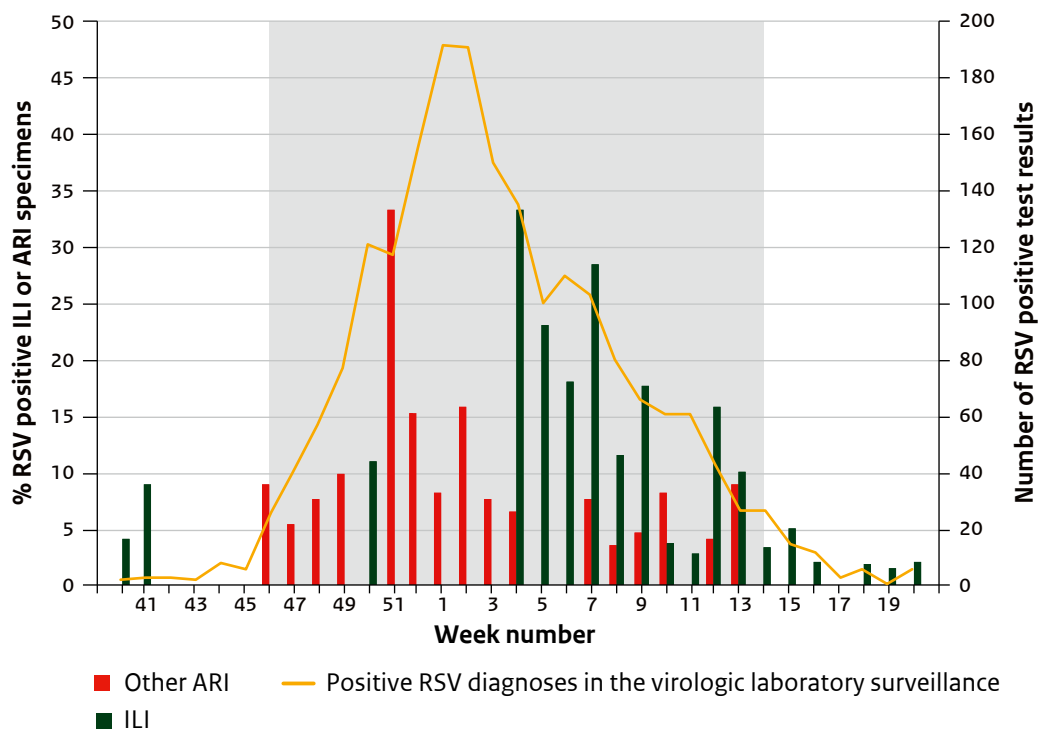
Footnote: The grey area represents the RSV season based on the virological laboratory surveillance. From week 18 of 2018 onwards, the number of collected ILI and other ARI specimens were each below 10 per week. Green bars represent specimens from ILI cases, red bars from other ARI cases.
Please note that for the virological surveillance, the ARI patients do not include the ILI patients, therefore other ARI.
ILI = influenza-like illness; ARI= acute respiratory infection; RSV = respiratory syncytial virus.

Figure 4.3 Percentage of RSV-A and RSV-B positive specimens from patients with ILI (A) and other ARI (B), and the number of tested specimens, taken by sentinel GPs during the respiratory season of 2017/2018 (week 40 of 2017 through week 20 of 2018), displayed for six age groups. (Source: Nivel Primary Care Database, RIVM).

Figure 4.4 Number of weekly reported RSV diagnoses (black line) and total number of RSV diagnoses in the respiratory season (blue dot) in the virological laboratory surveillance for the period 2013/2014-2017/2018 (until week 20) (Source: virological laboratory surveillance).

— Weekly number of RSV diagnoses

● Total number of RSV diagnoses per respiratory season (week 40 - week 20)
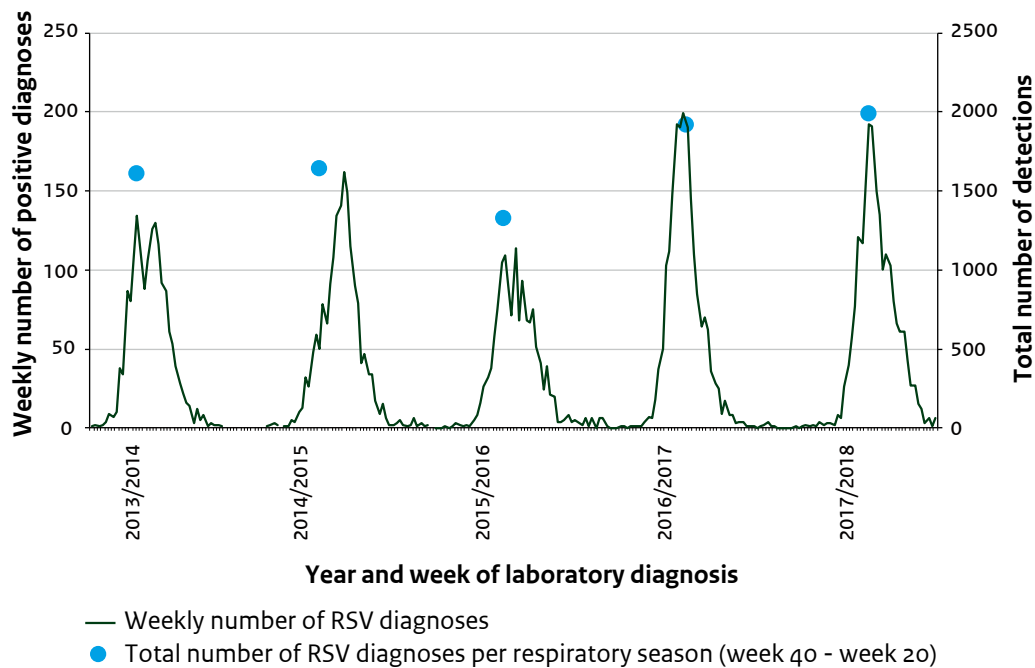
Table 4.1 Number of reported respiratory syncytial virus (RSV) diagnoses in the virological laboratory surveillance for the period 2008/2009-2017/2018 (through week 20).

RSV diagnoses	weeks 40-20 (N)	weeks 21-39 (N)	weeks 40-39 (N)
2008/2009	2416	35	2451
2009/2010	3075	34	3109
2010/2011	2702	27	2729
2011/2012	1838	51	1889
2012/2013	2197	12	2209
2013/2014	1629	16	1645
2014/2015	1661	32	1693
2015/2016	1348	42	1390
2016/2017	1938	21	1959
2017/2018	2006[a]	_[b]	_[b]

[a] Data for weeks 40 of 2017 through week 20 of 2018 are preliminary.
[b] Data for weeks 21-39 of 2018 are not yet available.

Table 4.2 RSV seasonal trends in the virological laboratory surveillance for the period 2008/2009-2017/2018 (through week 20): season onset, duration and peak. Week is week of laboratory diagnosis report. Threshold for the epidemic period is 20 diagnoses per week.

	Onset week (week number)	Season duration (N weeks)	Peak:	
			Timing (week number-year)	RSV diagnoses (N)
2008/2009	43	22	50-2008	278
2009/2010	45	21	4-2010	297
2010/2011	45	22	3-2011	264
2011/2012	45	23	51-2011	125
2012/2013	46	22	2-2013	182
2013/2014	48	19	6-2014	130
2014/2015	49	20	8-2015	177
2015/2016	48	20	4-2016	114
2016/2017	45	18	52-2016	199
2017/2018	46	21	1-2018	192

Chapter 5
Notifiable Respiratory Diseases

5.1 Legionnaires' disease

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5.1.1 Key points
- Notifications of Legionnaires' disease (LD) continuously increased over the 2012–2017 period.
- In 2017, a total of 561 cases with Legionnaires' disease (LD) were notified, the highest ever reported.
- Most cases (72%) have acquired the infection in the Netherlands, of which the majority (355 cases) is community acquired.
- For most community acquired cases the source of infection remains unknown.
- The case fatality rate was unchanged, but due to the increase in domestic cases, the number of deaths reported increased substantially to 31 cases.
- In June, July and August a large increase in LD was observed, following a period of very warm weather in May and June and extensive rainfall in July.
- Improved diagnostics can explain only a small part of the annual increase in cases.
- The proportion of LD due to *Legionella pneumophila* non-serogroup 1 and *Legionella* non*pneumophila* is small, but increasing.
- Two biological wastewater treatment plants were identified as source of infections for clusters of community acquired cases.
- Biological wastewater treatment plants may be a source for sporadic LD and should be included in LD source finding investigations.

5.1.2   Background

Legionellosis is an infection caused by inhalation of *Legionella* bacteria. Symptoms may range from mild to severe disease, but most patients who are diagnosed with a *Legionella* infection have a severe pneumonia, and this is called Legionnaires' disease (LD). The incubation period is usually 2-10 days and rarely exceeds 14 days. The disease affects mostly the middle aged and elderly population, and men are more at risk than women. Furthermore, smoking, an impaired health status and travel are risk factors.

Legionella bacteria are common in the natural environment, usually in low numbers. At present 61 different species of *Legionella* have been described, and 28 species have been associated with human disease. Most LD outbreaks are associated with manmade water systems, such as wet cooling towers, whirlpools and water distribution systems. However, for the majority of non-outbreak cases (sporadic cases) the source of infection remains unknown. There is a seasonal pattern of LD with an increase during the warm months of the year. Furthermore, more cases are reported after warm weather with heavy rainfall.

Most LD cases are diagnosed with a urine antigen test for *Legionella pneumophila* serogroup 1, which is the causative agent in most LD patients. Other serogroups or *Legionella* species can be diagnosed using culture or PCR on sputum or bronchial lavage. Culture is also important to obtain a clinical isolate for typing. This is especially relevant for identification of sources through comparison of clinical strains to *Legionella* found in environmental sources. However a clinical isolate is usually available in less than one out of five Dutch patients, which is a limitation for source finding.

5.1.3   Epidemiological situation in 2017

The increasing trend in Legionnaires' disease (LD) observed since 2012, continued in 2017 with a 24% increase compared to 2016. In total 575 notifications of legionellosis were received in 2017, of which 561 were confirmed or probable cases of Legionnaires' disease in Dutch residents. The incidence in 2017 was 3.3 LD cases per 100,000 inhabitants. The seasonal peak during the summer months June, July and August was much higher than expected based on the average monthly notifications in the previous five years (2012-2016). The highest number of cases were reported in July with 116 notified cases, of whom 98 cases (85%) were domestic (infection acquired in the Netherlands). The cases in summer months were spread over multiple public health regions and no large outbreaks were detected. Furthermore, more cases than expected were reported in December 2017.

The steady increase of LD is mostly due to an increase in domestic cases. Domestic LD accounted for 72% of cases and 27% was associated with travel abroad. More domestic travel associated cases than usual were reported, but most domestic cases (87%, 355 cases) were community acquired.

The age and gender distribution was similar to previous years with a median age of 64 years and 71 % males. As usual, 95% of cases was 40 years or older. In total, 48% of cases had relevant underlying disease and 48% were smoker. No underlying disease or smoking was reported by 23% of cases. Significantly more domestic cases were smoker (51%) or had underlying disease (53%) than cases who had travelled abroad (smoking 38%, underlying disease 34%).

Thirty-one deaths were reported, 55% more than last year. The case fatality rate (CFR) is higher in domestic cases (6.8%) than in cases with travel abroad (1.3%). Domestic cases in the oldest age group (80 years or older) had the highest mortality (CFR 13%). The mortality in women in 2017 (CFR 9.2%) was higher than in men (CFR 6.3%).

Clusters
Two biological wastewater treatment plants were identified as source of infection for multiple clusters in Noord-Brabant (See box). A geographic cluster was detected in December in the south of the Netherlands with 7 cases in a period of three weeks. Despite sampling of potential environmental sources, no source of infection was found for this cluster. Furthermore, some small geographic clusters (2-5 cases) were detected during the year, for which no common source was found. Small clusters (2-3 cases) were also seen linked to a hotel, a leisure park, a work location and multiple small clusters with saunas, carwashes and garden centres as possible sources.

Environmental investigations
Environmental sampling was reported in relation to 73 domestic patients (18%) and *Legionella* was detected in potential sources linked to 34 of these patients (46%). For 29 patients with a clinical isolate, environmental sources were sampled by the *Legionella* Source Identification Unit (BEL), allowing comparison between clinical and environmental strains. This resulted in a match for 5 of 29 patients (17%). In addition to the matches linked to the wastewater treatment plants, sequence based typing (SBT) confirmed a whirlpool in a holiday home for a patient who stayed at the accommodation 15-17 days before onset of disease. Furthermore, typing by Amplified Fragment Length polymorphism (AFLP) identified potting soil as most likely source for a patient with a *Legionella longbeachae* isolate.

Diagnostics and pathogen
Urine antigen test, which only reliably detects *L. pneumophila* serogroup 1, is the most frequently used diagnostic method (89% of cases). For 70% of cases this was the only used diagnostic method. Sputum culture on *Legionella* was performed for only a minority of patients (41%) and a positive culture was available for only 16% of the 561 patients. The number of cases diagnosed with Polymerase Chain Reaction (PCR) was 103 (18%). The small increase in the proportion of cases diagnosed solely by PCR continued, but the majority of cases (64 cases) was also diagnosed with another diagnostic method.
L. pneumophila serogroup 1 is the most frequently found pathogen (based on clinical isolates), but its proportion is decreasing. *L. pneumophila* non-serogroup 1 increased to 9% and *Legionella* non*pneumopila* also increased to 9%. Since a few years, especially *Legionella longbeachae* is reported more often.

Travel associated cases
The number of cases with travel abroad during incubation time increased marginally to 152 cases, of which the majority (83%) were reported to the European Legionnaires' Disease Surveillance Network (ELDSNet). Cases who were not reported to ELDSNet, stayed at a private address (9%) or had insufficient data available for reporting. Most travel (74%) was within the EU and Spain,

Italy and France were the countries visited most frequent. Outside the EU the highest number of cases was reported from Dubai in the United Arab Emirates (5 Dutch cases) and Sri Lanka (5 Dutch cases) [https://ecdc.europa.eu/en/publications-data/rapid-risk-assessment-increase-legionnaires-disease-eu-travellers-returning-dubai] (Dabrera, Brandsema et al. 2017). ELDSNet detected a general increase of LD among European travellers from Dubai. History of domestic travel among LD cases increased considerably to 45 cases, of which 27 (60%) were reported to ELDSNet and 17 (38%) were linked to a private, non-commercial address and were not reported.

In the town of Boxtel, Noord Brabant, two consecutive clusters with a total of 14 LD cases were reported in 2016 and 2017. Typing of clinical isolates showed an identical *Legionella* strain (*L. pneumophila* sg1 ST1646) in five cases. No common source of exposure was identified based on patient interviews and sampling of potential sources in 2016. After continued search for possible sources in 2017, a biological wastewater treatment plant (BWTP) was identified with nutrient rich water and a temperature of 35° C degrees. In the aeration ponds of the BWTP, an identical *Legionella* strain (ST1646) was found. The genotypic match between clinical and environmental isolates, the high concentrations of *Legionella* in the BWTP aeration ponds and modelling results, all suggested the BWTP as the infection source for both clusters in Boxtel. After this finding, the region of Eindhoven was also searched for a BWTP. This region had an increased LD incidence since 2013 and an identical ST-type was found in patients in this region. A similar BWTP (biogas and anammox installation with aeration) was found and sampled, and ST1646 was also found in this installation. Based on residential addresses and movements of cases, and the sporadic nature of the outbreak we assume transmission by direct dispersal of aerosols from the aeration ponds over a distance of 1.6 km in Boxtel and about 3 km in the region of Eindhoven. The aeration ponds of both BWTP's were covered to prevent further transmission and sludge filters from the membrane bioreactor were repaired to clean the effluent. The investigations highlight the importance of BWTPs as sources for LD outbreaks and suggest they may also be a relevant source for sporadic LD.

5.1.4 Discussion

The LD increase in June, July and August 2017 and the high number of LD cases in December may be explained by weather conditions. The weather in May and June was extremely warm, while July was a very wet month. December was also warmer than average. The association between the Dutch LD incidence and warm, wet weather has been shown in previous studies (Brandsema, Euser et al. 2014, Beaute, Sandin et al. 2016). However, it remains unclear which sources of infection attribute to the weather associated increase. The majority of the notified LD cases are sporadic LD and the source of infection for these cases is rarely identified.

The increased mortality in 2017 is due to the increase in domestic cases. Like other years, the case fatality rate in the domestic cases is considerably higher than in cases with travel abroad. However, the case fatality ratio in both groups remained similar to previous years.

The use of PCR should be encouraged, because this may reduce the underdiagnosing of the disease, as PCR can detect all *Legionella* species, in contrast to the urinary antigen test. The proportion of patients with *Legionella pneumophila* serogroup 1 as clinical isolate has continually decreased in the last 5 years. This may be a result of the increased use of PCR: cases that were diagnosed by PCR more often had a positive culture than cases diagnosed by the urinary antigen test (28% versus 15%). The distribution of the clinical isolates is still biased, because the urinary antigen test remains the primary diagnostic method.

The most important finding this year was the identification of two biological wastewater treatments plants as the source of infection for the clusters in Boxtel and the increased incidence in the region of Eindhoven. BWTP's have been described as the source of outbreaks in other countries (van Heijnsbergen, Schalk et al. 2015). However, we observed some differences in the characteristics of the clusters in Boxtel and Eindhoven compared to outbreaks in other countries. Documented outbreaks related to aeration ponds usually describe short distance transmission or long distance transmission caused by indirect dissemination of aerosols, for example by a wet cooling tower using contaminated water from the river. This has caused more explosive outbreaks with many cases in a short time period. In the case of Boxtel and Eindhoven however, we assume direct dissemination of aerosols from the aeration ponds over a longer distance. Although wet cooling towers and air scrubbers were located near the aeration ponds, no *Legionella* was detected in these installations. Furthermore, in Eindhoven and Boxtel the onset of disease was spread over a long time period with only 0-2 LD cases per week. This pattern indicates a different, less efficient dispersal of *Legionella* and we believe this can be explained by direct dissemination from contaminated aerosols from the aeration ponds. In a larger city a temporary increase of 0-2 cases per week may be overlooked as an outbreak, especially if no typing results are available. This sporadic nature of the epidemic curve linked to the BWTP suggest that these installation may be a relevant source for sporadic LD. Future source finding investigations for sporadic LD should therefore also include biological wastewater treatment plants.

5.1.5   Tables and figures

Figure 5.1 Annual numbers of notified Legionnaires' disease, 2007 through 2017, by infection acquired abroad or domestic (within the Netherlands) (Source: Osiris).
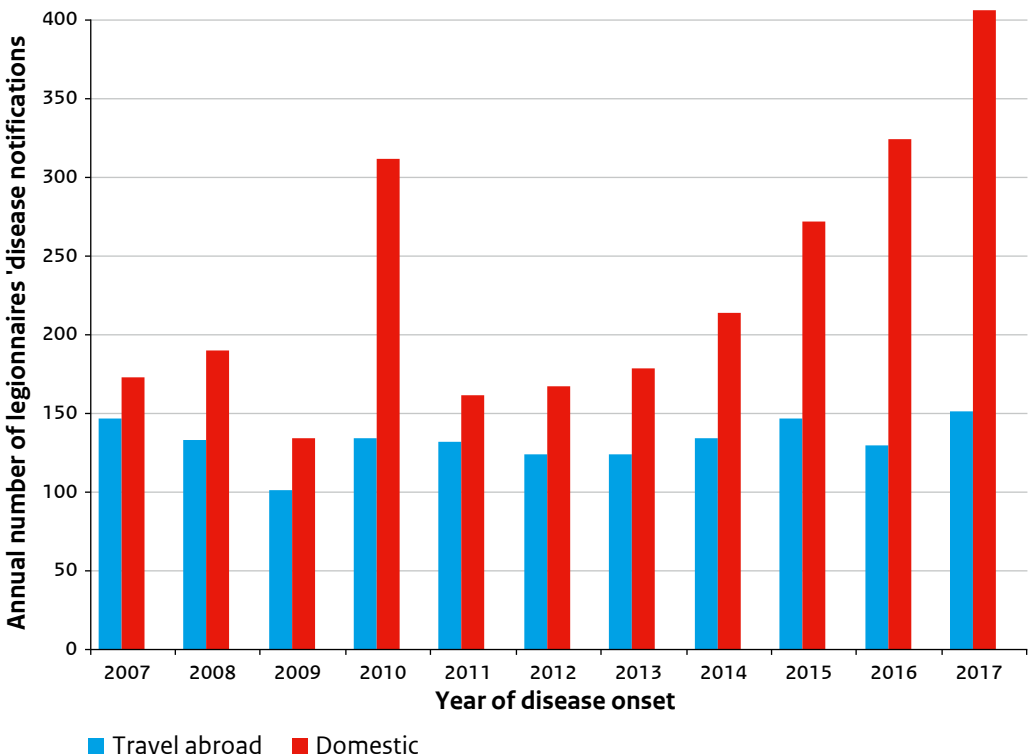
Figure 5.2 Notifications of Legionnaires' disease acquired abroad or acquired in The Netherlands (domestic), by month of disease onset in 2017 and the monthly average over 2012-2016. (Source: Osiris).
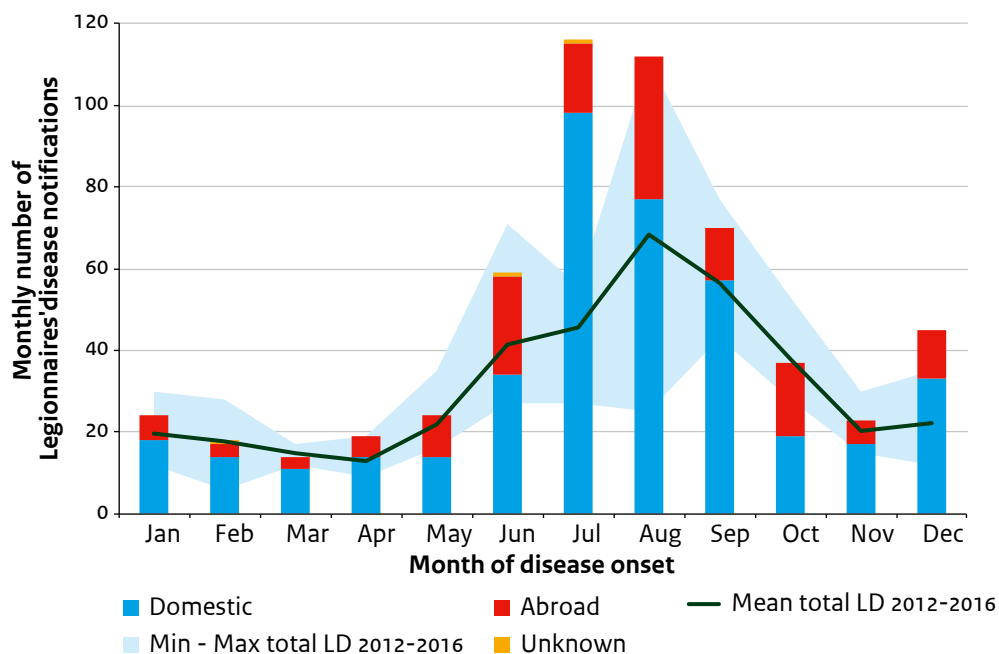
Table 5.1 Number of legionellosis notifications in 2013 – 2017, incidence, clinical and epidemiological background, mortality and diagnostics (Source: Osiris).

Year of onset disease[a]	2013	2014	2015	2016	2017
Number of legionellosis notifications [b]	310	370	438	468	575
Excluded from analysis [b]:	7	22	19	14	14
Total included:	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**
Legionnaires'disease (LD) (=100%) [b]	**303 (100)**	**348 (100)**	**419 (100)**	**454 (100)**	**561 (100)**
% difference to year before	+4%	+15%	+20%	+8%	+24%
Confirmed Legionnaires' disease[c]	288 (94)	327 (94)	393 (94)	422 (93)	519 (93)
Probable Legionnaires'disease[c]	15 (4)	21 (6)	26(6)	32 (7)	42 (7)
LD Incidence (per 100,000 inhabitants)	1.8	2.1	2.5	2.7	3.3
Male gender	202 (67)	255 (73)	293 (70)	327 (72)	401 (71)
Median age (Q1-Q3)	63 (54-72)	61 (53-71)	62 (53-69)	63 (55-72)	64 (54-73)
Hospital admission[d]	294 (97)	342 (98)	410 (98)	449 (99)	543 (97)
X-thorax confirmed pneumonia[d]	285 (98)	328 (94)	401 (96)	436 (96)	540 (99)
Deaths[d]	17 (6)	13 (4)	13 (3)	20 (4)	31 (6)
Setting of infection:					
Travel abroad[e]	124 (41)	134 (39)	145 (35)	130 (29)	152 (27)
% Difference to year before	0%	+8%	+8%	-10%	+17%
Domestic (acquired in The Netherlands)	179 (59)	214 (61)	273 [g] (65)	324	406 (72)
% Difference to year before	+8%	+20%	+28%	+19%	+25%
Setting unknown	-	-	1	-	3 (<1)
Domestic categories:					
Domestic travel[e]	12 (4)	20 (6)	24 (6)	17 (4)	45 (8)
Nosocomial	1 (<1)	4 (1)	2 (<1)	-	1 (<1)
Healthcare associated	-	6 (2)	3 (<1)	7(2)	5 (<1)
Community acquired	166 (55)	184 (53)	244 (58)	300 (66)	355 (63)
Diagnostics					
Legionella cultured performed (=yes)	122 (40)	156 (45)	181 (43)	209 (46)	229 (41)
Positive culture	49 (16)	67 (19)	79 (19)	84 (19)	92 (16)
Proportion *L.pneumophila* sg1 in culture (or PCR) positives [f]	96%	90%	87%	85%	82%

Year of onset disease[a]	2013	2014	2015	2016	2017
Positive urine antigen test	283 (93)	314 (90)	381 (91)	404 (89)	501 (89)
Positive PCR	43 (14)	54 (16)	65 (16)	88 (19)	103 (18)
of which PCR only [g]	11 (4)	15 (4)	21 (5)	26 (6)	39 (7)
Significant titer rise	5 (2)	5 (1)	6 (1)	6 (1)	6 (1)
Direct immunofluorescence	-	-	1(<1)	-	-
Diagnostic delay in days: median(Q1-Q3)	6 (4-8)	6 (4-8)	6 (4-7)	6 (4-8)	5 (4-7)
Notification delay in days: median (90% reported)	0 (2)	0 (2)	0 (2)	0 (2)	0 (2)

Analysis based on data as available on March 30, 2017, including all authorized notifications.

[a] If date of onset disease was unknown, date of diagnosis minus median diagnostic delay was used to estimate onset.

[b] Exclusion of cases in non-residents, cases without pneumonia and/or cases based on a single high titre.

[c] Confirmed and probable LD according to the European case definition (Commission Implementing Decision, 2012: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:262:0001:0057:EN:PDF).

[d] Percentage based on the number of patients for which this specific information was available.

[e] Travel Associated Legionnaires Disease (TALD) is defined as travel (including at least 1 overnight stay) in the period of 2-14 days before disease onset (2013-2015) or 2-10 days before disease onset (from 2016 onward), unless source finding suggests a non-travel associated source. A case with travel 11-14 days before onset will also be classified as travel associated if the case is part of a travel-associated cluster or when environmental sampling confirms the travel site as source. In 2016 and 2017 <= 1% of cases had travel reported during 11-14 days before onset.

[f] Proportion of clinical specimens (culture or PCR) available for typing at the reference lab.

[g] No other diagnostic method reported in Osiris.

Figure 5.3 Age and gender distribution of cases with Legionnaires' disease with onset of disease in 2017 and age and gender specific incidence (number of notified cases per 100,000 inhabitants). (source: Osiris and CBS statline).

Surveillance of influenza and other respiratory infections in the Netherlands: *winter 2017/2018*
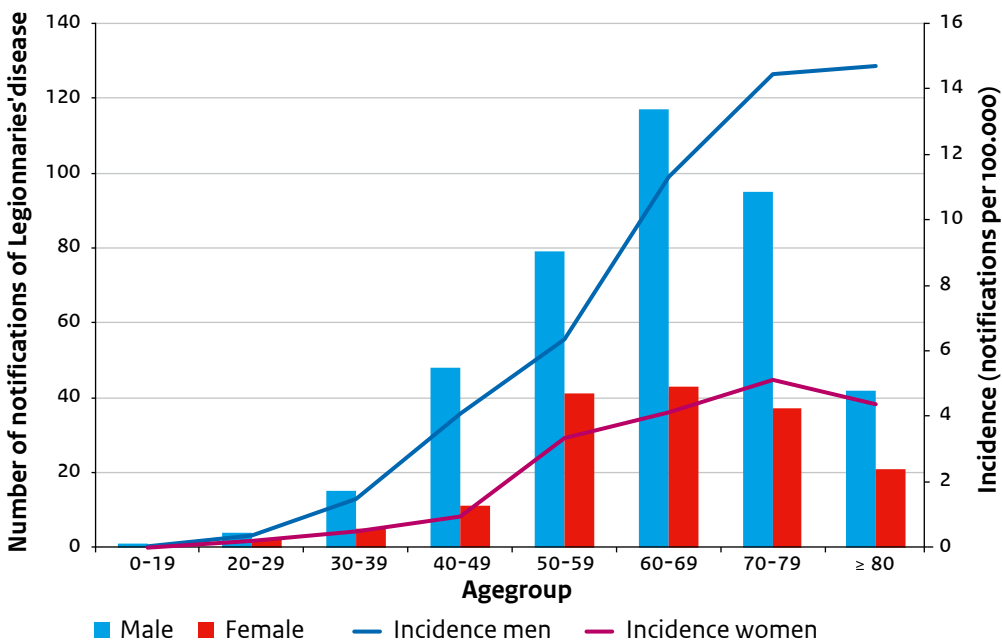
Figure 5.4 Distribution of the risk factors smoking and relevant underlying illness per age group reported in cases with Legionnaires' disease with onset disease in 2017. (source: Osiris).
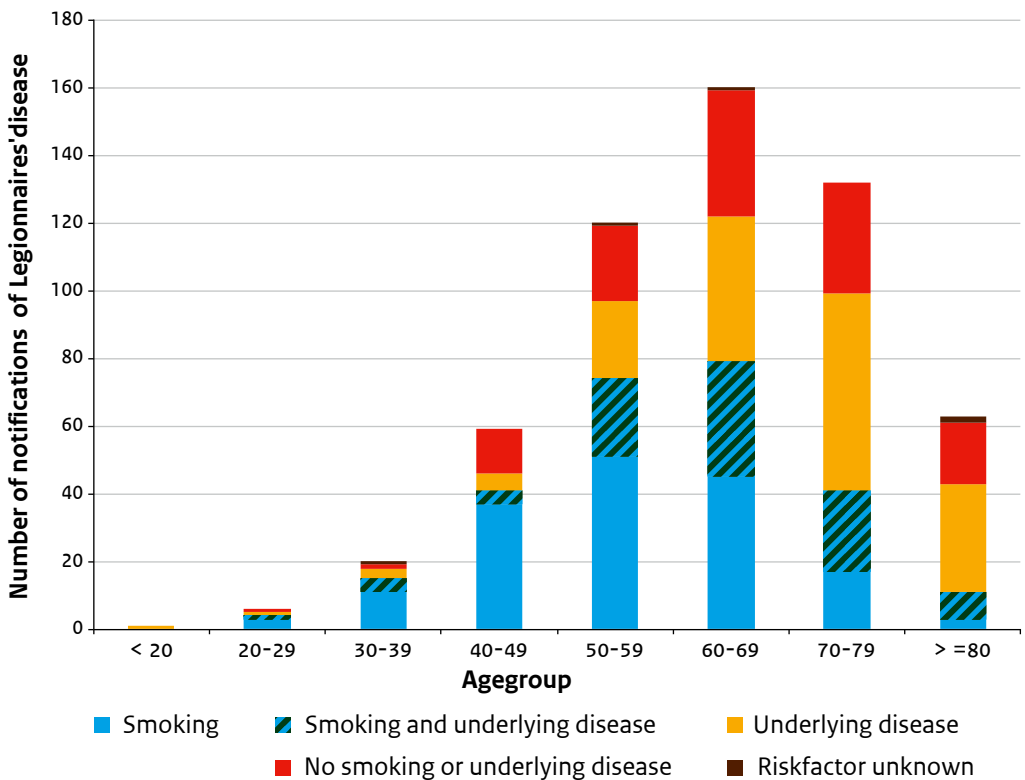
Figure 5.5 Disease outcome and case fatality ratio reported in cases with Legionnaires' disease with onset in 2017 by age group and gender.
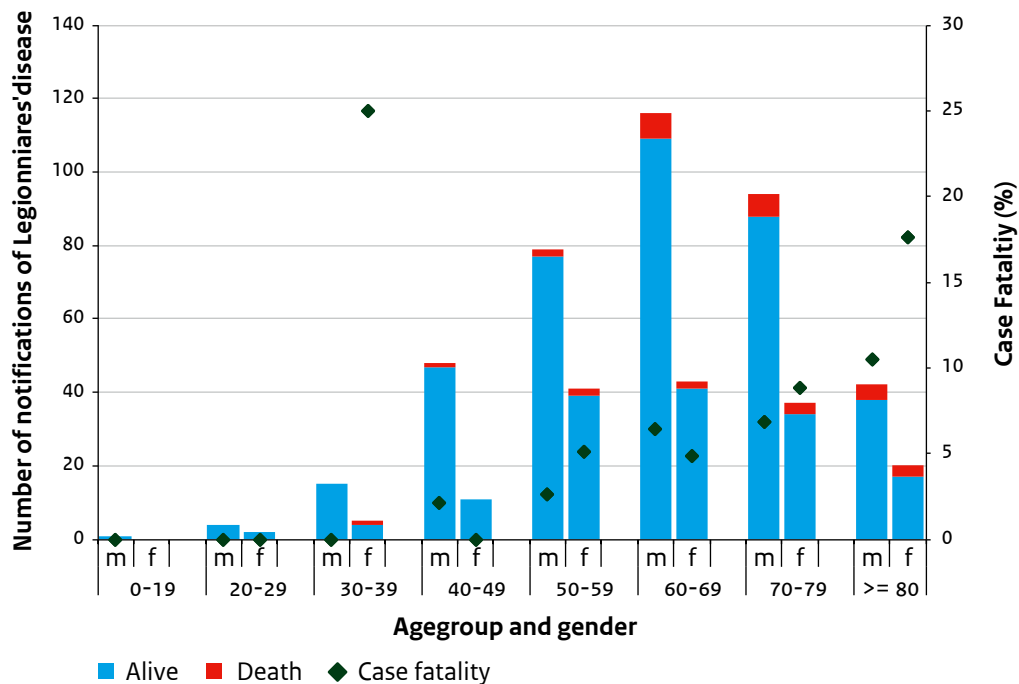
Footnote: m = male; f = female.

Tabel 5.2 Number of deaths and case fatality (CF) reported in cases of Legionnaires' disease with onset of disease in 2015-2017 by setting of infection.

Setting of infection	2015			2016			2017		
	Deaths n	Total n	CF %	Deaths n	Total n	CF %	Deaths n	Total n	CF %
Travel abroad	2	145	1.4	0	130	-	2	152	1.3
Domestic	11	273	4.0	20	324	6.2	28	406	6.9
Setting unknown	-	-	-	-	-	-	1	3	33
Domestic categories:									
Domestic travel	2	24	8.3	0	17	-	3	45	6.7
Community acquired	9	244	3.7	19	300	6.3	24	355	6.8
Nosocomial	0	2	-	-	-	-	0	1	-
Healthcare associated	0	3	-	1	6		1	5	20
Setting unknown	-	-	-	-	-	-	1	3	33
Total	13	419	3.1	20	454	4.4	31	561	5.5

Figuur 5.6 Regional incidence of domestic Legionnaires' disease per 100,000 inhabitants in 2017 by two-digit postcode area.

Incidence per 100,000 population

	0 – 0,5	(10)
	0,5 – 1,5	(18)
	1,5 – 2,5	(20)
	2,5 – 3,5	(19)
	3,5 – 5	(14)
	5 – 7	(9)
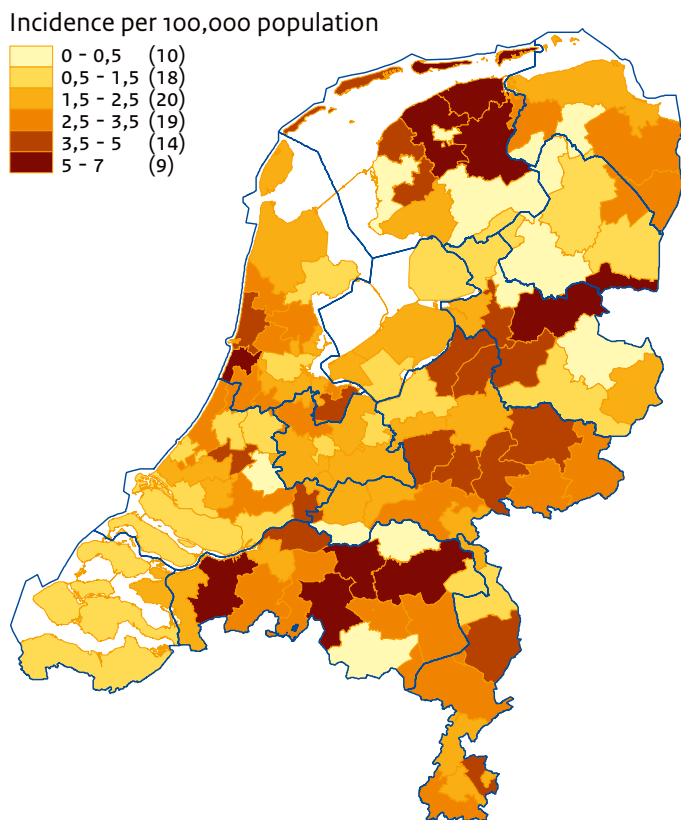
Tabel 5.3 Legionella species, serogroup and Sequence Based typing (ST-type) of patients with Legionnaires' disease with onset in 2017, compared to 2014-2016. (source: BEL, Osiris).

Type *Legionella* [a]	2014- 2016 n = 218	2017 n = 88
L. pneumophila serogroup 1	194 (89%)	72 (82%)
L. pneumophila serogroup 2	2 (<1%)	1 (1%)
L. pneumophila serogroup 3	2 (<1%)	3 (3%)
L. pneumophila serogroup 4	2 (<1%)	-
L. pneumophila serogroup 6	3 (1%)	2 (2%)
L. pneumophila serogroup 2-14 (sg not typed)	5 (2%)	2 (2%)
L. pneumophila **(total)**	**208 (95%)**	**80 (91%)**
L. longbeachae	8 (4%)	4 (5%)
L. bozemanii	1 (<1%)	1 (1%)
L. anisa	-	1 (1%)
L. jamestowniensis	-	1 (1%)
L. oakridgensis	-	1(1%)
Legionella nonpneumophila **(total)**	**9 (4%)**	**8 (9%)**
Most frequent ST-types	**n=199**	**n=76**
ST 47	56 (28%)	21 (28%)
ST62	15 (8%)	4 (5%)
ST82	9 (5%)	5 (7%)
ST42	8 (4%)	1 (1%)
ST1	8 (4%)	3 (4%)
ST1646	7 (4%)	4 (5%)
ST23	7 (4%)	1 (1%)
ST46	7 (4%)	5 (7%)
ST37	5 (3%)	3 (4%)
Total number different ST- types	53	34

[a] Based on the number of patients for whom clinical specimens were available at the reference lab for typing (mostly cultures, sporadically PCR with typing).

5.2 Psittacosis

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Contributors: Ingrid Keur en Edou Heddema

5.2.1 Key points
- In 2017, 52 patients with psittacosis were notified. This number is in line with the number of notifications in the years 2012-2016, in which the annual numbers ranged from 41 to 60.
- Six patients in two clusters were epidemiologically linked to one or more other notified patients. In both clusters, the patients were exposed to birds kept as hobby at home. The first cluster consisted of four patients: two family members and two neighbours of the bird owner. The second cluster consisted of two family members who had a bird from the same nest.
- Just as in 2016, the percentage of notified cases in which the diagnosis was confirmed with PCR was high (85%).
- 36 samples were sent for genotyping. Three samples were obtained from patients who were not notified.
- As in the previous 4 years, genotype A (mainly associated with parrot-like birds) and genotype B (mainly associated with doves and pigeons) were most prevalent among patients. Over the previous years, the relative proportion of these genotypes was more or less similar. In 2017, genotype B was slightly predominant.
- The genotyping and supplementary diagnostics also revealed less common (geno)types: two cases of a new *C. psittaci* genotype most similar to C (93% homology), two cases of *C. caviae* infection and a case of *C. felis* infection (both closely related Chlamydia species).
- For 45 patients (87%) at least one possible source location was reported by the public health service.
- In consultation between the public health service and the NVWA, it is decided whether sampling of a location is useful for tracing the source of a human case. For 25 patients at least one possible source location was sampled by the NVWA. For 17 patients at least one possible source location was tested positive for *C. psittaci* DNA. On 12 locations genotype A was found and on 7 locations genotype B was found.
- In addition to the human notifications that the NVWA receives for human source tracing, NVWA also receives notifications of clinical ill birds or positive laboratory test results of birds. In 2017, 24 of such veterinary notifications were received. 20 times a location was visited and birds were sampled (cloaca and/or faecal swabs). In 11 cases the suspected birds were not yet treated with an antibiotic and in four of these cases, *C. psittaci* DNA was detected. Four times a location was visited after the birds were given an antibiotic treatment, in all cases *C. psittaci* DNA was not detected. In seven cases the suspected bird had already died at the time of notification, five of these locations were visited to sample contact birds. In two cases *C. psittaci* DNA was detected. The genotype of five of the six positive samples taken by the NVWA were genotyped, and type A was found in all five cases. One sample could not be determined.

Figure 5.7 Number of notifications of human psittacosis by year and mode of confirmation of laboratory diagnosis, 2008 through 2017 (Source: Osiris).
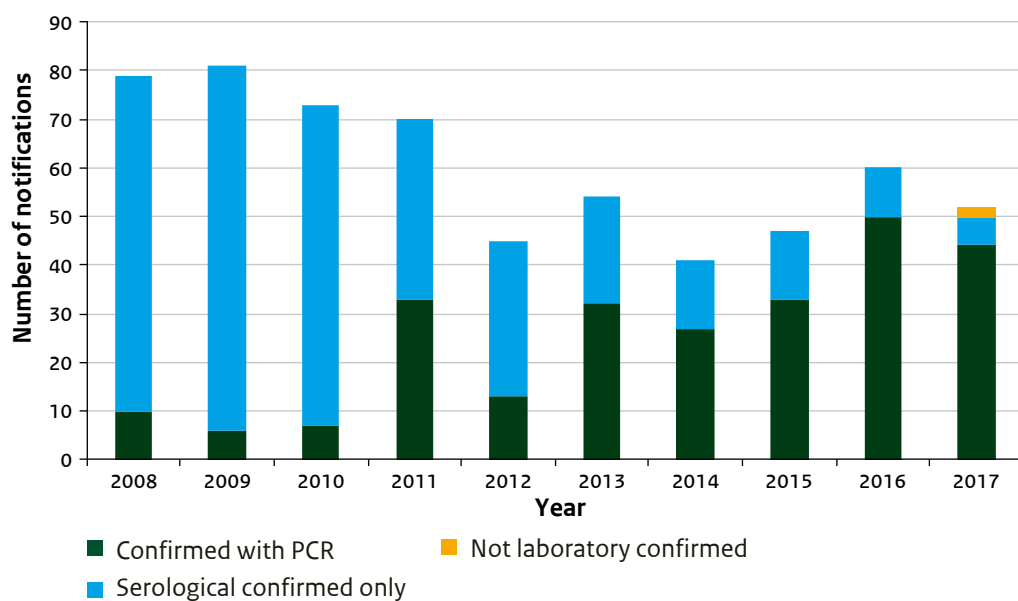
Table 5.4 Demographic, clinical and diagnostic characteristics of notified patients with psittacosis and positive diagnoses in the virological laboratory surveillance, in 2013-2017 (Source: Osiris and virological laboratory surveillance).

N (%), unless otherwise specified	2013	2014	2015	2016	2017
Osiris notifications:					
Number of notifications[a]	54 (100)	41 (100)	47 (100)	60 (100)	52 (100)
Incidence per 100,000 inhabitants	0.32	0.24	0.28	0.35	0.30
Median age in years (Q1-Q3)	59 (43 – 70)	58 (47 -71)	57 (41 – 68)	58 (45 – 71)	55 (39 – 69)
Male gender[b]	36 (67)	32 (78)	32 (68)	48 (80)	27 (52)
Hospitalised[b]	41 (76)	38 (93)	37 (79)	49 (82)	44 (85)
Deaths[b]	0	1 (2)	1 (2)	1 (2)	0
Infected abroad[b]	2 (4)	1 (2)	0	4 (7)	0
Median notification delay in days (Q1-Q3)[c]	0 (0 – 2)	0 (0 – 1)	0 (0 – 1)	0 (0 – 2	0 (0 – 1)
Diagnostics used for notifications:					
Median diagnostic delay in days (Q1-Q3)[d]	18 (9 – 29)	12 (7 – 21)	10 (8 – 14)	9 (6 – 14)	11 (7 – 27)
Mode of confirmation of laboratory diagnosis:					
PCR[e]	32 (59)	27 (66)	33 (70)	50 (83)	44 (85)
Serological only	22 (41)	14 (34)	14 (30)	10 (17)	6 (12)
None	0	0	0	0	2 (4)
Number of patients eligible for genotyping[f]	33	28	36	50	44
Notified patients for whom diagnostic material for genotyping was received by Zuyderland MC	31 (94)	24 (86)	30 (83)	37 (74)	36 (82)
Typing outcomes:					
C. psittaci genotype A	16 (52)	9 (38)	11 (37)	12 (32)	11 (31)
C. psittaci genotype B	11 (36)	11 (46)	9 (30)	13 (35)	13 (36)
C. psittaci genotype C	0	1 (4)	2 (7)	1 (3)	0

N (%), unless otherwise specified	2013	2014	2015	2016	2017
C. psittaci genotype E/B	0	1 (4)	2 (7)	0	0
New *C. psittaci* genotype most similar to C (93% homology)	0	1 (4)	0	0	2 (6)
Previously unknown genotype of *C. psittaci*, with characteristics of B and E	0	0	1 (3)	2 (5)	0
Negative for any *C. psittaci* genotype	2 (7)	1 (4)	2 (7)	7 (19)	0
Of which further diagnostics revealed:					
C. caviae	1 (3)	1 (4)	1 (3)	0	2 (6)
C. felis	0	0	0	0	1 (3)
No assessement possible	2 (7)	0	3 (10)	2 (5)	7 (19)
Virological laboratory surveillance:					
Number of positive diagnoses	23	16	18	30	15

a Date used for statistics = date of onset of disease or, if missing, date of notification or date of laboratory confirmation (depending on which of these dates was first). Both notifications with status 'definite' and 'authorised' (i.e. not definite) are included.

b Percentage based on the number of patient for whom this specific information was available.

c Notification delay = number of days between date of laboratory confirmation and date of notification at the Public Health Service. Negative delays and delays of more than a year are excluded.

d Diagnostic delay = number of days between onset of disease illness and date of laboratory confirmation. Negative delays and delays of more than a year are excluded.

e PCR= 'PCR only' or 'combination of PCR and serological confirmation'.

f Genotyping of notified patients was started on 27 Augustus 2012. *C. psittaci* strains of notified psittacosis patients are genotyped at the Zuyderland MC in Sittard-Geleen/Heerlen using ompA genotyping. This method distinguishes at least nine avian genotypes of *C. psittaci* (A – F, E/B, M56, and WC). Each genotype is relatively bird type specific. This method can furthermore identify *C. abortus*. Genotyping is only possible if diagnosis is based on PCR. In the table, the number of notified patients eligible for genotyping is used as denominator to calculate the percentage for the years 2012-2015. This number is calculated as the sum of the number of patients confirmed with PCR and the number of patients from whom material for genotyping was received, although the diagnosis was based on serological results.

5.3 Q fever

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5.3.1 Key points
- In 2017, 22 patients with acute Q fever were notified. This number is in line with the number of notifications in the years 2013-2016, in which the annual numbers varied from 14 to 26.
- Eight patients (36%) were probably infected abroad. This is somewhat higher than in the years 2013-2016, in which the percentage of patients infected abroad fluctuated between 10 and 21. During the epidemic years 2007-2010, the percentage of patients infected abroad was much lower (between 0.2 and 2.7%).
- Three notifications were epidemiological related. They were all part of the same family and all three shared the same house for residence and/or worked in the municipality of Bodegraven-Reeuwijk. GGD, NVWA (Netherlands Food and Consumer Product Safety Authority), RIVM, WBVR (Wageningen Bioveterinary Research) and GD (GD Animal Health) collaborated in source tracing. Despite these efforts, no common source could be demonstrated.
- Except for the family cluster mentioned above, there was no geographic clustering of domestic cases (i.e. patient who were not infected abroad). These patients were from 11 different public health services regions.
- The decreasing trend in the median diagnostic delay from 33 days in 2013 to 14 days in 2016 did not continue. Instead, in 2017 the median diagnostic delay increased to 29 days.
- The difference in the number of notifications and the number of diagnoses reported in the virological laboratory surveillance decreased. In 2017, 65 Q fever diagnoses were reported in the virological laboratory surveillance (versus 22 notifications), while in 2016 89 Q fever diagnoses were reported in the virological laboratory surveillance (versus 14 notifications).
- Possible animal sources of infection can be sampled in the following situations:
  – *Bulk milk monitoring:*
    In 2017, the NVWA received 4 notifications of a positive sample in the bulk milk monitoring from the GD Animal Health (GD). NVWA took official samples on 3 of these farms, but *C. burnetii* could not be demonstrated. The fourth farm could not be sampled by the NVWA in the spring of 2018, since there was no bulk milk available at the farm. All the animals at the farm have been vaccinated. The farm will keep a suspect status and will be officially sampled by the NVWA as soon as bulk milk is available again.
  – *Investigation of veterinary abortion waves:*
    In 2017, the NVWA received no notifications of a deviating number of abortions among sheep and/or goats.
  – *Source finding following human cases:*
    In 2017, public health services reported 8 human cases to the NVWA for source finding. For 5 human cases no likely/possible source could be identified. The other 3 human cases were the 3 family members as explained above.

5.3.2 Tables and figures

Figure 5.8 Number of notifications of acute Q fever by case classification[a] and year, 2005-2017 (Source: Osiris). The insert zooms in on the years 2011 through 2017.
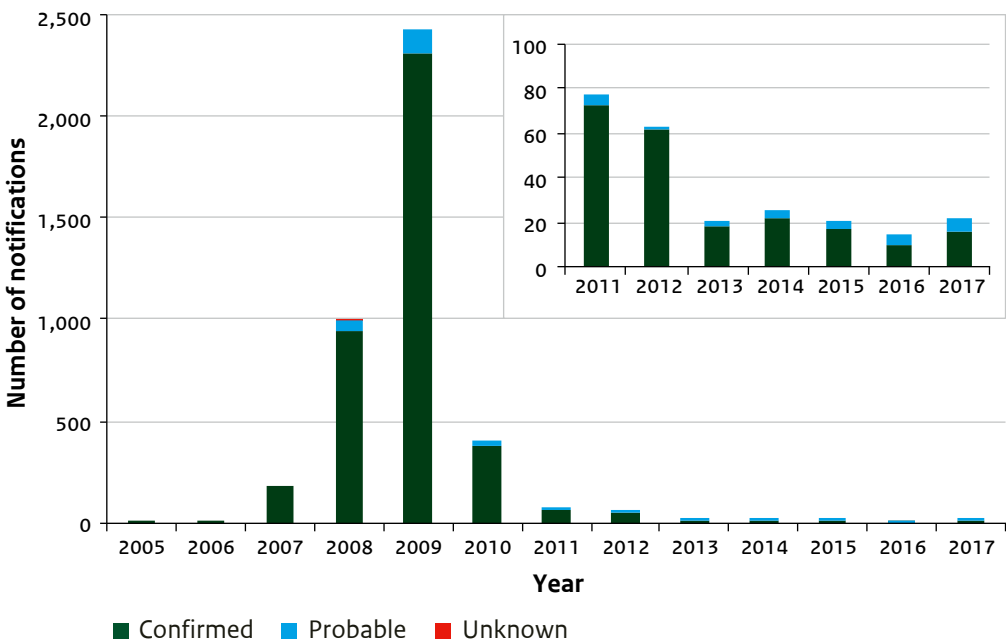
a The distinction between confirmed and probable notifications has been made since 1 July 2008.

Table 5.5 Demographic, clinical and diagnostic characteristics of notified acute Q fever patients and positive diagnoses in the laboratory surveillance, 2013-2017 (Source: Osiris and virological laboratory surveillance).

N (%), unless otherwise specified	2013	2014	2015	2016	2017
Notifications (Osiris):					
Number of notifications[a]	20 (100)	26 (100)	20 (100)	14 (100)	22 (100)
Confirmed[b]	18 (90)	22 (85)	17 (85)	9 (64)	16 (73)
Probable[c]	2 (10)	4 (15)	3 (15)	5 (36)	6 (27)
Incidence per 100,000 inhabitants	0.12	0.15	0.12	0.08	0.13
Median age in years (Q1-Q3)	52 (39 – 64)	57 (39 – 70)	58 (39 – 70)	49 (30 – 66)	53 (28 – 64)
Male gender[d]	13 (65)	21 (81)	9 (45)	11 (79)	16 (73)
Hospitalised[d]	15 (75)	17 (65)	12 (60)	7 (50)	13 (59)
Deaths notified in Osiris[d]	0	0	1 (5)	0	0
Infected abroad[d]	3 (15)	5 (19)	2 (10)	3 (21)	8 (36)
Median notification delay in days (Q1-Q3)[e]	1 (0 - 2)	0.5 (0 - 6)	1 (0 – 3)	1 (0 – 3)	0 (0 – 5)
Median diagnostic delay in days (Q1-Q3)[f]	33 (8 – 52)	25 (14 – 48)	27 (12 – 44)	14 (11 – 31)	29 (15 – 43)
Virological laboratory surveillance:					
Number of positive diagnoses	89	130	125	89	65

[a] Date used for statistics = date of onset of disease or, if missing, date of notification or date of laboratory confirmation (depending on which of these dates was first). Both notifications with status 'definite' and 'authorized' (i.e. not definite) are included.

[b] Confirmed case = a patient with clinical and laboratory diagnostic confirmation (seroconversion or a fourfold increases in IgG titre or PCR or isolation).

[c] Probable case = a clinical confirmed case with IgM antibodies against phase 2 of C. burnetii.

[d] Percentage based on the number of patients for whom this specific information was available.

[e] Notification delay = number of days between date of laboratory confirmation and date of notification at the Public Health Service. Negative delays and delays of more than a year are excluded.

[f] Diagnostic delay = number of days between onset of disease illness and date of laboratory confirmation. Negative delays and delays of more than a year are excluded.

5.4 Tuberculosis

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5.4.1 Key points 2017

- In 2017, the number of patients with tuberculosis (TB) in the Netherlands declined to less than 800, which was the first time since registration started in 1950. 787 TB patients were notified, a decrease of 11% compared to 2016 (887 notifications).TB has been steadily declining since 1997, with an increase in some years (2009, 2015 and 2016) related to migration.
- Most patients were foreign born (74%), mainly from Eritrea (n=94), followed by Morocco (n=73), Somalia (n=58), Ethiopia (n=32) and India (n=25).
- The incidence rate was 4.6 per 100,000 inhabitants.
- 463 patients (59%) had pulmonary TB, 203 with microscopy-positive sputum, the most contagious form of TB. The remaining 324 patients (41%) had extrapulmonary TB.
- 19% of all TB patients were detected by active case-finding (19% in 2016 and 20% in 2015).
- 11 patients had rifampicin-resistant TB, including 10 patients with multidrug-resistance (MDR). Eight of these 11 patients were foreign born.
- 526 TB patients (67%) were tested for HIV in 2017[1], of whom 22 were positive (4.2% of TB patients tested and 2.8% of all TB patients).
- In 2017, 89% of all TB patients with rifampicin-susceptible TB completed treatment successfully, which is similar to the treatment outcome for the years 2011-2015[2].
- 32 of 39 patients (82%) diagnosed in 2013-2015 with rifampicin-resistant TB completed treatment successfully.

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[1] Preliminary data.

[2] Treatment takes at least 6 months for drug-susceptible TB and often 20 months for rifampicin-resistant TB. Treatment outcome of drug-susceptible TB of 2017 and rifampicin-resistant TB of 2016 have not been reported yet.

5.4.2 Tables and figures

Figure 5.9 Tuberculosis incidence (per 100,000 inhabitants) in 2017 by two-digit postcode area

Incidence per 100,000 population

- 0 - 2
- >2 - 5
- >5 - 10
- >10 - 15
- TB-regions
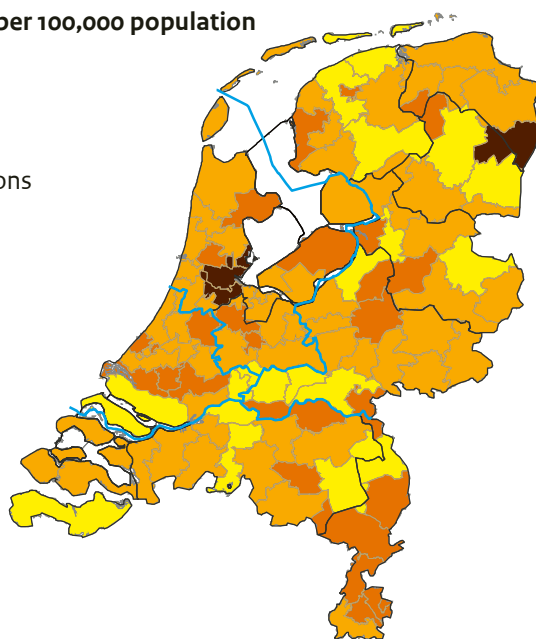
The incidence of tuberculosis was highest in Amsterdam and in Groningen in the area with a large asylum seekers' centre (Ter Apel).

Table 5.6 Summary tuberculosis data the Netherlands, 2015, 2016 and 2017

	2015 N(%)	2016 N(%)	2017 N(%)
Number of notifications	861	887	787
Incidence per 100,000 inhabitants	5.1	5.2	4.6
Mean age (years)	40	39	39
Age <15 years	42 (4.8)	49 (5.5)	34 (4.4)
Age ≥65 years	127 (15)	133 (15)	102 (13)
Male to female ratio	1.5	1.4	1.6
Foreign born	625 (73)	670 (76)	586 (74)
Residence in 1 of 4 largest cities [a]	233 (27)	256 (29)	212 (27)
Previous episode of TB (treatment)	41 (4.6)	33 (3.7)	27 (3.4)
HIV status known [3]	637 (74)	639 (72)	526 (67)
HIV positive	36 (4.2)	21 (2.4)	22 (2.8)
TNF-alpha inhibitors	16 (1.9)	11 (1.2)	11 (1.4)
Active case finding	170 (20)	167 (19)	149 (19)
Pulmonary tuberculosis (PTB & EPTB)	496 (58)	485 (55)	463 (59)
Sputum-positive PTB	217 (25)	175 (20)	203 (26)
Culture-confirmed TB	576 (67)	584 (66)	542 (69)
Rifampicin resistant TB (incl. MDR TB) [b]	11 (1.7)	16 (2.6)	11 (2.0)
Isoniazid resistance [b]	25 (4.3)	37 (6.3)	31 (5,7)
TB contacts	89 (10)	111 (13)	100 (13)
Immigrant <2.5 yr. in the Netherlands	93 (11)	75 (8)	85 (11)
Asylum seeker <2.5 yr. in the Netherlands	149 (17)	162 (18)	134 (17)
Latent tuberculosis Infection	1,468	1,741	1.773

TB=tuberculosis, PTB= pulmonary TB, EPTB= combination of pulmonary and extrapulmonary TB
HIV= Human Immunodeficiency Virus, TNF = Tumor Necrosis Factor, MDR = Multidrug-resistant
[a]   Amsterdam, Rotterdam, The Hague and Utrecht
[b]   percentage of culture-confirmed TB

[3] 2017: preliminary data

Figure 5.10 Number of tuberculosis (TB) patients and incidence per 100.000 inhabitants, 1997-2017
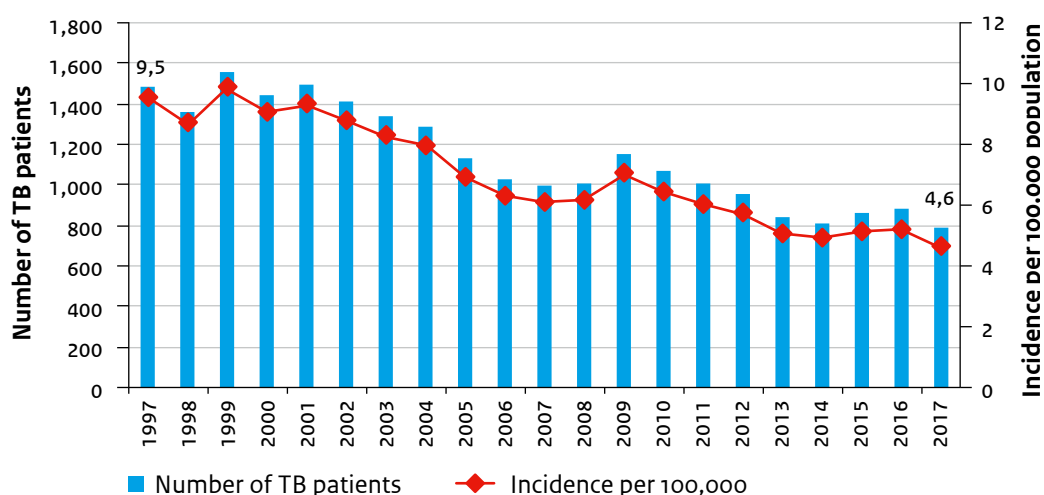
More detailed information about surveillance of tuberculosis in the Netherlands and the latest surveillance report 'Tuberculose in Nederland, 2016' is available through **the tuberculosis webpage of the RIVM** ([http://www.rivm.nl/Onderwerpen/T/Tuberculose], only available in Dutch). The next surveillance report 'Tuberculose in Nederland, 2017' will be published in December 2018.

The web-based application TBC-online [http://www.tbc-online.nl] provides information about tuberculosis in the Netherlands. TBC-online offers the opportunity to make tables and graphs of selected variables in the NTR.

5.5 Animal influenza viruses

Authors: Marit de Lange, Adam Meijer

5.5.1 Key points
In the Netherlands, no humans were tested because of exposure to an infected farm or because of possible infected bird exposure during foreign travel and therefore no infections with animal influenza virus were notified from 22 May 2017 through 20 May 2018.

5.5.2 Background
Many different animals, including ducks, chickens and pigs, can host influenza A viruses. These viruses also have the capacity to cause infection in humans, sometimes with high morbidity and mortality. Worldwide, the WHO reports once a month an overview of the worldwide animal influenza virus infection in humans. Last years, human infection by influenza virus types A(H5N1) and A(H7N9) (the vast majority from China) are most reported from a distinct number of countries. In the Netherlands, human infection with an animal influenza virus is a notifiable disease group B1, meaning that the attending physician and the laboratory are obliged to report a patient suspected of being infected with an animal influenza virus to the Public Health Service within 24 hours. This allows timely implementation of legal measures if necessary, such as forced hospitalisation or isolation, forced investigation and prohibition of profession as possible options for containment. In case of suspicion of human infection, diagnostics are performed by RIVM (CIb/IDS).

5.5.3 Epidemiological situation
At the end of 2017 and beginning of 2018, three commercial poultry holdings were infected with the highly pathogenic avian influenza virus type A(H5N6) in the Netherlands. From 22 May 2017 through 20 May 2018, no people were tested with influenza-like illness that was associated with an infected farm. Additionally, no returning travellers with possible animal influenza virus exposure were tested within the same time period.

5.6   MERS-CoV

Authors: Rianne van Gageldonk-Lafeber, Adam Meijer

5.6.1   Background

In 2012, a new type of coronavirus was discovered in the Kingdom of Saudi Arabia (KSA): the Middle East respiratory syndrome corona-virus (MERS-CoV). This virus can cause Acute Respiratory Distress Syndrome (ARDS). Most common symptoms are fever, cough and shortness of breath. There is no evidence of sustained human-to-human transmission, although a large outbreak of nosocomial transmission starting with one imported case occurred in South-Korea. Dromedary camels are a major reservoir host for MERS-CoV and an animal source of MERS infection in humans, although the route of transmission from animals to humans is not fully understood.

5.6.2   Epidemiological situation

Since July 2013, MERS-CoV is a group A notifiable disease for hospital care providers in the Netherlands, meaning that a specialist is obliged to immediately report a patient suspected of being infected with the MERS-CoV to the Public Health Service [http://www.rivm.nl/en/Topics/M/MERS_Coronavirus]. This enables the Public Health Service to take immediate appropriate action aimed at preventing further transmission by tracing and follow-up of potential contacts. In case of suspected MERS-CoV infection in the Netherlands, diagnostics are performed at ErasmusMC. In May 2014, Middle East respiratory syndrome coronavirus (MERS-CoV) infection, with closely related viral genomes, was diagnosed in two Dutch residents, returning from a pilgrimage to Medina and Mecca, Kingdom of Saudi Arabia (Fanoy, van der Sande et al. 2014, Kraaij-Dirkzwager, Timen et al. 2014).

In 2017, a total of 18 patients with severe acute respiratory illness, returning from countries where exposure to MERS-CoV is possible, were tested for MERS-CoV as well as 3 patients in 2018. None of them had an infection with MERS-CoV.

Chapter 6
Other respiratory infections reported in the weekly virological surveillance

Authors: Rianne van Gageldonk-Lafeber
Contributors: Adam Meijer, Sofie Mooij

6.1 Key points

- The total number of positive rhinovirus (N=2,706) test results in 2017 was the highest reported since five years (range 2013-2016: 2,049-2,589), especially because of high numbers of positive test results between week 32 and 42 of 2017.
- The total number of positive coronavirus (N=708) test results in 2017 was comparable to that in 2016 (N=712). The relatively high numbers of positive test results at the end of 2016 were followed by high numbers in the first quarter of 2017.
- As in previous years, the total number of positive parainfluenza virus test results was highest for type 3. The total number of positive tests for this specific type was higher than in the previous four years (N=585, range 2013-2016: 218-411), because of high numbers of positive test results in the first half of 2017.
- Also for parainfluenza virus type 1 and 4, the total number of positive tests were higher than in the previous four years (N=208, range 2013-2016: 55-149 and N=145, range 2013-2016: 53-122; respectively). High number of positive parainfluenza virus type 1 test results were reported in the fourth quarter of 2017, while relatively high number of positive parainfluenza virus type 4 test results were seen all year round.
- The total number of positive bocavirus (N=255) test results in 2017 was higher than the past four years (range 2013-2016: 107-159).
- The numbers of positive diagnoses for *Mycoplasma pneumoniae*, hMPV, parainfluenza virus type 2, *Chlamydia pneumoniae* and adenovirus were within the range of the four previous years.

6.2 Discussion

The virological laboratory surveillance includes weekly data on the number of positive test results for respiratory pathogens originating from both primary care and hospitals. Patient's background and information on clinical presentation is lacking in the virological laboratory surveillance, and no distinction can be made between data from primary care and hospitals (Bijkerk, de Gier et al. 2016). It is likely that patient population and disease severity differs between primary care and hospitals. In 2017, the total numbers of positive test results for rhinovirus, parainfluenza virus type 1, 3 and 4 and bocavirus were the highest reported since five years. Changes in the number of positive test results in the virological laboratory surveillance data are not necessarily caused by actual changes in the incidence of infection, but can also be caused by changes in the policy of testing and testing procedures by the physicians and/or microbiological laboratories. One such change in testing might be the increased application of respiratory panels, which can be used for detection of the causative agent of disease in patients displaying a respiratory disease syndrome. In these panels, molecular detection of the most common viruses is performed in one test. However, which viruses are included in the respiratory panels and the extent to which the panels are used, differs between laboratories and between years.

6.3 Tables and figures

Table 6.1 Number of reported positive tests of rhinovirus, *Mycoplasma pneumoniae*, human metapneumovirus (hMPV), coronavirus, parainfluenza virus (PIV) type 1-4, *Chlamydia pneumoniae*, adenovirus and bocavirus in the virological laboratory surveillance for the period 2013-2017.

Year:	Number of positive diagnoses:										
	Rhinovirus	M.pneumoniae	hMPV	Coronavirus	PIV type 1	PIV type 2	PIV type 3	PIV type 4	C. pneumoniae	Adeno-virus	Bocavirus
2013	2049	325	469	377	138	74	291	76	27	1244	111
2014	2194	436	385	318	76	66	218	53	20	1268	107
2015	2410	525	651	575	149	72	344	122	31	1322	114
2016	2589	608	542	712	55	108	411	65	19	1612	159
2017	2706	400	629	708	208	70	585	145	17	1379	255

M. pneumoniae = Mycoplasma pneumoniae
hMPV= human metapneumovirus
PIV= parainfluenza virus
C. pneumoniae = Chlamydia pneumonia

Figure 6.1 Number of weekly reported positive test results of rhinovirus in the virological laboratory surveillance for the calendar year 2017 and the trend lines* for the calendar years 2013 – 2017.
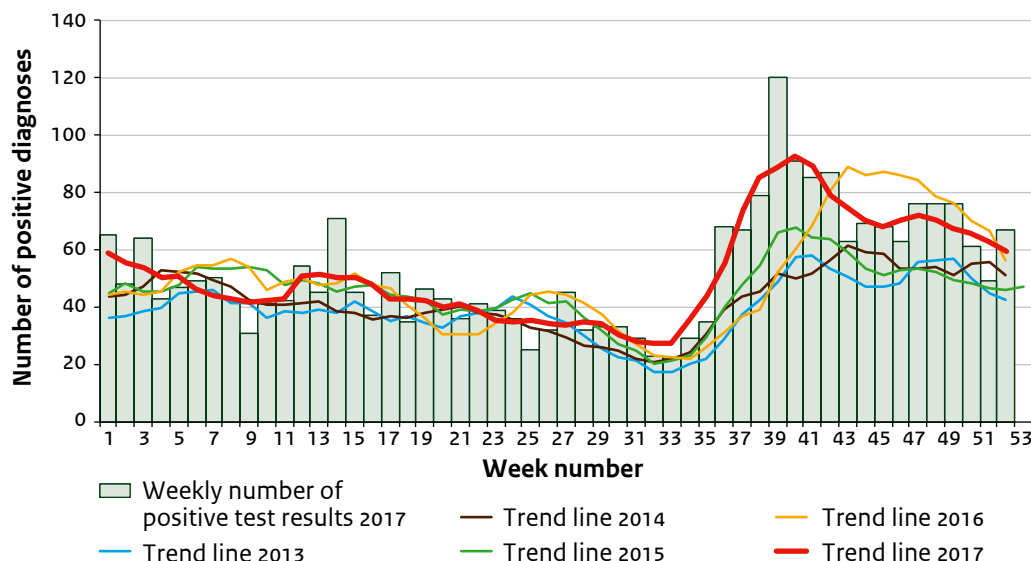
* 5-week moving average

Figure 6.2 Number of weekly reported positive tests *Mycoplasma pneumoniae* in the virological laboratory surveillance for the calendar year 2017 and the trend lines* for the calendar years 2013 – 2017.
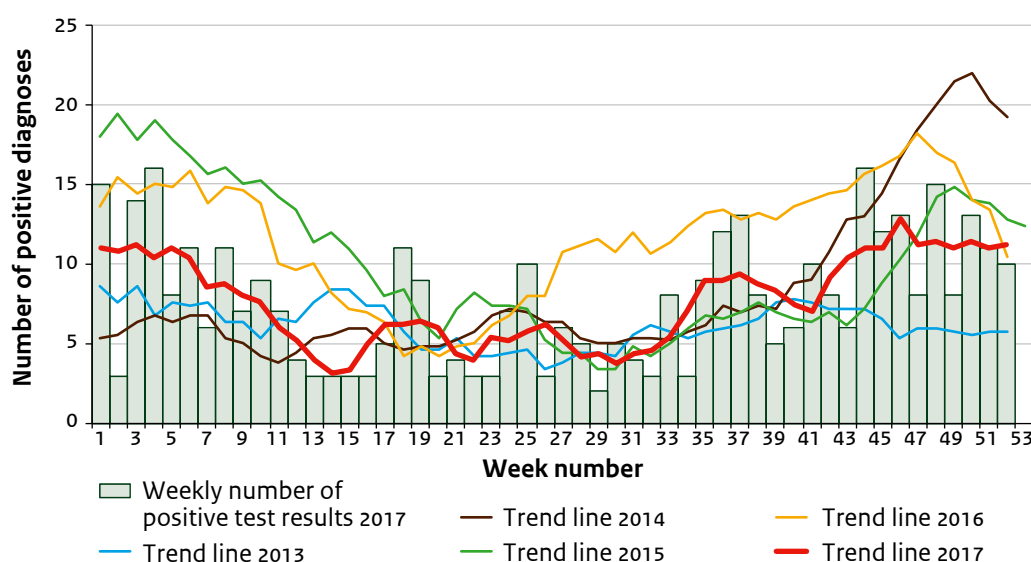
* 5-week moving average

Figure 6.3 Number of weekly reported positive tests of human metapneumovirus (hMPV) in the virological laboratory surveillance for the calendar year 2017 and the trend lines[*] for the calendar years 2013 – 2017.

- Weekly number of positive test results 2017
- Trend line 2013
- Trend line 2014
- Trend line 2015
- Trend line 2016
- Trend line 2017

* 5-week moving average
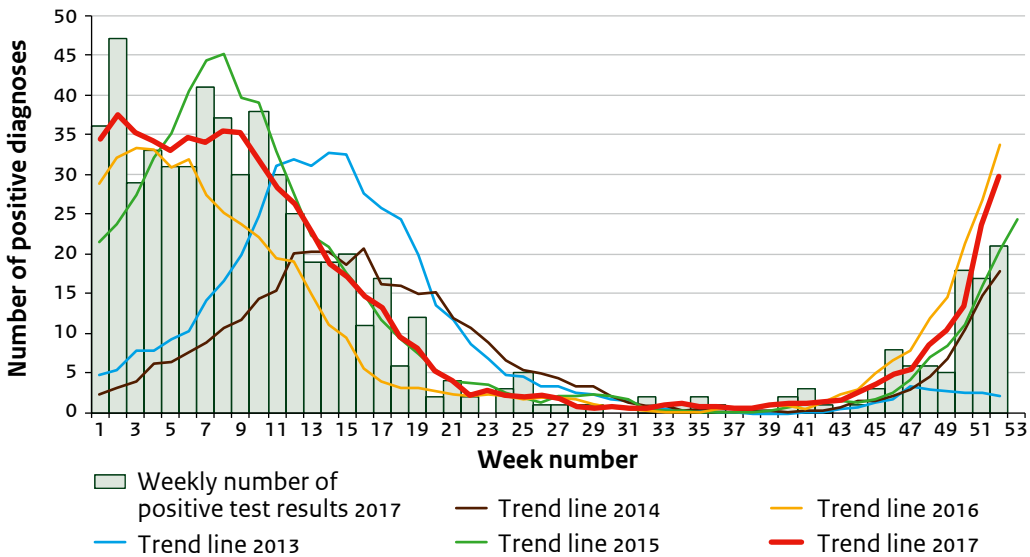
Figure 6.4 Number of weekly reported positive tests of coronavirus in the virological laboratory surveillance for the calendar year 2017 and the trend lines[*] for the calendar years 2013 – 2017.

- Weekly number of positive test results 2017
- Trend line 2013
- Trend line 2014
- Trend line 2015
- Trend line 2016
- Trend line 2017

* 5-week moving average

Figure 6.5 Number of weekly reported positive tests of parainfluenza virus type 1 in the virological laboratory surveillance for the calendar year 2017 and the trend lines* for the calendar years 2013 – 2017.

* 5-week moving average

Figure 6.6 Number of weekly reported positive tests of parainfluenza virus type 2 in the virological laboratory surveillance for the calendar year 2017 and the trend lines* for the calendar years 2013 – 2017.

* 5-week moving average
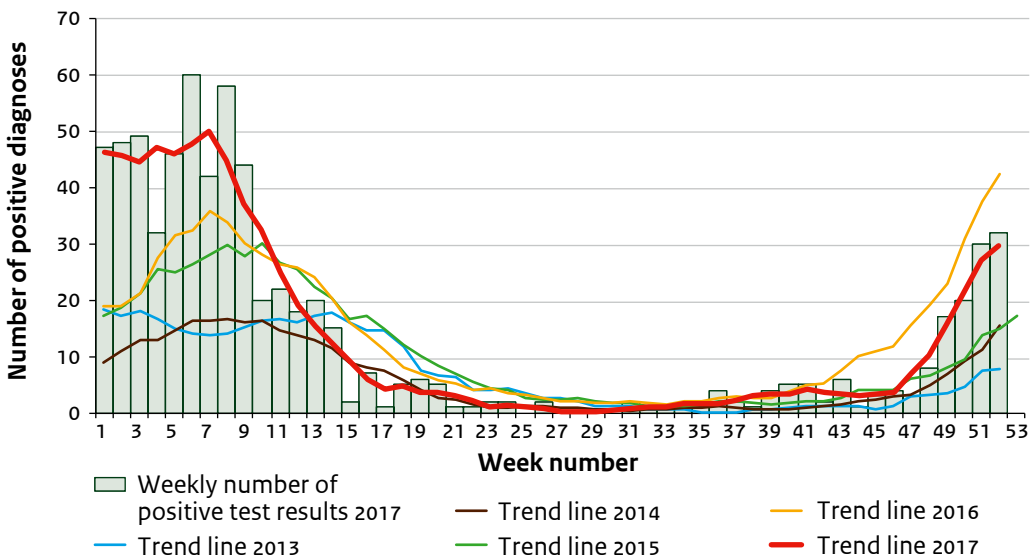
Figure 6.7 Number of weekly reported positive tests of parainfluenza virus type 3 in the virological laboratory surveillance for the calendar year 2017 and the trend lines[*] for the calendar years 2013 – 2017.

* 5-week moving average

Figure 6.8 Number of weekly reported positive tests of parainfluenza virus type 4 in the virological laboratory surveillance for the calendar year 2017 and the trend lines* for the calendar years 2013 – 2017.
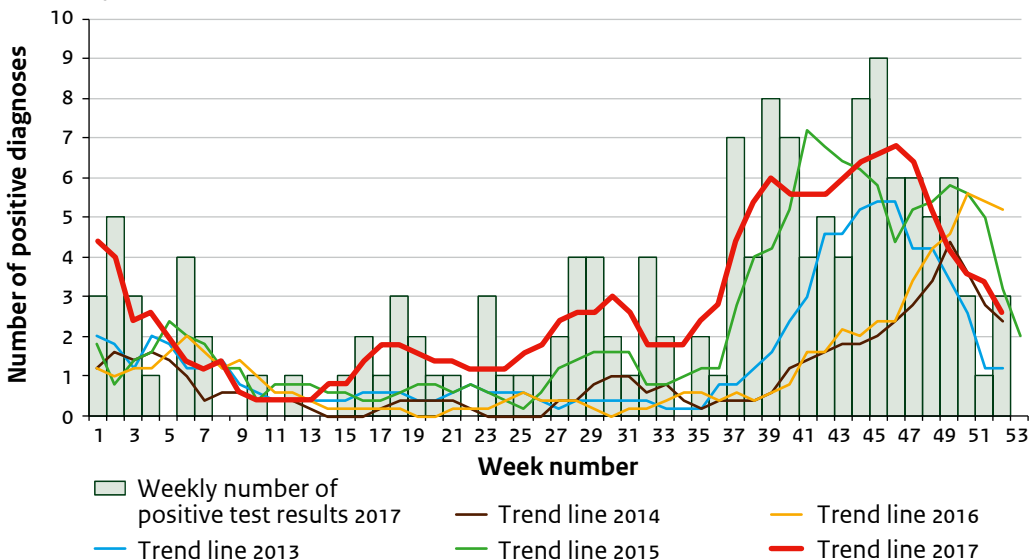
* 5-week moving average

Figure 6.9 Number of weekly reported positive tests of *Chlamydia pneumoniae* in the virological laboratory surveillance for the calendar year 2017 and the trend lines[*] for the calendar years 2013 – 2017.
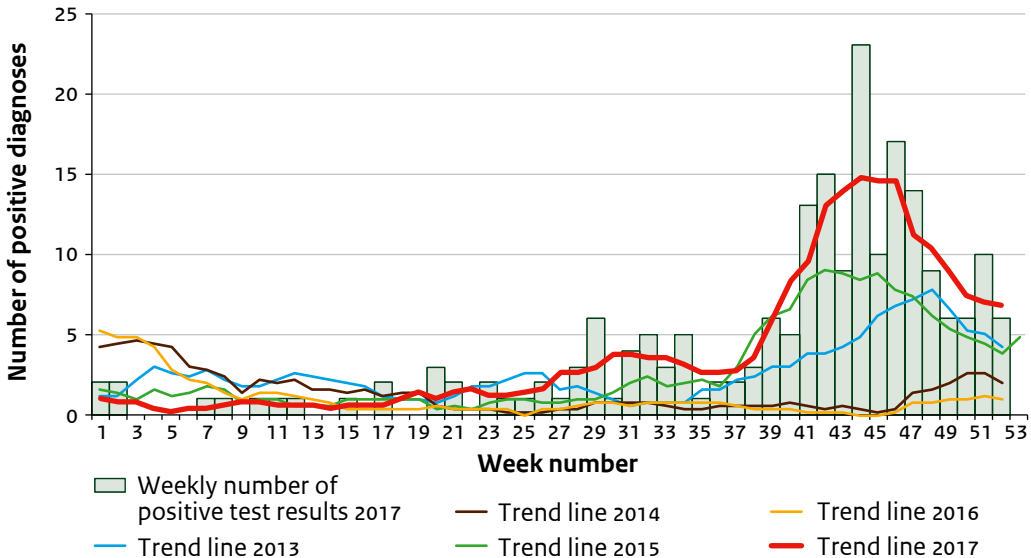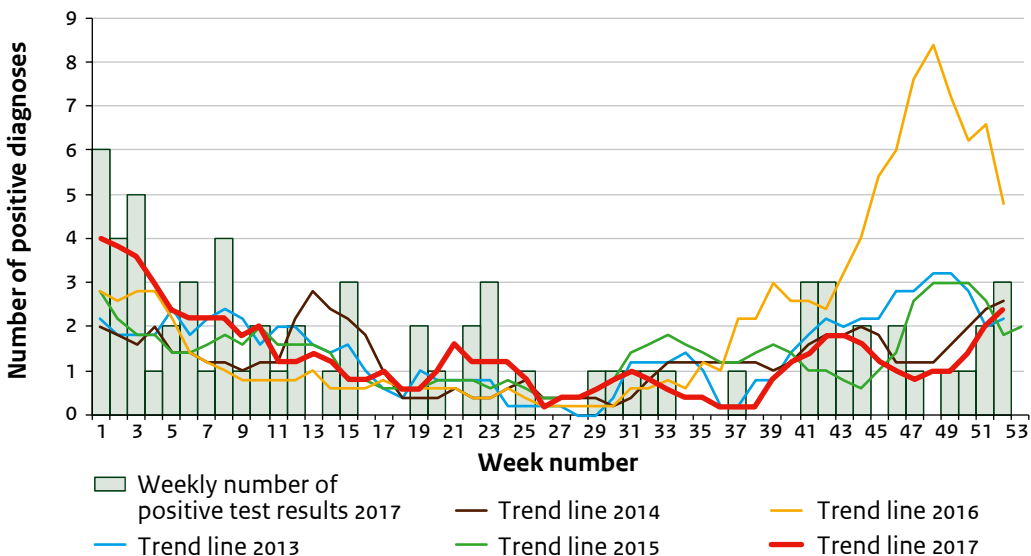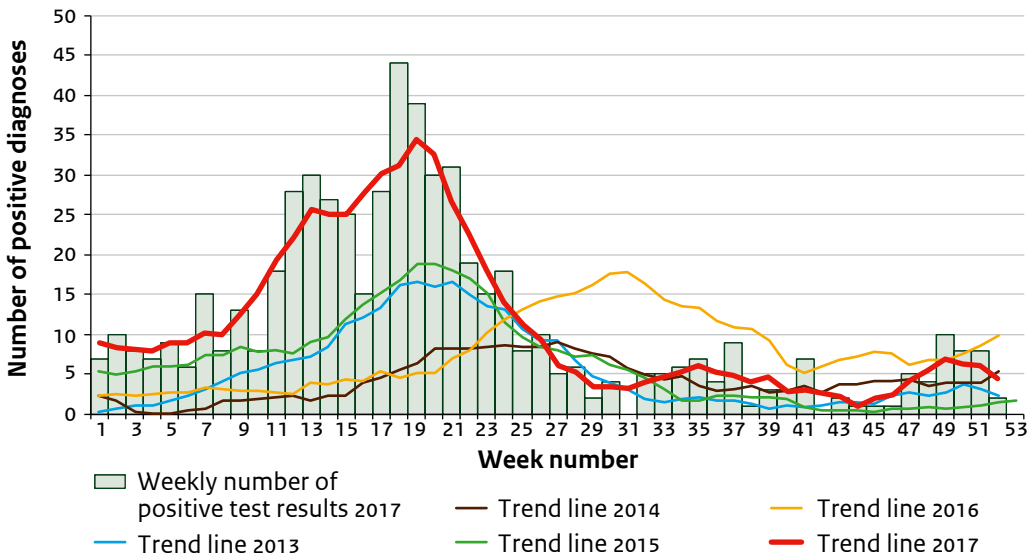

* 5-week moving average

Figure 6.10 Number of weekly reported positive tests of adenovirus in the virological laboratory surveillance for the calendar year 2017 and the trend lines[*] for the calendar years 2013 – 2017.

* 5-week moving average

Figure 6.11 Number of weekly reported positive tests of bocavirus in the virological laboratory surveillance for the calendar year 2017 and the trend lines* for the calendar years 2013 – 2017.
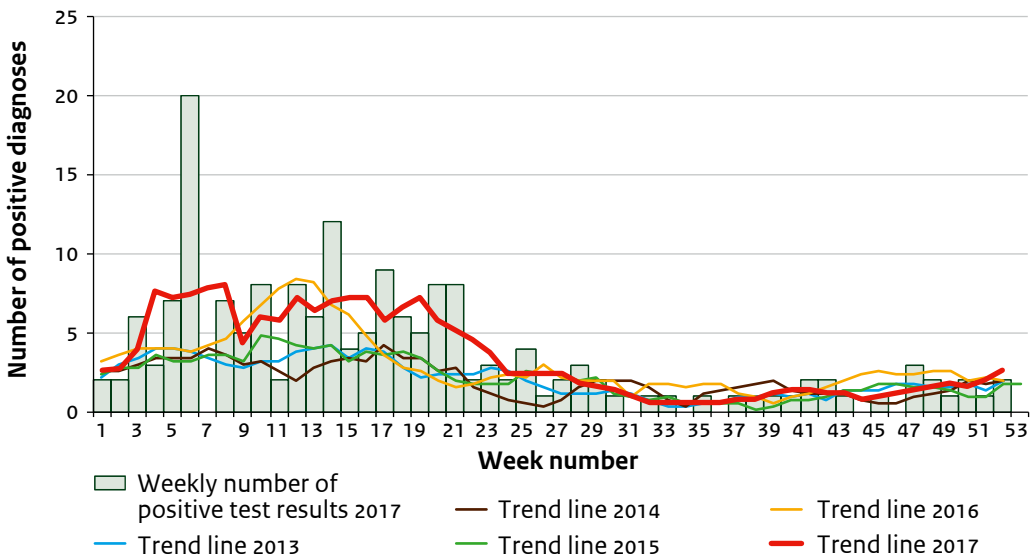
* 5-week moving average
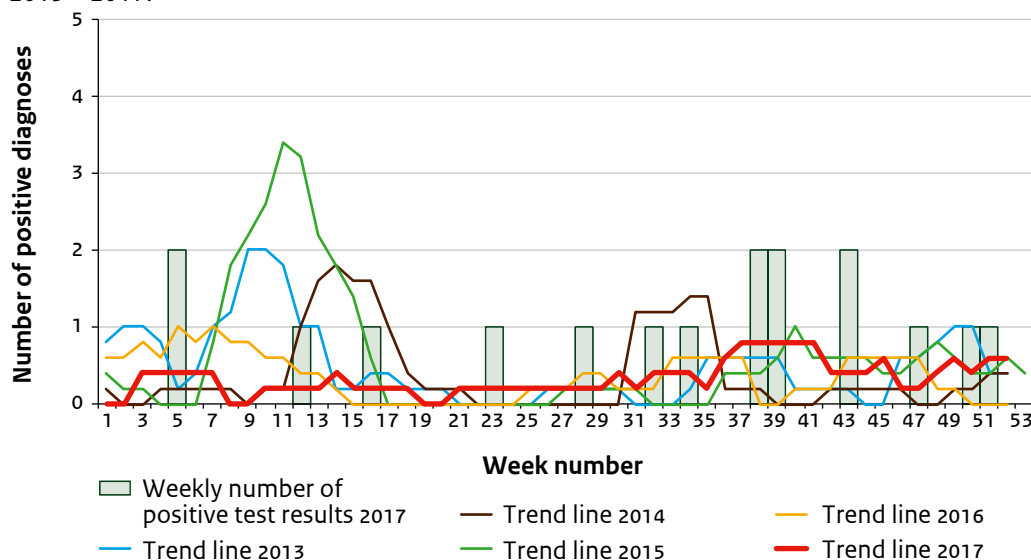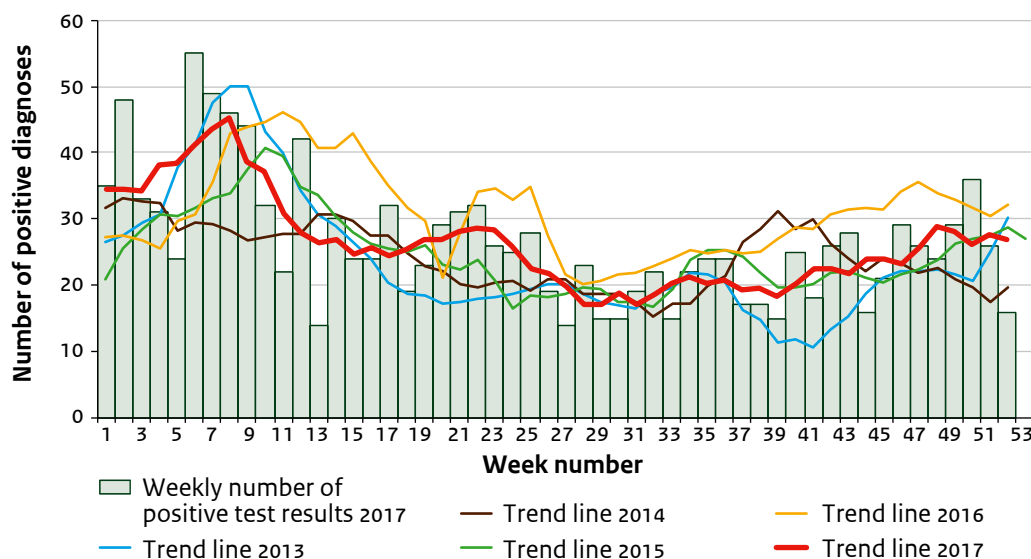
Chapter 7
Burden of respiratory infectious diseases in the Netherlands

Authors: Brechje de Gier
Contributors: Scott McDonald, Gerard de Vries, Erika Slump, Petra Brandsema, Frederika Dijkstra, Marit de Lange, Adam Meijer

7.1   Keypoints

- The respiratory infectious disease with the highest disease burden was influenza, with an estimated 18,600 DALY (95% CI 17,500-19,600) for season 2017/2018. Disease burden in 2017 was estimated at 8,100 DALY (7,200-8,900) for legionellosis; 2,300 DALY (2,300-2,400) for tuberculosis; 220 DALY (170-280) for psittacosis, and 72 DALY (60-86) for Q fever.
- For both influenza and legionellosis, the most recent burden estimate is the highest since 2013. The burden of influenza is highly variable across the years, while the burden of legionellosis has steadily increased during the past five years.
- When assessing the average burden per individual case, the burden is highest for tuberculosis and lowest for influenza.

7.2 Background

Estimates of the burden of infectious diseases are used to compare health impact between different infectious diseases in the Dutch population and to follow trends in time. The burden of a disease is a combination of incidence and severity. Disease burden is expressed here in disability-adjusted life years (DALY), which indicates the number of healthy life years lost due to a disease. DALY is the sum of years of life lost due to mortality (YLL) and years lived with disability due to morbidity (YLD) (Mangen, Plass et al. 2013). The burden of infectious diseases in the Netherlands was estimated using the Burden of Communicable Diseases in Europe (BCoDE) methodology, which entails a pathogen- and incidence-based approach (Mangen, Plass et al. 2013). This means that all health loss due to an infection is attributed to the event of infection and (future) long-term sequelae of infection are included in the burden assigned to the year of infection. The DALY estimates presented in this chapter can be interpreted as the disease burden that is and will be suffered due to the average annual respiratory infections that occurred in the years 2013 to 2017, or the disease burden that theoretically could have been avoided by preventing infections in those years.
See Chapter 9 for an overview of changes in burden estimation methods.

7.3 Tables and figures

Figure 7.1 Average annual DALY, caused by respiratory infectious diseases in the Netherlands, split by YLL (years of life lost due to mortality) and YLD (years lived with disability), ranked by the average disease burden caused by the annual incident cases in 2013-2017 (seasons 2013-2017 through 2017-2018 for influenza).
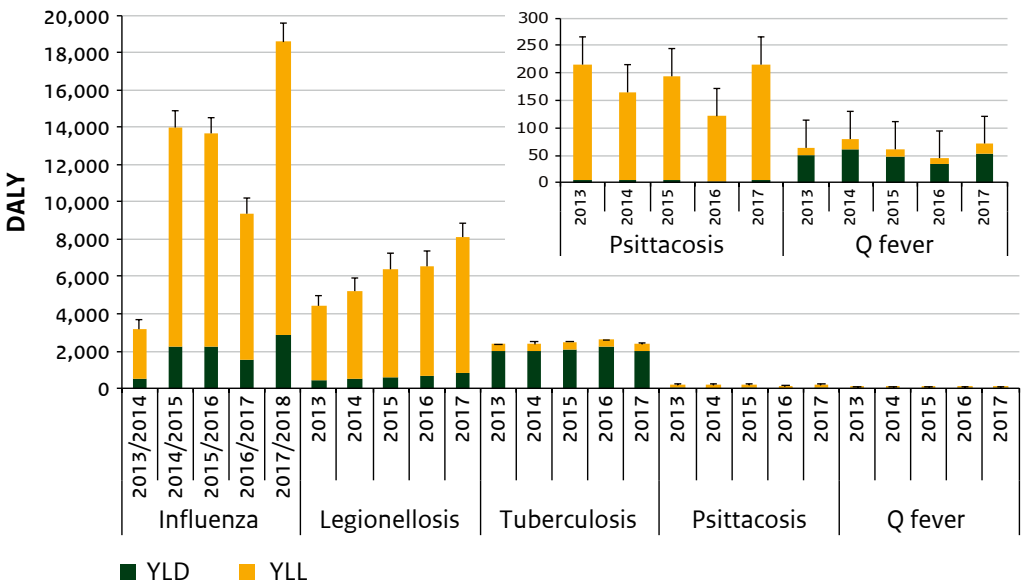
Note: Error bars indicate 95% confidence intervals. The insert zooms in for psittacosis and Q fever.

Figure 7.2 Ranking of respiratory diseases by estimated burden at population (DALYs/year) and individual level (DALYs/100 cases) in 2017 (for influenza respiratory season 2017/2018). The area of each bubble is proportional to the estimated incidence of the disease.
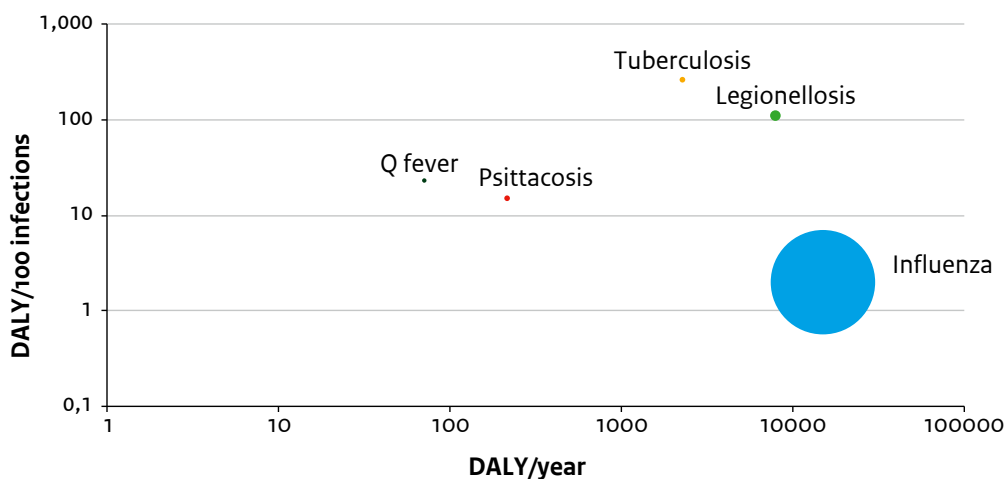
Note: both axes are on a logarithmic scale.

Table 7.1 Estimated annual disease burden in YLD per year, YLL per year, DALY per year, DALY per 100 cases (with 95% confidence intervals) and estimated annual number of acute infections in the years 2013 to 2017 (season 2017/2018 for influenza) in the Netherlands in order of highest to lowest average DALY/year in 2017.

Disease	YLD/ year	YLL/ year	DALY/ year	DALY/ 100 cases[ab]	Annual acute infections[c]
Influenza					
2013/ 2014	510 (420-600)	2,700 (2,300-3,100)	3,200 (2,700-3,700)		158,000
2014/ 2015	2200 (2,000-2,300)	11,800 (11,100-12,500)	14,000 (13,100-14,900)		700,000
2015/ 2016	2,200 (2,000-2,300)	11,500 (10,800-12,200)	13,700 (12,800-14,500)		682,000
2016/ 2017	1,500 (1,300-1,600)	7,900 (7,300-8,600)	9,400 (8,600-10,200)		471,000
2017/ 2018	2,900 (2,700-3,100)	15,700 (14,800-16,600)	18,600 (17,500-19,600)	2.0 (2.0 -2.0)	933,000
Legionellosis					
2013	430 (390-470)	4,000 (3,600-4,500)	4,500 (4,000-5,000)		4,000
2014	490 (440-540)	4,700 (4,100-5,200)	5,100 (4,600-5,800)		4,500
2015	590 (540-650)	5,800 (5,100-6,500)	6,400 (5,700-7,200)		5,500
2016	640 (580-700)	5,900 (5,200-6,600)	6,500 (5,800-7,300)		5,900
2017	790 (720-870)	7,300 (6,500-8,100)	8,100 (7,200-8,900)	110 (100-120)	7,300
Tuberculosis					
2013	2,000 (2,000-2,000)	380 (350-420)	2,400 (2,400-2,400)		950
2014	2,000 (2,000-2,000)	380 (340-420)	2,300 (2,300-2,400)		910
2015	2,100 (2,100-2,100)	390 (350-430)	2,500 (2,400-2,500)		960

Disease	YLD/ year	YLL/ year	DALY/ year	DALY/ 100 cases[ab]	Annual acute infections[c]
2016	2,200 (2,200-2,200)	400 (360-440)	2,600 (2,500-2,600)		1,000
2017	2,000 (2,000-2,000)	360 (320-390)	2,300 (2,300-2,400)	260 (260-270)	880
Psittacosis					
2013	6 (5-7)	210 (160-280)	220 (160-280)		1,500
2014	4 (4-5)	160 (120-210)	170 (130-210)		1,100
2015	5 (4-5)	190 (140-250)	190 (140-250)		1,300
2016	3 (3-4)	120 (91-160)	130 (94-170)		950
2017	5 (5-6)	210 (160-270)	220 (170-280)	15 (12-18)	1,500
Q fever					
2013	49 (41-57)	15 (13-18)	64 (55-74)		270
2014	62 (52-71)	18 (15-21)	80 (68-92)		360
2015	48 (41-56)	14 (12-17)	62 (52-72)		280
2016	34 (27-43)	11 (9-14)	46 (36-56)		190
2017	54 (45-64)	18 (15-22)	72 (60-86)	23 (19-27)	302

[a] for Q fever, asymptomatic acute infections can lead to disease burden from sequelae, the estimated annual DALY were therefore divided by the sum of both symptomatic and asymptomatic acute infections per year.
[b] DALY/ 100 cases is only shown for 2017 since this measure is a characteristic of the disease and is independent of time.
[c] this number includes asymptomatic acute infections for Q fever.

Chapter 8
General discussion and conclusion

Authors: Daphne Reukers, Wim van der Hoek

Influenza

The influenza epidemic in the 2017/2018 season lasted 18 weeks, which is much longer than the average nine weeks duration over the past 20 years. The ILI incidence reported by GPs and the peak in ILI incidence of 17.0 per 10,000 inhabitants in week 10 was higher than the previous four seasons. However, the ILI incidence in nursing homes was similar to the four previous seasons, as well as the number of ARI patients and GP consultations for pneumonia for children in the age group 0-4 years. Remarkably, a type B influenza virus (of the Yamagata-lineage) was the dominant influenza virus during most of the epidemic, while only in the last weeks of the epidemic influenza viruses of type A predominated, with slightly more subtype A(H1N1)pdm09 than subtype A(H3N2).

Peak ILI and ARI incidence among the 0-4 year age group was several weeks before the peak among the elderly. An explanation for this age difference is the RS-virus circulation early in the season, mainly affecting young children. The initial dominance of influenza B virus may also have played a role, while influenza A viruses became more prevalent later in the season. This pattern corresponds with the late peak of community-acquired pneumonia (CAP) in primary care, mainly consisting of elderly patients.

During the 2017/2018 season, many regional and national media reported a high burden on hospitals due to influenza. The sudden increase in the number of mostly elderly patients requiring hospital care for severe acute respiratory infections (SARI) as complication from influenza virus infection posed a significant burden for hospitals in managing bed and staff capacity. Unfortunately, it is not possible to provide a nationally representative quantitative confirmation of these hospital-specific and anecdotal reports. Surveillance of SARI is still in a pilot phase and testing of SARI patients for influenza virus infection is very limited in many hospitals. However, from the influenza viruses that were submitted by medical microbiological

laboratories to the Erasmus Medical Centre for antigenic characterisation, we can assume that most of the infections of hospitalised cases were caused by influenza virus type B (Yamagata-lineage). This does not provide an explanation for the severity of the epidemic, because type B influenza viruses are mostly considered to cause mild symptoms and with higher burden in children than in elderly. A possible explanation for a high burden in the 2017/2018 season might be the high number of susceptible persons in the population, as most people would not have been exposed to naturally circulating type B (Yamagata-lineage) influenza virus. Hospital capacity problems can have different causes, such as the increasing number of elderly that continue to live at home. Community-dwelling elderly with complications from influenza virus infection may have to be admitted to a hospital, while this could be less urgent for elderly that are already institutionalised in nursing homes. A problem mentioned by many hospitals was shortage of nurses and other qualified hospital staff, due to high rates of sick leave. This may partly be attributed to the very low influenza vaccine uptake among hospital workers.

The surveillance pyramid of influenza and other respiratory infections is displayed in Figure 8.1. Surveillance on severe acute respiratory infections (SARI) has been the missing link in the Dutch respiratory surveillance system. A pilot study on SARI surveillance has started in 2015 in two Dutch hospitals and has provided meaningful insights in the occurrence of hospitalised influenza cases. The results are added to the weekly surveillance report on the RIVM website and are reported to ECDC and WHO on a weekly basis. In the Jeroen Bosch hospital SARI surveillance is now embedded in a quality of care management strategy, resulting in the 'flu monitor', the implementation of point-of-care tests (POCT) for influenza and the establishment of a separate ward for influenza-positive patients. These initiatives, including an economic evaluation of influenza POCTs, will be further evaluated and the feasibility to extend this to other hospitals will be assessed.

Figure 8.1 The respiratory infections surveillance pyramid in the Netherlands
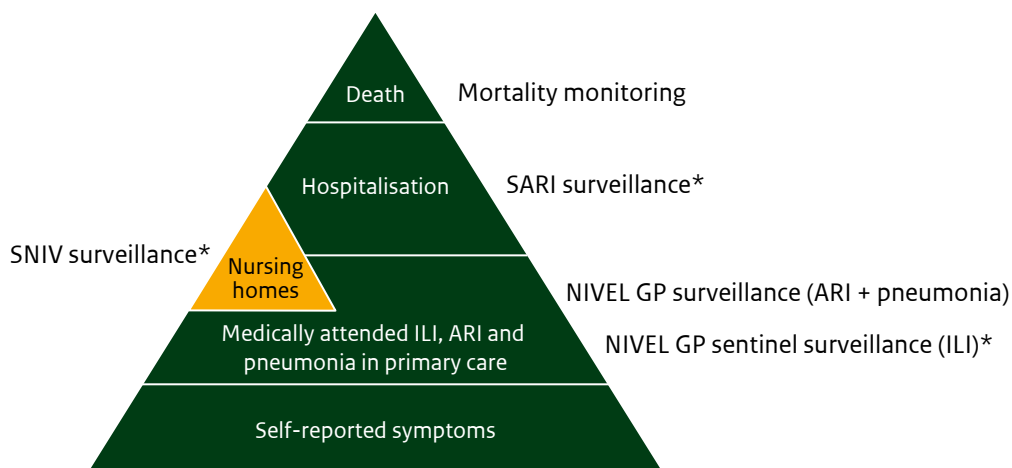
Footnote: Systems with * also include virological surveillance

We again present the estimated annual incidence of symptomatic influenza virus infection for the entire Dutch population, based on sentinel GP influenza surveillance data and self-reported data from Influenzanet. This outcome is derived using a statistical modelling approach, which combines multiple sources of evidence and, therefore, provides a useful estimate of symptomatic influenza incidence in the population that can be compared across seasons (McDonald, Presanis et al. 2014). This method also enables a direct comparison of influenza incidence between age groups, and the burden attributable to the various strains across seasons in the population

In the 2017/2018 season, the dominant influenza type B (Yamagata-lineage) was not included in the trivalent influenza vaccine (TIV). However, the vaccine effectiveness was still moderate against this subtype, likely because of cross protection by vaccination against type B (Victoria-lineage), which was included in the vaccine. The World Health Organization (WHO) has selected the same A(H1N1)pdm09 strain for the 2018/2019 season in the northern hemisphere, because of the good match with the circulating virus. The vaccine will again include a B (Victoria-lineage) virus, but updated to B/Colorado/06/2017. In the WHO vaccine recommendations, the composition of the quadrivalent influenza vaccine (QIV) is now mentioned first. In this QIV, a B/Victoria as well as a B/Yamagata virus are included [http://www.who.int/influenza/vaccines/virus/recommendations/2018_19_north/en/]. On influenza vaccine-effectiveness, RIVM will continue to participate in the European I-MOVE consortium. This makes it possible to pool data from different European countries and provide robust estimates of vaccine effectiveness early in the influenza season, so that public health measures can still be taken. Over the 10-years of existence of the I-MOVE programme, the overall influenza vaccine effectiveness was 35%, based on I-MOVE data, but weighed for circulating strains in the Netherlands.

Notifiable respiratory diseases
Notifiable infectious diseases that present as pneumonia are under-reported, because most cases of community-acquired pneumonia (CAP) are managed in primary care, without specific diagnostic laboratory tests. Even in patients admitted to hospital with CAP, presumptive treatment with antibiotics is provided and the causative pathogen often remains unknown.

In the virological laboratory surveillance 65 diagnoses of *C. burnetii* were reported which is higher than the 22 acute Q fever cases notified in Osiris. This discrepancy is not unexpected, as in the virological surveillance, many positive laboratory results indicate a past infection with *C. burnetii* and therefore do not fulfil the national notification criteria for acute Q fever. The number of notified cases is in line with the number of notifications from 2013-2016 (varying from 14 to 26), which is comparable to the levels before the large 2007-2010 Q fever epidemic.

In recent years, the number of notified tuberculosis cases showed a slight increase after years of steady decline. However, in 2017, the number of notified tuberculosis cases was below 800 patients (n=787) for the first time since the first registration in 1950. This pattern can largely be explained by the fluctuations in number of asylum seekers from high incidence countries. Most TB patients notified in 2017 were foreign born (74%).

The increasing trend in incidence of Legionnaires' disease (LD), which was observed in domestic cases from 2012 to 2016, continued in 2017. There was a record number of 561 patients in 2017 without major outbreaks but with several smaller clusters. Two of these clusters in the province of Noord-Brabant have now been linked to industrial biological wastewater treatment plants. As biological aeration ponds are increasingly used in modern (energy producing) wastewater treatment installations, this is a concern and needs further evaluation.

The report provides an update on the burden of respiratory infectious diseases expressed in disability-adjusted life years (DALY). Also when considering a larger group of infectious diseases, influenza remains the infectious disease with the highest burden in the Netherlands (van Lier, McDonald et al. 2016). This is also the case for the European (EU) region, with influenza responsible for 30% of the total burden from infectious diseases (Cassini, Colzani et al. 2018).

An overall objective of RIVM is to make surveillance information available to the public as quickly as possible. The RIVM website already provides weekly updated information on influenza and RSV trends and all-cause mortality. Information on tuberculosis is updated every quarter, data on psittacosis and Q fever monthly, or more frequently if indicated, such as during outbreaks. For other subjects, including legionellosis and pneumonia, the webpages are still under development. Up-to-date information on the incidence of legionellosis, psittacosis and Q fever is also available at https://www.atlasinfectieziekten.nl/.

Chapter 9
Methods for respiratory surveillance

9.1 Respiratory season, respiratory year and calendar year

The aim of this annual report is to describe the surveillance of influenza and other respiratory infections in the Netherlands. Since influenza, influenza-like-illness (ILI), acute respiratory infections (ARI), pneumonia, respiratory syncytial virus (RSV) infection, and all-cause mortality mainly occur in winter, data is usually presented for the respiratory season or the respiratory year. A respiratory season is defined as the period from week 40 through week 20 of the next year and the respiratory year is defined as the period from week 40 through week 39 of the next year. In this report, data on the respiratory year 2017/2018 is limited to the respiratory season to allow a timely reporting. These respiratory infections may occur outside this winter period to a limited extend. Because the notifiable diseases legionellosis, tuberculosis, Q fever and psittacosis as well as the majority of pathogens monitored in the virological laboratory surveillance occur without typical winter seasonality, the results of these diseases refer to the 2017 calendar year (weeks 1-52).

9.2   Data sources

Nivel Primary Care Database
Nivel (Netherlands institute for health services research) holds the integral monitoring and information services for primary care, called 'Nivel Primary Care Database' (Verheij and Koppes 2013). The Nivel Primary Care Database holds longitudinal data registered by general practitioners (GPs) and other primary health care providers. For the surveillance of respiratory infectious diseases, the following data of Nivel is used:

- Near real-time (weekly) surveillance data concerning pneumonia and acute respiratory infections, based on consultation data in electronic medical records from about 400 participating general practices spread over the country [http://www.nivel.nl/NZR/ wekelijkse-surveillance-gezondheidsproblemen].
- In the 2017/2018 respiratory year, the coverage was about 1.3 million persons (8% of the Dutch population, representative for age). These GPs do not actively report patients and do not take laboratory specimens for surveillance purposes but make their electronic patient information systems available for automatic, anonymised, data extraction (Hooiveld, ten Veen et al. 2013).
- A proportion of the GPs participating in Nivel Primary Care Database take part in 'sentinel surveillance'. These GPs actively report on the number of patients who consult them for ILI. From a subset of patients, they collect a throat swab and nose swab and send it to RIVM for virological laboratory diagnostics (influenza virus, RSV, rhinovirus and enterovirus). The population of these 40 sentinel practices covers approximately 0.8% of the Dutch population and is representative for age, sex, regional distribution and population density (Donker 2016).

National sentinel surveillance network for infectious diseases in nursing homes (SNIV)
The nursing homes participating in this network serve as sentinels for the national surveillance of infectious diseases in nursing homes. In the 2017/2018 respiratory year, 32 locations from 19 different institutions participated. The participating nursing homes weekly report the number of residents with ILI and pneumonia and annually report the total bed capacity in the nursing home. Due to reporting delay in the weekly reports, the incidence measures for the current season are not yet complete and should be considered preliminary data. The annual total bed capacity is reported retrospectively, i.e. after closure of the calendar year. Therefore, the total bed capacity of the current calendar year is not yet definite and based on the number reported in the previous calendar year. We assume 100% coverage of the total number of beds for every week that data has been registered. According to protocol, from a subset of ILI patients, or if not available/possible from patients with another acute respiratory infection (ARI), a throat swab and nose swab is collected for virological laboratory diagnostics. However, compliance with this procedure is low and only very few specimens are received from nursing homes.

Death notification data, Statistics Netherlands (CBS)
In the Netherlands, deaths are notified to municipalities and then reported to 'Statistics Netherlands' (In Dutch: Centraal Bureau voor de Statistiek: CBS), which collects and monitors all Dutch vital statistics. Weekly, RIVM receives data and analyses updated data that includes date of death, report-delay, age-group and region. The report-delay is the number of days between the date of death and the date that the death notification was received by CBS. Of all death notifications, 44% (median) is received by CBS within 1 week after the date of death, 97% within 2 weeks after date of death and 99% within 3 weeks of date of death.

Virological laboratory surveillance
On a weekly basis, about 19 virological laboratories, all members of the Working Group for Clinical Virology of the Dutch Society for Medical Microbiology (NVMM), report the number of diagnoses of several viral pathogens and certain obligatory intracellular (i.e. only growing within a cell) bacteria to RIVM. Data are reported by week of laboratory diagnosis. No distinction can be made between specimens originating from primary care or hospital care, or between the used diagnostic methods, such as culture, molecular diagnostic, serology or rapid tests. Data are therefore reported in an aggregated format. Although no background information concerning patient status, clinical data and type of diagnostic method is available, the weekly laboratory surveillance can be used as an additional source to follow trends of respiratory infections over a prolonged period because of their relative robust reporting history.

Osiris
According to Dutch legislation, legionellosis, psittacosis, Q fever, tuberculosis, Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and human infections with an animal influenza virus are notifiable diseases. Medical doctors and medical-microbiological laboratories notify cases to the Public Health Services, who subsequently report these to the RIVM via the online registration program Osiris. Tuberculosis is reported to the Dutch Tuberculosis Registry (NTR), which is integrated in Osiris. Furthermore, latent tuberculosis infections (LTBI) are reported voluntarily by the Public Health Services and registered in Osiris-NTR. Osiris is a dynamic system and due to corrections and additions of the Public Health Services, small differences may exist between the data reported here and earlier or elsewhere reported data. Osiris notifications consist of anonymous patient data, date of disease onset, diagnostic information (dates, diagnostic methods and outcome) and information on source finding and contact tracing. For tuberculosis, Osiris also registers information regarding treatment and treatment outcome.

New respiratory virus infections
In case of a suspected human infection with animal influenza virus, such as influenza A(H5N1) virus or influenza A(H7N9) virus, diagnostics are performed by the RIVM (CIb/IDS). For suspected infection with the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), diagnostics are performed by the ErasmusMC. Both human infection with animal influenza and MERS-CoV are notifiable in the Netherlands.

9.3 Data analysis

Influenza-like-illness (ILI)
ILI incidence is estimated using two data sources: 1) Nivel Primary Care Database - sentinel GP practices and 2) SNIV nursing homes. These two data sources use different ILI case definitions.

In the Nivel Primary Care Database - sentinel GP practices, ILI is defined according to the 'Pel-criteria' (Pel 1965):
- Sudden onset of symptoms
- Fever (at least 38 °C, rectal temperature)
- At least one of the following symptoms:
  – cough
  – rhinorrhoea
  – sore throat
  – frontal headache
  – retrosternal pain
  – myalgia

ILI incidence is calculated as the number of patients with a new episode of ILI, divided by the total number of enlisted patients of the participating sentinel GP Practices times 10,000 persons (Donker 2016). For chapter 2.1 and 3, the preliminary weekly numbers as reported during the season are used. The influenza epidemic threshold is set at an ILI incidence of 5.1 per 10,000 persons per week, based on historical data (Vega Alonso, Lozano Alonso et al. 2004). An influenza epidemic is defined as a period of at least two consecutive weeks with ILI incidence above the influenza epidemic threshold, during which influenza virus is detected in nose swabs and throat swabs of ILI patients.

The ILI incidence in SNIV nursing homes is calculated using the number of residents with ILI as numerator, and the number of observed resident weeks as denominator. The case definition of ILI used by SNIV surveillances is according to the ECDC case definition for ILI and is as follows:
- Sudden onset of symptoms
And at least one of the following four systemic symptoms:
- Fever or feverishness
- Malaise
- Headache
- Myalgia
And at least one of the following three respiratory symptoms:
- Cough
- Sore throat
- Shortness of breath

Acute respiratory infections (ARI)

Weekly numbers on patients consulting for an acute respiratory infection (including acute/chronic sinusitis, acute laryngitis/tracheitis, acute bronchitis/bronchiolitis or influenza) are obtained from Nivel Primary Care Database. Although ARI is less specific for an influenza virus infection than ILI, seasonal estimates are highly correlated. ARI surveillance figures are calculated as the number of patients consulting their GP in a given week, divided by the total number of enlisted patients. This produces weekly prevalence numbers. To allow for cumulation of weekly surveillance data we report the results as 'number of consultations', rather than prevalence.

Pneumonia

Pneumonia data are obtained from Nivel Primary Care Database, in a similar way as acute respiratory infections described above and is defined as the weekly number of patients consulting their GP for pneumonia (ICPC code R81), regardless of being a new or already existing pneumonia episode. The total practice population of participating GP practices serves as the denominator. Pneumonia data are also obtained from nursing homes (SNIV), in which the incidence of pneumonia is based on the weekly number of residents with new clinical diagnosis pneumonia, registered by the SNIV nursing homes. The denominator is the number of observed resident weeks.

Severe acute respiratory infections (SARI)

An active surveillance system is implemented at Jeroen Bosch Hospital (JBZ) and UMC Utrecht (UMC Utrecht) versus a passive surveillance system at the Leiden University Medical Centre (LUMC). This SARI surveillance pilot study makes a distinction between syndromic surveillance and surveillance based on laboratory-confirmed outcomes. Laboratory-confirmed outcomes are essential for pathogen detection and vaccine effectiveness calculations.

The SARI case definition as defined as:
a hospitalised person with:
- at least one systemic symptom or sign: fever or feverishness, malaise, headache or myalgia or deterioration of general condition (asthenia or loss of weight or anorexia or confusion or dizziness)

AND
- at least one respiratory symptom or sign (cough, sore throat or shortness of breath)

AND
- the symptoms should not have started (or clearly worsened, if chronic) more than 7 days ago

Leiden University Medical Centre

The passive SARI surveillance is embedded in an automated cluster detection system "Integrated Crisis Alert and Response System (ICARES)", which was implemented in the region of Leiden in 2013. General practitioners (GPs), general practitioner out-of-hours services and hospitals including ICU departments send a minimal dataset from patients with a respiratory tract infection using a routinely used Dutch coding system. The data are presented on a dashboard available for the research team and public health care authorities in the Leiden-The Hague region. The dashboard is updated daily in order to have real-time insight in occurrence of respiratory tract infection. DBC/DOT (Diagnose Behandel Combinatie Op weg naar Transparantie) is the routinely used coding system dictated by the national Dutch Healthcare Authority (NZa). The accompanying minimal dataset supplied by the hospitals consists of age cohort, gender, ICU admission, date of consultation, and an encrypted patient ID code. However, it has to be noted that ICARES not only reports absolute numbers of SARI patients admitted to the regular ward or ICU, but also outpatients discharged from the emergency ward with an acute respiratory infection. An historic cohort (8 years) is available for epidemiological and mathematical modelling. Microbiological laboratory test results are not part of the passive surveillance system in the region of Leiden (Groeneveld, Dalhuijsen et al. 2017).

Jeroen Bosch Hospital

Since October 2015, an active SARI surveillance is implemented at JBZ. On-site inclusion of any patient fulfilling the SARI case definition take place by research nurses. In February 2017, the SARI surveillance pilot study changed from research to a quality-of-care management strategy. The quality-of-care of SARI patients is now evaluated based on quality indicators, such as diagnostics, infection control measures, and treatment. The included SARI patient had to answer a short online questionnaire about symptoms, influenza and pneumococcal vaccination status, comorbidities and several risk factors. In addition, routinely collected respiratory- and urine specimens were used for influenza virus detection and a pneumococcal urinary antigen test respectively. If influenza virus diagnostics were not requested by the treating physician, influenza detection, influenza virus type A subtyping and type B lineage determination were performed in research setting at NIC, location RIVM, Centre for Infectious Disease Research, Diagnostics and laboratory Surveillance (IDS). SARI patients of all ages are included in the SARI surveillance pilot study at JBZ. No outpatients are included in the SARI surveillance at the JBZ. Retrospectively, the weekly total number of SARI patients is based on a selection of DBC/DOT codes related to SARI and provided with a lag of one week.

University Medical Centre Utrecht

The active SARI surveillance system implemented in UMC Utrecht is identical as in JBZ. Questionnaire data together with analysis on routinely collected urine- and respiratory samples are exactly the same. The only differences are that only adult SARI patients, aged 18 years and older, are included and the quality-of-care management strategy is not adopted at UMC Utrecht. Therefore, a notice of no objection from every study patient for study participation is required. The total number of SARI patients, retrospectively based on DBC/DOT codes related to SARI, is not available yet.

Determining excess mortality

Every Thursday the number of reported deaths, as provided by Statistics Netherlands (CBS), is evaluated for the presence of significant excess deaths above the expected levels of death (the baseline), at 2 different time-lags: deaths reported within 1 week (44% of all deaths) and deaths reported within 2 weeks after date of death (97% of all deaths). The baselines and prediction limits are calculated using a Serfling type algorithm on historical mortality data from the 5 previous years. In the historical data, any weeks with extreme underreporting were removed (the 7.5% most underreported values, often coinciding with public holidays). Also periods with high excess mortality in winter and summer were removed so as not to influence the calculated baseline with time-periods with previous excess mortality. When the observed number of deaths exceeds the upper limit of the prediction interval mortality is considered to be significantly increased (excess deaths calculated as the number of deaths above the baseline).

Influenza virus, RS-virus and other respiratory viruses

Surveillance of circulating viruses

At the National Influenza Centre (NIC) location RIVM the respiratory specimens are analysed that are taken for the influenza virus surveillance at the GP sentinel practices and the SNIV sentinel nursing homes. Additionally, Dutch laboratories submit all or a subset of their influenza virus positive clinical specimens to the NIC location Erasmus MC, for further subtyping, lineage determination, antigenic characterization and antiviral susceptibility testing. Since the beginning of 2018, the laboratories have been asked to send only a representative set of influenza virus positive samples per week (5-6 specimens) to the Erasmus MC. Therefore, the trend in the samples received by Erasmus MC is no longer a reflection of the course of the epidemic. In addition, since week 7 2018, the Erasmus MC has decided not to subtype all submitted viruses anymore, due to the large numbers received viruses. The laboratory in the region where the A(H1N2) reassortant virus was detected has been asked to send all influenza viruses type A to the Erasmus MC that were detected in the month preceding confirmation of the A(H1N2) case 18 March 2018.

Until the 2014/2015 season, the GP sentinel practices from Nivel Primary Care Database were requested to take specimens (combined throat swabs and nose swabs) of at least two ILI patients per week, of which one patient should be a child below the age of ten years. If no ILI patients were encountered or willing to participate, specimens should be taken from patients with an acute respiratory infection other than ILI (ARI), defined as:
- acute onset of symptoms;
- at least one respiratory symptom, e.g. cough, rhinorrhoea, sore throat.

Since the 2015/2016 season, RIVM and Nivel participate in the international I-MOVE and I-MOVE+ studies. These studies aim to estimate the influenza vaccine effectiveness in all age groups (I-MOVE) and in persons of 65 years or older (I-MOVE+), by pooling data from several European countries. Because of this study, the instructions for the GPs to swab ILI patients were adapted in 2015:

- Swab the first two ILI patients on Monday through Wednesday;
- When on Monday through Wednesday no ILI patients younger than 65 years attend the GP, than swab on Thursday through Sunday the first two ILI patients or ARI patients who are younger than 65 years of age;
- Swab all patients of 65 years and older with an ILI or ARI throughout the week.

The instructions for elderly care physicians participating in SNIV surveillance receive remained the same: to take specimens (combined throat swabs and nose swabs) of at least two ILI patients per week. If no ILI patients are encountered or willing to participate, specimens should be taken from patients with an ARI.

The GP and SNIV specimens are analysed by NIC location RIVM for influenza viruses, RSV, rhinoviruses and enteroviruses. The reason to test for RSV is that the clinical presentation is similar for RSV and influenza and that RSV infections can have a severe progression, both in young children and in the elderly. Rhino- and enteroviruses are important causes of acute respiratory infections, and the clinical presentation often resembles that of ILI. Influenza virus and RSV are genetically typed as influenza virus A, influenza virus B, RSV type A and RSV type B. Influenza virus type A is subsequently subtyped, and for influenza virus type B the phylogenetic lineage is assessed. The type of enterovirus is also determined.

Influenza virus antigenic and genetic characterization
Antigenic characterization of a subset of influenza viruses and influenza virus positive clinical specimens, submitted by peripheral laboratories and from the sentinel GP surveillance, is performed by NIC location Erasmus MC in Rotterdam. This provides an indication of the degree of antigenic match between the circulating influenza viruses and the vaccine virus. Furthermore, a subset of influenza viruses are characterized genetically by sequence analysis of the haemagglutinin genome segment at both NIC locations. At NIC location RIVM this is done on a systematic sample of the dominant influenza virus subtype and on all sporadically detected types and subtypes from the GP sentinel surveillance. This phylogenetic and amino acid substitution analysis gives information about the evolution of influenza viruses and changes that might lead to the emergence of potential antigenic variants. In addition, this type of information complements the antigenic analysis, especially when antigenic characterization is cumbersome, as was the case with the sporadic A(H3N2) viruses that could be antigenically characterised during the 2017/2018 season.

Antiviral susceptibility of influenza viruses

Infection with an influenza virus with a reduced susceptibility for an antiviral agent can lead to a reduced effectiveness of treatment. The antiviral susceptibility of influenza viruses is systematically monitored. Of the influenza virus isolates obtained in the Nivel and SNIV influenza surveillance, the phenotypic antiviral susceptibility for neuraminidase inhibitors (oseltamivir and zanamivir) is determined by NIC location RIVM. For a subset of virus isolates derived from specimens sent to NIC location Erasmus MC, the phenotypic antiviral susceptibility for neuraminidase inhibitors is determined at that location. Of viruses that appear reduced susceptible, the neuraminidase genome segment is sequenced to determine the amino acid substitution that explains the reduced susceptible phenotype In addition, the virus in the clinical specimen is sequenced to exclude the reduced inhibited amino acid substitution has been induced by the virus isolation procedure. Molecular markers for resistance to adamantanes (M2 ion channel blockers: amantadine and rimantadine) are assessed in a subset of influenza virus type A positive clinical specimens by sequencing at NIC location RIVM. For all influenza virus type A positive specimens, the most important molecular markers for reduced sensitivity for neuraminidase-inhibitors are determined by a rapid molecular test at both NIC locations. From a systematic sample of influenza virus positive clinical specimens the whole genome is sequenced at the NIC location RIVM in order to screen for other and new molecular markers for reduced sensitivity for antivirals. In case of mutations with previously unknown impact on antiviral susceptibility, the phenotypical neuraminidase inhibition test is the final proof for the degree of inhibition. This is done at both locations of the NIC for their own set of viruses. Data from viruses analysed at location RIVM and data from viruses analysed at location Erasmus MC are combined on a weekly basis to achieve one overall picture of the current situation.

Influenza vaccine effectiveness

The influenza vaccine effectiveness (VE) for the 2017/2018 season is calculated using data from patients of the Nivel sentinel surveillance, using the test-negative (case control) design (Jackson and Nelson 2013). Cases are defined as influenza virus positive patients with ILI or another acute respiratory infection, controls as influenza virus negative ILI or ARI patients. Only specimens taken within 7 days after day of onset were included in the analysis. Using this method, the odds of being vaccinated as a case is divided by the odds of being vaccinated as a control. With logistic regression this odds ratio (OR) is adjusted for confounding factors. Multilevel analysis is used, to take clustering within general practices into account. The VE is calculated as (1-OR) x 100%. As there was one very dominant virus subtype, B (Yamagata lineage), circulating during the 2017/2018 season, detailed stratification of VE by virus type, subtype or lineage was not possible. The analysis is restricted to the period that influenza virus was circulating in the Netherlands (for any subtype: week 48 in 2017 to week 16 in 2018, for B (Yamagata lineage): week 48 of 2017 to week 15 of 2018). Patients were excluded if it was unknown whether they had received influenza vaccination in the current season or if they received the influenza vaccination less than 15 days before the consultation. Patients who had antivirals prescribed in the 2 weeks before the consultation are also excluded. The following factors were regarded as potential confounders: period in the season (3 categories of 7 weeks each), age group (penalized spline with two degrees of freedom), gender, smoking (classified

as 'yes, or quitted smoking <1 year ago', 'quitted smoking >1 year ago' and 'never smoked'), obesity, pregnancy, chronic medical condition, and a proxy variable for frailty (combination variable of need for assistance with showering, need for assistance with walking, and stay in an elderly care home). The association between the potential confounders and influenza virus positivity was analysed with univariate logistic regression. Variables with a p-value of <0.20 were considered in the multivariable analysis. Variables that changed the OR by at least 5% were included in the final multivariable logistic regression model for any influenza subtype (forward selection). Age and comorbidity were chosen a priori as potential confounders. Therefore, they were both kept into the model, since these variables are associated with increased susceptibility to influenza (Madjid, Aboshady et al. 2004, Kurai, Saraya et al. 2013, Sansonetti, Sali et al. 2014, McElhaney, Garneau et al. 2015, Bahadoran, Lee et al. 2016).

Estimating symptomatic influenza incidence in the general population
We extended previously published methods for estimating the incidence of symptomatic infection with influenza virus by combining all relevant data sources via Bayesian evidence synthesis (McDonald, Presanis et al. 2014). This estimation procedure can be viewed as similar to the 'multiplier method' or 'direct method', but with correct propagation of the uncertainty inherent in each data source to the final estimate. The relevant data sources are: (i) ILI: number of ILI patients per season and per age-group, with catchment population size (<5, 5-14, 15-44, 45-64, 65+ years) (definite data for the seasons 2012/2013 through 2016/2017 and weekly data for the 2017/2018 season from Nivel Primary Care Database, as reported during the season, because the denominator was not yet finalised; see chapter 2.1); (ii) underascertainment: age-group specific number of respondents reporting ILI and number of respondents reporting ILI and who contacted their GP (from the InfluenzaNet; (Friesema, Koppeschaar et al. 2009, Koppeschaar, Colizza et al. 2017)), (iii) influenza positivity rate: number of positive tests and number tested, per age-group (from virological surveillance; see chapter 3); and (iv) sensitivity of virological testing: estimated at 95-100%. As an improvement over previous work, analysis was restricted to the winter season (week 40 through week 20 of the next year).

As an extension to the previous method, we estimated season-specific symptomatic infection incidence allowing for the non-independence in ILI incidence rates between seasons. To show variation in symptomatic influenza incidence by virus subtype/lineage across seasons, we also fitted a model in which data were stratified by subtype A(H1N1)pdm09 and A(H3N2) and lineage (B/Victoria, B/Yamagata) rather than age-group.

Virological laboratory surveillance
To describe trends over time in adenovirus, bocavirus, coronavirus, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, para-influenza virus, rhinovirus and human metapneumovirus (hMPV), we use the weekly number of positive diagnoses reported in the virological laboratory surveillance. Trends are reported for the 2017 calendar year. Number of diagnoses of psittacosis, Q fever, influenza and RSV as reported in virological laboratory surveillance are given in their respective chapters.

Burden of disease

To estimate disease burden in DALY, an incidence- and pathogen-based approach was applied to quantify the burden due to illness, disability and premature mortality associated with all short and long-term consequences of infection. The underlying outcome trees, disease progression probabilities, and other parameters have been previously described (Mangen, Plass et al. 2013, Bijkerk, van Lier et al. 2014, de Gier, Nijsten et al. 2017). DALY estimates incorporate both years of life lost (YLL) due to premature mortality and years lived with disability (YLD) (Murray and Lopez 2013). YLD were calculated by multiplying the number of acute cases, duration of a health state and the disability weight of the health state. The disability weight is a value between 0 (perfect health) and 1 (death). We used the newly available European disability weights collected by Haagsma et al. (Haagsma, Maertens de Noordhout et al. 2015). A full overview of the disability weights and durations used in the disease models can be found in the State of infectious diseases, 2016 (de Gier, Nijsten et al. 2017). To estimate YLL, remaining life expectancy tables were taken from the GBD 2010 study (WHO 2013).

The disease progression model for tuberculosis has been revised since State of infectious diseases 2016 (de Gier, Nijsten et al. 2017). Previously, both active and latent tuberculosis cases were included in the model, as a proportion of the latter cases develop active disease in the future. This resulted in 'double counting' of disease burden, as cases can appear again in surveillance sources when active disease develops and therefore would be included in the disease burden estimate of that year. In the revised model, only active tuberculosis cases are included. This results in a more interpretable estimate of the DALY/100 cases measure. Furthermore, the revised model separates acute pulmonary from extrapulmonary cases, and includes long-term sequelae (respiratory problems) that can occur following pulmonary tuberculosis (PTB). The proportion of PTB among acute tuberculosis was set to 57% (average of 2006-2016). Duration of active disease was set to 0.5 years. Probabilities of sequelae were based on (Vecino, Pasipanodya et al. 2011), and set to 37% mild respiratory problems, 11% moderate and 9% severe respiratory problems of PTB cases. The disability weights "COPD and other chronic respiratory problems, mild, moderate and severe" respectively 0.025, 0.284 and 0.418, were applied (Haagsma, Maertens de Noordhout et al. 2015). Case fatality rates per age were derived from a recent Dutch study (de Vries, Slump et al. 2017).

For all other diseases, models as first described in the State of Infectious Diseases 2013 and model modifications as reported in State of Infectious Diseases 2015 were maintained for the current estimations (Bijkerk, van Lier et al. 2014, Bijkerk, de Gier et al. 2016).

The incidence of symptomatic infection with influenza was estimated as described in the method of estimating influenza incidence in the general population. We estimated the disease burden associated with infections occurring in 2013, 2014, 2015, 2016 and 2017 separately. We estimated the burden of influenza for respiratory seasons (week 40 to week 20) for the seasons 2013-2014 through 2017-2018. No time discounting was applied.

Acknowledgements

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Abbreviations

ARDS	Acute Respiratory Distress Syndrome
ARI	acute respiratory infection
BCoDE	burden of communicable diseases in Europe
BEL	*Legionella* Source Identification Unit
	(NL: Bronopsporingseenheid legionellapneumonie)
BWTP	biological wastewater treatment plant
CAP	community-acquired pneumonia
CBS	Statistics Netherlands
	(NL: Centraal Bureau voor de Statistiek)
CFR	case fatality rate
CIb	Centre for Infectious Disease Control (Centre of RIVM)
	(NL: Centrum Infectieziektebestrijding)
CIb/EPI	Centre for Infectious Diseases, Epidemiology and Surveillance of CIb
	(NL: Centrum Epidemiologie en Surveillance van Infectieziekten)
CIb/IDS	Centre for Infectious Disease Research, Diagnostics and Screening of CIb
	(NL: Centrum Infectieziekteonderzoek, Diagnostiek en Screening)
CIb/LCI	National Coordination Centre for Communicable Disease Control of CIb
	(NL: Landelijke Coördinatie Infectieziektebestrijding)
DALY	disability-adjusted life years
DBC/DOT	NL: Diagnose Behandel Combinatie Op weg naar Transparantie
ECDC	European Centre for Disease Prevention and Control
EISN	European Influenza Surveillance Network
ELDSNet	European Legionnaires Disease Surveillance Network
EPTB	combination of pulmonary and extrapulmonary TB
ETB	extrapulmonary tuberculosis
EuroMOMO	European monitoring of excess mortality
GGD	Public Health Services
	(NL: Gemeentelijke Gezondheidsdienst)
GP	general practitioner
HIV	Human Immunodeficiency Virus
hMPV	human metapneumovirus
ICARES	Integrated Crisis Alert and Response System
ICU	intensive care unit
ILI	influenza-like illness
I-MOVE	influenza monitoring vaccine effectiveness
JBZ	Jeroen Bosch Hospital
LD	Legionnaires' Disease
LTBI	latent tuberculosis infection
LUMC	Leiden University Medical Centre
MDR-TB	Multi Drug Resistant tuberculosis
MERS-CoV	Middle East Respiratory Syndrome Coronavirus

NVWA	the Netherlands Food and Consumer Product Safety Authority
	(NL: Nederlandse Voedsel- en Waren Autoriteit)
NIC	National Influenza Centre
Nivel	Netherlands institute for health services research
	(NL: Nederlands instituut voor onderzoek van de gezondheidszorg)
NTR	Dutch Tuberculosis Registry
	(NL: Nederlands Tuberculose Register)
NVMM	Dutch Society for Medical Microbiology
	(NL: Nederlandse Vereniging voor Medische Microbiologie)
NZa	Dutch Healthcare Authority
	(NL: Nederlandse Zorgautoriteit)
PCR	Polymerase Chain Reaction
PIV	parainfluenza virus
POCT	point-of-care test
PTB	pulmonary tuberculosis
QIV	quadrivalent influenza vaccine
RIVM	National Institute for Public Health and the Environment
RSV	respiratory syncytial virus
SARI	severe acute respiratory infections
SNIV	national sentinel surveillance network for infectious diseases in nursing homes
TALD	Travel Associated Legionnaires' disease
UMCU	University Medical Centre Utrecht
VE	vaccine effectiveness
WHO	World Health Organization
YLD	years lived with disability due to morbidity
YLL	years of life lost due to mortality

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