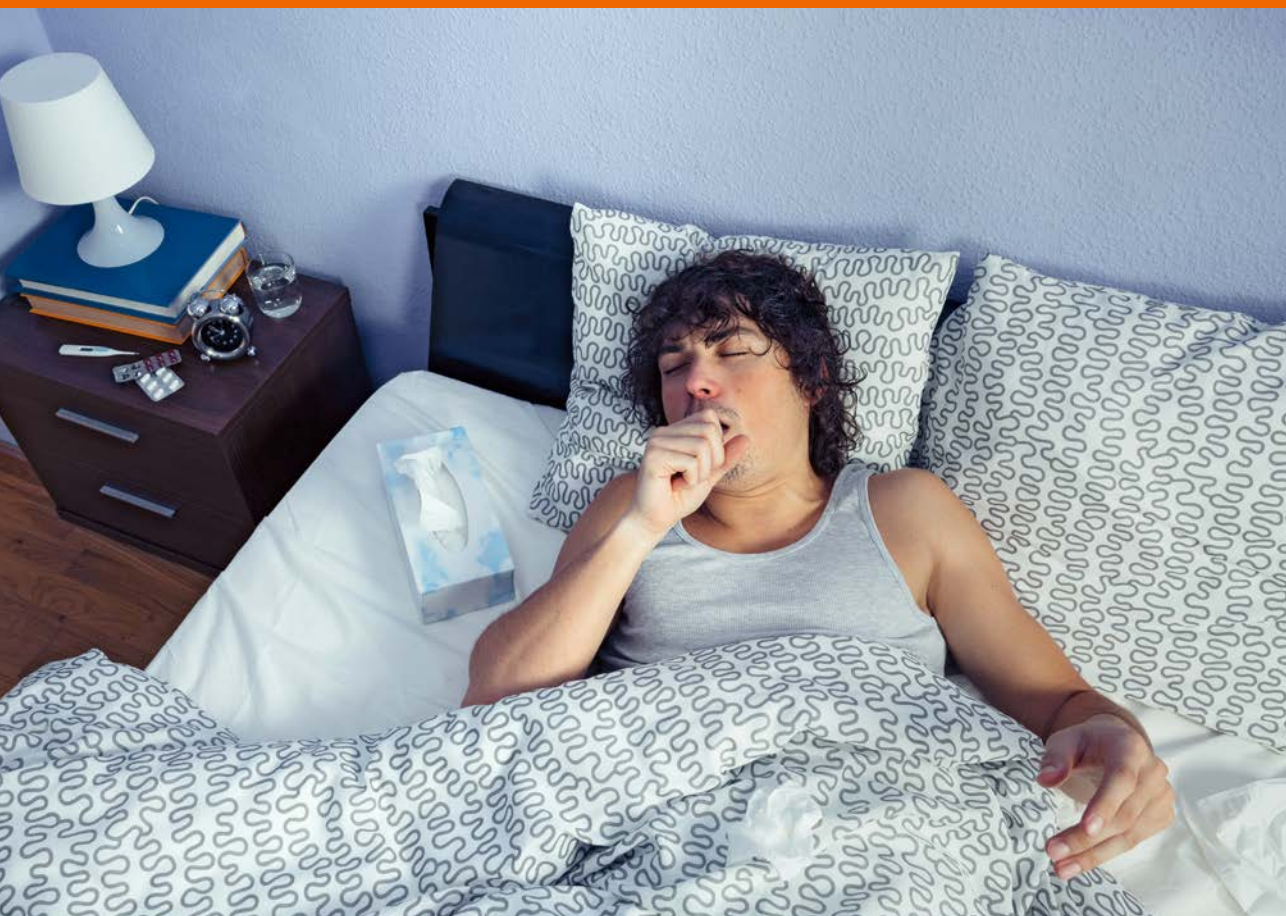
National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Annual report Surveillance of influenza and other respiratory infections in the Netherlands: *winter 2018/2019*



Annual report Surveillance of influenza and other respiratory infections in the Netherlands: *winter 2018/2019*

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Colophon

RIVM report number: 2019-0079

DOI 10.21945/RIVM-2019-0079

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Cover picture: Thinkstock

This investigation has been performed by order and for the account of the Ministry of Health, Welfare and Sport (VWS), within the framework of the project 'Epidemiologie en surveillance van Respiratoire infecties', project number V/150207/19/RI, and 'Labfunctie Respiratoire Virologie', project number V/150304/19/RE.

Report prepared by: Centre for Infectious Disease Control, National Institute for Public Health and the Environment with contributions of:
National Influenza Centre - Erasmus Medical Centre
Netherlands institute for health services research (Nivel)
Statistics Netherlands (CBS)
KNCV Tuberculosis Foundation
Legionella Source Identification Unit (BEL) at Regional Public Health Laboratory Kennemerland
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Synopsis

Surveillance of influenza and other respiratory infections: winter 2018/2019

Influenza epidemic

The influenza epidemic of the 2018/2019 winter was mild and lasted 14 weeks. That is longer than the average period of nine weeks during the last 20 years, but it is shorter than the extended influenza epidemic of 2017/2018 which lasted 18 weeks. Between October 2018 and May 2019, a total of approximately 400,000 people became ill due to the influenza virus. Approximately 165,000 people consulted their general practitioner with influenza-like symptoms. Fewer people were admitted to the hospital as a result of influenza complications (mostly pneumonia). This number was estimated to be around 11,000, compared to 16,000 during the 2017/2018 flu season. Type A influenza virus was responsible for the majority of illnesses. There were 2,900 more deaths during the influenza epidemic than would normally be expected during this period.

Influenza vaccine effectiveness

During the 2018/2019 flu season, the influenza vaccine in the Netherlands reduced the risk of developing flu by 57%. This is about the same effect as in the previous flu seasons. In Europe, the vaccine was less effective against one of the most common circulating influenza viruses. An international study is being carried out to determine the reason for this. The effectiveness of the influenza vaccine can differ greatly from season to season. This is because the decision on the composition of the flu vaccine is made half a year beforehand. This is based on the viruses that were most common globally during the previous flu season. However, influenza viruses can change or other influenza viruses may dominate by the time the flu season breaks out in the Netherlands. This is why it is not possible to predict exactly which influenza viruses will circulate in the Netherlands in the next season.

Notifiable respiratory infections

Some respiratory infections have to be reported to the Public Health Services. They can then intensively monitor such infections and, if necessary, take timely action to prevent their further spread. The number of reports of legionella increased further in 2018 and reached 584, which is the highest number ever reported. The number of reports of tuberculosis (806), Q fever (18) and psittacosis (64) remained stable. Q fever, psittacosis and legionella generally manifest themselves in the form of pneumonia. The number of cases reported is an underestimation of the actual number. This is because tests are often not carried out for these illnesses if 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 2018/2019

Griepepidemie

De griepepidemie in de winter van 2018/2019 was mild en duurde 14 weken. Dat is langer dan het gemiddelde van negen weken in de afgelopen 20 jaar, maar korter dan de lange griepepidemie van 2017/2018 (18 weken). In totaal zijn tussen oktober 2018 en mei 2019 ongeveer 400.000 mensen ziek geworden door het griepvirus. Ongeveer 165.000 mensen gingen naar de huisarts met griepachtige klachten. Minder mensen moesten vanwege complicaties van griep (meestal longontsteking) in het ziekenhuis worden opgenomen. Naar schatting waren dit er ruim 11.000, tegenover 16.000 in het griepseizoen 2017/2018. Mensen zijn vooral ziek geworden van het type A griepvirus. Tijdens de griepepidemie zijn er 2900 mensen meer overleden dan normaal is in deze periode.

Effectiviteit griepvaccin

In het griepseizoen 2018/2019 hadden gevaccineerden in Nederland 57 procent minder kans op griep. Dat is ongeveer hetzelfde als in vorige griepseizoenen. In Europa werkte het vaccin minder goed tegen een van de meest voorkomende griepvirussen. Internationaal wordt uitgezocht wat de reden daarvan is. De effectiviteit van het griepvaccin kan per seizoen sterk verschillen. Dat komt omdat een half jaar van tevoren wordt bepaald welke virussen in het griepvaccin komen. Dat gebeurt op basis van de virussen die het griepseizoen ervoor in de wereld het meest voorkwamen. Maar griepvirussen kunnen veranderen, of andere griepvirussen kunnen overheersen tegen de tijd dat het griepseizoen in Nederland begint. Daardoor kan van tevoren nooit precies worden voorspeld welke griepvirussen hierin omloop zullen zijn.

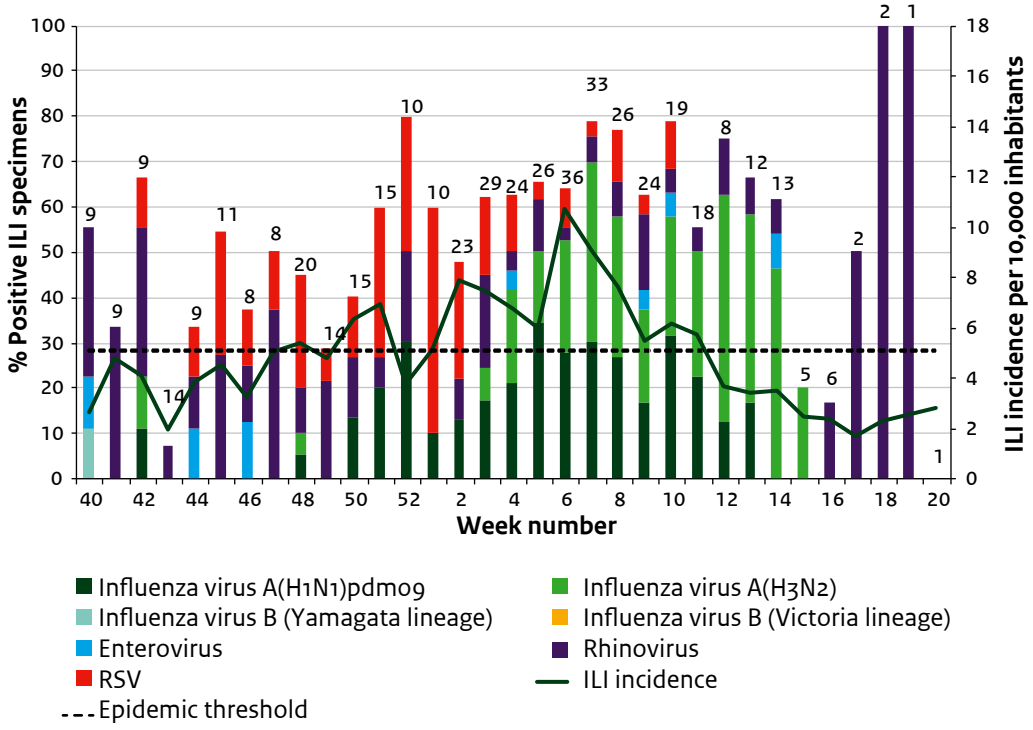
Meldingsplichtige luchtweginfecties

Sommige luchtweginfecties moeten bij de GGD worden gemeld. De GGD kan ze dan intensief volgen en als het nodig is op tijd actie ondernemen om te voorkomen dat ze zich verder verspreiden. Het aantal meldingen van legionella is in 2018 nog verder gestegen naar 584, het hoogste aantal ooit gerapporteerd. Het aantal gemelde gevallen van tuberculose (806), Q-koorts (18) en psittacose (64) bleef stabiel. Q-koorts, psittacose en legionella uiten zich meestal in de vorm van longontstekingen. Het aantal gemelde gevallen is lager dan het werkelijke aantal. Dat komt doordat 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 2018/2019 respiratory season (week 40 of 2018 through week 20 of 2019), displayed by week of sampling (Source: Nivel Primary Care Database; RIVM).



Footnote: ILI = influenza-like illness; GP = general practitioner.
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 the Nivel Primary Care Database 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 2018/2019 respiratory season, i.e. week 40 of 2018 through week 20 of 2019.

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 2018 calendar year. Q fever and psittacosis will be described in greater detail in the report 'State of Zoonotic Diseases 2018' (manuscript in preparation). More details on tuberculosis will be described in the next surveillance report on tuberculosis, 'Tuberculose in Nederland, 2018' that will be published in December 2019. 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 2018 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, Paul Bergervoet

2.1.1 Key points

- In the 2018/2019 winter season, the influenza epidemic lasted 14 weeks (week 50 of 2018 through week 11 of 2019), which is longer than the on average 9 weeks in the last 25 years.
- The seasonal number of patients with ILI and ARI that were reported by GPs in 2018/2019 (ILI: 159 per 10,000 inhabitants, ARI: 783 per 10,000 inhabitants) was lower than four preceding seasons (ILI range: 185-265 per 10,000 inhabitants, ARI range: 882-1058 per 10,000 inhabitants).
- The ILI incidence and ARI consultations reported by GPs, and the ILI incidence of nursing home residents peaked in week 6 of 2019.
- The seasonal ILI incidence among nursing home residents was relatively low in the 2018/2019 season (269 per 10,000 residents) in comparison with four previous seasons (range: 145-546 per 10,000 residents; the seasonal ILI incidence was only lower in the 2015/2016 season.
- The weekly number of ARI consultations and ILI incidence was highest in young children (0-4 years), followed by the elderly (65 years or older), which is in line with the four previous seasons.
- The ILI incidence reported by GPs among young children (0-4 years) peaked twice in the 2018/2019 season, in week 51 of 2018 and week 4 of 2019. The first peak coincides with the peak in ARI consultations in the same age group. In the oldest age group (65 years or older), also two peaks are seen in the ILI incidence, in consecutively week 2 and 7 of 2019.

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 with virological testing of a combined nose/throat swab of a subset of the ILI patients, to give insights in the main causes of ILI and the influenza virus circulation. Based on these data and using the MEM method (Vega, Lozano et al. 2013), the start of an influenza epidemic is defined as an ILI incidence above 5.1/10,000 inhabitants during 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, using data from electronic medical records of 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 participate in the ARI surveillance and no specimens are taken. 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 from geriatricians. Similar to the GP sentinel surveillance, a subset of ILI patients is swabbed to determine the cause of ILI.

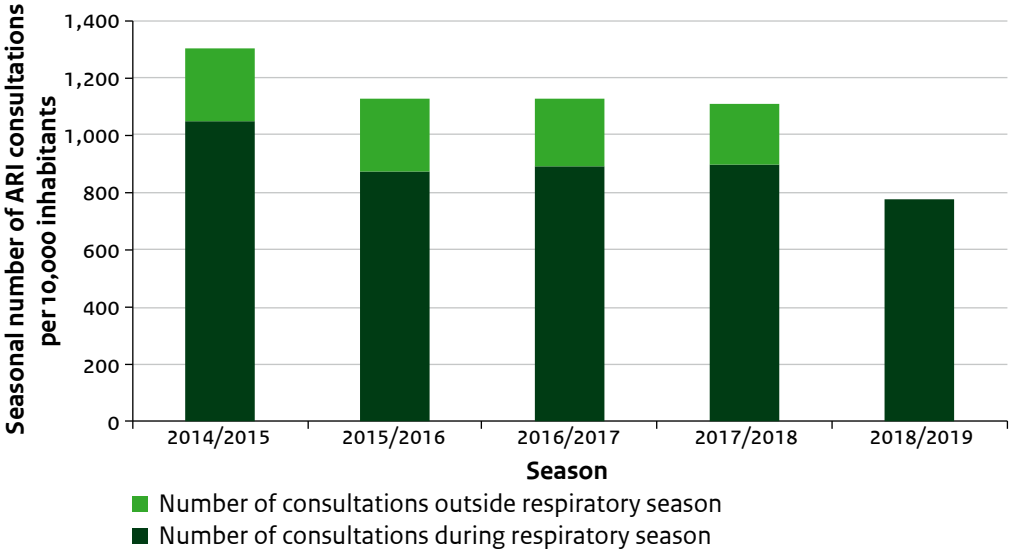
2.1.3 Discussion

The influenza epidemic lasted long in the 2018/2019 season, with 14 weeks compared to on average 9 weeks in the last 25 years. However, the epidemic was mild, as the seasonal ILI and ARI numbers were low in comparison to the four preceding seasons. The first peak in ILI incidence and the ARI peak in the young children could be explained by a greater 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) and the peaks seen in the older age groups are likely better explained by influenza virus circulation (Chapter 3).

2.1.4 Figures

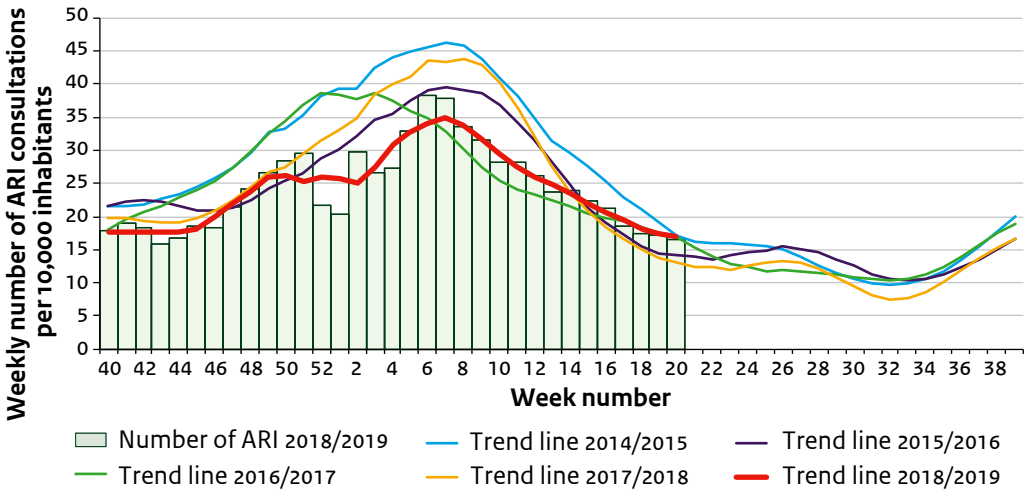
GP consultations for ARI

Figure 2.1 Seasonal cumulative number of patients consulting a GP because of ARI within the respiratory season (week 40 through week 20) and outside the respiratory season (week 21 through week 39) of 2014/2015 - 2018/2019 (Source: Nivel Primary Care Database).



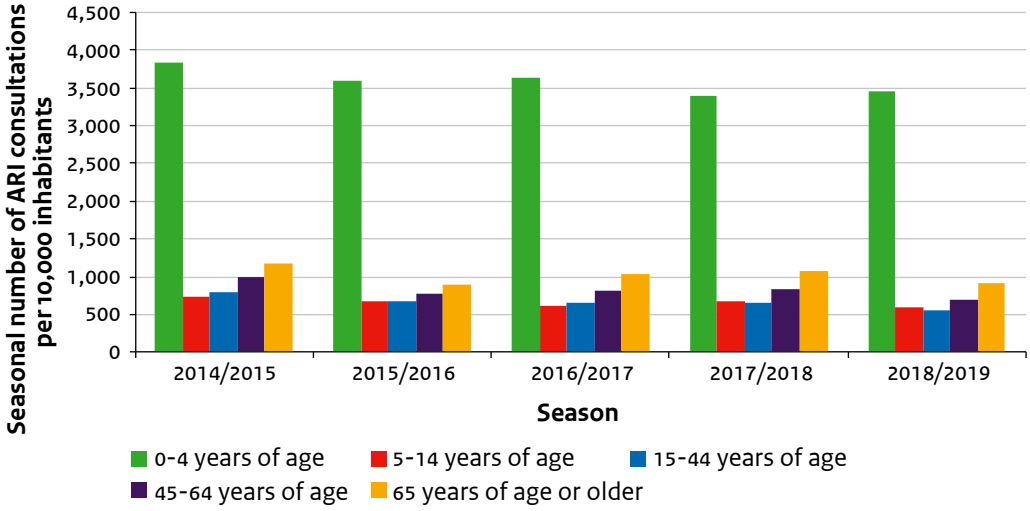
Footnote: ARI = acute respiratory infections (including influenza-like illness); GP = general practitioner.
For the 2018/2019 season, numbers for outside the respiratory season were not available yet.

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 2018/2019 and trend lines for seasons 2014/2015 - 2018/2019 (Source: Nivel Primary Care Database).



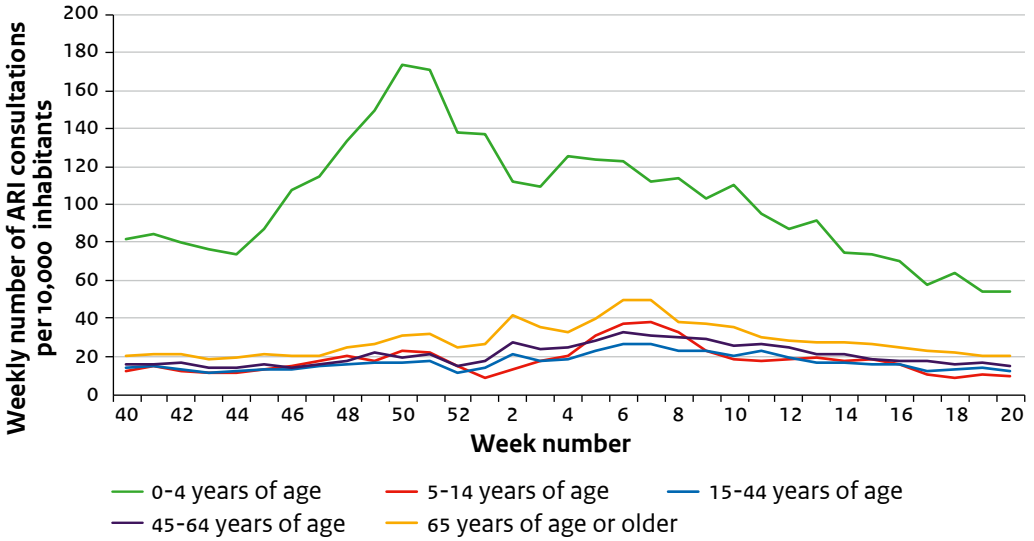
Footnote: Trend lines indicate a 5-weeks moving average. ARI = acute respiratory infection, including influenza-like illness; GP = general practitioner.

Figure 2.3 Seasonal cumulative number of patients consulting a GP because of ARI in the respiratory seasons (weeks 40 through 20) of 2014/2015 through 2018/2019 per 10,000 inhabitants by age group (Source: Nivel Primary Care Database).



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

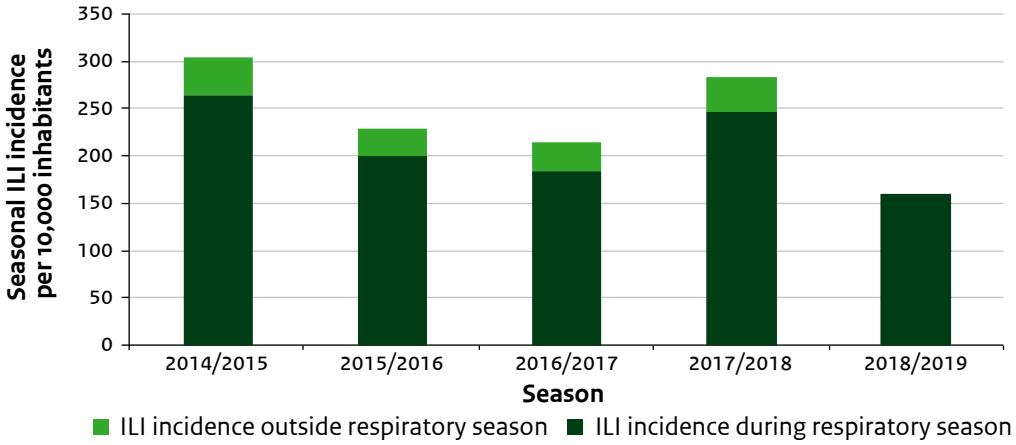
Figure 2.4 Weekly number of patients consulting a GP because of ARI per 10,000 inhabitants in 2018/2019 (through week 20 of 2019) by age group (Source: Nivel Primary Care Database).



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

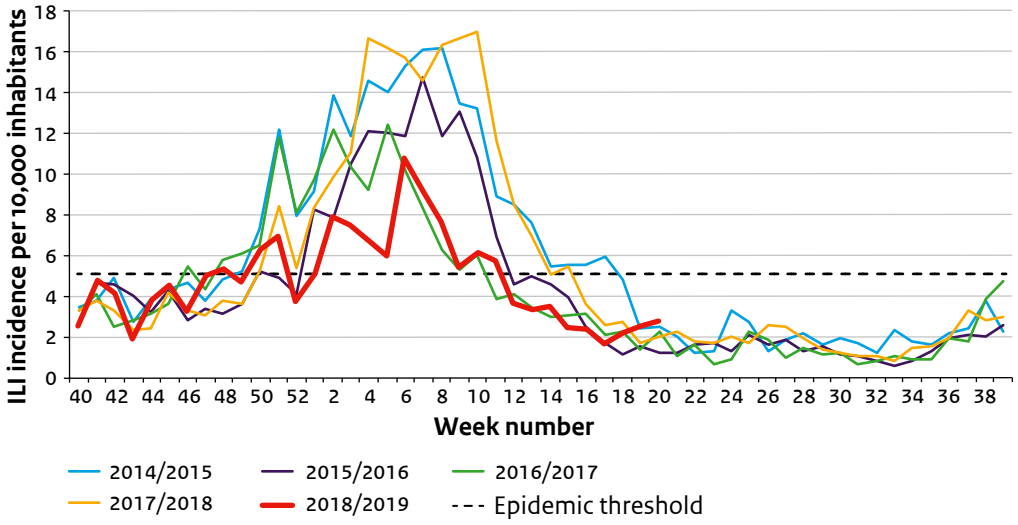
ILI incidence: sentinel GP practices

Figure 2.5 Seasonal ILI incidence within the respiratory season (week 40 through week 20) and outside the respiratory season (week 21 through week 39) of 2014/2015 - 2018/2019 (Source: Nivel Primary Care Database).



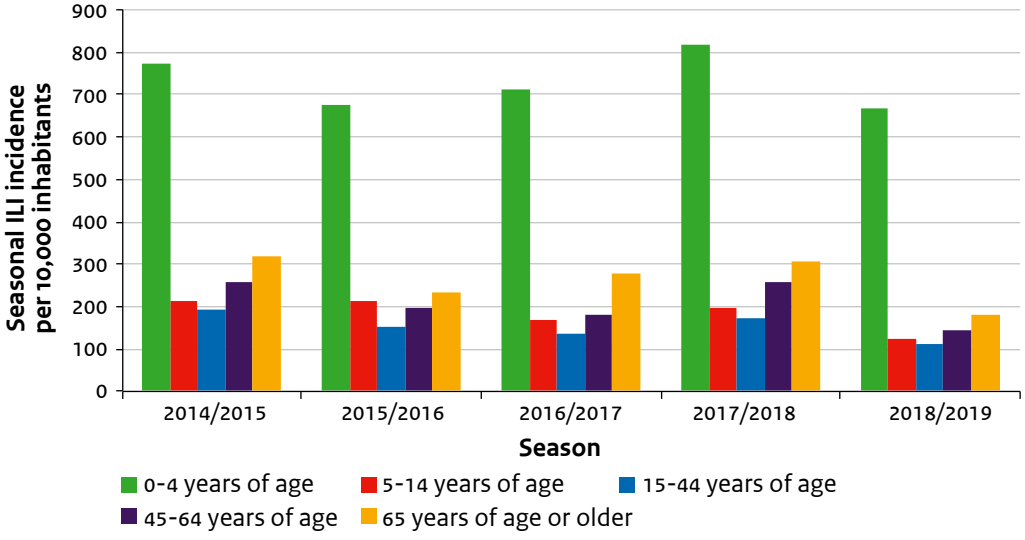
Footnote: ILI = influenza-like illness.
For the 2018/2019 season, numbers for outside the respiratory season were not available yet.

Figure 2.6 Weekly ILI incidence during the seasons 2014/2015 - 2018/2019 (through week 20 of 2019) (Source: Nivel Primary Care Database).



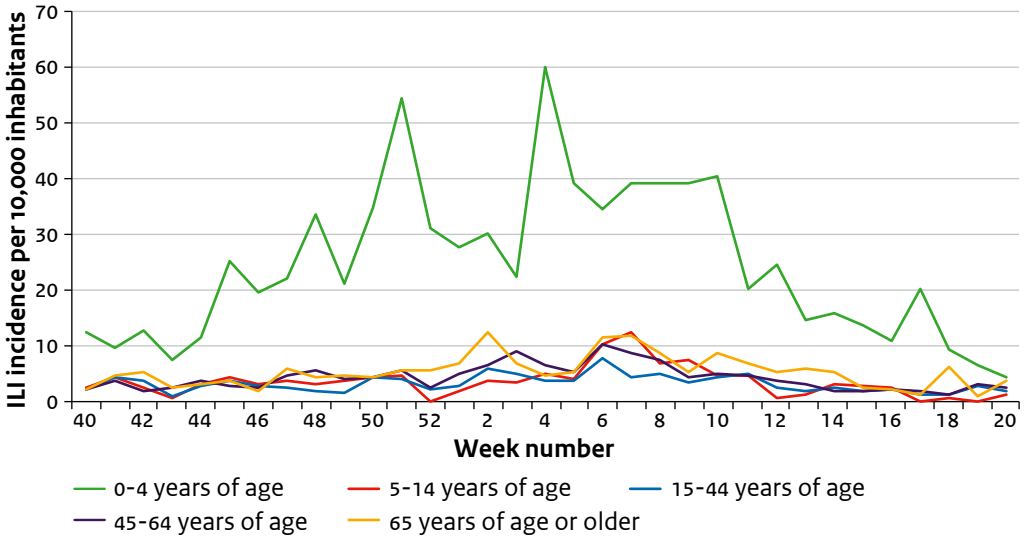
Footnote: ILI = influenza-like illness.

Figure 2.7 Seasonal ILI incidence in the respiratory seasons 2014/2015 - 2018/2019 per 10,000 inhabitants by age group (Source: Nivel Primary Care Database).



Footnote: ILI = influenza-like illness.

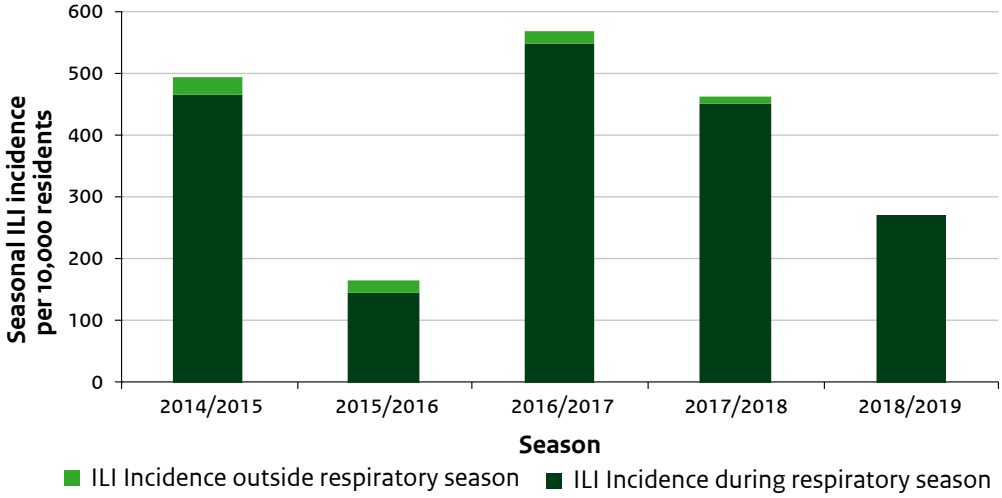
Figure 2.8 Weekly ILI incidence per 10,000 inhabitants in respiratory season 2018/2019 by age group (Source: Nivel Primary Care Database).



Footnote: ILI = influenza-like illness.

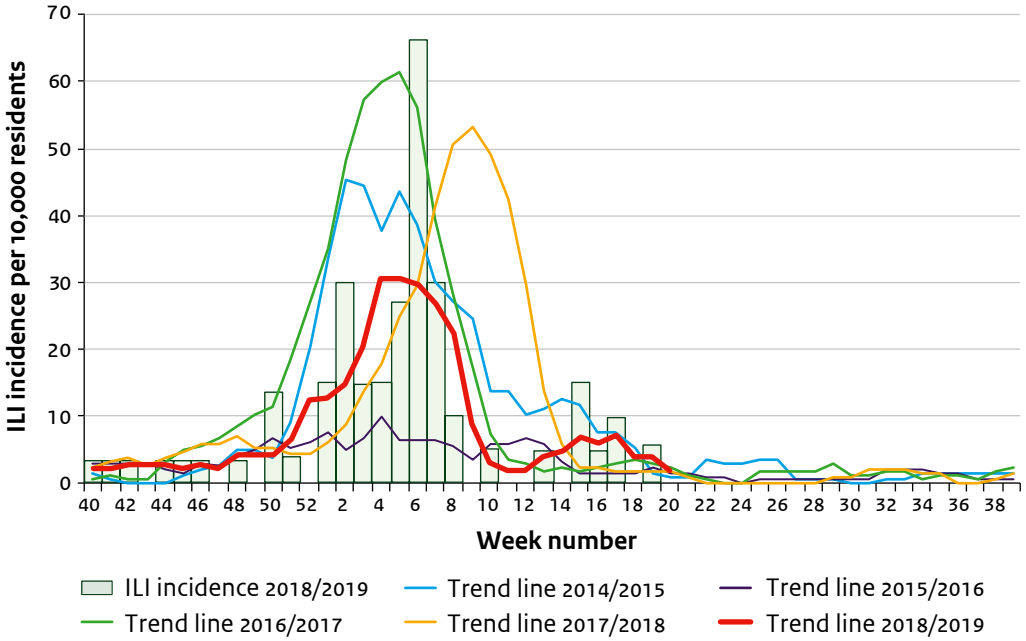
ILI incidence: in nursing homes

Figure 2.9 Seasonal ILI incidence in SNIV nursing homes per 10,000 residents within the respiratory season (week 40 through week 20) and outside the respiratory season (week 21 through week 39) of 2014/2015 - 2018/2019 (Source: SNIV, RIVM).



Footnote: ILI = influenza-like illness.
For the 2018/2019 season, numbers for outside the respiratory season were not available yet.

Figure 2.10 Weekly ILI incidence in SNIV nursing homes per 10,000 residents in the 2018/2019 respiratory season (week 40 of 2018 through week 20 of 2019) and trend lines for the seasons 2014/2015-2018/2019 (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: Daphne Reukers, Mariëtte Hooiveld
Contributors: Marit de Lange, Sierk Marbus, Paul Bergervoet

2.2.1 Key points

- The seasonal number of GP consultations for pneumonia (week 40 2018 through week 20 2019) in 2018/2019 was 97 per 10,000 inhabitants, which was lower than the previous four seasons.
- The peak in weekly pneumonia GP consultations (6 per 10,000 inhabitants) was observed in week 7 of 2019.
- The seasonal number of GP consultations for pneumonia in 2018/2019 (week 40, 2018 through week 20, 2019) for the age groups 0-4 years, 15-44 years and 45-64 years (11.1, 2.2 and 5.6 per 10,000 inhabitants, respectively) was lower than the previous four seasons.
- The weekly numbers of GP consultations for persons 5-14 years and persons aged 65 or older (2.9 and 21.0 per 10,000 inhabitants, respectively) were comparable to the previous four seasons.
- The seasonal incidence (week 40 2018 through week 20 2019) of pneumonia in nursing homes was 1,454 per 10,000 residents. Which was comparable to the previous four seasons (range: 1,239-1,587 per 10,000 residents).
- The peak in the weekly incidence for pneumonia (104 patients per 10,000 residents) reported by the SNIV nursing homes was observed in week 7 of 2019.
- In conclusion, fewer cases of pneumonia were registered during the 2018/2019 season in general practices compared to the previous four seasons. However, the incidence of pneumonia in nursing homes was average compared to previous seasons.

2.2.2 Background

Pneumonia is an infection 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 (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, there is a lack of guidelines on diagnostic testing in CAP patients. Therefore, the causative pathogens remain unknown in the majority of CAP patients, since microbiological tests are not systematically used and are usually limited to blood and sputum cultures for bacterial causes. Developing hospital or national guidelines could lead to a more systematic diagnostic testing policy in CAP patients and minimize the amount of testing bias.

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

The influenza epidemic in 2018/2019 was mild compared to the previous four seasons, which resulted in relatively low numbers of patients consulting their GP with pneumonia. The peak in weekly pneumonia GP consultations in 2018/2019 coincided with the peak of influenza-like illness in week 6, 2019 and was lower than the peaks in the four previous seasons.
The number of pneumonia consultations was low or average in all age groups. In children younger than five years, the number of pneumonia consultations peaked in week 51 2018. This relatively early peak coincided approximately with the peak in the number of RSV diagnoses (week 1 2019, Chapter 4). Nevertheless, because 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.
The peak in the weekly incidence for pneumonia in week 7 was higher than the peak incidences in the four previous seasons. However, there was a steep increase and decrease in the pneumonia incidence in nursing homes, which resulted in an average seasonal incidence (week 40 2018 through week 20 2019) of pneumonia in SNIV nursing home residents.

2.2.4 Figures

GP consultations for pneumonia

Figure 2.11 Seasonal cumulative numbers 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 2014/2015 - 2018/2019 (Source: Nivel Primary Care Database).

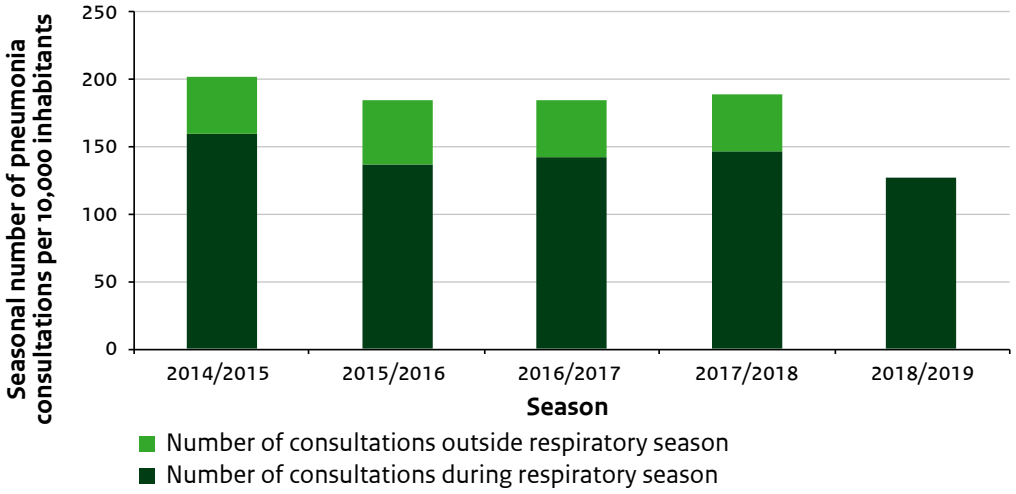


Figure 2.12 Weekly numbers of patients consulting their GP for pneumonia per 10,000 inhabitants in 2018/2019 (week 40, 2018 through week 20, 2019) and the trend lines for 2014/2015 - 2018/2019 (2018/2019: through week 20). Trend lines are based on a 5-week moving average (Source: Nivel Primary Care Database).

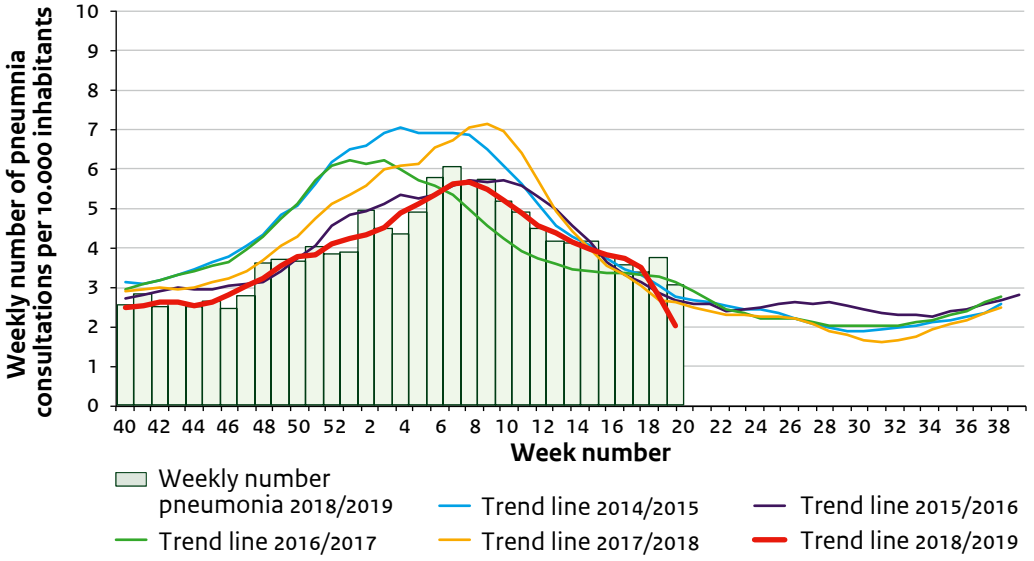
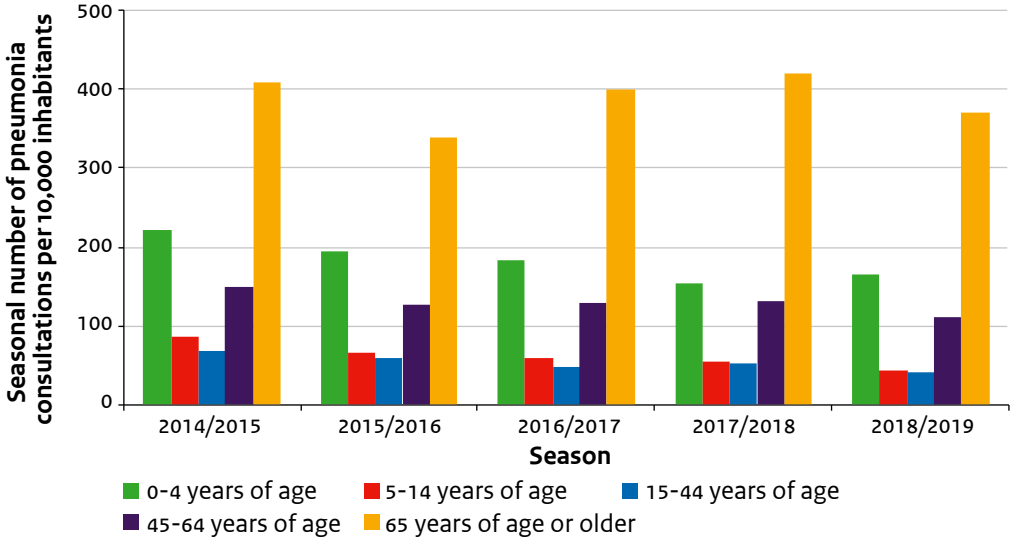


Figure 2.13 Seasonal cumulative number of GP consultations for pneumonia per 10,000 inhabitants by age group in the respiratory seasons 2014/2015 – 2018/2019 (week 40 through week 20) (Source: Nivel Primary Care Database).



Incidence of pneumonia (nursing homes)

Figure 2.14 Seasonal incidence of pneumonia in SNIV nursing homes per 10,000 residents within the respiratory season (week 40 through week 20) and outside the respiratory season (week 21 through week 39) of 2014/2015 - 2018/2019 (Source: SNIV, RIVM).

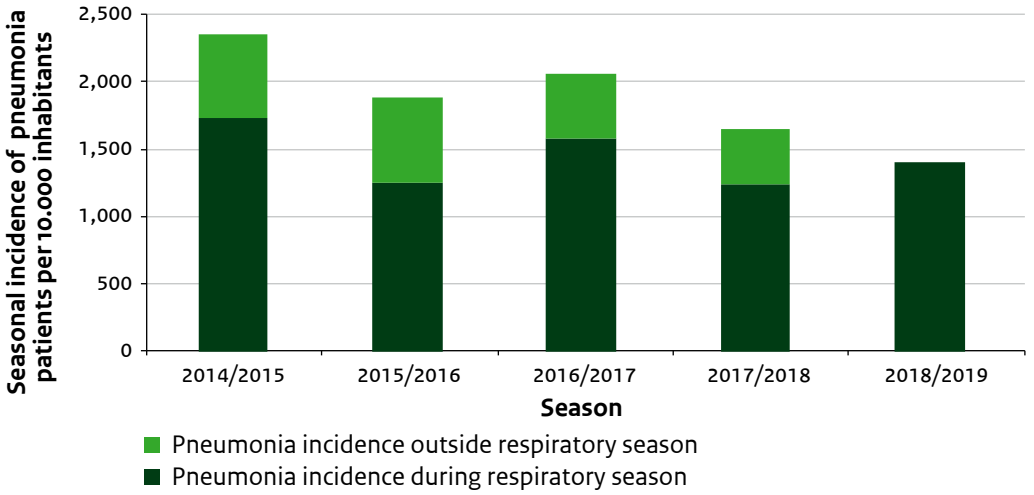
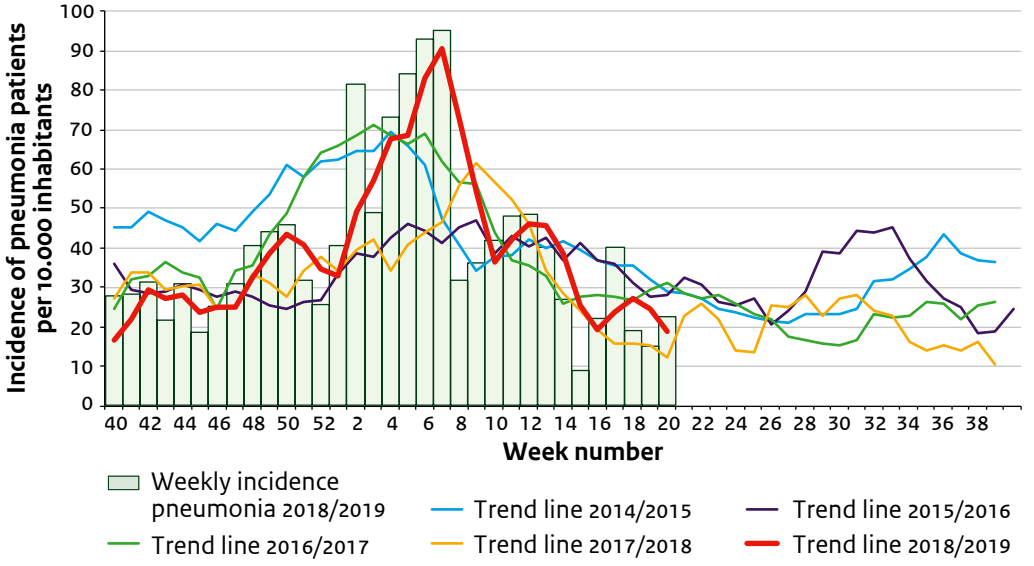


Figure 2.15 Weekly incidence of pneumonia patients in SNIV nursing homes per 10,000 residents in 2018/2019 and trend lines for the seasons 2014/2015 – 2018/2019 (through week 20). Trend lines are based on a 5-week moving average (Source: SNIV, RIVM).



2.3 Severe acute respiratory infections (SARI)

Authors: Sierk Marbus, Rianne van Gageldonk-Lafeber
Contributors: Inge Roof, Rianne van Hunen-Aarnoudse, Peter Schneeberger

2.3.1 Key points

- The seasonal cumulative SARI incidence was 28 per 10,000 inhabitants in the 2018/2019 season (week 40 of 2018 through week 20 of 2019). Compared to the season 2017/2018 (33 per 10,000 persons), the seasonal cumulative SARI incidence was lower. However, it was higher than in season 2016/2017 (16 per 10,000).
- The peak in weekly SARI incidence was reached in week 1 of 2019 (2 SARI patients per 10,000 persons.
- In 250 of the 915 SARI patients (27%) more detailed information was available:
  - The median age of SARI patients was 71 years (IQR 61-80).
  - In 11% (27/250) of SARI patients an ICU admission was required.
  - In SARI patients of 65 years and older, 59% (67/113) had received an influenza vaccination this season.

2.3.2 Background

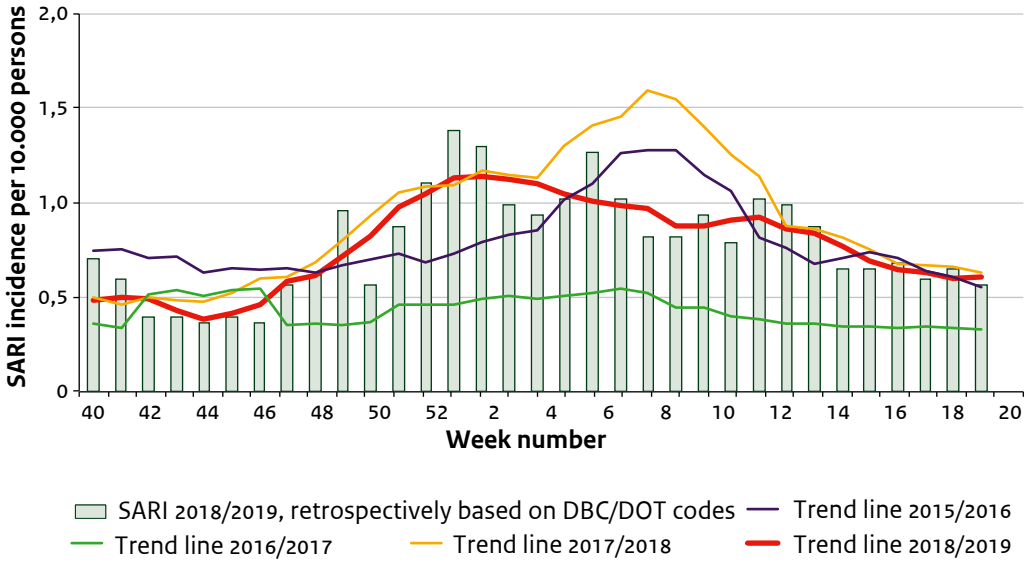
Severe acute respiratory infections requiring hospitalization (SARI) are an important cause of morbidity and mortality worldwide. After the 2009 influenza A(H1N1) pandemic, the World Health Organization (WHO) and European Centre of Disease Prevention and Control (ECDC) recommended every country to implement a SARI surveillance system for pandemic preparedness. Therefore, a pilot study started in 2015 in Leiden University Medical Center (LUMC) and Jeroen Bosch Hospital (JBZ) in the Netherlands with the main objective to set up a sentinel surveillance system for SARI. In LUMC, a passive syndromic SARI surveillance was in effect until October 2018, after which the collaboration with the ICT provider ended. Currently, only an active SARI surveillance with laboratory-confirmed outcome is operational in JBZ.
In Chapter 3, data on influenza virus infections in JBZ are reported.

2.3.3 Discussion

Based on seasonal cumulative SARI incidence, the season 2018/2019 was less severe than 2017/2018. However, it has to be taken into consideration that the SARI incidence is based on only one hospital and might not reflect the situation on national level. In addition, similar to previous seasons, more detailed information is collected for only a subset of SARI patients, who have unknown representativeness for the total SARI population in the Netherlands.
In our experience, a potential sustainable SARI surveillance system for the long-term is an automated, passive surveillance system. The advantages are that syndromic SARI surveillance data can be reported real-time and the administrative burden for medical personnel is minimalized. Therefore, in collaboration with several hospitals, the RIVM is working towards an automated, passive SARI surveillance system.

2.3.4 Figure

Figure 2.16 SARI incidence at the Jeroen Bosch Hospital during influenza seasons 2015/2016 through 2018/2019.



Footnote: SARI=severe acute respiratory infection

2.4 Mortality Monitoring

Author: Liselotte van Asten
Contributors: Marit de Lange, Anne Teirlinck, Ursula de Bruijn- van Leijden, Felicia Minnaard, Lenny Stoeldraijer, Carel Harmsen

2.4.1 Key Points

- An average of 2,833 deaths occurred weekly in the Netherlands over the past 5 years, 2014-2018.
- During the 2018/2019 influenza epidemic (of 14 weeks), increased mortality started in the 6th week of the influenza epidemic (week 3 of 2019). The 9 weeks thereafter (until one week after the influenza epidemic) showed intermittent increased mortality (5 weeks of increased mortality in weeks 3, 4, 7, 11, and 12 of 2019).
- Mortality peaked in week 7 of 2019 with 3,249 deaths, which was 1,000 lower than the peak of 2017/2018. The mortality in week 7 showed an excess of 345 deaths above expected deaths.
- Cumulative excess mortality during the 14 weeks of the 2018/2019 influenza epidemic was an estimated 2,894 (range in the previous 5 epidemics: 0 to 9,375 excess deaths), roughly half of the 5,757 average excess in the past 5 epidemics.
- Excess mortality was estimated at 3,124 during the respiratory season (week 40 through week 20, and was on average 6,112 in the past 5 respiratory seasons).
- Excess mortality was mostly observed in persons aged 75 years and older.

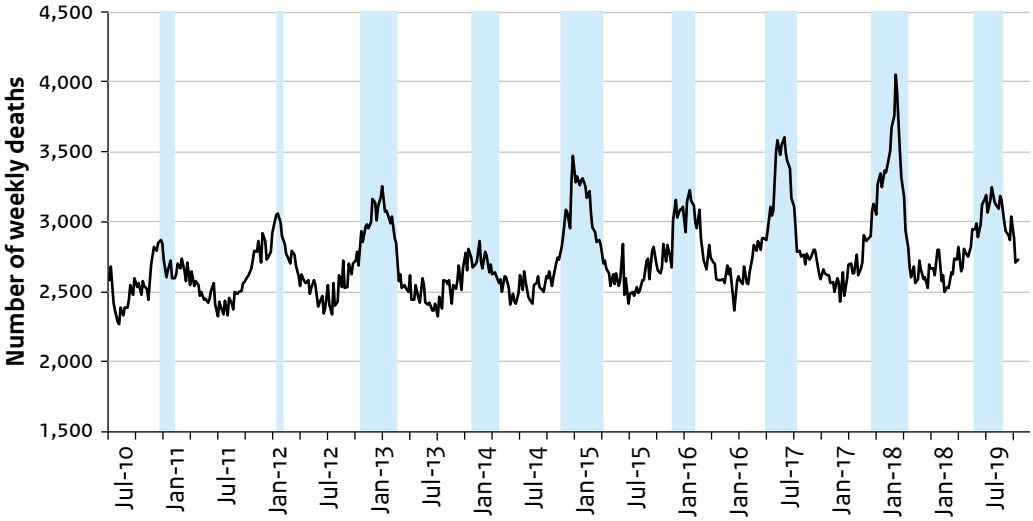
2.4.2 Background

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 45%, 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.

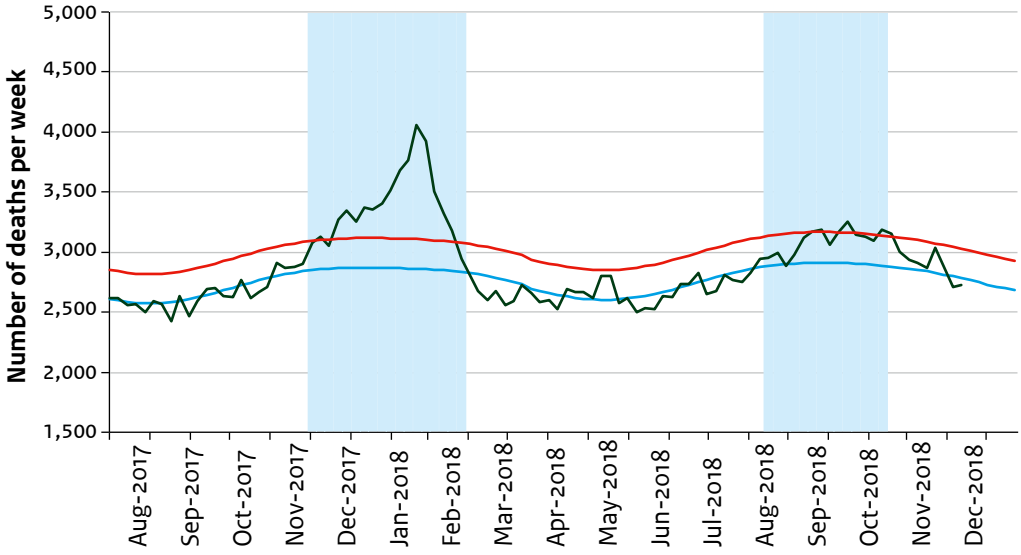
2.4.3 Figures

Figure 2.17 Weekly number of deaths from 2010 to 2019 (through week 20 of 2019) by date of death (notified within three weeks from date of death) (Source: Statistics Netherlands).



Legend: Black line: deaths notified within three weeks. Blue shading: influenza epidemic weeks.

Figure 2.18 Observed and expected ('baseline') weekly number of deaths, July 2017 to May 2019 (Source: Statistics Netherlands).



Footnote
Blue shading: influenza epidemic weeks.
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

Authors: Marit de Lange, Gé Donker, Sierk Marbus, Scott McDonald, Frederika Dijkstra, Adam Meijer
Contributors: Anne Teirlinck, Daphne Reukers, Ron Fouchier

3.1 Key points

- In the 2018/2019 winter season, the influenza epidemic lasted 14 weeks.
- In the first six weeks of the epidemic, a low percentage influenza virus (average 18%) was detected in specimens taken from people with influenza-like-illness (ILI).
- From week seven of the epidemic, influenza virus was detected more frequently. Influenza type A virus was the predominant influenza virus type detected, with A(H1N1)pdm09 and A(H3N2) detected in approximately equal proportions, both in ILI patients visiting the GP and in severe acute respiratory infection (SARI) patients admitted to the hospital.
- Despite genetic diversity, the antigenic match of circulating A(H1N1)pdm09 viruses was good with the A(H1N1)pdm09 vaccine virus. Three major groups of A(H3N2) circulated of which two within one clade (40% each) that had moderate to good antigenic match with the A(H3N2) vaccine virus. The third group is an older clade that re-emerged this season (17%), which had a poor match with the vaccine virus. A representative virus of the latter group has been recommended for the composition of the 2019/2020 vaccine.
- Except for three A(H1N1)pdm09 viruses, all 756 viruses tested for antiviral susceptibility were sensitive for neuraminidase inhibitors.
- In the 2018/2019 respiratory season 232 (95% uncertainty interval (UI): 194 – 277) per 10,000 inhabitants had symptoms of an influenza virus infection, which was lower than in the four previous seasons. This corresponds to an estimated 400,000 cases. Symptomatic influenza incidence in respiratory season 2018/2019 was highest for the age group 0-4 years.
- In the Netherlands, the vaccine effectiveness (VE) against laboratory confirmed influenza virus (all A subtypes and B lineages) infection was estimated at 57% (95% confidence interval (CI): 16% – 78%) overall. The VE against influenza virus type A(H1N1)pdm09 was 60% (95% CI: -16% – 86%), and against type A(H3N2) 75% (95% CI: 13 – 93%).

- Preliminary end-of-season analysis of the European I-MOVE study, in which the Netherlands participates, estimated a lower influenza VE of 27% (95% CI: 13% – 39%) for patients at the primary care level against any influenza type A, 57% (95% CI: 44% – 66%) against influenza virus type A(H1N1)pdm09 and -1% (95% CI: -24% - 18%) against influenza virus type A(H3N2).
- The influenza vaccination programme of 2018 was estimated to have averted 4,340 (95% CI: 215 – 9,920) GP ILI consultations caused by an influenza virus in the age group 65 years and older in the 2018/19 season.

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). Different combinations of HA and NA proteins result in various subtypes, for example H1N1 and H3N2, the subtypes currently causing seasonal 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 natural or vaccine induced immunity.

3.3 Epidemiological situation, season 2018/2019

In the 2018/2019 season, there was an influenza epidemic from week 50 of 2018 through week 11 of 2019. Data on the influenza-like illness (ILI) incidence, obtained through sentinel general practitioner (GP) surveillance, can be found in Chapter 2.1. In the beginning of the epidemic, a low percentage influenza virus was detected in specimens taken from people with influenza-like-illness (ILI). Corona viruses and RSV particularly explained an additional part of the observed increased ILI incidence in the beginning of the epidemic. Later in the epidemic, influenza virus was detected more frequently. Influenza virus type A was the predominant influenza virus type detected, with A(H1N1)pdm09 and A(H3N2) in approximately equal proportions, both in ILI patients visiting the GP and in severe acute respiratory infection (SARI) patients admitted to the hospital. In the virological laboratory surveillance, the number of influenza virus type A detections was higher than eight preceding seasons, and was in the last ten seasons only higher during the 2009 pandemic.

SARI surveillance with laboratory confirmation for influenza continued its fourth season at Jeroen Bosch Hospital (JBZ). During the influenza season 2018/2019, 167 respiratory specimens of 250 SARI patients in JBZ were tested for influenza virus (67%). In 74 of 167 respiratory specimens, influenza A virus was detected (44%), of which 41% type A(H1N1)pdm09 and 49% type A(H3N2). The median age of SARI patients with a positive influenza virus test was 71 years (IQR 58-80). Influenza vaccination status was only collected in the 65-plus age group (see Chapter 2.3, Key points).

All characterised type A(H1N1)pdm09 influenza viruses belonged to clade 6B.1, although the viruses allocated to many subclades. Despite the genetic diversity, the circulating A(H1N1) pdm09 influenza viruses were antigenically indistinguishable from the A(H1N1)pdm09 vaccine virus. The A(H3N2) viruses were more diverse. In the Netherlands, about 80% of the A(H3N2) viruses were two variants of the 3C.2a1b clade, like in other parts of Europe. Similar to previous seasons, antigenic characterisation of A(H3N2) viruses was difficult due to lack of hemagglutination, therefore virus neutralisation assays had to be used instead. Limited virus neutralisation data showed, despite the genetic diversification of clade 3C.2a1b viruses, a moderate antigenic match with the A(H3N2) vaccine strain. As the season progressed, an increasing number of A(H3N2) viruses belonged to clade 3C.3a, a clade that re-emerged this season and to which the A(H3N2) vaccine strain for the 2015/2016 season belonged. About 17% of the total number A(H3N2) characterised belonged to this clade. Recent viruses in this clade did not antigenically match the virus in the vaccine for 2018/2019. These 3C.3a clade viruses were more often and increasingly detected in the US. Together with the limited availability of appropriate candidate vaccine strains this led to the selection of a clade 3C.3a virus for inclusion in the 2019/2020 vaccine. Type B viruses were only detected sporadically in the 2018/2019 season.

The vaccine effectiveness (VE) against all influenza viruses detected by sentinel GP surveillance was good with 57% (95% confidence interval (CI): 16% – 78%) in Dutch estimates for all ages. The influenza VE was slightly higher for people of 60 years and older compared to people younger than 60 years (70% (95% CI: -40% – 93%) and 55% (95% CI: -12% – 82%), respectively), and slightly higher against type A(H3N2) compared to type A(H1N1)pdm09 (75% (95% CI: 13% – 93%) and 60% (95% CI: -16% – 86%) respectively). The VE against all type A influenza viruses in preliminary end-of-season European estimates, to which the Netherlands also contributed data, was lower compared to the Dutch estimates, namely 27% (95% CI: 13% – 39%). The European estimated VE against influenza type A(H1N1)pdm09 was higher than against influenza A(H3N2) (57% (95% CI: 44% – 66%) and -1% (95% CI: -24% – 18%) respectively).

Influenza incidence estimated using statistical modelling was 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 (Teirlinck, de Gier et al. 2018). During the 2018/2019 season, an estimated 232 (95% uncertainty interval (UI): 194 – 277) per 10,000 inhabitants had ILI symptoms caused by an influenza virus infection, which was lower than in the four previous seasons. This corresponds to an estimated 400,000 people.

The estimated symptomatic influenza incidence in the 2018/2019 respiratory season was highest in children in the age group 0-4 years (627 per 10,000 inhabitants of 0-4 years (95% UI: 338 – 1125)). The incidence was comparable for influenza virus type A(H3N2) and type A(H1N1) pdm09 (113 (95% UI: 88 – 142), and 117 (95% UI: 92 – 142) respectively).

The influenza vaccination programme of 2018 was estimated to have averted 4,340 (95% CI: 215 – 9,920) GP ILI consultations caused by an influenza virus in the age group 65 years and older in the 2018/19 season. This estimate is based on an assumed vaccination coverage of 60.4 (95% CI: 53.9 – 66.5), a VE of 32.4 (95% CI: 8.4 – 56.5) and an estimated incidence of GP ILI consultations caused by an influenza virus of 17,830 (95% CI: 11,090 – 25,870). The number of averted GP ILI consultations caused by an influenza virus was much lower than in the seasons 2015/16 and 2017/18, but twice as high as in the season 2016/17. The influenza vaccination programme was estimated to have prevented 20% (95% CI: 1 – 33) of the total number of these consultations in the population aged 65 years and older that would have been expected without the vaccination programme. With these estimates, to prevent one GP consult for ILI caused by an influenza virus, 462 (95% CI: 164 – 2,730) persons aged 65 years and older should be vaccinated.

3.4 Discussion

In the beginning of the 14-week epidemic in the 2018/2019 season, a low percentage of influenza virus was detected in specimens taken from ILI patients. Later during the epidemic, influenza virus was detected more frequently. Influenza type A virus was the predominant influenza virus type detected, with A(H1N1)pdm09 and A(H3N2) detected in approximately equal proportions. Circulating A(H1N1)pdm09 viruses showed a good antigenic match with the vaccine virus using ferret sera studies. However, globally, a reduced serological response against the circulating A(H1N1)pdm09 viruses that predominated worldwide was found in people that were vaccinated with the 2018/2019 vaccine which included the A/Michigan/45/2015 vaccine strain. [http://www.who.int/influenza/vaccines/virus/recommendations/2019_20_north/en/]. Therefore, the new strain A/Brisbane/02/2018 is recommended by WHO as the A(H1N1)pdm09 component for the 2019/2020 season.

From the influenza viruses type A(H3N2) viruses that circulated in the Netherlands, most belonged to two variants of the clade 3C.2a1b. About one fifth of the Dutch A(H3N2) viruses in season 2018/2019 belonged to the re-emerging clade 3C.3a that was the dominant clade in the US but not in Europe. Because of this heterogeneous pattern the WHO recommendation for the A(H3N2) vaccine strain for the 2019/2020 vaccine was delayed with a month. Available candidate clade 3C.2a1b vaccine strains elicited antibodies in ferrets that did not react well with recent 3C.2a1b and 3C.3a viruses. Because of the dominance of re-emerging clade 3C.3a virus in the US and the availability of a good 3C.3a candidate vaccine virus, A/Kansas/14/2017 (H3N2)-like virus was selected for the 2019/2020 vaccine. Unfortunately, ferret sera raised against this virus do not react with clade 3C.2a1b viruses suggesting poor vaccine efficacy against clade 3C.2a1b viruses. For the efficacy of the A (H3N2) component of the vaccine in

2019/2020 season, it will therefore depend on whether the trend being seen in the US with an increasing percentage of clade 3C.3a viruses, will continue in the 2019/2020 season in Europe and the Netherlands. Nevertheless, according to Derek Smith's Antigenic Distance Hypothesis (Smith, Forrest et al. 1999), clade 3C.3a vaccination may eventually induce sufficient immunity against clade 3C.2a1b viruses in humans. However, this cannot be concluded from studies of antigenic similarity of viruses with ferret sera as presented in the WHO report. The influenza virus type B components remain the same for the 2019/2020 vaccine [http://www.who.int/influenza/vaccines/virus/recommendations/2019_20_north/en/].

As discussed in the outbreak management team, and advised by the administrative coordination meeting (BAO), from the 2019/2020 season onwards, the quadrivalent vaccine will be provided in the Netherlands, within the National Influenza Prevention Program. [https://www.rijksoverheid.nl/documenten/brieven/2018/10/14/advies-aan-bao-n.a.v.-55e-omt-influenza-d.d.-4-september-2018] Additionally, they recommended to increase the vaccination rate of healthcare personnel to 100% if possible, to protect them against influenza infection, to protect the health of their patients, and to prevent dropout rate among healthcare workers. Last, they also advised to further develop a severe-acute respiratory (SARI)-surveillance to be able to among others monitor severe influenza infections. [https://www.rijksoverheid.nl/documenten/vergaderstukken/2018/09/20/advies-bao-bestuurlijk-afstemmingsoverleg]

With influenza point-of-care-testing (POCT) in place at the emergency department of JBZ in 2018/2019, a similar amount of SARI patients was tested for influenza virus infection compared to season 2017/2018. The new influenza clinical pathway in JBZ includes a clinical algorithm for influenza diagnostics, PCR-based point-of-care testing for influenza type A and B and respiratory syncytial virus (RSV) and referring to a temporary influenza ward for cohort isolation. A cost efficiency study of this new influenza clinical pathway is in preparation.

The low number of specimens that is generally available from sentinel GP surveillance results in broad confidence intervals in VE analyses, especially in subtype-stratified and 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. Interestingly, for the season 2018/2019, the Dutch national VE point estimate of subtype A(H3N2) differed substantially from the European outcome. While the Dutch and European point estimates of the influenza VE for subtype A(H1N1)pdm09 were similar and relatively high, the influenza VE for subtype A(H3N2) was high in the Dutch estimates and low in the European estimates. There were no large differences in circulating A(H3N2) viruses (clades and subclades) in the Netherlands and elsewhere in Europe. The lack of vaccine effectiveness against A(H3N2) among working age adults that was observed in the I-MOVE primary care multicentre study for 2018-19, is a reason for concern. The I-MOVE consortium together with public health experts in Canada and the US, where similar results as in Europe were obtained, is now evaluating this. 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 compared to the virus strains included in the vaccine. 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). However, in spite of the suboptimal VE, the influenza vaccination programme was estimated to have prevented 20% of the total number of GP ILI consultations caused by an influenza virus in the population aged 65 years and older that would have been expected without the vaccination programme (i.e. 4,340 consultations).

3.5 Tables and figures

Virus surveillance

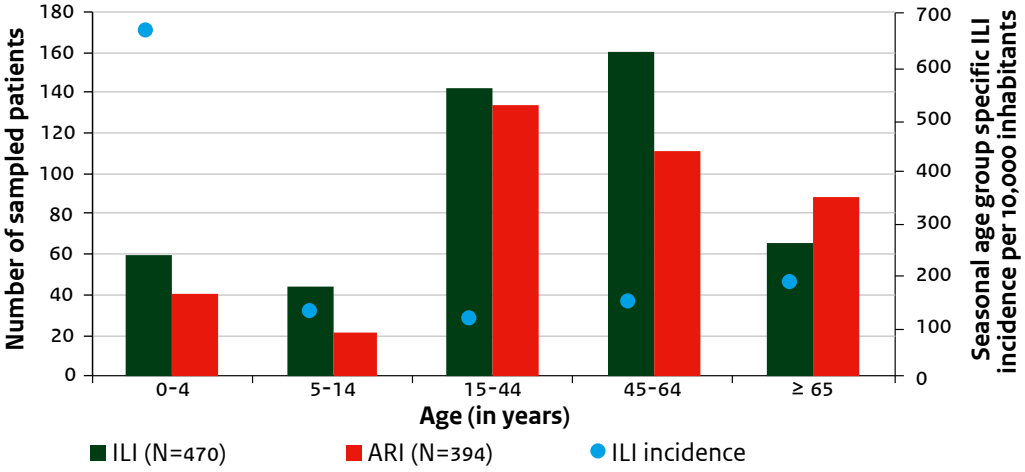
Table 3.1 Characteristics of influenza-like illness (ILI) and other acute respiratory infection (ARI) patients, who are sampled in the Nivel GP sentinel surveillance in the 2018/2019 season (through week 20 of 2019) (Source: NIC location RIVM).

Characteristics	ILI patients n/N (%)	Other ARI patients n/N (%)
Male gender	194/470 (41)	162/394 (41)
Vaccinated against influenza	101/470 (21)	106/394 (27)
If yes, brand was Influvac	40/64 (63)	35/84 (42)
If yes, brand was Vaxigrip	24/64 (37)	49/84 (58)
Belongs to target group for vaccination	169/470 (36)	168/394 (43)
Lung disease (e.g. asthma, COPD)	65/169 (38)	69/168 (41)
Immune deficiency due to treatment (e.g. chemotherapy and radiotherapy)	7/169 (4)	6/168 (4)
Immune deficiency due to disease (e.g. HIV)	4/169 (2)	3/168 (2)
Cardiac disease (myocardial infarction, angina pectoris, arrhythmias, valvular heart disease, heart failure)	24/169 (14)	27/168 (16)
Diabetes mellitus	28/169 (17)	20/168 (12)
Obesitas	50/468 (11)	33/393 (8)
Smoking		
Yes or stopped < 1 year	49/455 (11)	59/382 (15)
No, stopped > 1 year	66/455 (14)	61/382 (16)
Never	340/455 (75)	262/382 (69)
Women		
Pregnant	4/276 (1)	2/232 (1)
Delay in sampling, in days[a]	4 (2-6)	4 (3-7)

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

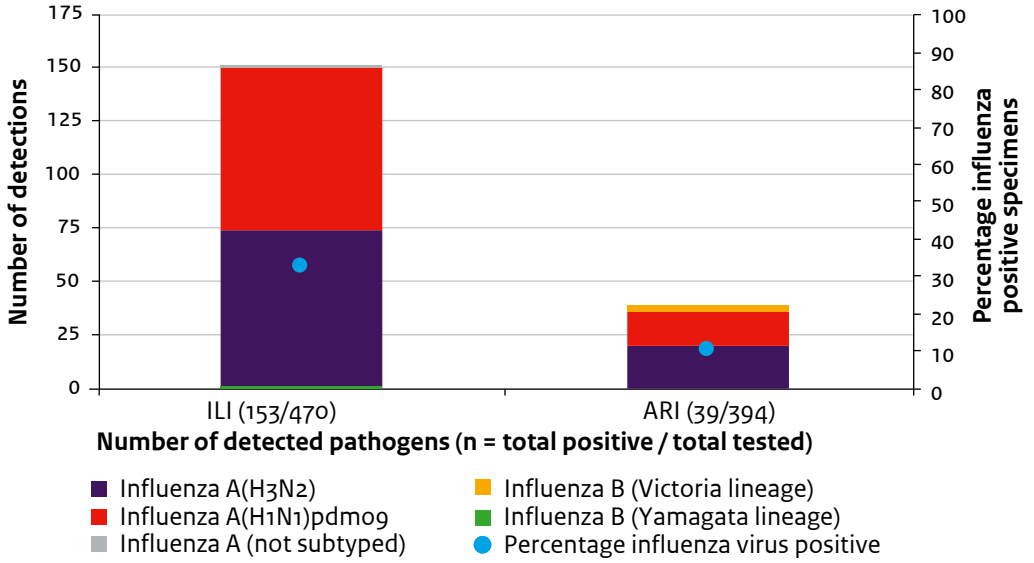
Footnote: ILI =influenza-like illness; ARI = acute respiratory tract infection; GP = general practitioner; NIC = national influenza centre; n = the number in the corresponding group; N = total number of patients, for whom the information was available. Please note that for the virological surveillance, 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 2018/2019 respiratory season (week 40 of 2018 through week 20 of 2019) (Source: Nivel Primary Care Database, NIC location RIVM).



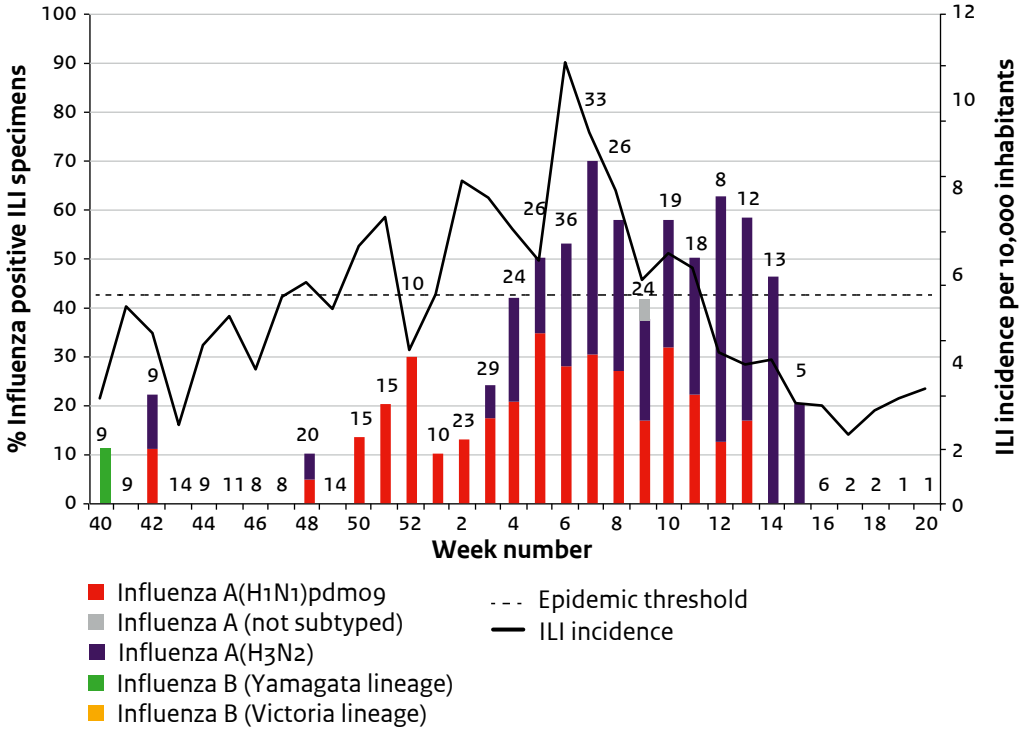
Footnote: ILI = influenza-like illness; ARI = other acute respiratory tract infections; GP = general practitioner; NIC = national influenza centre.
Please note that for the virological surveillance, the ARI patients do not include the ILI patients, hence the notation 'other ARI'.

Figure 3.2 Number and proportion of detected influenza viruses detected in specimens taken from ILI and other ARI patients, who were sampled in the Nivel GP sentinel surveillance in the 2018/2019 respiratory season (through week 20 of 2019) (Source: NIC location RIVM).



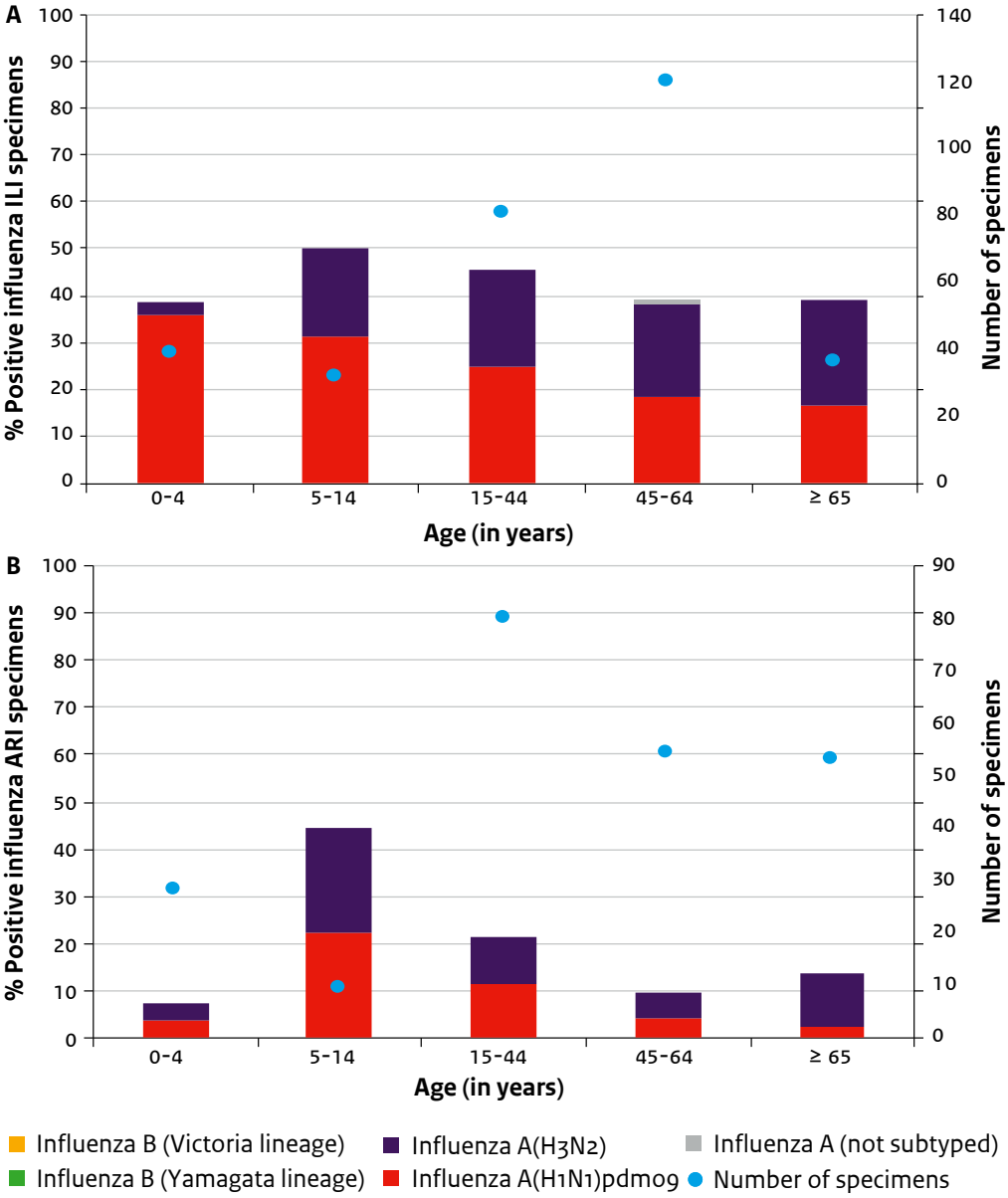
Footnote: ILI = influenza-like illness; ARI = other acute respiratory tract infection; GP = general practitioner; NIC = national influenza centre.
Please note that for the virological surveillance, the ARI patients do not include the ILI patients, hence other ARI.

Figure 3.3 Percentage of specimens taken from ILI patients by sentinel GPs positive for influenza virus, and ILI incidence with epidemic threshold during the 2018/2019 respiratory season (week 40 of 2018 through week 20 of 2019), displayed by week of sampling (Source: Nivel Primary Care Database, NIC location RIVM).



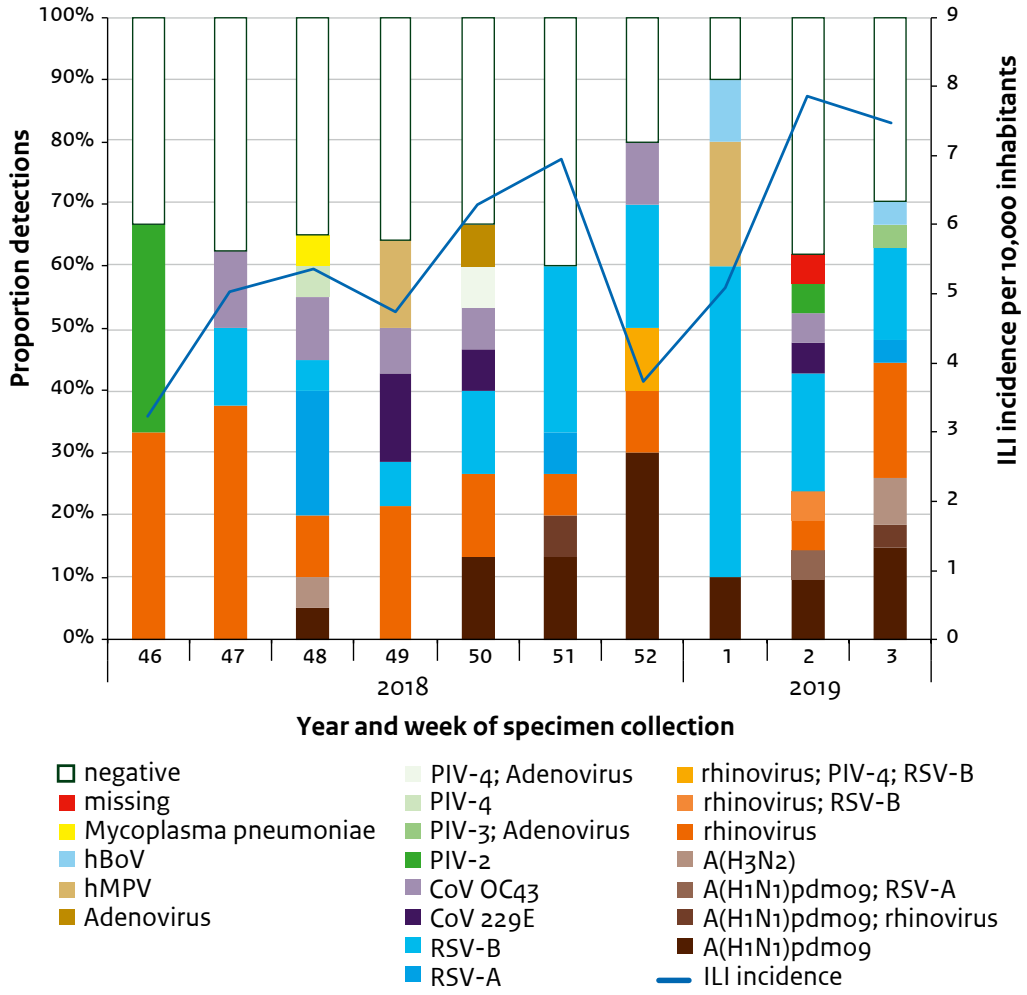
Footnote: ILI = influenza-like illness; GP = general practitioner; NIC = national influenza centre.
The numbers above the bars are the total number of tested specimens.

Figure 3.4 Percentage of influenza virus positive specimens taken from ILI (graph A) and other ARI (graph B) patients per age group, taken by sentinel GPs, during the epidemic weeks (week 50 of 2018 through 11 of 2019) of the 2018/2019 season (Source: NIC location RIVM).



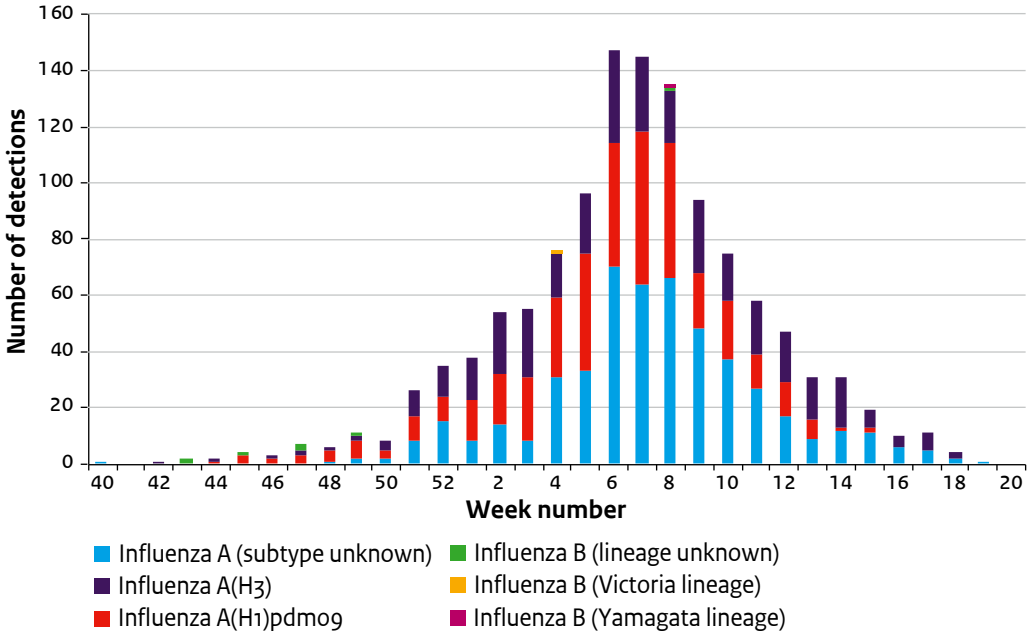
Footnote: ARI = acute respiratory tract infection; ILI = influenza-like illness; GP = general practitioner; NIC = national influenza centre.
Please note that for the virological surveillance, the ARI patients do not include the ILI patients, hence other ARI.

Figure 3.5 Detection of pathogens in specimens from ILI patients for surveillance purposes with in-house PCR assays (influenza virus, RSV, rhinovirus, and enterovirus), and retrospective with a commercial multiplex PCR on specimens negative for influenza virus, RSV, rhinovirus and enterovirus, for the period of week 46 of 2018 through week 3 of 2019 including the first 6 weeks (week 50/2018 onwards) of the start of the influenza epidemic as signaled by an ILI incidence above 5.1 ILI cases per 10,000 inhabitants (Source: NIC location RIVM).



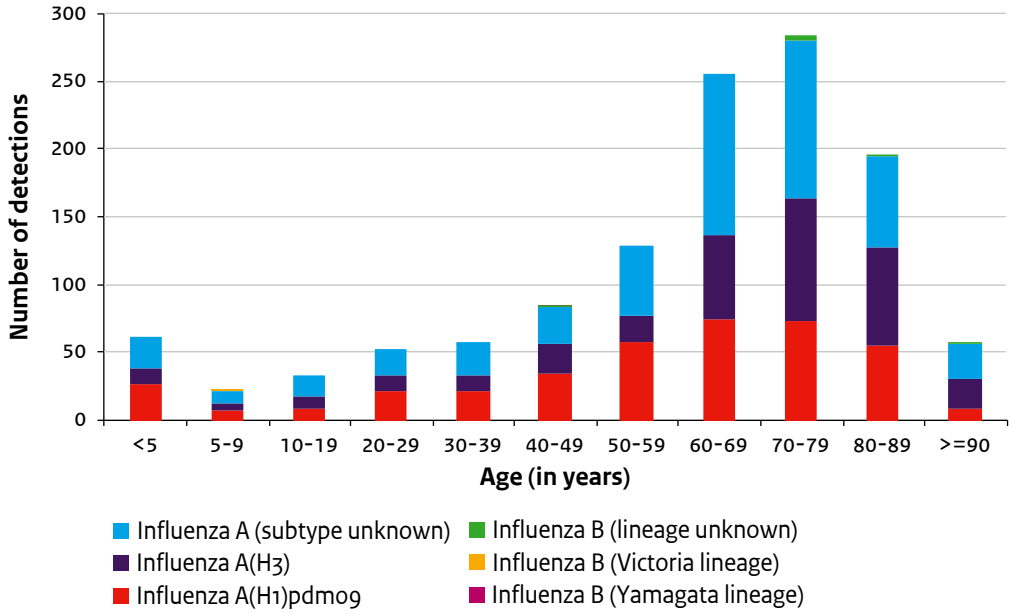
Footnote: ILI = influenza-like illness; NIC = national influenza centre; hBoV = human bocavirus; hMPV = human metapneumovirus; PIV = parainfluenza virus; CoV = coronavirus; RSV = respiratory syncytial virus.

Figure 3.6 Subtyping of influenza viruses submitted by Dutch laboratories to the NIC location Erasmus MC during the 2018/2019 season, displayed by week of specimen collection, excluding specimens taken for sentinel GP surveillance and submitted to NIC location Erasmus MC for antigenic characterisation (Source: NIC location Erasmus MC).



Footnote: NIC = national influenza centre; GP = general practitioner.
Note: Since the beginning of 2018, the laboratories were requested 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 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 to subtype only 5-6 viruses per week for laboratories that continue to submit all influenza virus positive specimens (displayed in the figure as subtype or lineage unknown; these include also specimens that had a too low viral load for subtype/lineage determination by MinION sequencing).

Figure 3.7 Subtyping of influenza viruses submitted by Dutch laboratories to the NIC location Erasmus MC during the 2018/2019 season, displayed by week of specimen collection, excluding specimens taken for sentinel GP surveillance and submitted to NIC location Erasmus MC for antigenic characterisation, per age group (Source: NIC location Erasmus MC).



Footnote: NIC = national influenza centre; GP = general practitioner.
Note: Since the beginning of 2018, the laboratories were requested 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 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 to subtype only 5-6 viruses per week for laboratories that continue to submit all influenza virus positive specimens (displayed in the figure as subtype or lineage unknown; these include also specimens that had a too low viral load for subtype/lineage determination by MinION sequencing).

Table 3.2 Genetic characterisation of influenza viruses, week 40 of 2018 through week 20 of 2019 (Source: NIC location RIVM, NIC location Erasmus MC; status by 22 May 2019).

Virus (sub)type	Clade[a]	Defining amino acid substitutions in HA gene[b]	Antigenic match with 2018/2019 vaccine strains[c]	Source	
				RIVM[d]	Virology labs[e]
A(H1N1) pdm09 (n=307)	**6B.1**	na	na	na	na
	6B.1A	S74R, S164T, I295V	Good	1	5
	6B.1A	+S183P	Good	2	7
	6B.1A1	Genetic group	Good	0	0
	6B.1A2	+L233I	Good	3	11
	6B.1A3	+T120A	Good	0	2
	6B.1A4	+N129D, A141E	Good	0	0
	6B.1A5	+N260D	Good	57	130
	6B.1A6	+T120A; genetic distinct from 6B.1A3	Good	15	25
	6B.1A7	K302T, *I77M, N169S, E179D;* Many have S183P	Good	15	34
A(H3N2) (n=404)	**3C.2a1**	N121K, *N171K, I77V, G160E*	Moderate to good[f]	na	na
	3C.2a1	+H311Q	Moderate to good[f]	0	1 (not allocating to subgroup)
	3C.2a1b	+K92R, R142G	Moderate to good[f]	0	1 (not allocating to subgroup)
	3C.2a1b	+E62G, T128A	Moderate to good[f]	0	3 (not allocating to subgroup)
	3C.2a1b +135K grp 1	+E62G, T128A, T135K, R142G	Moderate to good[f]	8	40

Continued on next page

Virus (sub)type	Clade[a]	Defining amino acid substitutions in HA gene[b]	Antigenic match with 2018/2019 vaccine strains[c]	Source	
				RIVM[d]	Virology labs[e]
	3C.2a1b +135K grp 2	+E62G, T128A, T135K, R142G	Moderate to good[f]	31	83
	3C.2a1b +131K	+E62G, T131K, R142G, *V200I*	Moderate to good[f]	41	120
	3C.2a1b +135N	+K92R, T135N	Moderate to good[f]	0	0
	3C.2a2	T131K, R142K, R261Q	Moderate to good[f]	3	1
	3C.2a3	N121K, S144K	Moderate to good[f]	0	3
	3C.2a4	N31S, D53N, R142G, S144R, N171K, I192T, Q197H	Poor[f]	0	1
	3C.3a	T128A, A138S, R142G	Poor[f]	16	52
B-Yamagata (n=2)	3, subgroup	L172Q and M251V	Absent[g]	1	1
B-Victoria (n=2)	1A, subgroup 1	I117V, N129D, V146I Without deletions	Poor[h]	0	0
	1A, subgroup 2	I180V, R151K (HA2), 162-163 amino acid deletion	Moderate to good[h]	0	0
	1A, subgroup 3	K136E, (many have K52N, E198G), 162-164 amino acid deletion	Poor[h]	1	1
	1A, subgroup 4	I180T, K209N, 162-164 amino acid deletion	Poor[h]	0	0

Footnote: NIC = national influenza centre.

[a] Bold font type indicates the clade to which the strain in the vaccine 2018/2019 belongs.

[b] Normal font is amino acid in HA1 protein, italics font is amino acid in HA2 protein.

[c] Composition 2018/2019 vaccine: an A/Michigan/45/2015 (H1N1)pdm09-like virus; an A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus; and a B/Colorado/06/2017-like virus (Victoria lineage; with) virus. Antigenic match based on a limited number of Dutch viruses analysed and the WHO CC, London, interim report (https://www.crick.ac.uk/sites/default/files/2019-04/Crick%20VCMFeb2019%20report_toPost.pdf).

[d] Source NIC location RIVM; viruses from GP ILI/ARI surveillance and from hospital SARI surveillance.

[e] Source NIC location Erasmus MC.

[f] Clade 3C.2a viruses and most of its subclades match antigenic moderately to good with the egg-grown vaccine strain A/Singapore/INFIMH-16-0019/2016. Clade 3C.3a viruses match antigenic badly with the egg-grown vaccine strain A/Singapore/INFIMH-16-0019/2016. Egg-grown viruses are used for vaccine production.

[g] A B-Yamagata lineage virus was not included in the trivalent influenza vaccines used in the Dutch National Programme for prevention of Influenza in the 2018/2019 season.

[h] In the 2016/2017 Northern Hemisphere and 2017 Southern Hemisphere season haemagglutinin amino acid deletion variants of the Victoria lineage of influenza type B viruses emerged, resulting in current circulation of four groups, one without deletions, one with two deletions (position 162-163) and two with three deletions (position 162-164) resulting in antigenic distinction between all four groups.

Table 3.3 Influenza virus diagnostics of SARI patients; comparison influenza season 2015/2016, 2016/2017, 2017/2018 and 2018/2019 at the Jeroen Bosch Hospital.

Total	Influenza season[a]			
	2015/2016[b] N=138	2016/2017 N=175	2017/2018 N=427	2018/2019 N=250
	N (%)	N (%)	N (%)	N (%)
Influenza test performed	90 (65)	101 (58)	304 (71)	167 (67)
Influenza virus positive	32 (36)	38 (38)	130 (43)	74 (44)
type A and B	0	0	2	0
type A	24 (75)	38 (100)	42 (31)	74 (100)
H3N2[c]	0 (0)	32 (84)	18 (43)	30 (41)
H1N1pdm09[c]	17 (71)	0 (0)	10 (24)	36 (49)
Not subtyped[d]	7 (29)	6 (16)	14 (33)	8 (11)
type B	8 (25)	0 (0)	90 (69)	0 (0)
Yamagata[c]	0 (0)	0 (0)	67 (74)	0 (0)
Victoria[c]	4 (50)	0 (0)	0 (0)	0 (0)
Not characterized[d]	4 (50)	0 (0)	23 (26)	0 (0)
Influenza virus negative	58 (64)	74 (42)	174 (57)	93 (56)

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

[a] Influenza season = week 40 through week 20 the following year.

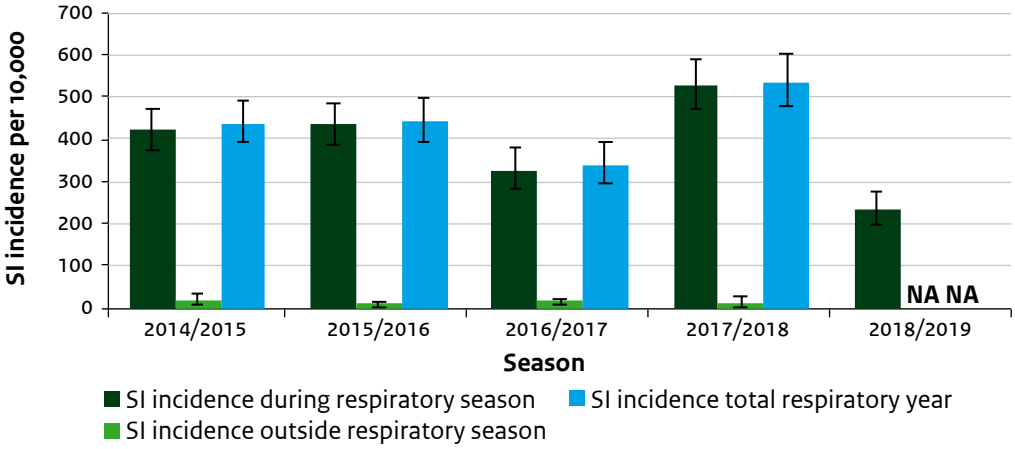
[b] Influenza season 2015/2016 is limited from week 42 of 2015 through week 20 of 2016.

[c] Influenza virus A subtype and B lineage determined at NIC location RIVM.

[d] Not all influenza viruses could be subtyped or lineage determined, because SARI surveillance pilot study is dependent on routinely collected, residual respiratory material that can be used for further analyses and was not always available.

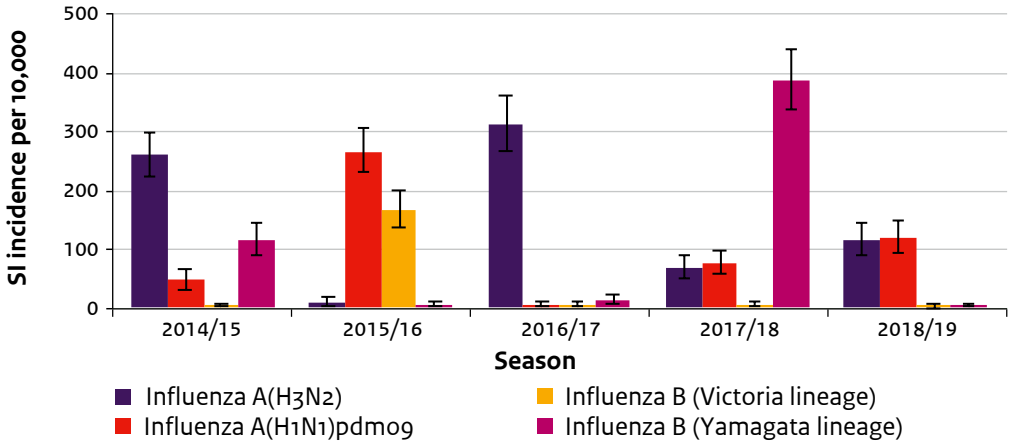
Symptomatic influenza incidence estimation

Figure 3.8 Estimated symptomatic influenza (SI) incidence per 10,000 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 2014/2015 through 2018/2019 (Source: Nivel Primary Care Database, NIC location RIVM, Influenzanet).



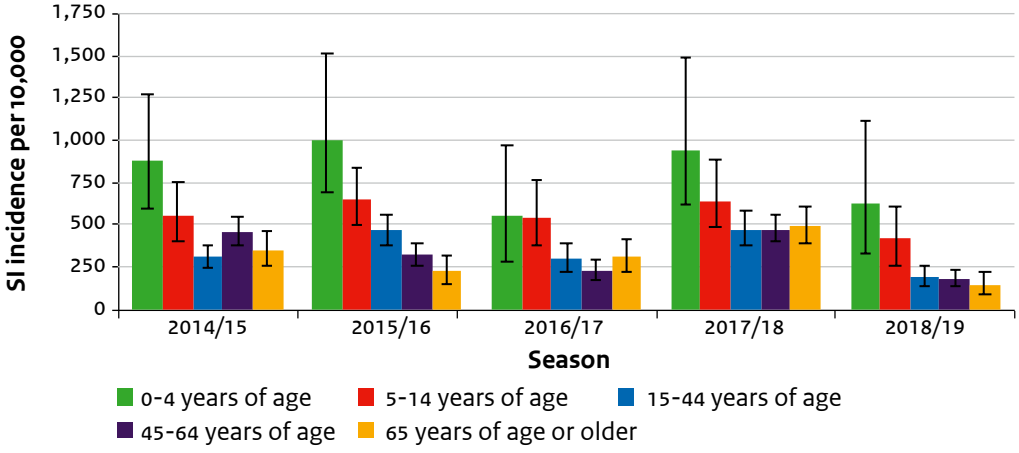
Footnote: NA= not applicable; NIC =national influenza centre.
Error bars represent 95% uncertainty intervals (UI). For the 2018/2019 season, no numbers for outside the respiratory season were yet available.

Figure 3.9 Estimated symptomatic influenza (SI) incidence per 10,000 inhabitants by subtype for the respiratory seasons (week 40 through week 20) 2014/2015 through 2018/2019 (Source: Nivel Primary Care Database, NIC location RIVM, Influenzanet).



Footnote: NIC = national influenza centre. Error bars represent 95% uncertainty intervals (UI).

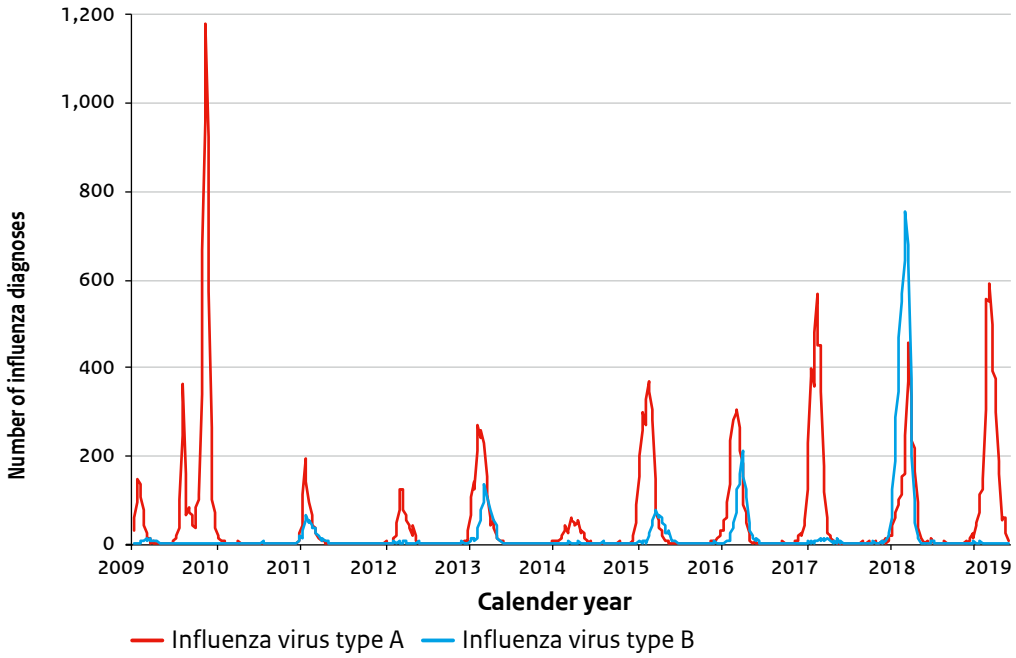
Figure 3.10 Estimated symptomatic influenza (SI) incidence per 10,000 inhabitants by age group for the respiratory seasons (week 40 through week 20) 2014/2015 through 2018/2019 (Source: Nivel Primary Care Database, NIC location RIVM, Influenzanet).



Footnote: NIC = national influenza centre. Error bars represent 95% uncertainty intervals (UI).

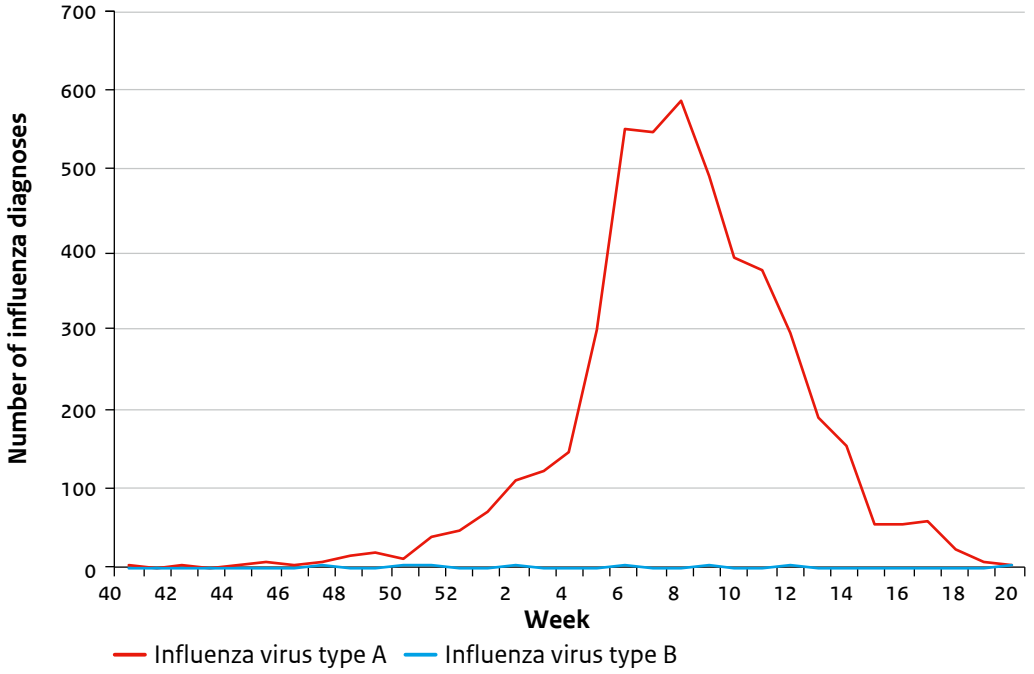
Influenza diagnostics in virological laboratories

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 2009 through week 20 of 2019 (Source: Virological laboratory surveillance, NWKV).



Footnote: NWKV = Dutch Working Group for Clinical Virology of the Dutch Society for Medical Microbiology (NVMM).

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 2018 through week 20 of 2019 (Source: Virological laboratory surveillance, NWKV).



Footnote: NWKV = Dutch Working Group for Clinical Virology of the Dutch Society for Medical Microbiology (NVMM)

Antiviral susceptibility

Table 3.4 Reduced inhibition of influenza viruses by neuraminidase inhibitors and M2 ion-channel blockers, 2016/2017 – 2018/2019 (Source: NIC location RIVM, NIC location Erasmus MC)[a].

Antiviral Influenza virus (sub)type	Viruses with reduced inhibition by season		
	2016/2017 n/N (%)	2017/2018 n/N (%)	2018/2019 n/N (%)[b]
Neuraminidase inhibitor			
A(H1N1)pdm09	2/11 (18)[c]	1/233 (1)[d]	3/331(1)[e]
A(H3N2)	0/911 (0)	0/355 (0)	0/421 (0)
B	0/14 (0)	0/156 (0)	0/4 (0)
M2 ion-channel blocker			
A(H1N1)pdm09	2/2 (100)	12/12 (100)	None tested
A(H3N2)	56/56 (100)	13/13 (100)	3/3 (100)

Footnote: NIC = national influenza centre; n = the number in the corresponding group; N = total number of patients.

[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 40/2018 through week 20/2019; status by 23 May 2019.

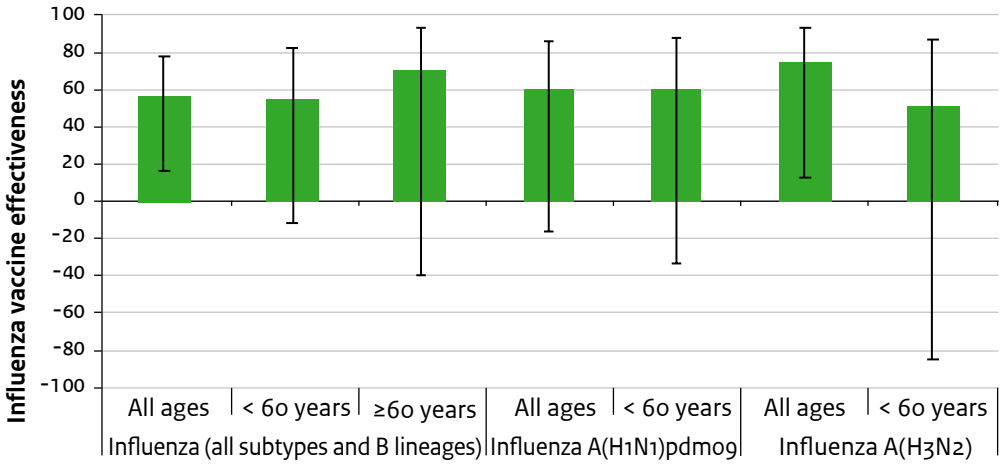
[c] Two viruses from one patient taken 10 days apart with both highly reduced inhibition by oseltamivir due to a H275Y amino acid substitution. The patient was treated with oseltamivir prior to specimen collection.

[d] 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.

[e] Three viruses with highly reduced inhibition by oseltamivir due to H275Y (n=1) or mixture 275H/Y (n=2) amino acid substitution. Two patients were admitted to ICU of which one was treated with oseltamivir prior to specimen collection and the other had an unknown treatment status. One community patient had no prior treatment with oseltamivir.

Influenza vaccine effectiveness

Figure 3.13 Influenza vaccine effectiveness in the 2018/2019 season in the Netherlands, measured in GP sentinel surveillance, against laboratory confirmed influenza virus type A (all subtypes), A(H1N1)pdm09, and A(H3N2) infection, and influenza virus type A (all subtypes) in people of younger than 60 years and 60 years or older (Source: Nivel Primary Care Database, NIC location RIVM).



Footnote: GP = general practitioner; NIC = national influenza centre.

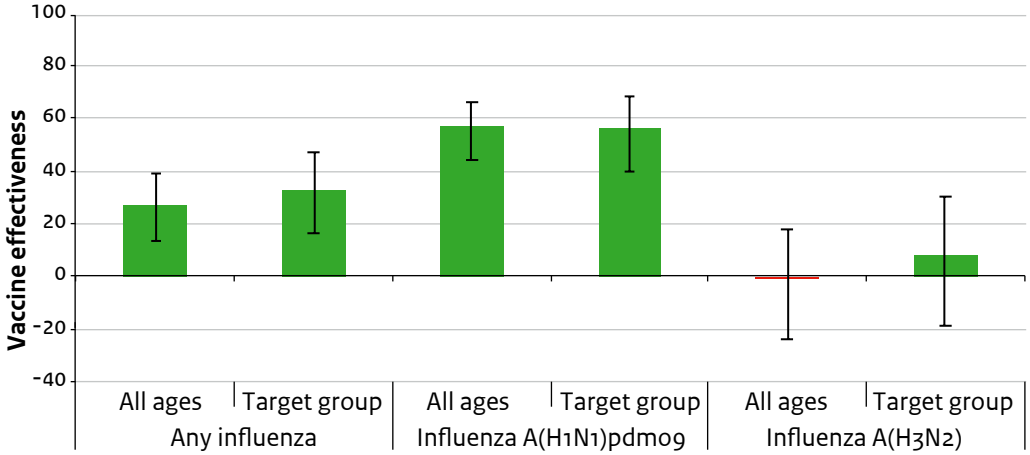
Table 3.5 Estimation of vaccine effectiveness (VE) against laboratory confirmed influenza for all ages, based on influenza virus positive and influenza virus negative ILI and other ARI patients (test negative design), which were collected for the Dutch sentinel GP surveillance in the 2018/2019 season (Source: Nivel Primary Care Database, NIC location RIVM).

	Age group / adjustment	Cases			Controls			Adjusted VE	95% CI
		All	Vaccinated	%	All	Vaccinated	%		
Any influenza	All ages[a]	178	38	21	377	100	27	57	16 – 78
	< 60 years[a]	138	14	10	294	38	13	55	-12 – 82
	≥ 60 years	40	24	60	83	62	75	70	-40 – 93
A(H1N1)pdm09	All ages[a]	88	16	18	360	96	27	60	-16 – 86
	< 60 years[a]	73	6	8	281	37	13	60	-33 – 88
A(H3N2)	All ages[a]	87	20	23	257	83	32	75	13 – 93
	< 60 years[b]	63	7	11	195	33	17	51	-85 – 87

Footnote: VE= vaccine effectiveness, ILI = influenza-like illness, ARI = other acute respiratory tract infection, GP = general practitioner; NIC = national influenza centre.
Please note that for the virological surveillance, the ARI patients do not include the ILI patients, hence other ARI. Due to very wide confidence intervals, the VE for people of 60 years or older against influenza subtypes A(H1N1)pdm09 and A(H3N2) were not displayed.

[a] Adjusted by age, comorbidity, period.
[b] Adjusted by age, comorbidity, gender.

Figure 3.14 Influenza vaccine effectiveness in the 2018/2019 season in Europe, measured in, I-MOVE multicentre case control studies, against laboratory confirmed influenza virus A (all subtypes A(H1N1)pdm09, and A(H3N2), per age group (Source: I-MOVE study).



Footnote: All results are from preliminary end-of-season data.

Table 3.6 Influenza vaccine effectiveness in the 2018/2019 season in Europe, measured in, I-MOVE multicentre case control studies, against laboratory confirmed influenza virus A (all subtypes A(H1N1)pdm09, and A(H3N2), per age group (Source: I-MOVE study).

		Cases			Controls				
	Age group	All	Vaccinated	%	All	Vaccinated	%	Adjusted VE	95% CI
Any influenza	All ages	3618	375	10	4032	507	13	27	13 – 39
	< 15 years	1164	41	4	1370	62	5	58	32 – 74
	15-64 years	2119	185	9	2208	202	9	14	-9 – 32
	≥ 65 years	335	149	44	454	243	54	39	14 – 57
	Target group	905	271	30	1104	398	36	33	16 – 47
A(H1N1) pdm09	All ages	1643	100	6	3683	481	13	57	44 – 66
	< 15 years	493	9	2	1221	61	5	76	47 – 89
	15-64 years	1036	56	5	2047	191	9	49	29 – 64
	≥ 65 years	114	35	31	415	229	55	63	38 – 78
	Target group	387	75	19	1010	375	37	56	40 – 68
A(H3N2)	All ages	1917	265	14	3885	485	12	-1	-24 – 18
	< 15 years	668	33	5	1340	62	5	46	8 – 68
	15-64 years	1038	123	12	2115	194	9	-26	-66 – 4
	≥ 65 years	211	109	52	430	229	53	20	-20 – 46
	Target group	497	189	38	1051	377	36	8	-19 – 30

Footnote: All results are from preliminary end-of-season data.

Table 3.7 Impact estimations for ILI GP consultations caused by influenza virus, 2015/16 – 2018/19. Number between brackets are 95% CIs. (Sources: Nivel Primary Care Database, I-MOVE/I-MOVE+ study and NIC location RIVM).

	2015/16	2016/17	2017/18	2018/19
Input parameters				
Vaccine coverage	66.5 (59.3 – 73.1)	62.9 (56.1 – 69.2)	60.4 (53.9 – 66.5)	60.4 (53.9 – 66.5)[a]
Vaccine effectiveness[b]	37.1 (21.7 – 52.5)	9.7 (-8.4 -27.8)	19.5 (4.7 – 34.4)	32.4 (8.4 – 56.5)
Incidence	25,900 (15,510 - 37,740)	33,760 (20,570 - 48,840)	65,120 (48,100 – 80,770)	17,830 (11,090 – 25,870)
Estimated impact				
NAE	8,483 (3,396 – 16,255)	2,194 (-2,141 – 7,524)	8,694 (1,158 -17,487)	4,340 (215 – 9,920)
NAE (per 100,000 pop.)	275 (110 – 527)	69 (-68 – 238)	268 (36 – 540)	131 (6 – 299)
NNV	242 (127 – 598)	906 (-9,053 – 9,680)	225 (105 – 1,093)	462 (164 – 2,730)
PF	0.25 (0.13 – 0.36)	0.06 (-0.07 – 0.17)	0.12 (0.02 – 0.20)	0.20 (0.01 – 0.33)

Footnote: ILI = influenza-like illness; GP = general practitioner; CI = confidence interval; ; NIC = national influenza centre; NAE = number of averted events; Pop.= population; NNV = number of vaccinated persons needed to avoid one influenza-associated event;
PF = prevented fraction

[a] Vaccination coverage of 2018/19 is not available yet. Instead, the vaccination coverage of 2017/18 was used.

[b] See table 3.8.

Table 3.8 Weighted overall vaccine effectiveness (VE) against influenza confirmed ILI for the population of 65 years and older in the Netherlands as used for the impact estimations. Number between brackets are 95% CIs. (Sources: I-MOVE/I-MOVE+ study and NIC location RIVM).

	2015/16	2016/17	2017/18	2018/19
Input parameters				
I-MOVE+ pooled VE against H1N1	42.8 (19.6 – 59.3)[a]	42.8 (19.6 – 59.3)[a]	42.8 (19.6 – 59.3)[a]	62.8% (37.5 – 77.9[c]
I-MOVE+ pooled VE against H3N2	8.4 (-13.1 – 25.8)[b]	8.4 (-13.1 – 25.8)[b]	8.4 (-13.1 – 25.8)[b]	19.9% (-19.6 – 46.3)[c]
I-MOVE+ pooled VE against B	21.3 (0.9 – 37.5)[a]	21.3 (0.9 – 37.5)[a]	21.3 (0.9 – 37.5)[a]	n.a.
Proportion H1N1/H3N2/B in NL (sentinel)	0.74/ 0.00/ 0.27	0.02/ 0.93/ 0.05	0.03/ 0.18/ 0.79	0.29/0.71[d]
Weighted overall VE against influenza confirmed ILI for NL	37.1 (21.7 – 52.5)	9.7 (-8.4 -27.8)	19.5 (4.7 – 34.4)	32.4 (8.4 – 56.5)

Footnote: VE = vaccine effectiveness; ILI = influenza-like illness; CI = confidence interval; NIC = national influenza centre; n.a. = not available.

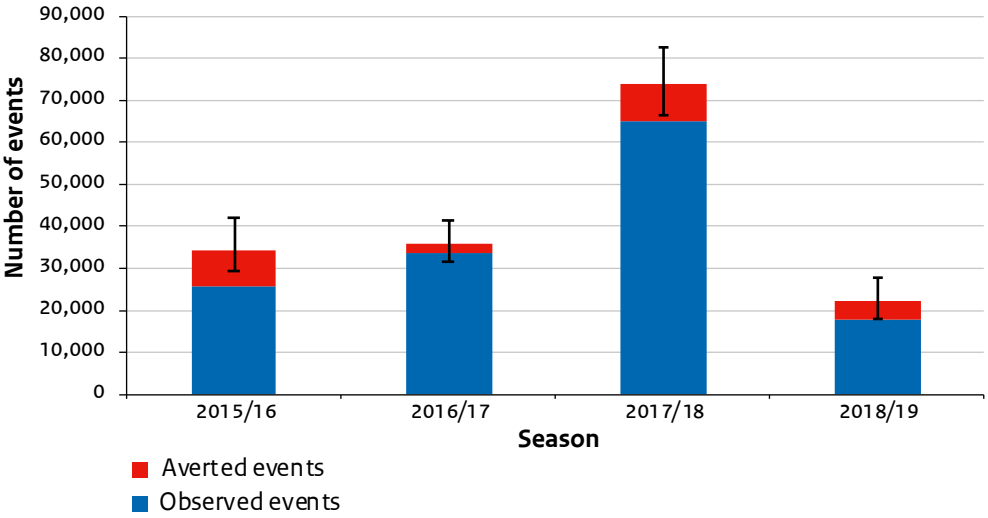
[a] Based on pooled I-MOVE+ primary care data over the seasons 2015-16/2017-18.

[b] Based on pooled I-MOVE+ primary care data over the seasons 2016-17/2017-18.

[c] Based on pooled I-MOVE+ primary care data over the seasons 2018/19 (near final end-of-season data, per 7-6-2019)

[d] Because of very low number of influenza virus B among sentinel ILI- and ARI patients of 65 years and older (n=1), influenza virus B was excluded from the calculation of the proportion.

Figure 3.15 Impact estimations for ILI GP consultations caused by influenza virus, 2015/16 – 2018/19. Blue bars represent the estimated number of observed cases. Red bars represent the estimated number of cases averted by the 2018 influenza vaccination campaign, with 95% CIs. (Sources: Nivel Primary Care Database, I-MOVE/I-MOVE+ study and NIC location RIVM).



Footnote: ILI = influenza-like illness; GP = general practitioner; CI = confidence interval; NIC = national influenza centre.

Chapter 4
RS-Virus

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Contributors: Marit de Lange, Daphne Reukers, Sofie Mooij

4.1 Keypoints

- We have defined the RSV season using the Moving Epidemic Method (MEM) based on the number of RSV diagnoses reported by the virological laboratory surveillance. The MEM pre- and post-epidemic thresholds for respiratory season 2018/2019 based on the previous 12 seasons were 26 and 36 RSV diagnoses per week, respectively.
- The RSV season started in week 47 of 2018 and lasted 16 weeks. The average length of RSV seasons from 2009/2010 – 2017/2018 was 18 weeks (range 16 – 20 weeks). In week 1 and 2 of 2019, the epidemic was above the medium intensity threshold of 172 diagnoses.
- During the respiratory season, the number of RSV diagnoses in the virological laboratory surveillance peaked in week 1 of 2019 (n=186).
- A total of 104 (12.1%) RS-viruses were detected in 863 combined nose swabs and throat swabs taken from ILI and other ARI patients, collected by sentinel GPs in the 2018/2019 respiratory season. The peak percentage of RSV positive ILI and other ARI samples (46% in week 1 2019) was higher than the peak percentages of previous seasons.
- The overall percentage of RSV positive specimens taken by the GPs was highest in children in the age group 0-1 years with 30% in ILI patients and 54% in other ARI patients. In the age group 65 years or older, 17% of ILI patients and 17% of other ARI patients was positive for RSV. As usual, the percentage of RSV positive specimens was lowest in the age groups 15-44 and 45-64 (taken both age groups together 7% in ILI patients and 7% in other ARI patients).

4.2 Background

Respiratory Syncytial Virus (RSV) causes respiratory infection and is commonly contracted by children, 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 preterm infants, infection can lead to severe illness, hospitalization and even death. Studies suggest that RSV is also a common cause for respiratory infections in the elderly causing outbreaks in elderly care facilities (Meijer, Overduin et al. 2013). RSV is subdivided in RSV-A and RSV-B, based on the different antigenic properties of their attachment glycoprotein G. These two types may circulate simultaneously in the population. Currently, no vaccine for RSV is available, but many 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/resources/rsv-vaccine-and-mab-snapshot/]. Recently, Novavax has published the first results of a clinical trial on their maternal vaccine against RSV. The primary endpoint (medically significant symptomatic RSV lower respiratory tract infection (LRTI) through 90, 120, 150 and 180 days of life in infants) was not met. However, 44% efficacy (95% CI 19.6-61.5) was found against RSV LRTI hospitalizations in the first 90 days [https://novavax.com/presentation.show].

4.3 Epidemiological situation, season 2018/2019

The RSV season as defined using virological laboratory surveillance data lasted 18 weeks from week 47 of 2018 through week 10 of 2019 and was above the medium intensity threshold of 172 reports in week 1 and 2 of 2019. The total number of positive RSV diagnoses reported by the 19 Dutch virological laboratories participating in the virological laboratory surveillance in 2018/2019 (n=1807; through week 20 of 2019) was within the range of the last ten seasons. The number of RSV-diagnoses peaked in week 1 of 2019 (n=186). In the 2018/2019 respiratory season (week 40 through week 20), 104 of 863 total ARI (ILI plus other ARI) patients that were sampled in the GP sentinel surveillance tested RSV positive (12.1%), of which two patients had an infection with both RSV-A and B. Among the 106 RS-viruses detected, 18 were RSV-A (17%) and 88 were RSV-B (83%). The percentage of RSV positive patients, and especially the peak percentage of 46% in week 1 2019, is higher than previous years.

4.4 Discussion

Previously, we defined the RSV season as the period with at least 20 RSV-diagnoses per week reported by the virological laboratory surveillance. We now used the Moving Epidemic Method (MEM), that was originally developed to assess influenza seasonality (Vega, Lozano et al. 2015), to establish the epidemic thresholds for RSV, using the virological laboratory surveillance data of the previous 12 seasons (Vos, Teirlinck et al. 2019). Other advantages of this method are that the pre-epidemic threshold and post-epidemic threshold can be calculated separately, and that intensity levels can be used to provide a more detailed description of the RSV season. Generally, the post-epidemic threshold is higher than the pre-epidemic threshold and higher than the previously used number of 20 detections. The epidemic seasons are therefore slightly shorter than reported in previous seasons. For more details on the MEM method and the differences between the definitions of epidemic periods, see the methods section (chapter 9) of this report, and (Vos, Teirlinck et al. 2019). The virological laboratory surveillance provides real-time data on absolute number of RSV diagnoses, but a denominator, age, clinical background information, information on testing strategy by laboratory and RSV typing information is lacking. Such background information is available for ILI and other ARI patients that are swabbed by sentinel GPs. However, GPs are instructed to focus primarily on sampling ILI patients which includes fever as a pre-requisite. Many RSV cases are assumed to present without fever and should be captured as another ARI that does not include fever as a pre-requisite.

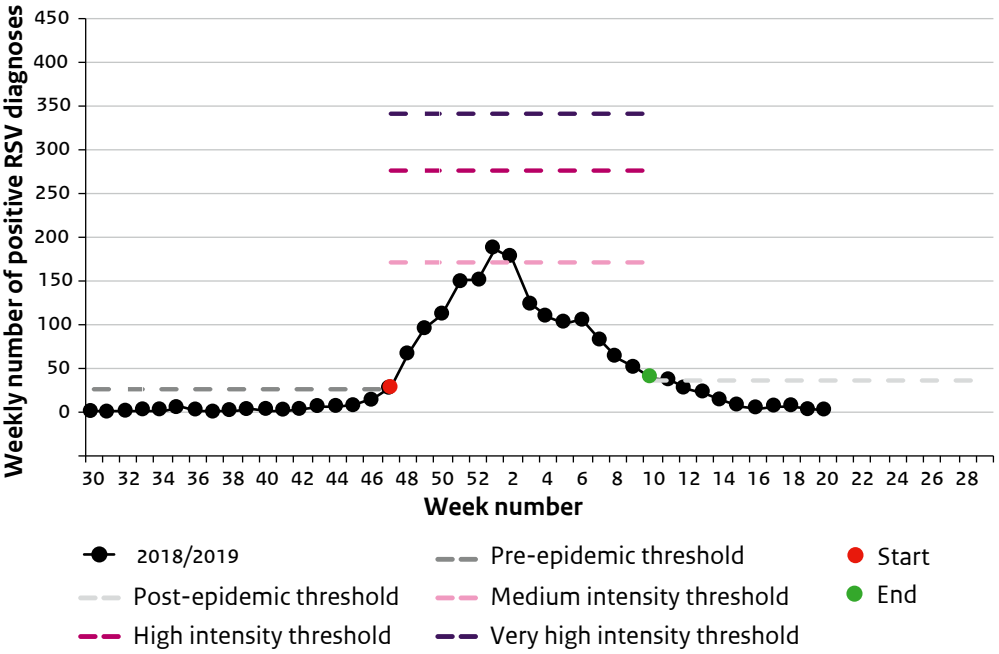
The high peak percentage of RSV-positive ARI (ILI + another ARI) samples that was found in the GP sentinel surveillance is in line with a trend of increasing percentages of RSV positives in the GP sentinel surveillance over the past years (Vos, Teirlinck et al. 2019). Interestingly, this is not found in the absolute counts of the virological laboratory surveillance, representing more severe RSV cases that are tested for clinical reasons, but mostly children. Testing policy in hospitals can vary from testing only to confirm that the season has started and further performing RSV diagnosis on clinical indication to testing every patient with a severe respiratory infection.

The need for a clear case definition for RSV has been emphasised in the previous annual reports. 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.

RESCEU has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement 116019. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and the European Federation of Pharmaceutical Industries and Associations.

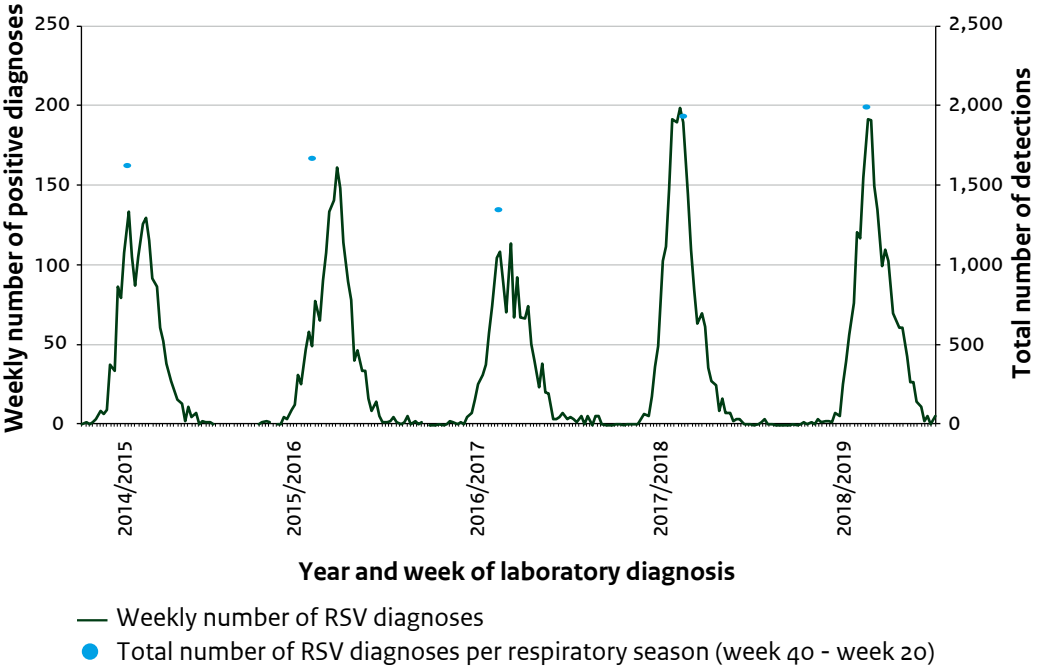
4.5 Tables and figures

Figure 4.1 Number of weekly reported RSV diagnoses in respiratory season 2018/2019, and epidemic thresholds and intensity levels, based on the number of RSV diagnosis in the period 2006/2007-2017/2018 (Source: virological laboratory surveillance, NWKV and MEM web application (Lozano 2018).



Footnote: The MEM epidemic and intensity thresholds were as follow: pre-epidemic threshold: 26; post-epidemic threshold: 36; medium intensity: 172, high intensity: 276; very high intensity; 340. NWKV = Dutch Working Group for Clinical Virology of the Dutch Society for Medical Microbiology (NVMM).

Figure 4.2 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 2014/2015-2018/2019 (until week 20) (Source: virological laboratory surveillance), NWKV.



Footnote: NWKV = Dutch Working Group for Clinical Virology of the Dutch Society for Medical Microbiology (NVMM).

Table 4.1 Number of reported respiratory syncytial virus (RSV) diagnoses in the virological laboratory surveillance for the period 2009/2010-2018/2019 (through week 20).

RSV diagnoses	weeks 40-20 (N)	weeks 21-39 (N)	weeks 40-39 (N)
2009/2010	3075	34	3109
2010/2011	2702	27	2729
2011/2012	1838	51	1889
2012/2013	2199	12	2211
2013/2014	1629	16	1645
2014/2015	1670	32	1702
2015/2016	1348	42	1390
2016/2017	1938	21	1959
2017/2018	2006	32	2038
2018/2019	1807	-[b]	-[b]

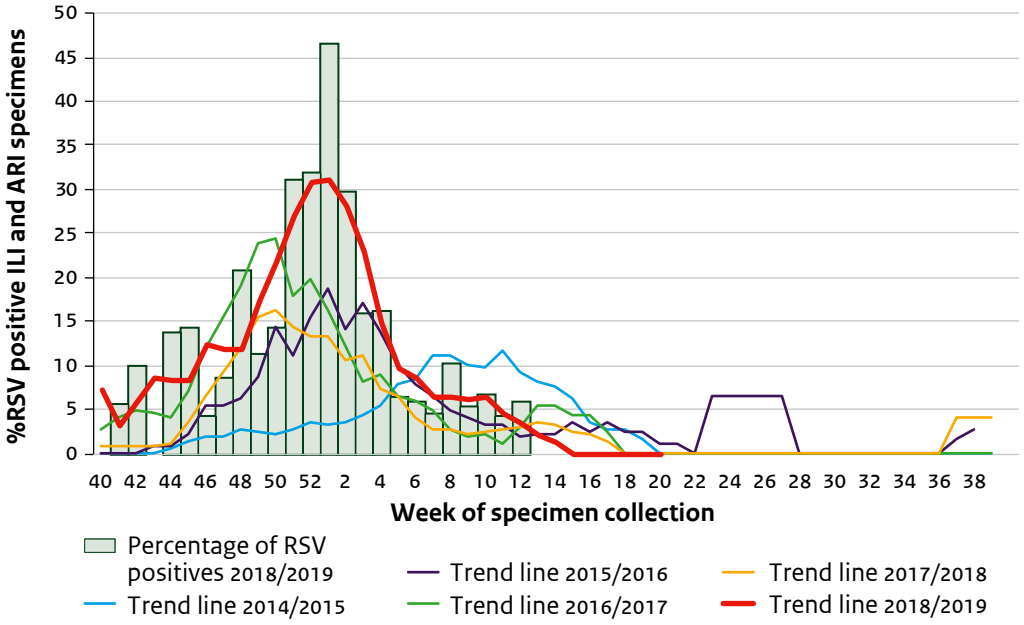
[a] Data for weeks 40 of 2018 through week 20 of 2019 are preliminary.
[b] Data for weeks 21-39 of 2019 are not yet available.

Table 4.2 RSV seasonal trends in the virological laboratory surveillance for the period 2009/2010-2018/2019 (through week 20): season onset and duration, epidemic intensity, and peak. Week is week of laboratory diagnosis report. Thresholds for the epidemic period and intensity are defined by MEM.

	Onset week (week number)	Season duration (N weeks)	Above medium intensity level (N weeks)	Above high intensity level (N weeks)	Peak	
					Timing (week number-year)	RSV diagnoses (N)
2009/2010	45	19	9	1	4-2010	297
2010/2011	46	20	6	0	3-2011	264
2011/2012	47	18	0	0	51-2011	125
2012/2013	46	20	4	0	2-2013	182
2013/2014	48	17	0	0	1-2014	134
2014/2015	49	18	0	0	8-2015	162
2015/2016	48	19	0	0	4-2016	114
2016/2017	45	16	4	0	52-2016	199
2017/2018	46	19	2	0	1-2018	192
2018/2019	47	16	2	0	1-2019	186

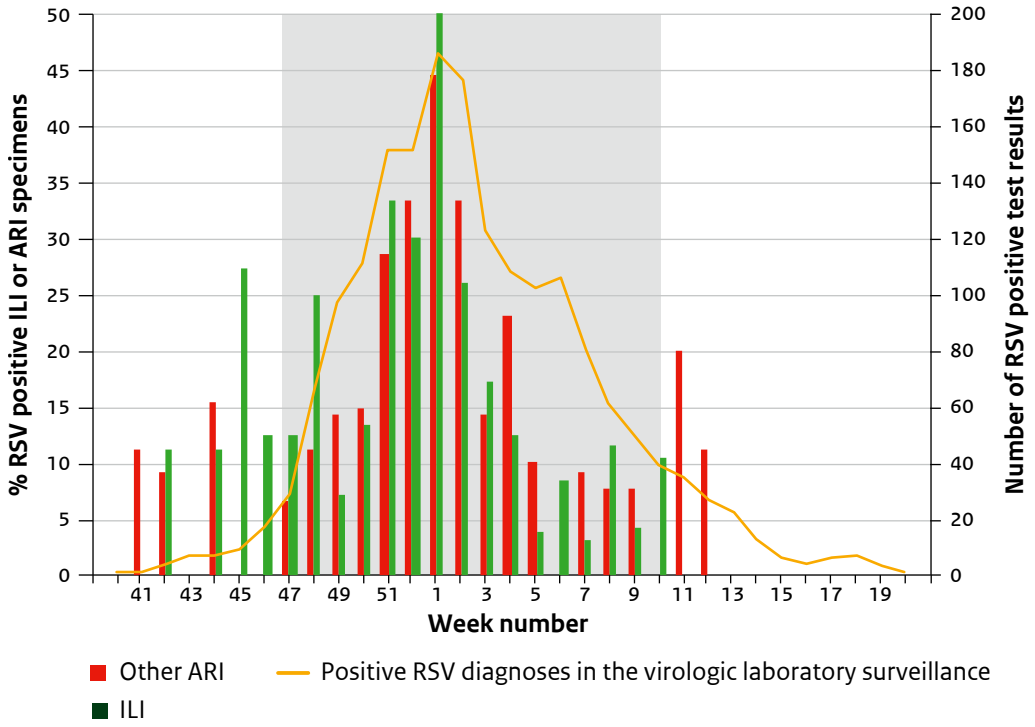
Note: The duration of the seasons are different than in previous reports, because a different method was used to define the epidemic thresholds. The same MEM thresholds were applied to all seasons for calculating the onset and duration and intensity and were as follow: pre-epidemic threshold: 26; post-epidemic threshold: 36; medium intensity: 172, high intensity: 276; very high intensity; 340.

Figure 4.3 Percentage of RSV-positive specimens from ILI and other ARI patients, taken by sentinel GPs during the seasons 2014/2015 – 2018/2019 (week 40 2018 through week 20 of 2019) (Source: Nivel Primary Care Database, RIVM).



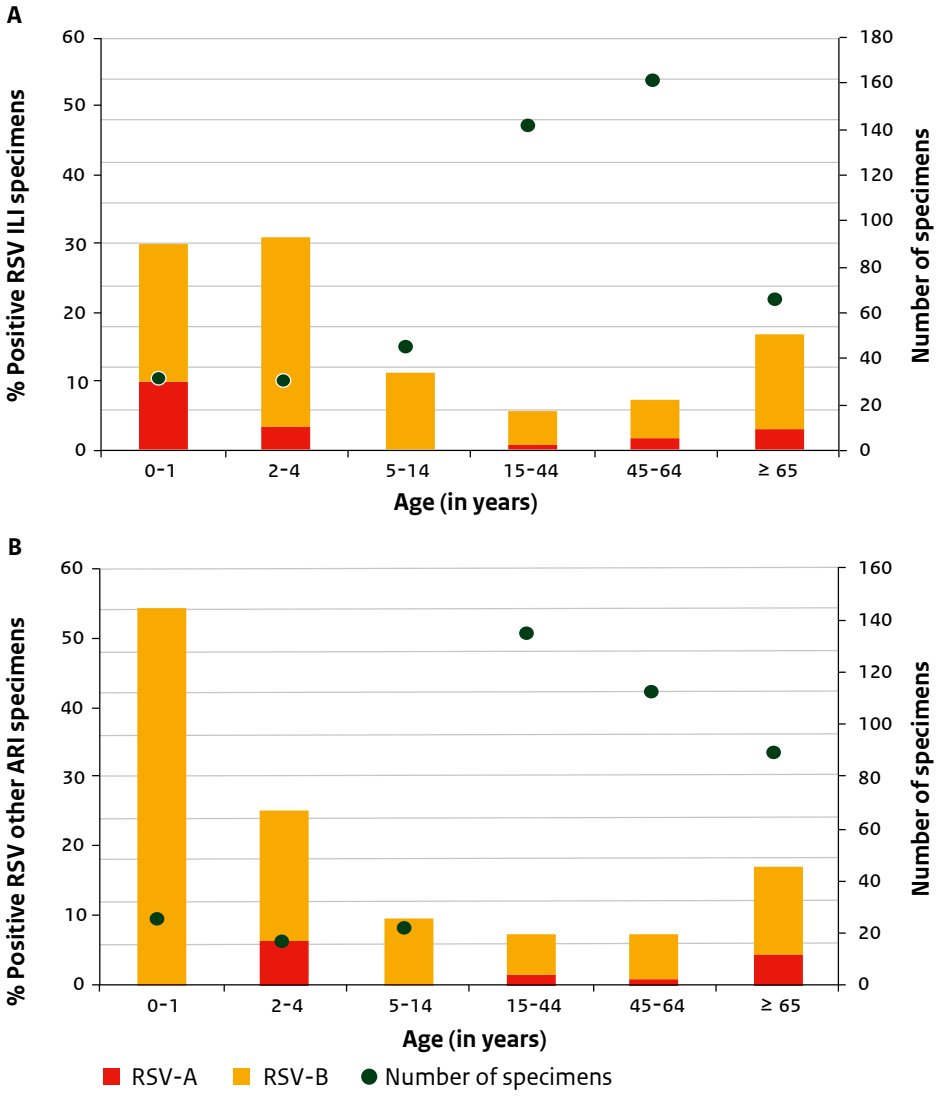
Footnote: Trend lines indicate a 5-weeks moving average. ILI= influenza-like illness; ARI = acute respiratory infection

Figure 4.4 Percentage of positive specimens from ILI and other ARI patients, taken by sentinel GPs, and number of RSV diagnoses as reported by the virological laboratory surveillance, during the 2018/2019 respiratory season (week 40 of 2018 through week 20 of 2019), displayed by week of sampling (Source: RIVM, virological laboratory surveillance, NWKV).



Footnote: The grey area represents the RSV season based on the virological laboratory surveillance, using MEM, and lasted from week 47 2018 through week 10 2019. From week 17 of 2019 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 other ARI patients do not include the ILI patients. NWKV = Dutch Working Group for Clinical Virology of the Dutch Society for Medical Microbiology (NVMM).

Figure 4.5 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 2018/2019 (week 40 of 2018 through week 20 of 2019), displayed for six age groups (Source: Nivel Primary Care Database, RIVM).



Footnote: Please note that for the virological surveillance, the other ARI patients do not include the ILI patients.

Chapter 5
Notifiable Respiratory Diseases

5.1 Legionnaires'disease

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Contributor: Sjoerd Euser

5.1.1 Key points

- In 2018, a total of 584 cases with Legionnaires' disease (LD) were notified, the incidence was 3,4 per 100.000.
- There was an unusual seasonal pattern with substantially more LD cases than expected in the first half of the year and from September to December, but a decrease in July and August.
- The unusually low number during summer may be explained by the drought during this period.
- Despite the strong decrease during the summer months the increasing trend from 2012-2017 continued in 2018, with 4% more cases in 2018 compared to 2017. Excluding July and August, 2018 had 45% more cases than 2017.
- Most cases (69%) have acquired the infection in the Netherlands, of which the majority (361 cases) is community acquired.
- The case fatality of 7.4 % in domestic cases and 0,6% in cases with travel abroad was similar to previous years. In females the case fatality (8,5%) was significantly higher than in men (3,6%).
- There were seven cases due to *Legionella longbeachae*. The source of this *Legionella* species is usually related to gardening and potting soil.
- Multiple jacuzzi's in private settings were identified as source of infection: An outdoor jacuzzi in a private holiday home was linked to a cluster of three patients and was confirmed by a genotypic match with a patient isolate. Two other outdoor Jacuzzi's at home addresses were confirmed for two single cases by a genotypic match.
- Other genotypic matches identified a gardenhose, a shower by a swimming pool, an industrial work location and wastewater treatment plants.

- After identifying a cluster linked to an industrial wastewater treatment plant in 2017, a biological wastewater treatment plant in the region of Eindhoven was identified as source of infection in 2018, explaining the increased incidence in this region. In autumn 2018 an identical *Legionella* ST-type (ST1646) was also found in two other wastewater treatment and in a cluster of patients. Additional studies on the risks of legionnaires' disease linked to biological wastewater treatment plants are ongoing.
- Multiple geographic clusters were identified for which no source was confirmed.

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 have a severe pneumonia (Legionnaires' disease (LD)). The incubation period is usually 2-10 days and rarely exceeds 14 days. LD 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. Since 2017 wastewater treatment plants in the Netherlands have been identified as source of infection for LD, and the possible contribution of these installations to the LD incidence is currently under investigation. For the majority of non-outbreak cases (sporadic cases) however the source of infection remains unknown. The common seasonal pattern of LD shows an increase during summer, especially after warm weather with heavy rainfall. These wet weather conditions are favorable for the survival of aerosolized *Legionella* bacteria , so this may lead to increased transmission. However, it remains unclear which environmental sources are driving the weather related increase of Legionnaires' disease.

Most LD patients 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 available for only one out of five Dutch patients, which is a limitation for source finding.

5.1.3 Tables and figures

Figure 5.1 Annual numbers of notified Legionnaires' disease, 2007 through 2018, by infection acquired abroad or domestic (acquired within the Netherlands) (Source: Osiris).

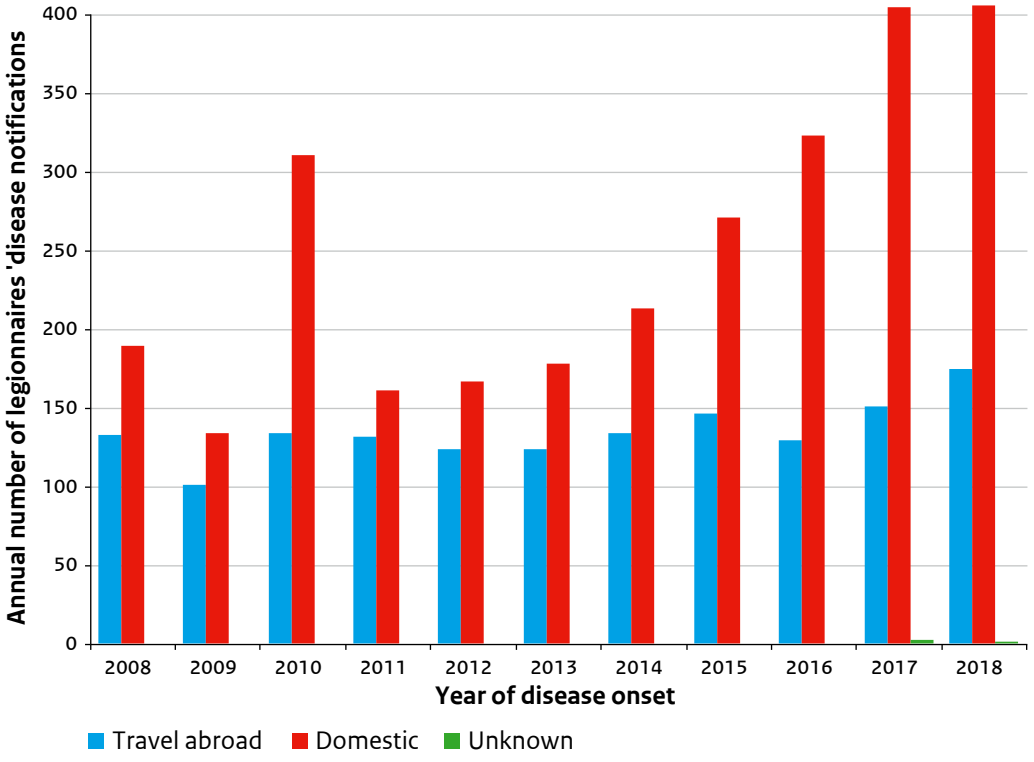


Figure 5.2 Notifications of Legionnaires' disease acquired abroad or acquired in The Netherlands (domestic), by month of disease onset in 2018 and the monthly average over 2013-2017 (Source: Osiris).

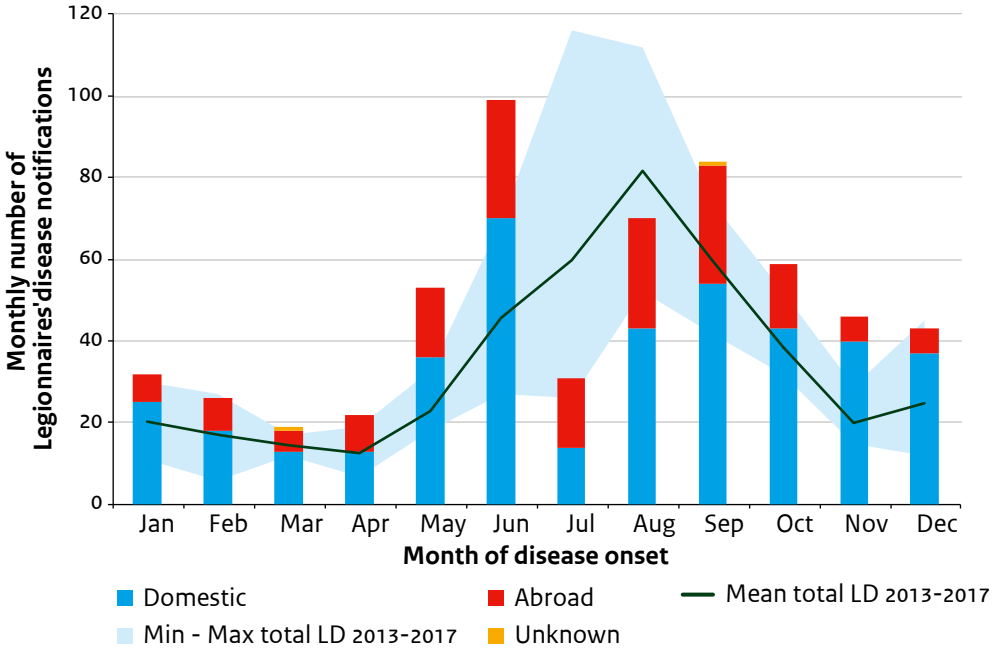


Table 5.1 Number of legionellosis notifications in 2014 – 2018, incidence, clinical and epidemiological background, mortality and diagnostics (Source: Osiris).

Year of onset disease[a]	2014	2015	2016	2017	2018
Number of Legionellosis notifications[b]	370	438	468	575	594
Excluded from analysis[b]: Of which based on single high titre[c]	22 12	19 13	14 6	14 5	10 -
Total included:	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**
Legionnaires'disease (LD) (=100%)[b]	**348 (100)**	**419 (100)**	**454 (100)**	**561 (100)**	**584 (100)**
% difference to year before	+15%	+20%	+8%	+24%	+4%
Confirmed Legionnaires' disease[d]	327 (94)	393 (94)	422 (93)	519 (93)	536 (92)
Probable Legionnaires'disease[d]	21 (6)	26(6)	32 (7)	42 (7)	48 (8)
LD Incidence (per 100,000 residents)	2.1	2.5	2.7	3.3	3.4
Male gender	255 (73)	293 (70)	327 (72)	401 (71)	420 (72)
Median age (Q1-Q3)	61 (53-71)	62 (53-69)	63 (55-72)	64 (54-73)	64 (57-74)
Hospital admission[e]	342 (98)	410 (98)	449 (99)	543 (97)	571 (98)
X-thorax confirmed pneumonia[e]	328 (94)	401 (96)	436 (96)	540 (99)	546 (98)
Deaths[e]	13 (4)	13 (3)	20 (4)	31 (6)	29 (5)
Setting of infection:					
Travel abroad[f]	134 (39)	145 (35)	130 (29)	152 (27)	177(30)
% Difference to year before	+8%	+8%	-10%	+17%	+17%
Domestic (acquired in The Netherlands)	214 (61)	273 g (65)	324	406 (72)	405(69)
% Difference to year before	+20%	+28%	+19%	+25%	-0.5%
Setting/ country Unknown	-	1	-	3 (<1)	6/2(1)
Domestic categories:					
Domestic travel[f]	20 (6)	24 (6)	17 (4)	45 (8)	35(6)
Nosocomial (hospital acquired)	4 (1)	2 (<1)	-	1 (<1)	-
Other healthcare facilities	6 (2)	3 (<1)	7(2)	5 (<1)	5(<1)
Community acquired	184 (53)	244 (58)	300 (66)	355 (63)	361(62)

Year of onset disease[a] Diagnostics	2014	2015	2016	2017	2018
Legionella cultured performed (=yes)	156 (45)	181 (43)	209 (46)	229 (41)	263 (45)
Positive culture	67 (19)	79 (19)	84 (19)	92 (16)	111 (19)
Proportion *L.pneumophila* sg1 in culture (or PCR) positives[g]	90%	87%	85%	82%	85%
Positive urine antigen test	314 (90)	381 (91)	404 (89)	501 (89)	515 (88)
Positive PCR	54 (16)	65 (16)	88 (19)	103 (18)	102(17)
of which PCR only[h]	15 (4)	21 (5)	26 (6)	39 (7)	46 (8)
Significant titer rise	5 (1)	6 (1)	6 (1)	6 (1)	2(<1)
Direct immunofluorescence	-	1(<1)	-	-	-
Diagnostic delay in days: median(Q1-Q3)	6 (4-8)	6 (4-7)	6 (4-8)	5 (4-7)	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 February 18, 2018, 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 .
[c] Diagnostic confirmation only based on a single high titre with polyvalent serology (usually L. pneumophila serogroup 1-6 or sg1-7, i.e. not specific for L. pneumophila serogroup1) or single high titre without information on type of serology. This diagnostic method is excluded from the European case definition 2012.
[d] 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).
[e] Percentage based on the number of patients for which this specific information was available.
[f] 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 in the 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 travelsite as source.
[g] Proportion of clinical specimens (culture or PCR) available for typing at the reference lab.
[h] No other diagnostic method reported in Osiris.

Figure 5.3 Age and gender distribution of cases with Legionnaires' disease with onset of disease in 2018 and age and gender specific incidence (LD notifications per 100,000 inhabitants) (Source: Osiris and CBS statline).

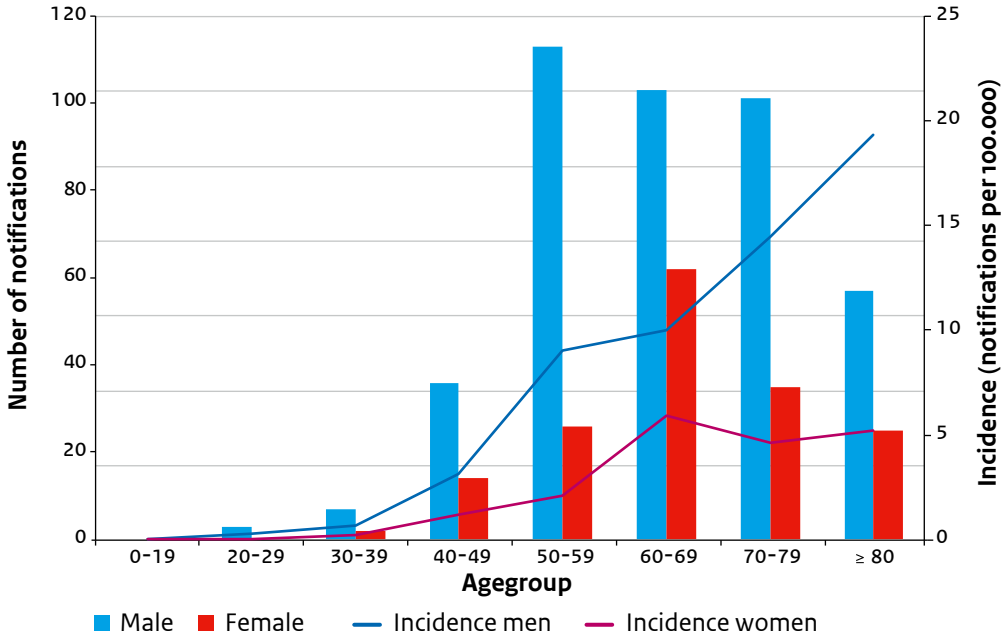


Figure 5.4 Distribution of the risk factors smoking and relevant underlying illness per age group reported in cases with Legionnaires' disease with onset disease in 2018 (Source: Osiris).

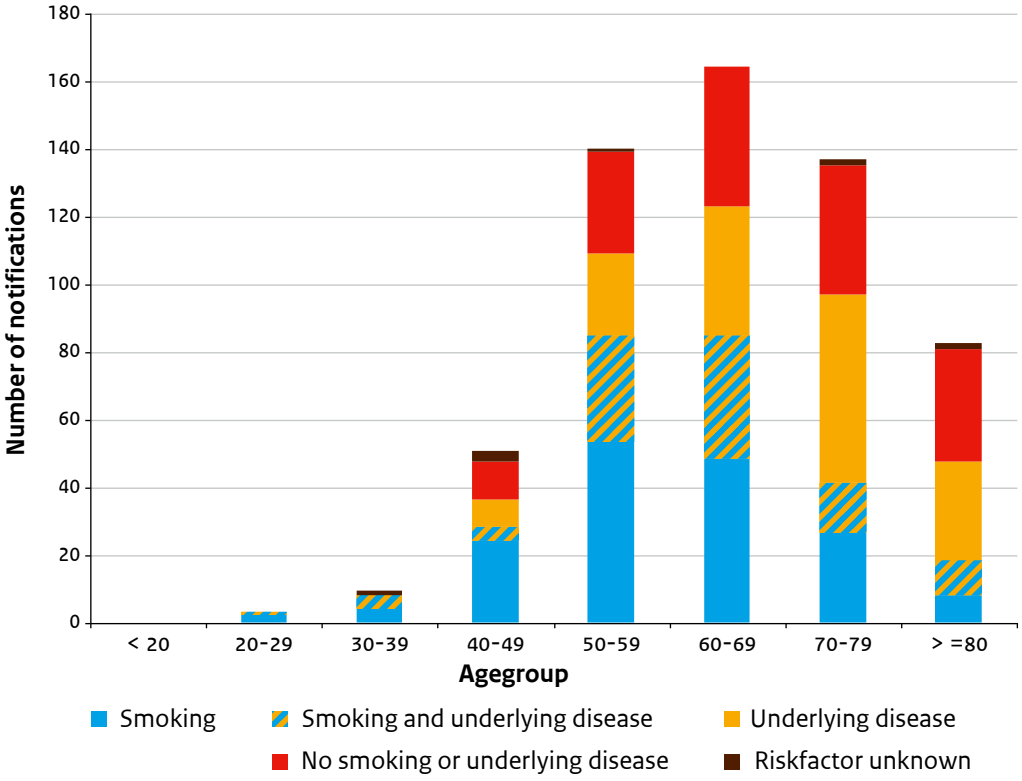
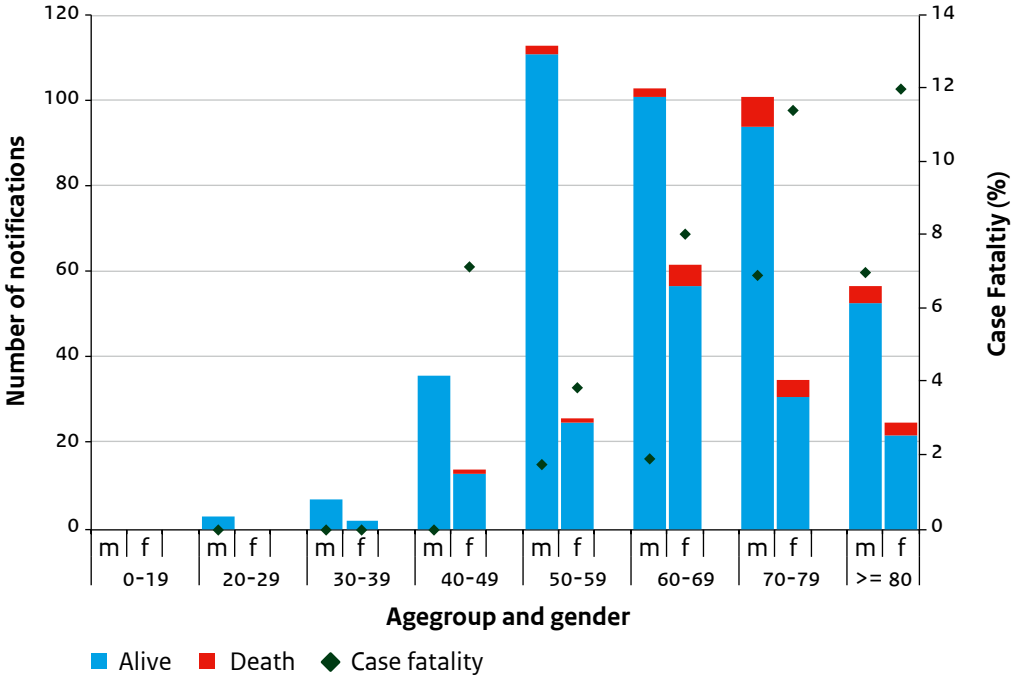


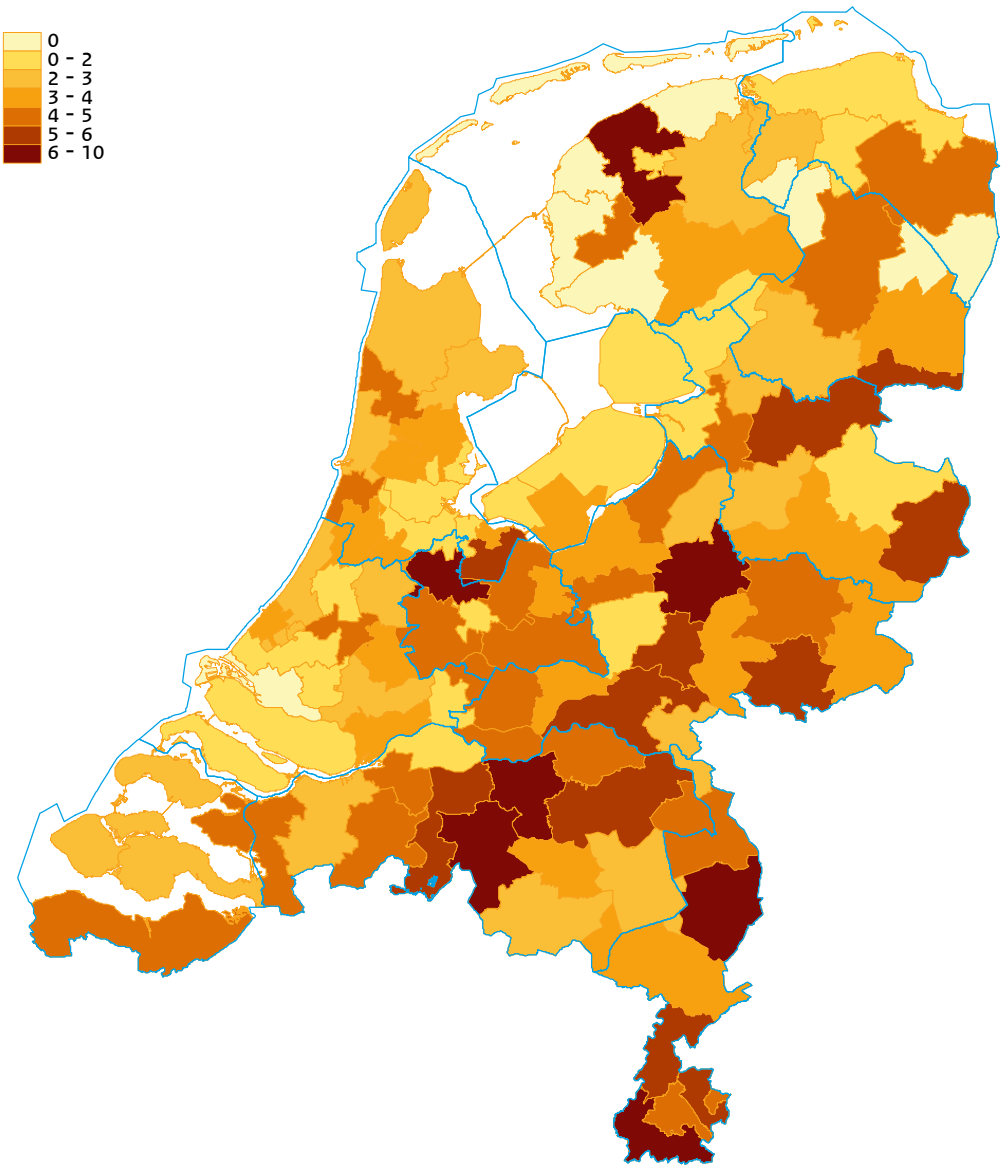
Figure 5.5 Disease outcome and case fatality reported in cases with Legionnaires' disease with onset in 2018 by age group and gender.



Tabel 5.2 Number of deaths and case fatality (CF) reported in cases of Legionnaires' disease with onset of disease in 2016-2018 by setting of infection.

Setting of infection	2016			2017			2018		
	Deaths n	Total n	CF %	Deaths n	Total n	CF %	Deaths n	Total n	CF %
Travel abroad	0	130	-	2	152	1.3	1	177	0.5
Domestic	20	324	6.2	28	406	6.9	28	405	6.9
Country unknown	-	-	-	1	3	33	0	3	0
Domestic categories									
Domestic travel	0	17	-	3	45	6.7	2	35	5.7
Community acquired	19	300	6.3	24	355	6.8	24	361	6.6
Nosocomial	-	-	-	0	1	-	-	-	-
Healthcare associated	1	6		1	5	20	0	5	0
Setting unknown	-	-	-	1	3	33	2	6	33
Total	20	454	4.4	31	561	5.5	29	584	5.0

Figuur 5.6 Regional incidence of domestic Legionnaires' disease per 100,000 inhabitants in 2018 by two-digit postcode area.



Tabel 5.3 Legionella species, serogroup and Sequence Based typing (ST-type) of patients with Legionnaires'disease with onset in 2018, compared to 2014-2016 and 2017 (Source: BEL, Osiris).

Type *Legionella*[a]	2014- 2016 n = 218	2017 n = 88	2018 N=98
L. pneumophila serogroup 1	194 (89%)	72 (82%)	83 (85%)
L. pneumophila serogroup 2	2 (<1%)	1 (1%)	2 (2%)
L. pneumophila serogroup 3	2 (<1%)	3 (3%)	2 (2%)
L. pneumophila serogroup 4	2 (<1%)	-	-
L. pneumophila serogroup 5	-	-	1 (1%)
L. pneumophila serogroup 6	3 (1%)	2 (2%)	3 (3%)
L. pneumophila serogroup 2-14 (sg not typed)	5 (2%)	2 (2%)	-
L. pneumophila (total)	208 (95%)	80 (91%)	91 (93%)
L. longbeachae	8 (4%)	4 (5%)	7 (7%)
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%)	7 (7%)
Most frequent ST-types	n=199	n=76	N=85
ST 47	56 (28%)	21 (28%)	29 (34%)
ST62	15 (8%)	4 (5%)	4 (5%)
ST82	9 (5%)	5 (7%)	1 (1%)
ST42	8 (4%)	1 (1%)	3 (4%)
ST1	8 (4%)	3 (4%)	2 (4%)
ST1646	7 (4%)	4 (5%)	4 (5%)
ST23	7 (4%)	1 (1%)	4 (5%)
ST46	7 (4%)	5 (7%)	2 (2%)
ST37	5 (3%)	3 (4%)	1 (1%)
ST2439	-	2 (3%)	3 (4%)
Total number different ST- types	53	34	37

[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).

Tabel 5.4 Travel associated cases who visited an accommodation site during the 2-10 days before onset disease are reported by the RIVM to the European Legionnaires' disease Surveillance Network (ELDSNet) at ECDC, in order to detect clusters and take control measures at accommodations sites (Source Osiris, Tessy (ECDC)).

2018	LD cases	Travel accommodations[b]
Travel associated (domestic and abroad)[a]	212	364
Reported by the Netherland to ELDSNet		
Travel accommodation in the Netherlands	27	32
Travel accommodation abroad	146	332
Not reported to ELDSnet		
Private location domestic or abroad	29	
Travel details unknown	13	
Dutch site reported by other country	5	6
Dutch LD cases linked to an accommodation cluster[c]	49	31 +11 complex[d]
Accommodation clusters in the Netherlands	7	3+1 complex
Travel countries visited most frequently by Dutch LD patients		
Total number (of which no other countries were visited)	LD cases	Clusters[c]
Italy	30 (22)	8
France	31 (20)	4
Germany	31 (18)	2
Spain	17 (11)	2
Belgium	12 (9)	1
Austria	12 (5)	0
Greece	10 (10)	4
Turkye	10 (10)	0

[a] Overnight stay 2-10 days before onset of disease reported in Osiris,
[b] A patient may have visited multiple accommodation sites in multiple countries,
[c] Cluster is defined as two or more cases who stayed at the same commercial accommodation site in the 2-10 days before onset of disease within the same two-year period.
[d] A complex cluster is a cluster associated with more than one accommodation site.

5.2 Psittacosis

Author: Frederika Dijkstra
Contributors: Ingrid Keur en Edou Heddema

5.2.1 Key points

- In 2018, 64 patients with psittacosis were notified. This number is in line with the annual number of notifications in the years 2009-2017 in which the annual numbers ranged from 41 to 81.
- Median age of the patients (65 years) was higher than in the years 2014-2017 (55 – 58 years).
- As in previous season, no clear seasonal pattern was observed.
- In 2018, three clusters of patients were identified: a clusters of seven patients who were related to a large bird fair in Zwolle, a clusters of five patients who were related to an animal shop in the southwest of the country and a cluster of three patients in whom the same rarely reported genotype was found (genotype with characteristics of genotype B and E, not being genotype E/B).
- The percentage of notified cases in which the diagnosis was confirmed with PCR has further increased from 70% in 2015 to 97% in 2018.
- 55 samples from notified patients were sent for genotyping. Strikingly, for almost one third of the samples, no assessment of genotype was possible. In most of these cases, the laboratory of the ZuyderlandMC could not demonstrate *C. psittaci* in these samples. Although this was also the case in a few samples in previous years, a much higher proportion was reported than in previous years. We do not exactly know why this happened in such a high proportion this year, although it was noted that in at least half of these cases a very low load (High Ct value) in the diagnostic PCR assay of the submitting lab was found.
- In the samples that could be genotyped, mainly genotype A (50%) and genotype B (34%) were found.
- Five samples from not-notified cases were sent for genotyping. In three cases genotype B was found, in one case genotype A and in one case no assessment was possible.
- In consultation between the public health service and the Netherlands Food and Consumer Product Safety Authority (NVWA), it is decided whether sampling of a possible location is useful for tracing the source of a human case. Data from the Source Tracing Tool showed that for 35 patients at least one possible source location was sampled by the NVWA.
  For 22 patients at least one possible source location was tested positive for *C. psittaci* DNA.
  For 1 patients two possible source locations tested positive (genotypes A found on one location and 'negative for any *C. psittaci* genotype' found on the other location). For the other 21 patients one possible source location tested positive (11 times genotypes A, 8 times genotype B and two times no assessment of genotype was possible).
- In addition, the NVWA was able to back trace in 6 of these cases to the previous location of the animals. Several animals were sampled at these locations. In three of these cases, the animals tested positive (all genotype A). In the 3 other cases negative.

- In addition to the human notifications that the NVWA received for human source tracing, NVWA also receives notifications of clinical ill birds or positive laboratory test results of birds. In 2018, 19 of such veterinary notifications were received. 13 times a location was visited and birds were sampled (cloaca and/or faecal swabs). In three cases concerning ill birds, *C. psittaci* DNA was not detected by the NVWA. In seven cases *C. psittaci* DNA was detected. Genotype A was found in six of these cases, and for one sample the genotype could not be determined. Two times a location was visited by the NVWA after the birds were given an antibiotic treatment, in both cases *C. psittaci* DNA was not detected. In one case the suspected bird had already died at the time of notification. This location was visited to sample contact birds, but no *C. psittaci* DNA could be detected.

5.2.2 Tables and figures

Figure 5.7 Number of notifications of human psittacosis by year and mode of confirmation of laboratory diagnosis, 2009 through 2018 (Source: Osiris).

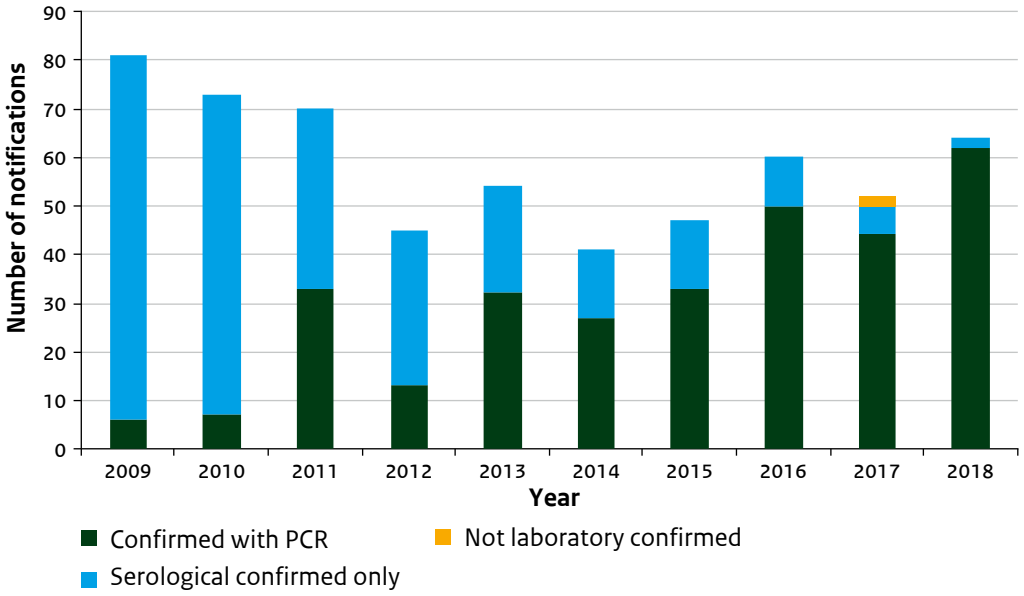


Table 5.5 Demographic, clinical and diagnostic characteristics of notified patients with psittacosis and positive diagnoses in the virological laboratory surveillance, in 2014-2018 (Source: Osiris and virological laboratory surveillance, NWKV).

N (%), unless otherwise specified	2014	2015	2016	2017	2018
Osiris notifications					
Number of notifications[a]	41 (100)	47 (100)	60 (100)	52 (100)	64 (100)
Incidence per 100,000 inhabitants	0.24	0.28	0.35	0.30	0.37
Median age in years (Q1-Q3)	58 (47 -71)	57 (41 – 68)	58 (45 – 71)	55 (39 – 69)	65 (56 – 72)
Male gender[b]	32 (78)	32 (68)	48 (80)	27 (52)	50 (78)
Hospitalised[b]	38 (93)	37 (79)	49 (82)	44 (85)	58 (91)
Deaths[b]	1 (2)	1 (2)	1 (2)	0	0
Infected abroad[b]	1 (2)	0	4 (7)	0	1 (2)
Median notification delay in days (Q1-Q3)[c]	0 (0 – 1)	0 (0 – 1)	0 (0 – 2	0 (0 – 1)	1 (0 – 2)
Diagnostics used for notifications					
Median diagnostic delay in days(Q1-Q3)[d]	12 (7 – 21)	10 (8 – 14)	9 (6 – 14)	11 (7 – 27)	11 (17 – 19)
Mode of confirmation of laboratory diagnosis					
PCR[e]	27 (66)	33 (70)	50 (83)	44 (85)	62 (97)
Serological only	14 (34)	14 (30)	10 (17)	6 (12)	2 (3)
None	0	0	0	2 (4)	0
Number of patients eligible for genotyping[f]	28	36	50	44	62
Notified patients for whom diagnostic material for genotyping was received by Zuyderland MC	24 (86)	30 (83)	37 (74)	36 (82)	55 (89)
Typing outcomes					
C. psittaci genotype A	9 (38)	11 (37)	12 (32)	11 (31)	19 (35)
C. psittaci genotype B	11 (46)	9 (30)	13 (35)	13 (36)	13 (24)
C. psittaci genotype C	1 (4)	2 (7)	1 (3)	0	1 (2)
C. psittaci genotype E/B	1 (4)	2 (7)	0	0	0

N (%), unless otherwise specified	2014	2015	2016	2017	2018
New *C. psittaci* genotype most similar to C (93% homology)	1 (4)	0	0	2 (6)	0
Previously unknown genotype of *C. psittaci*, with characteristics of B and E	0	1 (3)	2 (5)	0	3 (5)
Negative for any *C. psittaci* genotype	1 (4)	2 (7)	7 (19)	0	3 (5)
Of which further diagnostics revealed					
C. caviae	1 (4)	1 (3)	0	2 (6)	2 (4)
C. felis	0	0	0	1 (3)	0
No assessement possible	0	3 (10)	2 (5)	7 (19)	16 (29)
Virological laboratory surveillance[g]					
Number of positive diagnoses	16	18	30	15	26

[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.

[g] Participating laboratories: 21 laboratories in 2014 and 2015, 20 laboratories in 2016, and 19 laboratories in 2017 and 2018.

Footnote: NWKV = Dutch Working Group for Clinical Virology of the Dutch Society for Medical Microbiology (NVMM).

5.3 Q-fever

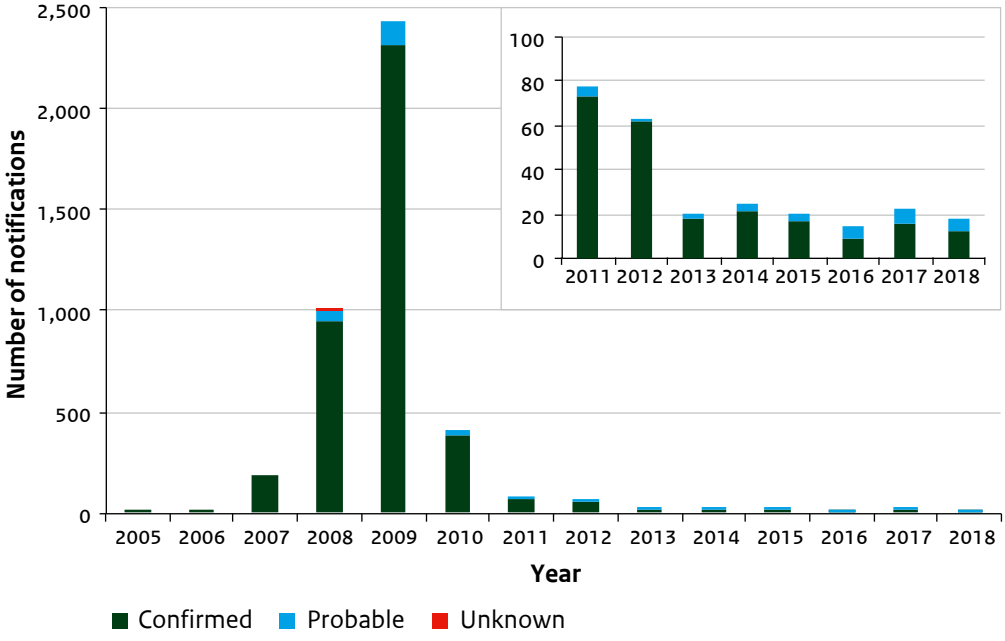
Author: Frederika Dijkstra
Contributor: Ingrid Keur

5.3.1 Key points

- In 2018, 18 patients with acute Q fever were notified. This number is in line with the number of notifications in the years 2013-2017, in which the annual numbers varied from 14 to 26.
- None of the patients were epidemiological linked to each other.
- The difference in the number of notifications and the number of diagnoses reported in the virological laboratory surveillance has decreased further. In 2018, 44 Q fever diagnoses were reported in the virological laboratory surveillance versus 18 notifications (proportion 2:1), while in the years 2013 – 2015 the proportion diagnoses reported in the virological laboratory surveillance to the number of notification varied between 5:1 and 6:1.
- Possible animal sources of infection can be sampled in the following situations:
  - *Bulk milk monitoring:*
    In 2018, the NVWA received one notification of a positive sample in the bulk milk monitoring from the GD Animal Health (GD). NVWA took official samples on this farm, but *C. burnetii* could not be demonstrated.
  - *Investigation of veterinary abortion waves:*
    In 2018, the NVWA received one notification of abortion among two goats at a petting zoo. One goat had died, the other goat aborted recently. The fetus and the placenta were sent to the GD for further diagnosis. The NVWA visited the location and took a sample of the animal. In none of the samples *C. burnetii* could be demonstrated. All the sheep and goats at this location were vaccinated against Q fever.
  - *Source finding following human cases:*
    In 2018, public health services reported four human cases to the NVWA for source finding. For these four human cases no likely/possible source could be identified.

5.3.2 Tables and figures

Figure 5.8 Number of notifications of acute Q fever by case classificationa and year, 2005-2018 (Source: Osiris). The insert zooms in on the years 2011 through 2018.



[a] The distinction between confirmed and probable notifications has been made since 1 July 2008.

Table 5.6 Demographic, clinical and diagnostic characteristics of notified acute Q fever patients and positive diagnoses in the laboratory surveillance, 2014-2018 (Source: Osiris and virological laboratory surveillance, NWKV).

N (%), unless otherwise specified	2014	2015	2016	2017	2018
Notifications (Osiris)					
Number of notifications[a]	26 (100)	20 (100)	14 (100)	22 (100)	18 (100)
Confirmed[b]	22 (85)	17 (85)	9 (64)	16 (73)	12 (67)
Probable[c]	4 (15)	3 (15)	5 (36)	6 (27)	6 (33)
Incidence per 100,000 inhabitants	0.15	0.12	0.08	0.13	0.10
Median age in years (Q1-Q3)	57 (39 – 70)	58 (39 – 70)	49 (30 – 66)	53 (28 – 64)	50 (40 – 71)
Male gender[d]	21 (81)	9 (45)	11 (79)	16 (73)	15 (83)
Hospitalised[d]	17 (65)	12 (60)	7 (50)	13 (59)	15 (83)
Deaths notified in Osiris[d]	0	1 (5)	0	0	0
Infected abroad[d]	5 (19)	2 (10)	3 (21)	8 (36)	3 (17)
Median notification delay in days (Q1-Q3)[e]	0.5 (0 - 6)	1 (0 – 3)	1 (0 – 3)	0 (0 – 5)	0 (0 – 2)
Median diagnostic delay in days (Q1-Q3)[f]	25 (14 – 48)	27 (12 – 44)	14 (11 – 31)	29 (15 – 43)	16 (7 – 32)
Virological laboratory surveillance[g]					
Number of positive diagnoses	130	125	89	65	44

[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.
[g] Participating laboratories: 21 laboratories in 2014 and 2015, 20 laboratories in 2016, and 19 laboratories in 2017 and 2018.

Footnote: NWKV = Dutch Working Group for Clinical Virology of the Dutch Society for Medical Microbiology (NVMM).

5.4 Tuberculosis

Authors: Erika Slump
Contributors: Henrieke Schimmel, Rianne van Hunen, Gerard de Vries

5.4.1 Key points 2018

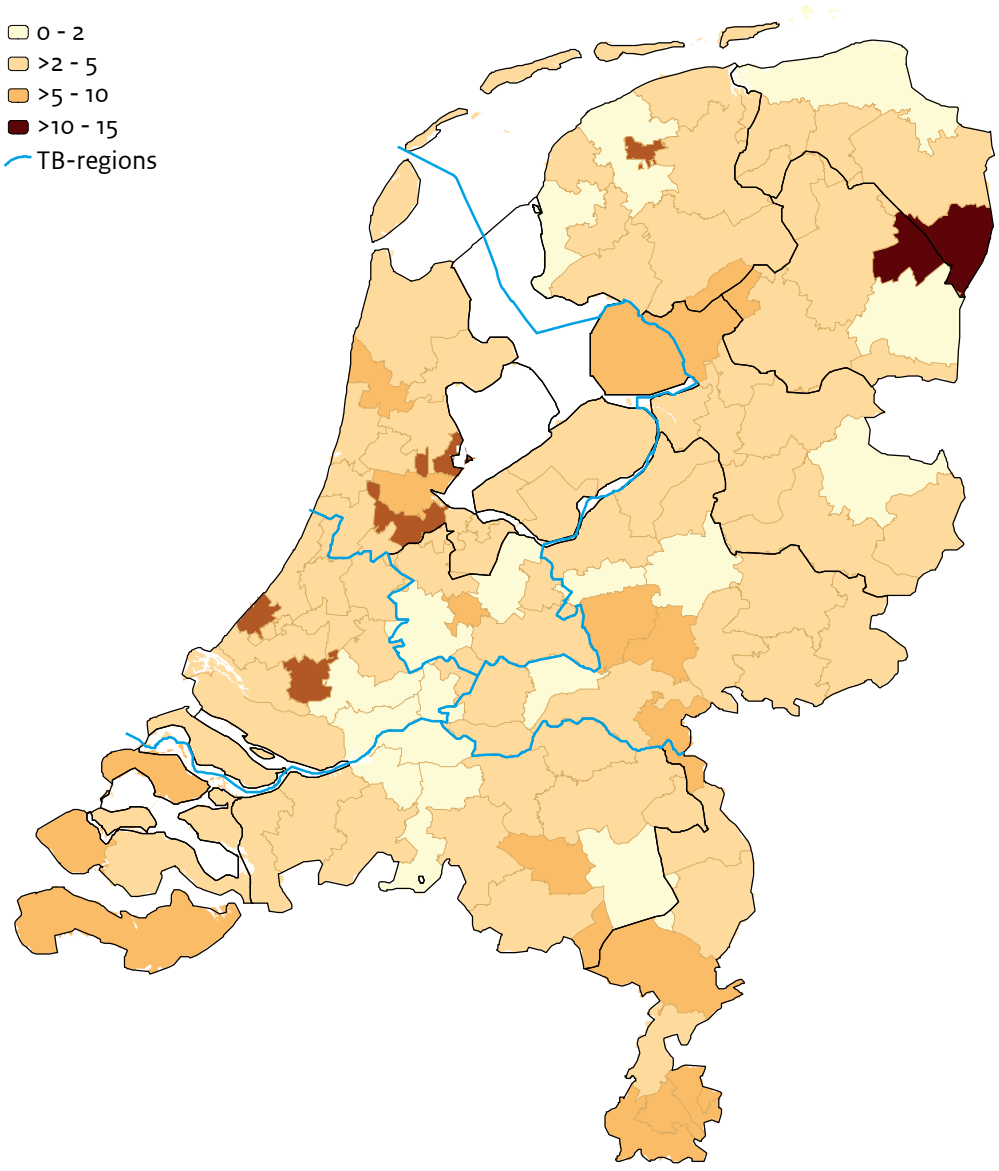
- In 2018, 806 tuberculosis (TB) patients were notified, a small increase of 3% compared to 2017 (783 notifications). TB in the Netherlands has been steadily declining since 1998, with an increase in some years (2009, 2015 and 2016) related to migration.
- The incidence rate of TB in 2018 was 4.7 per 100,000 population.
- Most patients were foreign born (77%), mainly from Eritrea (n=133), followed by Morocco (n=66), India (n=46), Somalia (n=43), Indonesia (n=30) and 68 other countries (n=300).
- In the first months of 2018 an increase of TB was observed among young asylum seekers (< 18 years) from Eritrea. Fifty-one young adults with TB were notified; 38 (75%) were detected by active case finding (screening at entry, follow-up screening or contact investigation)(Wolters, Aartsma et al. 2018). In response, advise was given to Municipal Health Services to screen these asylum seekers for latent TB infection.
- 469 patients (58%) had pulmonary TB, 204 with microscopy-positive sputum, the most contagious form of TB. The remaining 337 patients (42%) had extrapulmonary TB.
- 21% of all TB patients were detected by active case-finding (19% in 2016 and 2017).
- Six patients had rifampicin-resistant TB, five with multidrug-resistant (MDR) TB and one with extensively drug resistant (XDR) TB. All these patients were foreign born.
- 534 TB patients (66%) were tested for HIV in 2018[1], of whom 21 were HIV positive (2.6% of all TB patients and 3.9% of TB patients tested for HIV).
- In 2017, 88% of TB patients with rifampicin-susceptible TB completed treatment successfully (90% over the years 2012-2016[2]).
- 24 of 34 patients (71%) with rifampicin-resistant TB diagnosed in 2014-2016 completed treatment successfully.

[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 patients of 2018 and rifampicin-resistant TB patients of 2017 have not been reported yet.

5.4.2 Tables and figures

Figure 5.9 Tuberculosis incidence (per 100,000 population) in 2018 by two digit postcode area.



The incidence of tuberculosis was highest in Groningen in the area with a large reception centre for asylum seekers (Ter Apel).

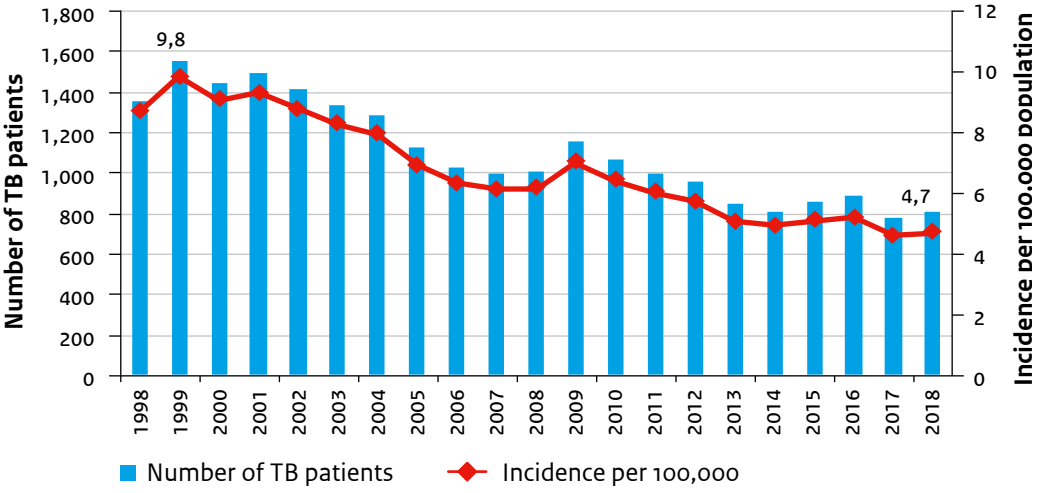
Table 5.7 Summary tuberculosis data the Netherlands, 2016, 2017 and 2018.

	2016	2017	2018
	N(%)	N(%)	N(%)
Number of notifications	886	783	806
Incidence per 100,000 population	5.2	4.6	4.7
Mean age (years)	39	39	39
Age <15 years	49 (5.5)	34 (4.4)	20 (2.5)
Age ≥65 years	132 (15)	102 (13)	115 (14)
Male to female ratio	1.4	1.6	1.7
Foreign born	669 (76)	586 (75)	619 (77)
Residence in 1 of 4 largest cities[a]	255 (29)	212 (27)	219 (27)
Previous episode of TB (treatment)	32 (3.6)	28 (3.6)	38 (4.7)
HIV status known[3]	645 (73)	599 (77)	534 (66)
HIV positive	20 (2.3)	23 (2.9)	21 (2.6)
TNF-alpha inhibitors	11 (1.2)	11 (1.4)	11 (1.4)
Active case finding	166 (19)	148 (19)	166 (21)
Pulmonary tuberculosis (PTB & EPTB)	484 (55)	461 (59)	469 (58)
Sputum-positive PTB	175 (20)	205 (26)	204 (25)
Culture-confirmed TB	583 (66)	544 (69)	554 (69)
Rifampicin resistant TB (incl. MDR TB/XDR TB)[b]	15 (2.6)	11 (2.0)	6 (1.1)
Isoniazid resistance[b]	38 (6.5)	34 (6.3)	33 (6.0)
TB patients in risk groups:			
-TB contacts	111 (13)	102 (13)	73 (9)
-Immigrants <2.5 years in the Netherlands	88 (10)	54 (7)	74 (9)
-Asylum seekers <2.5 years in the Netherlands	165 (19)	134 (17)	127 (16)
Latent tuberculosis Infection	1,796	1,898	1,397

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] 2018: preliminary data

Figure 5.10 Number of tuberculosis (TB) patients and incidence per 100.000 population, 1998-2018.



More detailed information about surveillance of TB in the Netherlands and the latest surveillance report 'Tuberculose in Nederland, 2017' is available through the tuberculosis webpage of the RIVM ([http://www.rivm.nl/Onderwerpen/T/Tuberculose], only available in Dutch). The 'TB Keypoints in the Netherlands 2018' infographic is available through the (English) webpage (https://www.rivm.nl/en/tuberculosis). The next surveillance report 'Tuberculose in Nederland, 2018' will be published in December 2019.

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 point

In the Netherlands, no humans were tested for animal influenza viruses because of exposure to an infected farm or because of possible infected bird exposure during foreign travel. Therefore, no infections with animal influenza virus were notified in 2018.

5.5.2 Background

Many different animals, including ducks, chickens and pigs, can host influenza A viruses. These viruses have the potential capacity to cause infection in humans, sometimes with high morbidity and mortality. 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) are most reported from a distinct number of countries, the vast majority from China. 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 highly pathogenic avian influenza virus type A(H5N6) in the Netherlands. Additionally, at the end of 2018, avian influenza virus type A(H5) was detected in waterfowl in a bird shop in the Netherlands. This was most likely a low pathogenic variant of the virus. No further infections were notified in animals in the Netherlands. In 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: Daphne Reukers, Adam Meijer

5.6.1 Key point

In the Netherlands from January 2018 through May 2019, ten patients have been tested for MERS-CoV. None of them was infected with MERS-Cov.

5.6.2 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 animals to humans is not fully understood.

5.6.3 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 Municipal Health Service [https://www.rivm.nl/en/mers-coronavirus]. This enables the Municipal 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 2018, a total of eight patients with (severe) acute respiratory illness, returning from countries where exposure to MERS-CoV is possible, were tested for MERS-CoV as well as two patients in 2019 (until May 2019). None of them had an infection with MERS-CoV.

Chapter 6
Other respiratory infections reported in the weekly virological surveillance

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

6.1 Key points

- In the first weeks of 2018, influenzavirus B, influenzavirus A and RSV were most often detected. In spring and summer, rhinovirus and adenovirus were the primary detections and towards the end of the year 2018 RSV was most detected.
- The total number of tests positive for rhinovirus (N=2,755 in 2018) steadily increased since 2014, when 2,196 positive test results were reported. Although the peak of reports was higher in 2017 than in 2018 (120 reports in week 39 2017 vs 86 reports in week 51 2018), the total number of reports was higher in 2018 than in 2017 (2,755 vs 2,706).
- The total number of positive hMPV (N=846) test results in 2018 was the highest reported since five years (range 2014-2017: 384-652), especially because of high numbers of positive test results between week 1 and 15 of 2018.
- The total number of positive adenovirus (N=1,623) test results in 2018 was the highest reported since five years (range 2014-2017: 1273-1612).
- The number of parainfluenza virus type 1 detections had been relatively high in the end of 2017 and remained high in the first weeks of 2018. In the remaining weeks of the year, the number of detections was very low. Parainfluenza virus type 2 was found more frequently in 2018 than the years before (N=150, range 2014-2017 66-108), mainly because of higher reported numbers in week 38 until week 52 2018. 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 type was within the range of the four previous years (N=476, range 2014-2017:

218-585). Also, the detections of parainfluenza virus type 4 were within the range of previous years, although in week 48, 49 and 50 of 2018, the weekly number of detections was higher than usual.
- The total number of positive *Mycoplasma pneumoniae* (N=328) test results in 2018 was the lowest reported since five years (range 2014-2017: 400-608).
- The numbers of positive diagnoses for bocavirus, coronavirus and *Chlamydia pneumoniae* 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 and 2018, generally higher numbers of positive test results were found than the years before. 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.

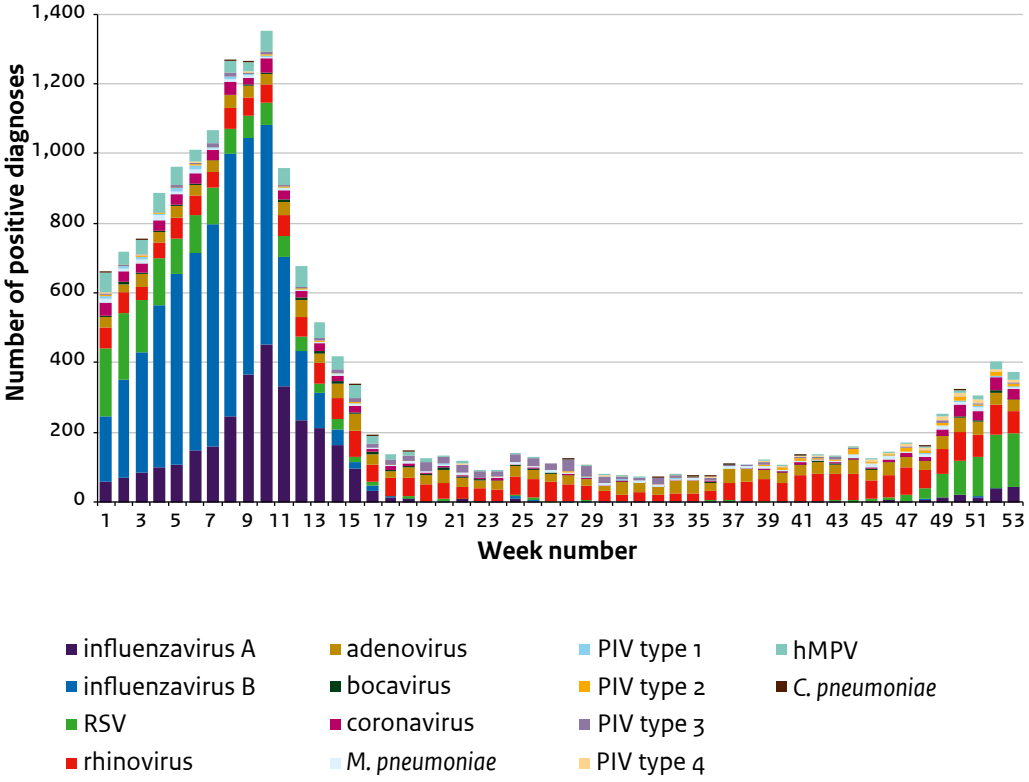
6.3 Tables and figures

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 2014-2018. (Source: Virological laboratory surveillance, NWKV)

Number of positive diagnoses											
Year	Rhinovirus	*M.pneumoniae*	hMPV	Coronavirus	PIV type 1	PIV type 2	PIV type 3	PIV type 4	*C. pneumoniae*	Adeno-virus	Bocavirus
2014	2196	436	384	320	76	66	218	53	20	1273	107
2015	2410	525	652	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	177
2018	2755	328	846	682	94	150	476	112	17	1623	150

M. pneumoniae = *Mycoplasma pneumoniae*
hMPV= human metapneumovirus
PIV= parainfluenza virus
C. pneumoniae = *Chlamydia pneumonia*
NWKV = Dutch Working Group for Clinical Virology of the Dutch Society for Medical Microbiology (NVMM).

Figure 6.1 Number of reported positive tests of influenzavirus type A and B, RSV, 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 year 2018. (Source: Virological laboratory surveillance, NWKV)



Footnote: *M. pneumoniae* = *Mycoplasma pneumoniae*; hMPV= human metapneumovirus; PIV= parainfluenza virus; *C. pneumoniae* = *Chlamydia pneumonia*; RSV= Respiratory Syncytial Virus.
NWKV = Dutch Working Group for Clinical Virology of the Dutch Society for Medical Microbiology (NVMM).

Figure 6.2 Number of weekly reported positive test results of rhinovirus in the virological laboratory surveillance for the calendar year 2018 and the trend lines* for the calendar years 2014 – 2018.

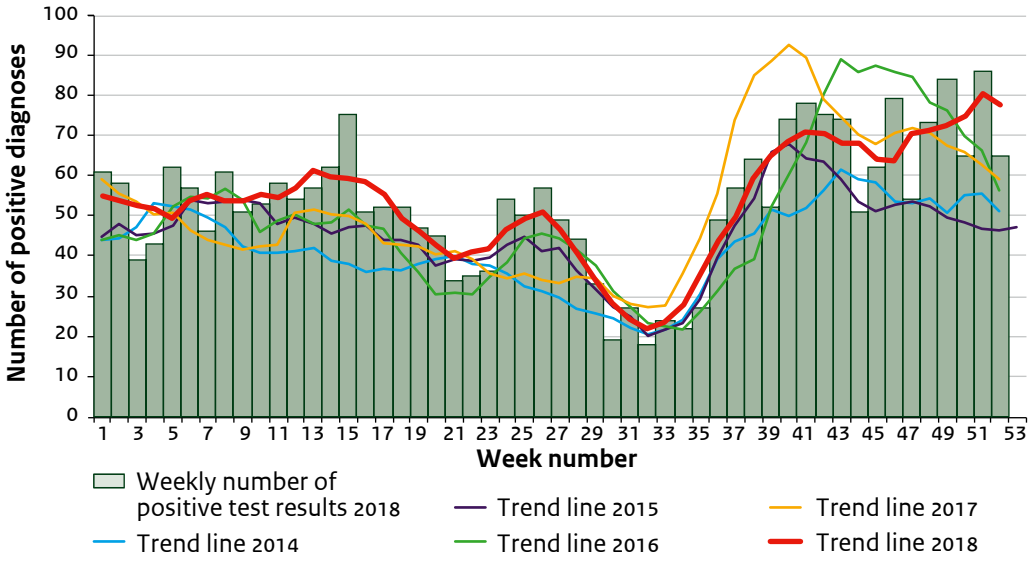
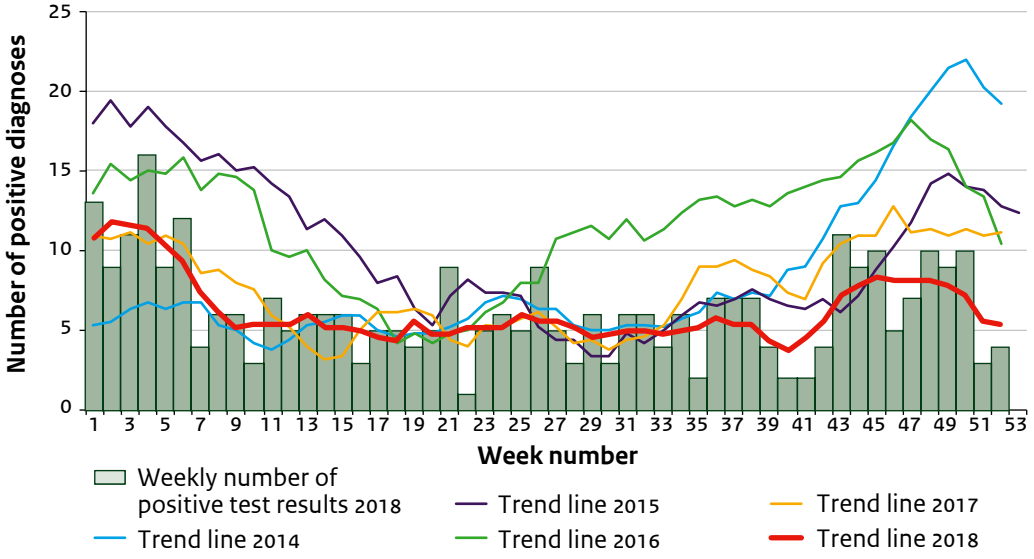


Figure 6.3 Number of weekly reported positive test results of *Mycoplasma pneumoniae* in the virological laboratory surveillance for the calendar year 2018 and the trend lines* for the calendar years 2014 – 2018.



*5-week moving average

Figure 6.4 Number of weekly reported positive test results of human metapneumovirus (hMPV) in the virological laboratory surveillance for the calendar year 2018 and the trend lines* for the calendar years 2014 – 2018.

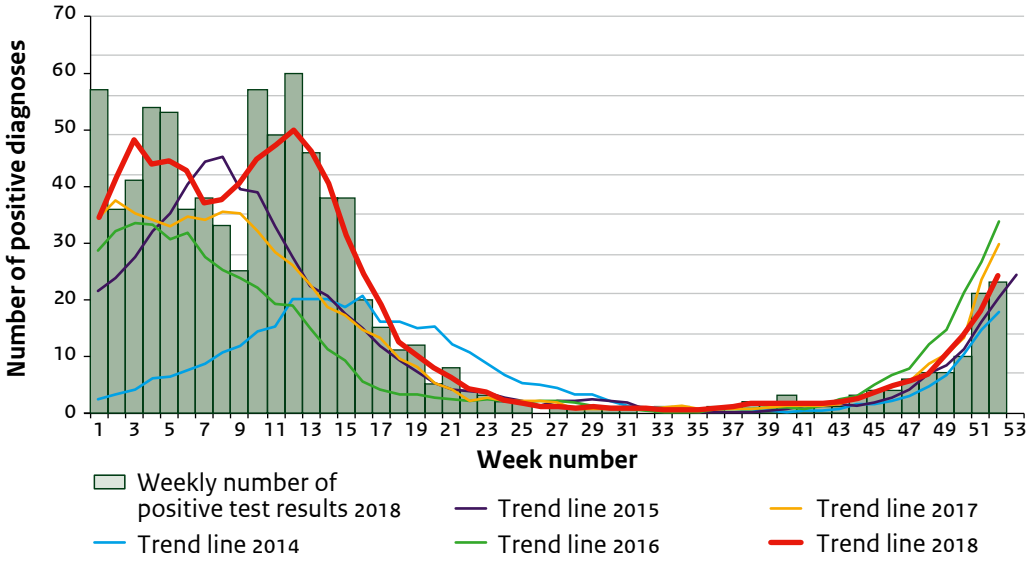
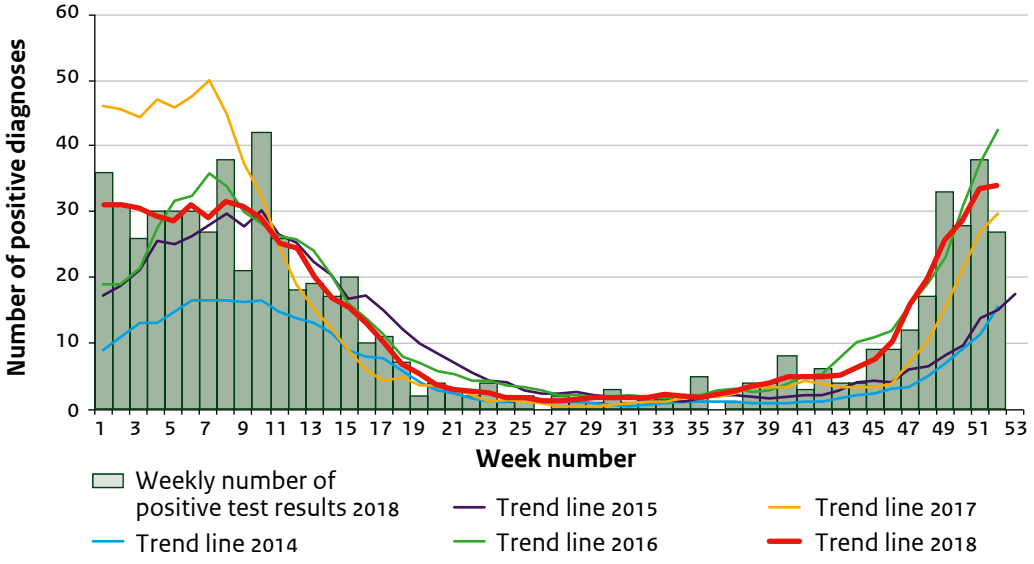


Figure 6.5 Number of weekly reported positive test results of coronavirus in the virological laboratory surveillance for the calendar year 2018 and the trend lines* for the calendar years 2014 – 2018.



5-week moving average

Figure 6.6 Number of weekly reported positive test results of parainfluenza virus type 1 in the virological laboratory surveillance for the calendar year 2018 and the trend lines* for the calendar years 2014 – 2018.

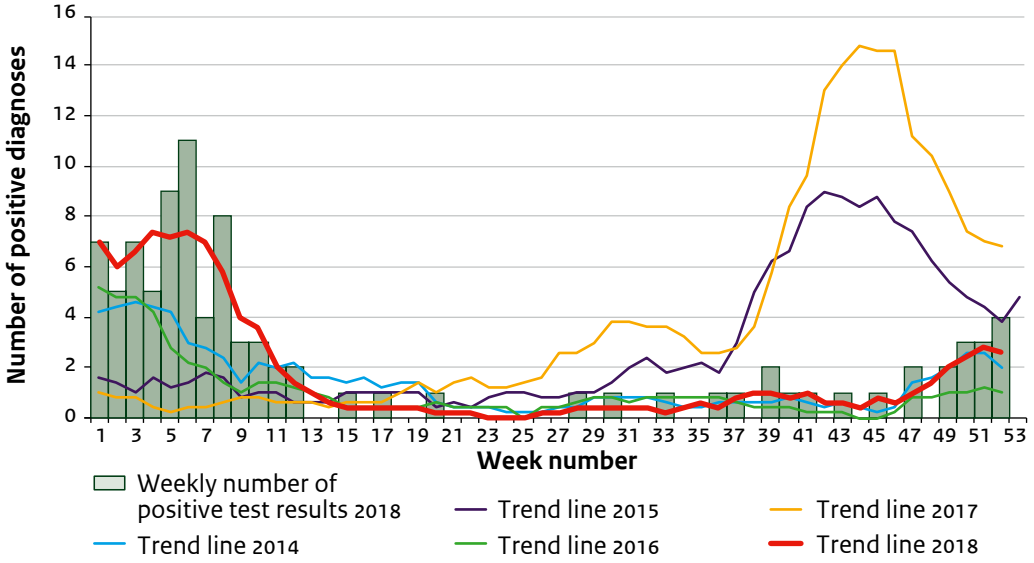
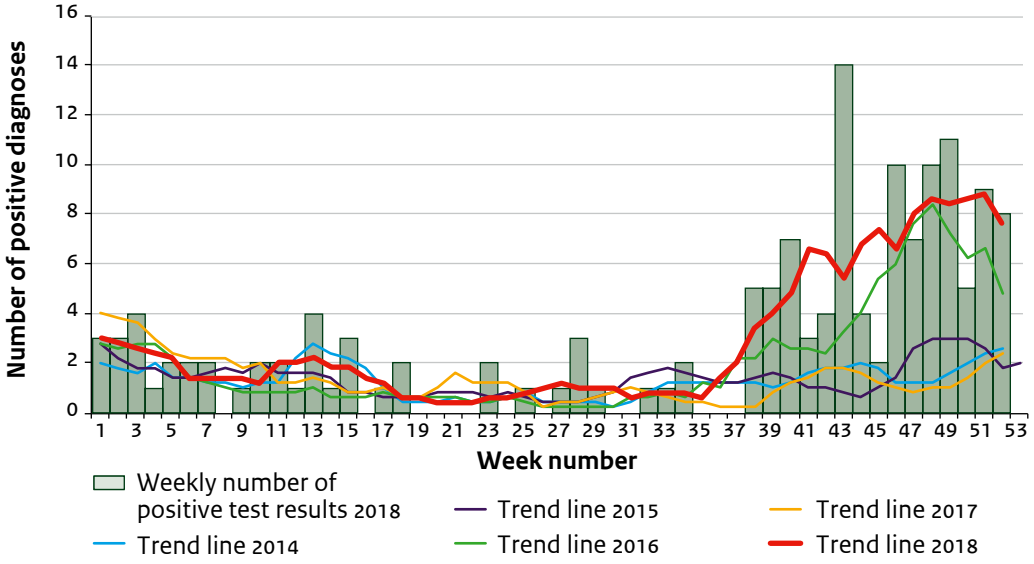


Figure 6.7 Number of weekly reported positive test results of parainfluenza virus type 2 in the virological laboratory surveillance for the calendar year 2018 and the trend lines* for the calendar years 2014 – 2018.



5-week moving average

Figure 6.8 Number of weekly reported positive test results of parainfluenza virus type 3 in the virological laboratory surveillance for the calendar year 2018 and the trend lines* for the calendar years 2014 – 2018.

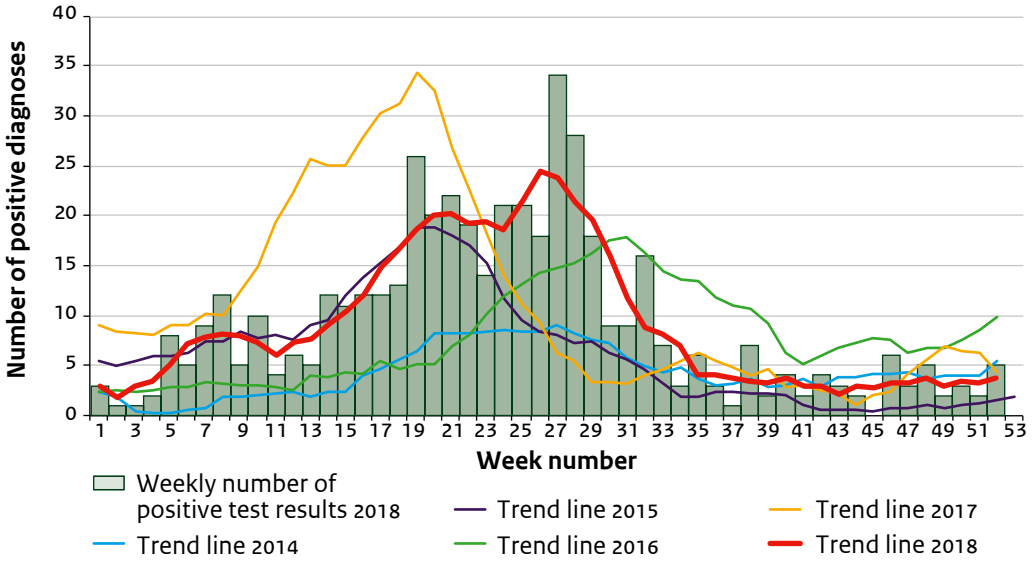
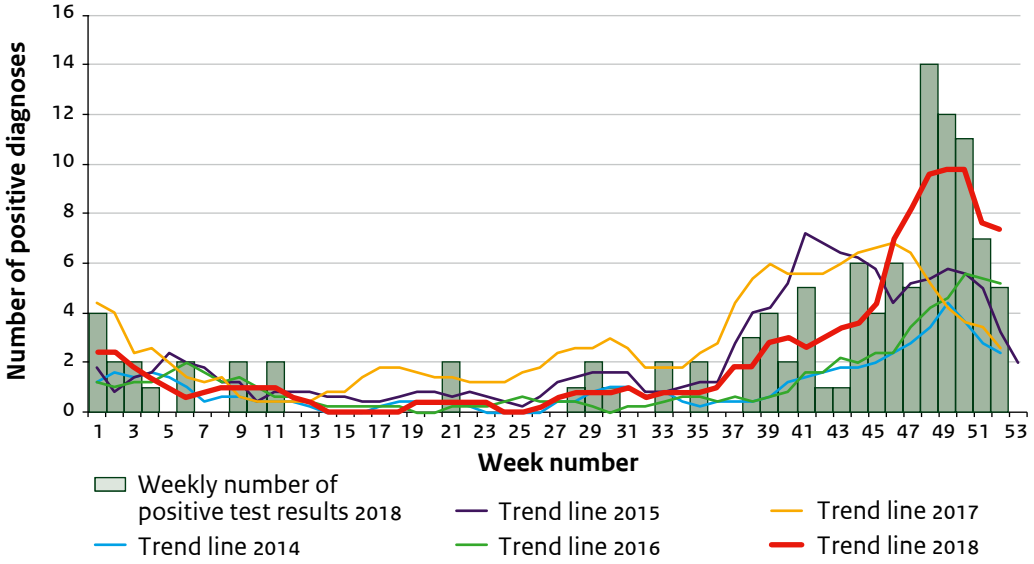


Figure 6.9 Number of weekly reported positive test results of parainfluenza virus type 4 in the virological laboratory surveillance for the calendar year 2018 and the trend lines* for the calendar years 2014 – 2018.



5-week moving average

Figure 6.10 Number of weekly reported positive test results of *Chlamydia pneumoniae* in the virological laboratory surveillance for the calendar year 2018 and the trend lines* for the calendar years 2014 – 2018.

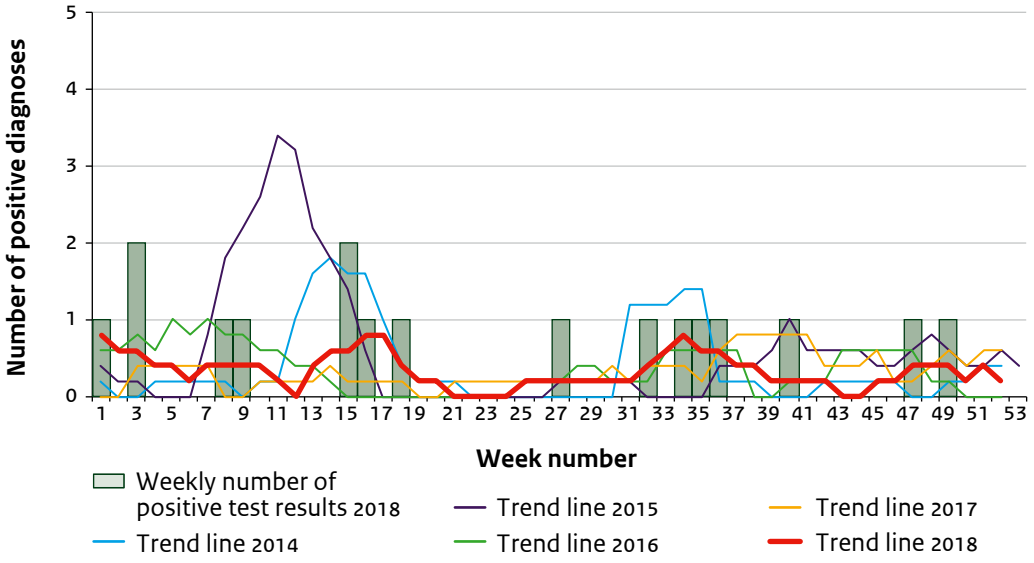
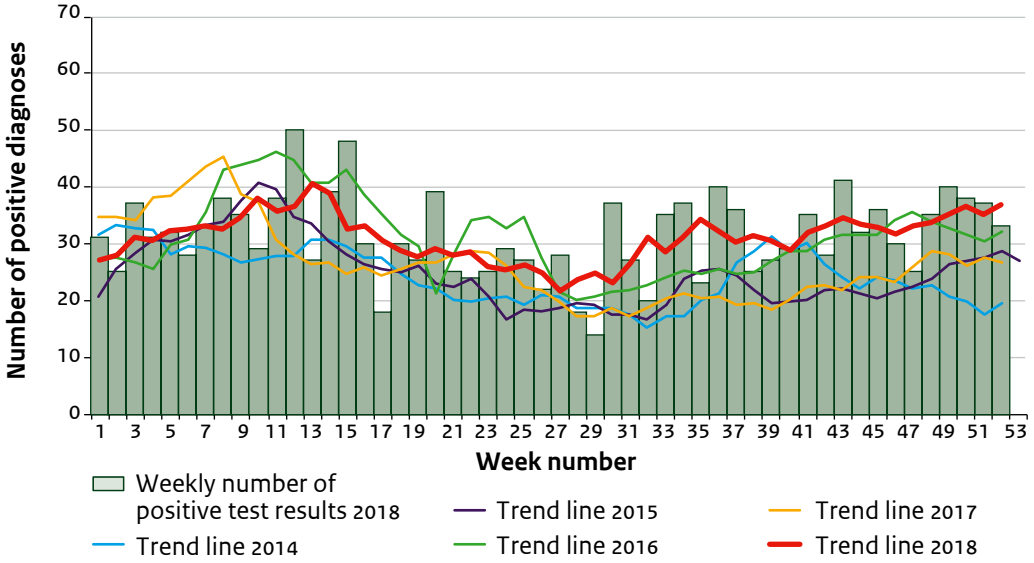
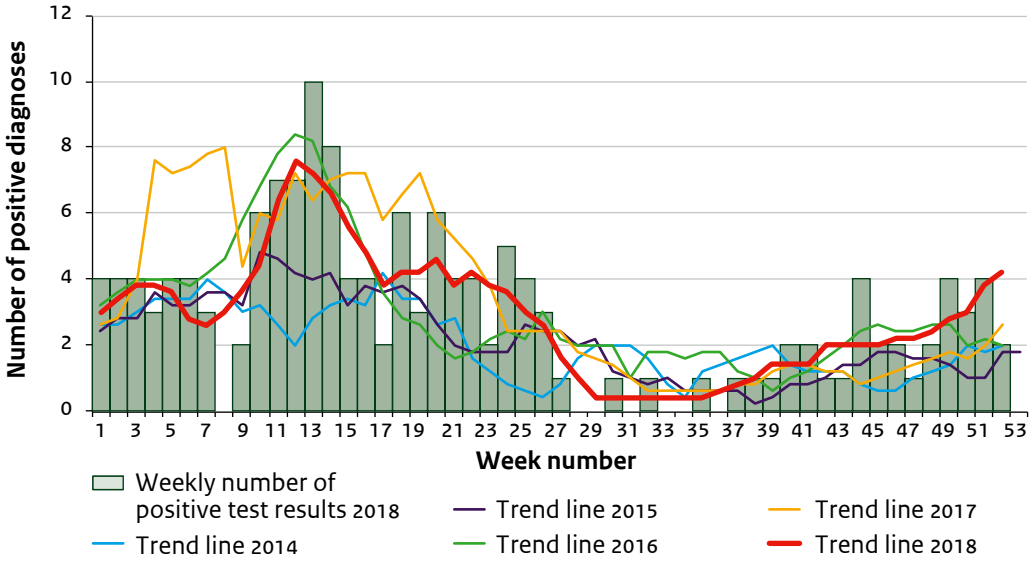


Figure 6.11 Number of weekly reported positive test results of adenovirus in the virological laboratory surveillance for the calendar year 2018 and the trend lines* for the calendar years 2014 – 2018.



*5-week moving average

Figure 6.12 Number of weekly reported positive test results of bocavirus in the virological laboratory surveillance for the calendar year 2018 and the trend lines* for the calendar years 2014 – 2018.



5-week moving average

Chapter 7
Burden of respiratory infectious diseases in the Netherlands

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

7.1 Keypoints

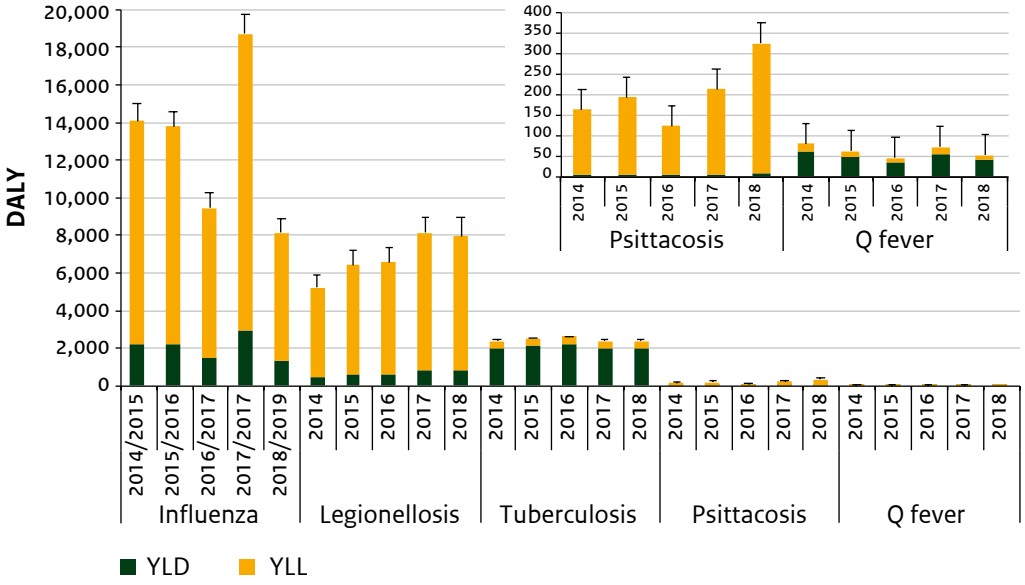
- The respiratory infectious disease with the highest disease burden in 2018 was influenza, with an estimated 8000 DALY (95% CI 7400-8700) for season 2018/2019. Disease burden in 2018 was estimated at 7900 DALY (7100-8900) for legionellosis; 2300 DALY (2300-2400) for tuberculosis; 330 DALY (250-430) for psittacosis, and 52 DALY (44-61) for Q fever.
- After a season with a very high burden for influenza in 2017/2018, the influenza burden of season 2018/2019 was low compared to the previous four seasons.
- For psittacosis, the burden estimate for 2018 is the highest reported since 2014. The burden of legionellosis has steadily increased during the past five years, but stabilized in 2018 compared to 2017.
- The burden of tuberculosis and Q-fever remained relatively the same during the last five years.
- When assessing the average burden per individual case, the burden is highest for tuberculosis and lowest for influenza. This burden per individual case is a characteristic of the disease and is independent of time.

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 2014 to 2018, or the disease burden that theoretically could have been avoided by preventing infections in those years. Trends in burden estimates can differ from trends in notification of the diseases that are described in previous chapters. This is due to the fact that the age distribution of the cases vary per year, which influences the burden estimates.

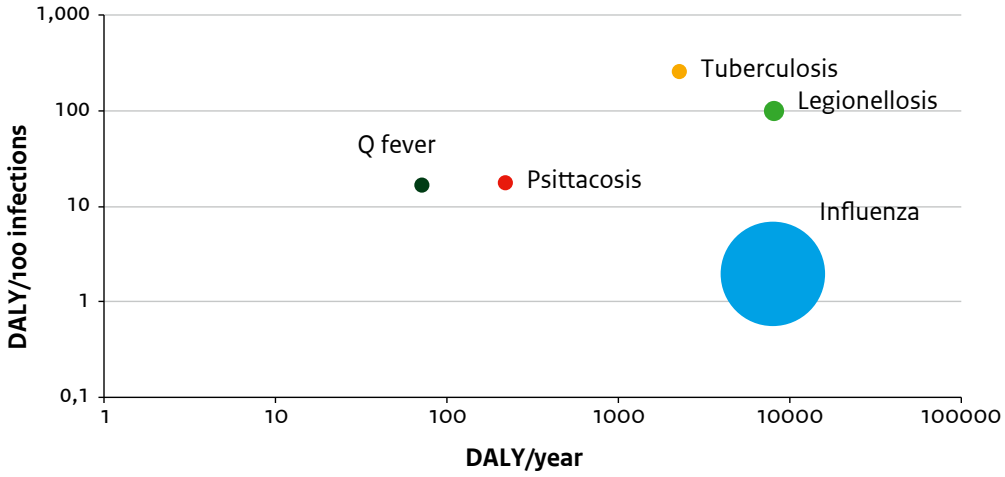
7.3 Tables and figures

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 2014-2018 (seasons 2014/2015 through 2018/2019 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 infections) in 2018 (for influenza respiratory season 2018/2019). 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 2014 to 2018 (season 2014/2015 to 2018/2019 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 casesab	Annual acute infections[c]
Influenza					
2014/ 2015	2200 (2000-2300)	11800 (11100-12500)	14000 (13100-14900)		700000
2015/ 2016	2200 (2000-2300)	11500 (10800-12200)	13700 (12800-14500)		682000
2016/ 2017	1500 (1300-1600)	7900 (7300-8600)	9400 (8600-10200)		471000
2017/ 2018	2900 (2700-3100)	15700 (14800-16600)	18600 (17500-19600)		933000
2018/ 2019	1300 (1200-1400)	6800 (6300-7300)	8000 (7400-8700)	2.0 (2.0 -2.0)	400000
Legionellosis					
2014	490 (440-540)	4700 (4100-5200)	5100 (4600-5800)		4500
2015	590 (540-650)	5800 (5100-6500)	6400 (5700-7200)		5500
2016	640 (580-700)	5900 (5200-6600)	6500 (5800-7300)		5900
2017	790 (720-870)	7300 (6500-8100)	8100 (7200-8900)		7300
2018	820 (740-900)	7100 (6300-8000)	7900 (7100-8900)	100 (96-110)	7600
Tuberculosis					
2014	2000 (2000-2000)	380 (340-420)	2300 (2300-2400)		910
2015	2100 (2100-2100)	390 (350-430)	2500 (2400-2500)		960
2016	2200 (2200-2200)	400 (360-440)	2600 (2500-2600)		1000

Disease	YLD/ year	YLL/ year	DALY/ year	DALY/ 100 casesab	Annual acute infections[c]
2017	2000 (2000-2000)	360 (320-390)	2300 (2300-2400)		880
2018	2000 (2000-2010)	350 (310-390)	2300 (2300-2400)	260 (250-260)	900
Psittacosis					
2014	4 (4-5)	160 (120-210)	170 (130-210)		1100
2015	5 (4-5)	190 (140-250)	190 (140-250)		1300
2016	3 (3-4)	120 (91-160)	130 (94-170)		950
2017	5 (5-6)	210 (160-270)	220 (170-280)		1500
2018	7 (5-8)	320 (240-420)	330 (250-430)	18 (15-22)	1800
Q fever					
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)		302
2018	40 (33-47)	12 (10-15)	52 (44-61)	17 (15-20)	250

[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 2018 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, Anne Teirlinck, Wim van der Hoek

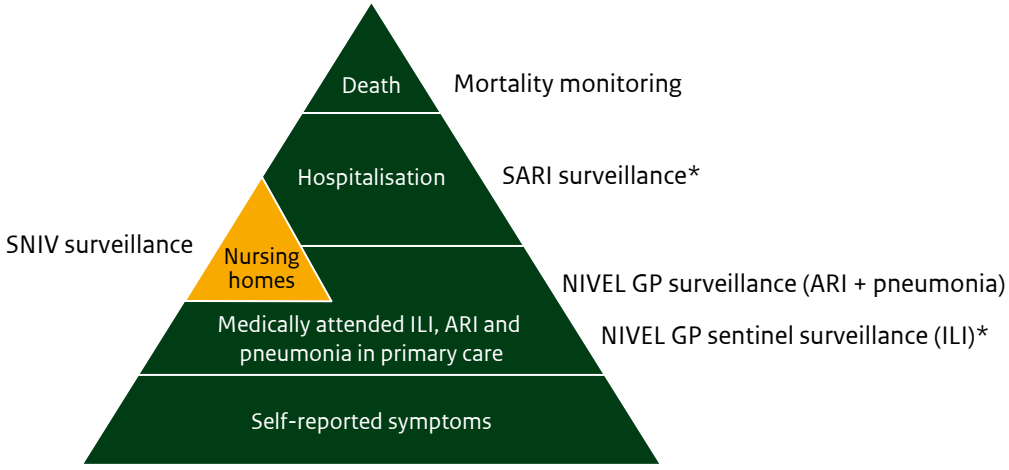
Influenza surveillance

The influenza epidemic in the 2018/2019 season had a milder course than the severe epidemic in the 2017/2018 season. Nevertheless, the epidemic lasted 14 weeks, which is longer than the average nine weeks duration over the past 20 years. Seasonal ILI incidence reported by GPs and the peak in ILI incidence of 10.8 per 10,000 inhabitants was lower than the previous four seasons. The ILI incidence in nursing homes was also relatively low compared to the previous four seasons, as well as the seasonal number of GP consultations for pneumonia. The season started with minimal detections of influenza at a time when more swabs collected by sentinel GPs were positive for RSV, rhinovirus and coronavirus than for influenza virus. Later during the epidemic, type A influenza virus became the dominant virus in the sentinel GP surveillance, with equal proportions of influenza subtype A(H3N2) and subtype A(H1N1)pdm09. In contrast to the 2017/2018 season, which was dominated by influenza B, hardly any type B influenza viruses were detected in the 2018/2019 season.

As described in previous editions of this annual report, surveillance of severe acute respiratory infections (SARI) remains the missing link in the Dutch respiratory surveillance system (Figure 8.1). From the pilot SARI surveillance that started in 2015 and in which three Dutch hospitals have participated, it has become clear that in order to be sustainable, SARI surveillance must be automated, rather than rely on active reporting by clinicians. As SARI surveillance should be based on real-time (weekly) data, in the next phase of establishing SARI surveillance, we are planning to make use of the Dutch national financial 'DBC-DOT' codes, which are assigned as soon as a patient is admitted to hospital. Improving SARI surveillance in order to get better insight into severe influenza disease, was a recommendation from the Outbreak Management Team that met in September 2018 in response to the hospital capacity problems that were encountered during the 2017/2018 influenza epidemic.

For a number of years, important information on the base of the surveillance pyramid, consisting of people with ILI or ARI, who do not visit their GP, was available from the 'Grote Griep Meeting', a private initiative that recorded self-reported ILI incidence in the general population. Unfortunately, the 'Grote Griep Meting' is not operational anymore since the 2016/2017 season. In the meantime, public health institutes in several European and non-European countries have copied the 'Grote Griep Meting' methodology and now use it for their national influenza surveillance.

Figure 8.1 The respiratory infections surveillance pyramid in the Netherlands.



Footnote: Systems with * also include virological surveillance

For the third year, the estimated annual incidence of symptomatic influenza virus infection for the entire Dutch population is presented. This outcome is derived using a statistical modelling approach, which combines multiple sources of evidence and provides a useful estimate of symptomatic influenza incidence in the population that can be compared across seasons (McDonald, Presanis et al. 2014). It was estimated that 400.000 persons had symptomatic influenza during the 2018/2019 respiratory season, compared to 900.000 in season 2017/2018 and 500.000 in season 2016/2017. This affirms that the past season was a mild season, especially compared to the 2017/2018 season, which had more than double the amount of symptomatic influenza cases.

Influenza vaccination

For the estimation of influenza vaccine-effectiveness, RIVM participates 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, for each circulating virus and for different age groups. On average, influenza vaccine effectiveness (VE) is only moderate. However, because of the high burden of disease from influenza, vaccination with a moderately effective vaccine can still prevent many influenza virus infections, complications such as pneumonia, and deaths. Within I-MOVE, RIVM together with colleagues from Portugal and Spain are developing methods to estimate the number of disease cases, hospital admissions, and deaths averted by vaccination, i.e. the impact of the vaccination programme.

Data from Europe (I-MOVE), the US, and Canada show an unusual very low 2018/2019 VE against influenza A(H3N2) among those aged 15-64 years. In contrast, the Dutch VE in the 2018/2019 season was good against all influenza viruses, with no large differences in circulating viruses (clades and subclades) with other countries. However, Dutch VE estimates have very wide confidence intervals, due to small sample sizes, therefore no definite conclusions can be drawn.

The World Health Organization (WHO) has selected a new strain (A/Brisbane/02/2018) as the A(H1N1)pdm09 component for the 2019/2020 season, as a reduced serological response was detected in persons vaccinated with the 2018/2019 vaccine (including the A/Michigan/45/2015 vaccine strain).
Different variants of the influenza virus type A(H3N2) circulated in Europe and the US, therefore the WHO recommendation for this vaccine strain in the 2019/2020 influenza vaccine was delayed with a month. Ultimately, A/Kansas/14/2017(H3N2)-like virus strain was selected for the 2019/2020 vaccine, because of the dominance in the US and the availability of a good candidate vaccine virus [http://www.who.int/influenza/vaccines/virus/recommendations/2019_20_north/en/]. This delay in vaccine virus selection might pose a problem for vaccine producers to deliver the vaccines in time for the 2019/2020 season. The start of the next (2019/2020) seasonal influenza epidemic cannot be predicted, but in 2019 the epidemic in some countries in the southern hemisphere, especially in Australia, started exceptionally early.

From the 2019/2020 season onwards, the National Influenza Prevention Program in the Netherlands will only use inactivated quadrivalent influenza vaccines (QIV) [https://www.rijksoverheid.nl/documenten/kamerstukken/2018/10/10/kamerbrief-over-maatregelen-griep]. These QIV's will include a B/Victoria, as well as a B/Yamagata virus and the WHO recommendation for influenza virus type B components remained the same as last season.

Notifiable respiratory diseases

As most cases of community acquired pneumonia are diagnosed based on clinical criteria and without laboratory diagnostics, at the GP as well as in a hospital setting, often the causative pathogen remains unknown. Therefore, notifiable infectious diseases that present as pneumonia are often underreported.

In the virological laboratory surveillance 65 diagnoses of *C. burnetii* were reported and 18 acute Q fever cases were notified in Osiris. The number of notified cases are often less than the number of cases in the virological surveillance, as a positive laboratory result can also indicate a past infection and these do not fulfil the national notification criteria for acute Q fever. In an analysis in one Public Health Service (PHS) region, only 8% of laboratory diagnoses received at the PHS fulfilled the notification criteria and were thus nationally notified in Osiris (Hanssen, Morroy et al. 2019) The number of notified cases is in line with the number of notifications from 2013-2017 (varying from 14 to 26), which is comparable to the levels before the large 2007-2010 Q fever epidemic.

The number of notified tuberculosis cases showed years of steady decline, however in recent years it has remained stable or even showed a slight increase. In 2017, the number of notified tuberculosis cases was below 800 patients (n=787) for the first time since registration started in 1950. In 2018, the number of notified tuberculosis cases increased with 3% to 806. Most TB patients notified in 2018 were foreign born (77%).

The increasing trend in incidence of Legionnaires' disease (LD) continued in 2018. A record number of 584 patients were notified in 2018 in several smaller clusters. Multiple private Jacuzzi's were identified as a source of infection, as well as a gardenhose, swimming pool shower, a work location and biological wastewater treatment plants. Studies on the risk of Legionnaires' disease linked to these biological wastewater treatment plants are ongoing. The report provides an update on the burden of respiratory infectious diseases expressed in disability-adjusted life years (DALY). 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, de Gier, Schimmer et al. 2019). 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. 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 respiratory illnesses mainly occur in winter, the 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 2018/2019 is limited to the respiratory season to allow a timely reporting. Respiratory infections may occur outside the respiratory season 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 2018 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 2019). The Nivel Primary Care Database holds longitudinal data recorded in electronic medical files 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 300 participating general practices spread over the country [https://nivel.nl/nl/zorgregistraties-eerste-lijn/surveillance].

- In the 2018/2019 respiratory season, 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 (de Gier, Nijsten et al. 2017).
- A proportion of the GPs participating in Nivel Primary Care Database take part in sentinel influenza 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 2018).

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 2018/2019 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. In previous years, the nursing homes were requested to collect throat swabs and nose swabs from patients with ILI or another respiratory infection (ARI). Due to low compliance this procedure was ineffective and not informative and therefore stopped in the 2018/2019 season.

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 is useful as an additional source. It can be used 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 in this report 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(H_5N_1) virus or influenza A(H_7N_9) 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 (Donker 2018).
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 (ICPC code R74), including acute/chronic sinusitis (ICPC code R75), acute laryngitis/tracheitis (ICPC code R77), acute bronchitis/bronchiolitis (ICPC code R78) or influenza (ICPC code R80) are obtained from Nivel Primary Care Database. Please note that the ILI syndrome is a subset of, and included in the ARI syndrome. Although ARI is less specific for an influenza virus infection than ILI, seasonal estimates are highly correlated. Weekly ARI consultation rates are calculated as the number of patients consulting their GP in a given week, divided by the total number of enlisted patients. Cumulation of this weekly surveillance data over the season (separated for week 40 through 20 and week 21 through 39) is reported as the seasonal number of consultations.

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). This SARI surveillance pilot study makes a distinction between syndromic surveillance and surveillance based on laboratory confirmed outcomes. Laboratory 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.

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. A short web-based questionnaire was completed by the research nurse about symptoms, influenza and pneumococcal vaccination status, comorbidities and several risk factors of every included SARI patient. In addition, routinely collected respiratory specimens were used for influenza virus detection.. 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.

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 (45% 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. Additionally, a selection of Dutch virology laboratories submit a representative set of influenza virus positive specimens (5-6 specimens per week is the request) to the Erasmus MC. For laboratories that continued to send all influenza virus positive specimen this selection of 5-6 specimens per week for further characterisation is done by Erasmus MC. Therefore, the trend in the specimens received by Erasmus MC is not a reflection of the course of the epidemic since 2018 when this procedure was installed.

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.

Since the 2018/2019 season, after I-MOVE+ stopped but I-MOVE continued, the GPs were instructed to:

- Swab at least the first two ILI patients on Monday through Wednesday;
- When on Monday through Wednesday no ILI patients attend the GP, than swab on Thursday through Sunday at least the first two ILI patients or ARI patients;
- Swab at least one child below the age of 10 with an ILI or ARI throughout the week.

The GP 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. At the start of the influenza epidemic, the proportion of influenza virus in specimens collected from ILI patients is often low. Although RSV explains a large proportion of these cases especially in very young children, a relatively large proportion of specimens remains negative for the pathogens tested. Therefore, a retrospective analysis was performed on specimens negative in our routinely used assays. We used a commercial multiplex PCR assay (Fast Track Diagnostics FTD Respiratory pathogens 21) diagnosing 21 pathogens: influenza A virus, influenza A(H1N1)pdm09 virus, influenza B virus, human rhinovirus, human coronavirus NL63, 229E, OC43 and HKU1, human parainfluenza 1, 2, 3 and 4, human metapneumoviruses A/B, human bocavirus, human respiratory syncytial viruses A/B, human adenovirus, enterovirus, human parechovirus, *Mycoplasma pneumoniae.*

Virus isolation
At both locations influenza viruses are isolated from PCR influenza virus positive clinical specimens in cell culture on MDCK-SIAT or MDCK mono culture cell lines at Erasmus MC or on mixed MDCK-SIAT and MDCK-I cell lines at RIVM. Successful grown viruses are used for antigenic characterisation and phenotypic determination of antiviral susceptibility.

Influenza virus antigenic and genetic characterization
Whereas subtyping and lineage determination at RIVM are performed using RT-PCR assays, Erasmus MC has changed for the 2018/2019 season to MinION next generation sequencing of the HA and NA genes for simultaneous subtyping/lineage determination and genetic characterisation of influenza viruses.
Antigenic characterization of a subset of influenza viruses and influenza virus positive clinical specimens after successful virus isolation, 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. Because new ferret sera have to be generated at Erasmus MC, the results of this thorough antigenic characterisation takes some time and is completed after this report has been published.
A subset of influenza viruses are characterized genetically by sequence analysis of the haemagglutinin genome segment at RIVM. At Erasmus MC as described above this is done using MinION sequencing of all received and selected specimens. At NIC location RIVM this is done on a systematic sample of the dominant influenza virus subtype and on all I-MOVE influenza cases, all sporadically detected types, subtypes and lineages and all of particular interest if multiple clades or subgroups emerge from the GP sentinel surveillance. Sequences from both locations are combined for detailed phylogenetic and amino acid substitution analysis giving 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 A(H3N2) viruses that could be antigenically characterised during the 2018/2019 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 Nivelinfluenza 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 locations RIVM and Erasmus MC. 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 NIC location RIVM. Of all viruses tested at Erasmus MC and a subset of viruses tested at RIVM, the neuraminidase gene is sequenced and analysed for any markers previously associated with reduced neuraminidase inhibitor susceptibility. 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 susceptibility for antivirals and markers for virulence. 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) was 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%. Influenza virus type A(H3N2) and type A(H1N1)pdm09 were the dominant subtypes in the 2018/2019 season, so stratification for those subtypes were performed. The analysis is restricted to the period that influenza virus was circulating in the Netherlands (for any subtype: week 48 in 2018 through week 15 in 2019, for A(H3N2): week 1 of 2019 through week 15 of 2019, for type A(H1N1)pdm09: week 48 2018 through week 13 2019). 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, and chronic medical condition. 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 estimated the incidence of symptomatic infection with influenza virus by combining all relevant data sources via Bayesian evidence synthesis (Teirlinck, de Gier et al. 2018). 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 from Nivel Primary Care Database was used); (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 (McDonald, Presanis et al. 2014), analysis was restricted to the winter season (week 40 through week 20 of the next year).

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.

Impact of the influenza vaccination programme

We estimated number of GP visits averted by the influenza vaccination programme in the Netherlands among those aged ≥65 years. First, the observed number of cases was estimated for GP visits based on incidence of ILI from sentinel GP surveillance, influenza virus positivity rate, and sensitivity of virological testing (i.e. the same method as described in the paragraph 'Estimating symptomatic influenza incidence in the general population', but without the correction for underascertainment based on data of InfluenzaNet). Secondly, the number of averted cases was calculated from the estimated observed cases, national vaccination coverage and VE. Vaccination coverage of the age group 65 years and older was sourced from pseudo-anonymized data from electronic medical files of general practices participating in Nivel Primary care Database. Using multilevel logistic regression analysis, the clustering of patients in GP practices is taken into account (Heins, Hooiveld et al. 2018).
During the data analysis for this Annual Report, the vaccination of the was published of the vaccination campaign of 2018 was not available yet. Therefore, for the 2018/19 season, the vaccination coverage of the season 2017/18 (vaccination campaign of 2017) was used instead. VE was based on subtype specific I-MOVE primary care study VEs, corrected for the proportion of subtypes circulating in the Netherlands.

The impact measures calculated were:

- Number of GP visits averted. This was calculated as:

$$NAE = N - n = \frac{n}{1-(VC*VE)} - n = n * (\frac{VC*VE}{1-(VC*VE)})$$

  where NAE = number of averted events,
  N = Expected number of events without the vaccination programme
  n = Observed number of events
  VC = vaccination coverage
  VE = Vaccine effectiveness
- Prevented fraction (PF), which was calculated as: PF = NAE/N
- Number needed to vaccinate to prevent one event, which was was calculated as: NVN = 1/(VE*N/population size).
  95% CIs were derived through Monte Carlo simulation.

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 2018 calendar year. Number of diagnoses of psittacosis, Q fever, influenza and RSV as reported in virological laboratory surveillance are given in their respective chapters.

Moving Epidemic Method (MEM) for RSV seasonality

Previously, we defined the RSV season as the period with at least 20 RSV-diagnoses per week reported by the virological laboratory surveillance. We now used the Moving Epidemic Method (MEM), that was originally developed to assess influenza seasonality (Vega, Lozano et al. 2013), to establish the epidemic thresholds for RSV, using the virological laboratory surveillance data of the previous 12 seasons (Vos, Teirlinck et al. 2019).
MEM was applied with the Moving Epidemic Method Web Application (Lozano 2018) and absolute detection numbers per week for all 12 seasons in the fixed criterium model and a manually optimised slope parameter of 1.4 that had been established previously (Vos, Teirlinck et al. 2019). We calculated the mean length, timing and coverage of the epidemic period by calculating pre-and postepidemic thresholds using the arithmetic mean and its one-sided 95% point confidence interval (CI). We also calculated epidemic intensity levels using the geometric mean and its one sided 40% (medium), 90% (high) and 97.5% (very high) point CI. For the MEM calculations, a season was defined from week 30 through week 29 of the next year to be able to include enough data points to calculate a precise pre-epidemic threshold as RSV circulation might start as early as week 40. For displaying results in this annual report, the respiratory season as defined for influenza (week 40- week 39) is used.

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 (Reukers, Van Asten et al. 2018). 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 European disability weights collected by Haagsma et al. (Haagsma, Maertens de Noordhout et al. 2015). To estimate YLL, remaining life expectancy tables were taken from the GBD 2010 study (WHO 2013).

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 tuberculosis, legionellosis, psittacosis and Q fever incident in 2014, 2015, 2016, 2017 and 2018 separately. We estimated the burden of influenza for respiratory seasons (week 40 to week 20) for the seasons 2014-2015 through 2018-2019. No time discounting was applied.

Acknowledgements

Many people have contributed to the present report. We especially thank the following persons for their contributions to respective chapters:

Guus Rimmelzwaan, Ruud van Beek, Ron Fouchier and **Mark Pronk** (NIC location Erasmus MC) for data on influenza viruses submitted by Dutch virology laboratories.

Paul Bergervoet, Marjolein Korndewal, Jeroen Alblas and Anja Haenen (CIb/EPI) for provision and analysis of pneumonia and ILI data in SNIV.

Inge Roof, Rianne van Hunen-Aarnoudse (CIb/EPI), **Peter Schneeberger, Peter de Jager, Florens Polderman, Tamara van Zuylen and Angela Bouman** (JBZ) for their cooperation in the SARI project.

Carel Harmsen, Lenny Stoeldraijer, Ursula de Bruijn- van Leijden and **Felicia Minnaard** (Statistics Netherlands, department demography) for providing weekly mortality data.

Ben Bom (RIVM/SSC Campus) for compiling the map for Legionnaires' disease and tuberculosis.

Julika Vermolen (CIb/Corporate Communication) for editing the 'Publiekssamenvatting'.

Willem Verdouw (CIb/Corporate Communication) for managing the production of this report.

In addition, we want to thank the following people or authorities for their contribution and/or cooperation for delivering data we used in this report:

- **Nivel Primary Care Database team** and participating general practitioners
- **Pieter Overduin (sequencing), Mariam Bagheri, Ton Marzec** and **Gabriel Goderski (virus isolation and phenotypic antiviral susceptibility testing)** and **Lisa Wijsman and Sharon van den Brink (molecular diagnosis group), Anne-Marie van den Brandt, Edin Jusic, Bas van der Veer** and **Jeroen Cremer**, technicians of the department respiratory and enteritic viruses (REV) respiratory viruses group and of the molecular diagnosis group of discipline Virology, CIb/IDS
- The medical microbiological laboratories and the laboratories which participated to the virological laboratory surveillance of the **Working Group for Clinical Virology**
- Medical doctors and nurses of the Public Health Services took care of the Osiris and the Osiris-NTR notifications
- **Inger Bregman and Lieke Blijboom** (CIb/EPI)
- **Miranda Kamst and Dick van Soolingen** (CIb/IDS, Bacterial and Parasitological Diagnostics)
- **SNIV** team and participating nursing homes.

- **Jeroen den Boer, Jacqueline de Vries, Wim Houtenbos, Arjen Veen, Ruud Jansen, Paul Badoux, Bjorn Herpers, Liane Kosten, Jan Willem Meester, Awatef Hamdan** (Regional Public Health Laboratory Kennemerland) of the *Legionella* Source Identification Unit (BEL) for their contribution to source investigation and environmental sampling for legionellosis.
- **Helma Ruijs, Alvin Bartels, Marijke van Cooten-Boot, Felix ter Schegget and Laura van Vossen** (CIb/LCI) and **Willemijn Lodder and Harrold van den Berg** (CIb/Z&O).

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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)
NWKV	Dutch Working Group for Clinical Virology (NL: Nederlandse Werkgroep Klinische Virologie)
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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RIVM report 2019-0079

Published by:

National Institute for Public Health and the Environment
PO Box 1 | 3720 BA Bilthoven
The Netherlands
www.rivm.nl/en

August 2019

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