



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 2016/2017*





# Annual report Surveillance of influenza and other respiratory infections in the Netherlands: *winter 2016/2017*

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## Synopsis

### Surveillance of influenza and other respiratory infections in the Netherlands: Winter 2016/2017

During the 2016/2017 winter season, the influenza epidemic in the Netherlands lasted for 15 weeks. This was longer than the nine-week average duration of epidemics in the twenty previous seasons. Influenza subtype A(H3N2) was the dominant influenza virus throughout the season. In general, baseline natural immunity against A(H3N2) is relatively low among the elderly. Indeed, the number of patients older than 65 years, who visited a general practitioner (GP) for influenza-like symptoms, was higher than last year when influenza A(H1N1)pdm09 predominated. In nursing homes, the number of patients with influenza-like symptoms was also high. In total, an estimated 500,000 patients had symptomatic influenza in the period between the beginning of October 2016 and the end of May 2017 and 6,500 patients were admitted to hospital for influenza-related symptoms. During the epidemic, there were 7,500 more deaths than expected in this 15-week period.

The effectiveness of the influenza vaccine against the A(H3N2) virus was 47 per cent. The circulating Dutch A(H3N2) viruses displayed a good to moderate match with the strain that was used in the 2016 vaccine. The WHO has recommended that the same strain be used for the trivalent vaccine for the 2017/2018 season in the northern hemisphere. The B component in the 2017 trivalent vaccine also remains the same as it was in 2016, but the A(H1N1)pdm09 component will be replaced with a more recent virus. The effectiveness of the vaccine varies every season because it is never known which influenza virus(es) will dominate in the next influenza season. Also, the circulating influenza viruses can evolve over time and deviate from the chosen vaccine viruses.

There were more reports of the notifiable respiratory infectious diseases made in the 2016 calendar year than in previous years: tuberculosis (889 notifications), psittacosis (60 notifications) and legionellosis (454 notifications). The increase in legionellosis notifications may be associated with the warm, wet weather conditions in 2016. However, several geographic clusters were observed whose existence could not be explained by heavy rainfall or other weather conditions and for none of these clusters could the source of infection be found. The number of notifications for Q fever (14 notifications) is still decreasing. However, the notifiable infectious diseases that present as pneumonia are notoriously underreported because most cases of community-acquired pneumonia are managed in primary care without specific diagnostic laboratory tests being made.

Keywords: respiratory infections, flu, influenza, RS-virus, pneumonia, Legionnaires' disease, *Legionella*, parrot fever, psittacosis, Q fever, tuberculosis

## Publiekssamenvatting

### Surveillance van influenza en andere luchtweginfecties: winter 2016/2017

In de winter van 2016/2017 duurde de griepepidemie 15 weken. Dit is langer dan het gemiddelde van negen weken in de afgelopen 20 jaar. Tijdens de gehele epidemie is vooral influenzavirus van het type A(H3N2) aangetroffen, waartegen ouderen over het algemeen minder weerstand hebben. Het aantal patiënten boven de 65 jaar dat de huisarts bezocht met griepachtige klachten was dan ook iets hoger dan vorig jaar, toen vooral influenza A(H1N1)pdm09 circuleerde. Vooral in verpleeghuizen waren er veel patiënten met griepachtige klachten. In totaal zijn naar schatting tussen begin oktober 2016 en eind mei 2017 ongeveer 500 duizend mensen ziek geworden door een infectie met het griepvirus en zijn ruim 6500 mensen in het ziekenhuis opgenomen vanwege griep gerelateerde problemen. Gedurende de epidemie overleden 7500 meer mensen dan in die periode was verwacht.

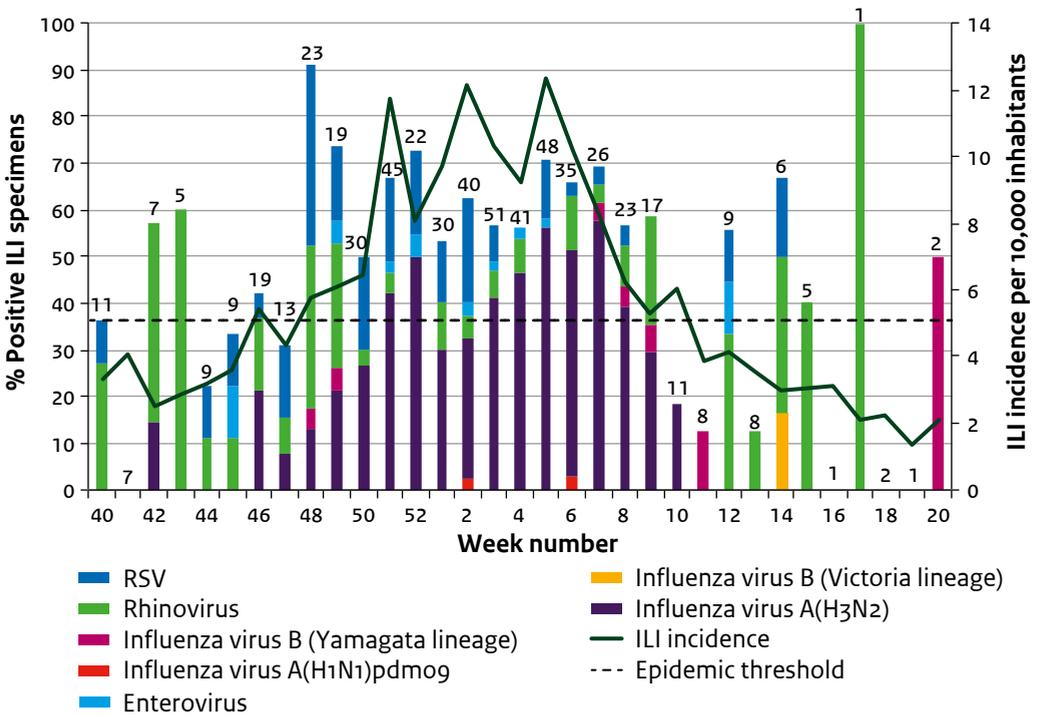
Gevaccineerden hadden een 47 procent verlaagd risico om griep te krijgen. Er was een redelijk tot goede match tussen het vaccin en het A(H3N2) virus dat dit jaar griep veroorzaakte. De Wereldgezondheidsorganisatie (WHO) heeft daarom geadviseerd om volgend jaar hetzelfde A(H3N2) vaccinvirus te gebruiken. Het B-virus in het griepvaccin van volgend jaar zal ook hetzelfde blijven, maar het vaccinvirus A(H1N1)pdm09 wordt wel door een recenter virus vervangen. De effectiviteit van het vaccin kan per seizoen sterk verschillen doordat nooit van tevoren bekend is welke virussen in het volgend seizoen overheersen. Ook kunnen deze virussen door de tijd heen evolueren en gaan afwijken van de gekozen vaccinvirussen.

Van de meldingsplichtige luchtweginfectieziekten zijn in 2016 zowel tuberculose (889 meldingen) als psittacose (60 meldingen) en legionellose (454 meldingen) vaker gemeld dan voorgaande jaren. De stijging bij legionellose kan deels worden toegeschreven aan het warme en natte weer. Bij enkele plaatselijke verhogingen was dit niet het geval en kon ook geen besmettingsbron worden gevonden. Het aantal meldingen van Q-koorts (14) bleef dalen. Het aantal gemelde gevallen van Q-koorts, psittacose en legionellose is altijd een onderschatting van het werkelijke aantal. Bij longontsteking wordt namelijk niet vaak de oorzaak vastgesteld, omdat ofwel niet altijd getest wordt of de test geen zekere oorzaak oplevert.

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 2016/2017 respiratory season (week 40 of 2016 through week 20 of 2017), displayed by week of sampling (Source: NIVEL Primary Care Database, NIC location RIVM).



**Footnote:** ILI = influenza-like illness; GP = general practitioner; RSV = respiratory syncytial virus. The numbers above the bars are the total number of tested specimens.



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# 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 Municipal Health Services and others working or interested in the field of respiratory infectious diseases. The national surveillance of respiratory infectious diseases that are 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 many syndromic surveillance systems used: influenza-like illness (ILI), acute respiratory infections (ARI), pneumonia, severe acute respiratory infections (SARI) and mortality. The diagnosis 'influenza-like illness' is based on the notion that symptoms of influenza may be caused by several pathogens, including other than influenza viruses. The causative pathogen remains unknown in the majority of patients with respiratory infections because most infections are not laboratory-confirmed, but based on clinical diagnosis only. This surveillance is important because of the high burden of disease, in terms of patient numbers, mortality and the impact on the health care system. The surveillance of ILI, ARI and pneumonia is currently mainly based on the registration of consultations by general practitioners (GPs) participating in NIVEL Primary Care Database (in Dutch: NIVEL Zorgregistraties eerste lijn). Elderly care physicians provide data within the context of the national sentinel surveillance network for infectious diseases in nursing homes (SNIV). Laboratory-confirmed influenza in these two networks is assessed by the National Influenza Centre (NIC), location RIVM (at the Centre for Infectious Disease Research, Diagnostics and Screening (IDS) of CIb). Laboratory-confirmed influenza cases reported by hospital and peripheral laboratories are monitored at NIC, location Erasmus Medical Centre. A new paragraph in Chapter 2 is on surveillance of SARI in pediatric intensive care units (PICU).

This is in collaboration with six of the eight PICUs in the Netherlands that weekly report the number of SARI patients on the PICU and laboratory outcome if diagnostics are performed. Respiratory infectious diseases such as influenza and pneumonia are important causes of death. As real-time, cause-specific data on deaths are not available, mortality surveillance is based on all-cause mortality, and is also reported in Chapter 2. Surveillance of mortality is based on data collected by Statistics Netherlands (CBS).

Chapters 3 and 4 show the surveillance data for, respectively, influenza virus infection and respiratory syncytial virus (RSV) infection. Since both the respiratory syndromes and influenza virus and RS-virus infections show winter seasonality, data in the Chapters 2-4 are reported for the 2016/2017 respiratory season, i.e. week 40 of 2016 through week 20 of 2017. Chapter 5 describes the summary of the results of the surveillance of the notifiable respiratory infectious diseases legionellosis, tuberculosis, Q fever, psittacosis and for animal influenza virus and MERS-CoV for the 2016 calendar year. Q fever and psittacosis will be described in greater detail in the report 'Staat van zoönosen 2016' (manuscript in preparation). More details on tuberculosis will be described in next surveillance report on tuberculosis, 'Tuberculose in Nederland, 2016' that will be published in December 2017. 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. In Chapter 6, diagnoses of other respiratory infections reported in the virological laboratory surveillance and the diagnosis of rhinovirus and enterovirus by the NIVEL GP surveillance are described, all for the 2016 calendar year. Chapter 7 provides an update on the burden of disease from five respiratory diseases: influenza, legionellosis, tuberculosis, Q fever and psittacosis. This chapter is based on another RIVM publication, entitled 'State of Infectious Diseases in the Netherlands, 2016' (de Gier, Nijsten et al. 2017). 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. In previous annual reports, we reported data from Influenzanet (in Dutch, De Grote Griepmeting) [[www.influenzanet.eu](http://www.influenzanet.eu) and [www.degrotegriepmeting.nl](http://www.degrotegriepmeting.nl)], that records the self-reported ILI incidence in the general population. Using this data, we also assessed vaccine effectivity against self-reported ILI. Because of technical problems with the data extraction, the Influenzanet data could not be included in this report.

## 1.2 Collaborations: national and international

For the surveillance of respiratory infectious diseases, the Clb 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; Influenzaneet; KNCV Tuberculosis Foundation; the Regional Public Health Laboratory Kennemerland, Haarlem (national reference laboratory for legionellosis); and Statistics Netherlands (CBS). The collaboration with the Municipal 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, also 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 LUMC. PICU surveillance is performed in collaboration with the PICUs of Emma Children's hospital/Academic Medical Center, Amsterdam (EKZ/AMC); VU Medical Center (VUMC); Amsterdam; Leiden University Medical Center (LUMC), Maastricht University Medical Center (MUMC+), Erasmus MC-Sophia, Rotterdam and UMCU Wilhelmina children's hospital, Utrecht.

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 (Clb/IDS and Clb/EPI) participates together with NIVEL and Erasmus MC in the European Influenza Surveillance Network (EISN) of ECDC collaborating with the WHO regional office for Europe in Copenhagen and reporting in the FluNews Europe Bulletin, and in FluNet and FLUID of the WHO (World Health Organization) in Geneva. Data on influenza and RSV is reported on a weekly basis. 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 infection (ARI) and influenza-like illness (ILI)

**Authors:** Marit de Lange, Gé Donker, Adam Meijer, Mariëtte Hooiveld

**Contributors:** Anne Teirlinck, Linda Verhoef

#### 2.1.1 Key points

- In the 2016/2017 winter season, the influenza epidemic lasted 15 weeks (week 48 of 2016 through week 10 of 2017). This season was comparable in length to four earlier seasons, however it was longer compared to the average duration of the twenty previous seasons (on average 9 weeks of epidemic).
- The peak in ILI incidence in week 5 of 2017 was later than the peak of ARI consultations (week 1 of 2017). The ILI incidence and the number of ARI consultations in children under the age of five peaked in week 51 and 50 respectively.
- The number of ARI consultations declined earlier compared to the four previous seasons.
- The peak in ILI incidence and the seasonal cumulative ILI incidence in nursing home residents was higher than in the four previous years.

#### 2.1.2 Background

Acute respiratory infection (ARI) and the subgroup of influenza-like illness (ILI) are clinical syndromes that can be caused by a range of viruses and bacteria. However, the case definition for ILI is more specific for influenza virus infection. For the surveillance of ARI and ILI, two data sources from NIVEL Primary Care Database are used. First, near real-time (weekly) surveillance data concerning ARI, based on consultation data retrieved from electronic medical records (EMR) from general practices. ARI is defined as a diagnosis of acute upper respiratory infection, acute/chronic sinusitis, acute laryngitis/tracheitis, acute bronchitis/bronchiolitis or influenza (and therefore also includes the ILI case definition). In the 2016/2017 respiratory season, the coverage was about 1.1 million persons (6.6% of the Dutch population). The participating general practitioners (GPs) do not actively report patients and do not take laboratory specimens for surveillance purposes, but make their EMR information systems available for

automatic, anonymized data extraction. Secondly, a proportion of the practices (sentinel practices) in NIVEL Primary Care Database participate in 'sentinel surveillance'. These GPs actively report on the number of patients who consult them for ILI, which is a subgroup of ARI, defined according to the 'Pel criteria' (Pel 1965): sudden onset of symptoms, fever  $\geq 38^{\circ}\text{C}$  and at least one of the symptoms cough, rhinorrhoea, sore throat, frontal headache, retrosternal pain, or myalgia. From a random subset of ILI and/or other ARI patients, sentinel GPs collect a throat swab and a nose swab and send it to RIVM for virological laboratory diagnostics. The population enlisted with the sentinel practices covers approximately 0.7% of the Dutch population and is representative for age, sex, regional distribution and population density. In the Netherlands, two additional systems register the ILI incidence in other populations. First, the RIVM estimates the ILI incidence in institutionalized elderly [<http://www.rivm.nl/Onderwerpen/S/SNIV>]. From a subset of patients, a throat swab and nose swab are analysed at RIVM for respiratory viruses. Secondly, Influenzanet (in Dutch, De Grote Griepmeting) [[www.influenzanet.eu](http://www.influenzanet.eu) and [www.degrotegriepmeting.nl](http://www.degrotegriepmeting.nl)], records the self-reported ILI incidence in the general population. Because of technical problems with the data extraction, the Influenzanet data could not be included in this report.

### 2.1.3 Epidemiological situation, season 2016/2017

#### **Acute respiratory infections (ARI)**

The trend line of weekly number of patients that consulted a GP participating in NIVEL Primary Care Database for an ARI peaked in week 1 of 2017 (39 per 10,000 inhabitants). The peak of the weekly numbers and the seasonal number of consultations for an ARI were within the range of the previous four seasons. However, the decline in ARI consultations was in the 2016/2017 season earlier than in the four previous seasons. The weekly number of ARI consultations was highest in children under the age of five, which is in line with the four previous seasons. This number peaked in week 50 of 2017.

#### **Influenza-like illness (ILI)**

For 15 weeks, from week 48 of 2016 through week 10 of 2017, there was an influenza epidemic, based on GP-attended ILI incidence above the epidemic threshold (5.1/10,000) in combination with circulating influenza virus (see Chapter 3). In week 5 of 2017, the peak of weekly ILI incidence as reported by sentinel GPs was 12/10,000, which was later than the peak in ARI consultations. The cumulative ILI incidence (weeks 40 through 20) in the 2016/2017 season was 184/10,000. Both the peak incidence and cumulative incidence were comparable to four previous seasons. The GP-attended ILI incidence was highest among the 0-4 year olds, followed by people aged 65 years or older. The ILI incidence among 0-4 year olds peaked in week 51. Among nursing home residents, the ILI incidence was higher than in the four previous seasons.

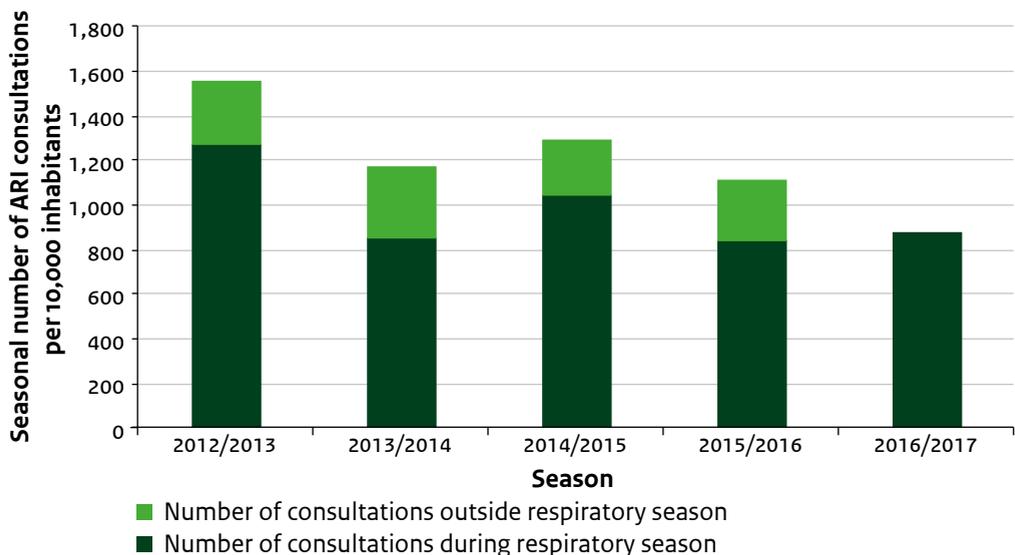
### 2.1.4 Discussion

Based on GP data, the 2016/2017 season was an average season with respect to ILI incidence and weekly numbers of ARI, compared with the four previous seasons. However, compared to the average duration of the epidemic in the past 20 years (average 9 weeks, range 2-21), the 2016/2017 epidemic was relatively long with 15 weeks of epidemic. Additionally, the ILI incidence among nursing home residents was high in the 2016/2017 season, which is typical for a season where influenza virus A(H3N2) is dominant or co-circulating (see chapter 3). This season, the ILI incidence in nursing homes is about two times higher than it is in patients aged 65 years or older in general practice. In the seasons 2012/2013-2015/2016 this was one to three times higher. The difference between elderly GP patients and nursing home is larger when comparing pneumonia consultations (see paragraph 2.2). ARI consultation rates are high relative to ILI incidence, because the contribution of viruses other than influenza is higher in ARI than in ILI.

### 2.1.5 Tables and figures

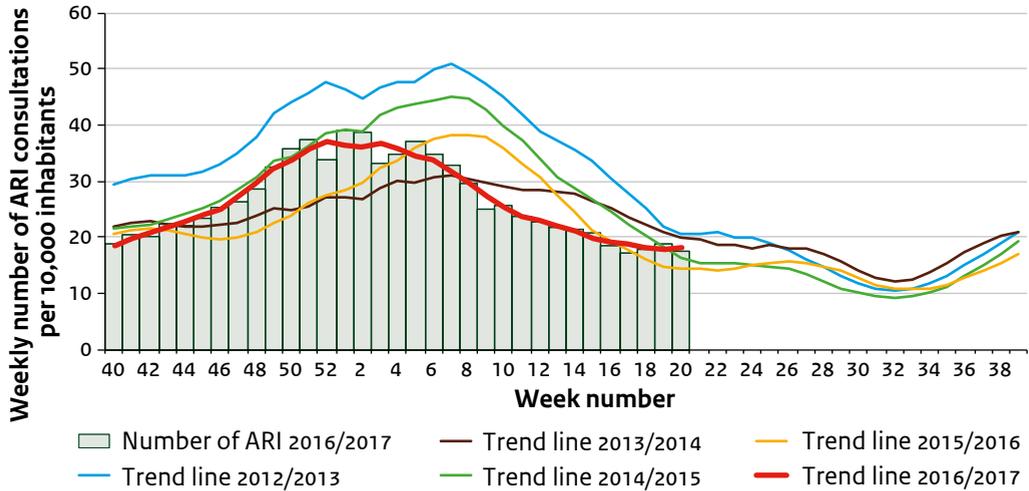
#### GP consultations for ARI

**Figure 2.1** Seasonal number of patients consulting a GP because of ARI within the respiratory season (week 40 through week 20 of the next year) and outside the respiratory season (week 21 through week 39) of 2012/2013-2016/2017 (Source: NIVEL Primary Care Database).



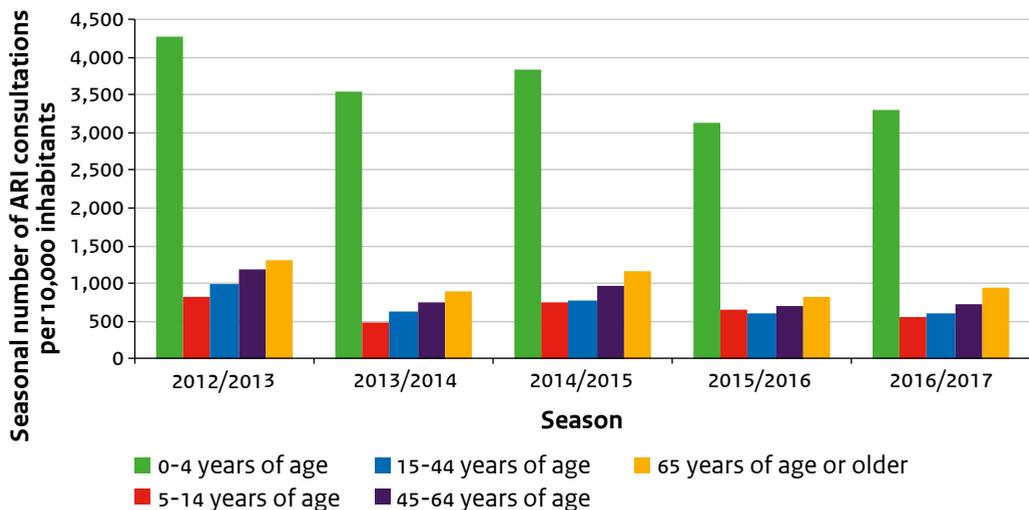
**Footnote:** ARI = acute respiratory infections (including influenza-like illness); GP = general practitioner.

**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 the next year) of 2016/2017 and the trend lines for seasons 2012/2013-2016/2017 (Source: NIVEL Primary Care Database).



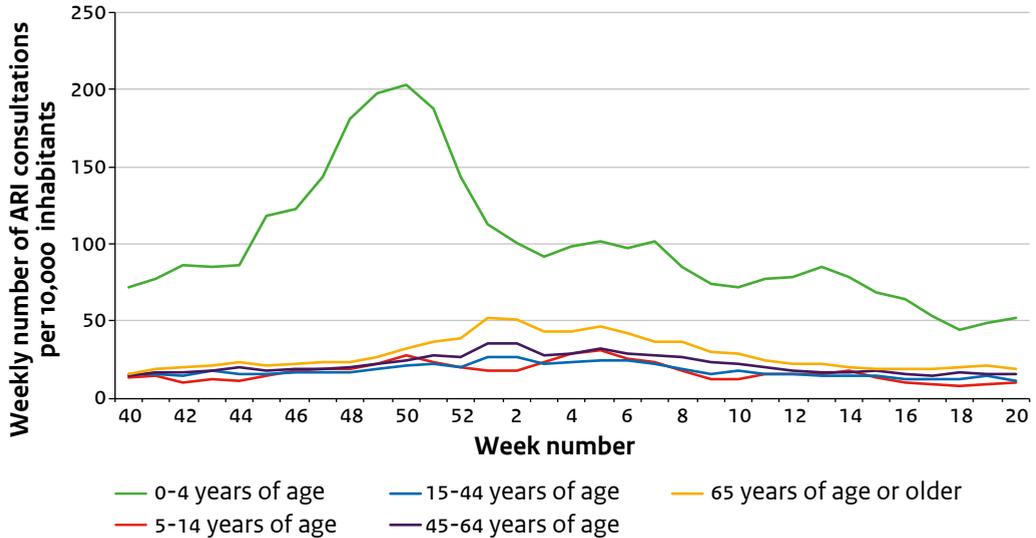
**Footnote:** Trend lines indicate a 5-weeks moving average. ARI = acute respiratory infection, including influenza-like illness; GP = general practitioner.

**Figure 2.3** Seasonal cumulative weekly number of patients consulting a GP because of ARI in the respiratory seasons (weeks 40 through 20 of the next year) of 2012/2013 through 2016/2017 per 10,000 inhabitants, per age category (Source: NIVEL Primary Care Database).



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

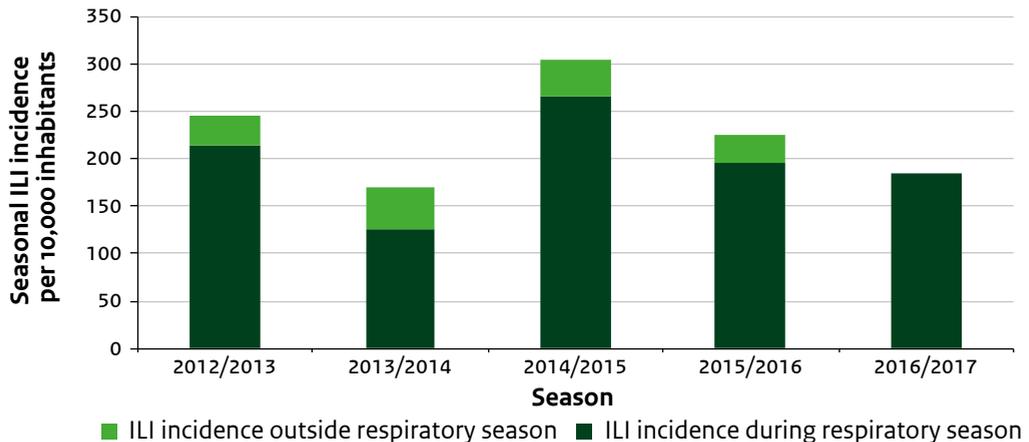
**Figure 2.4** Weekly number of patients consulting a GP because of ARI per 10,000 inhabitants in 2016/2017 (week 40 2016 through week 20 2017) per age group (Source: NIVEL Primary Care Database).



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

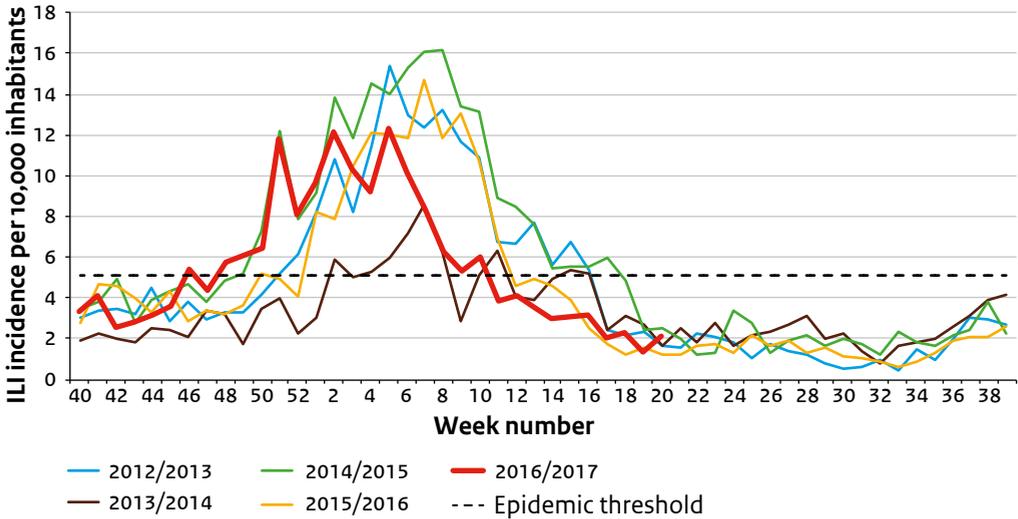
### ILI incidence: sentinel GP practices

**Figure 2.5** Seasonal cumulative ILI incidence within the respiratory season (week 40 through week 20 of the next year) and outside the respiratory season (week 21 through week 39) of 2012/2013-2016/2017 (Source: NIVEL Primary Care Database).



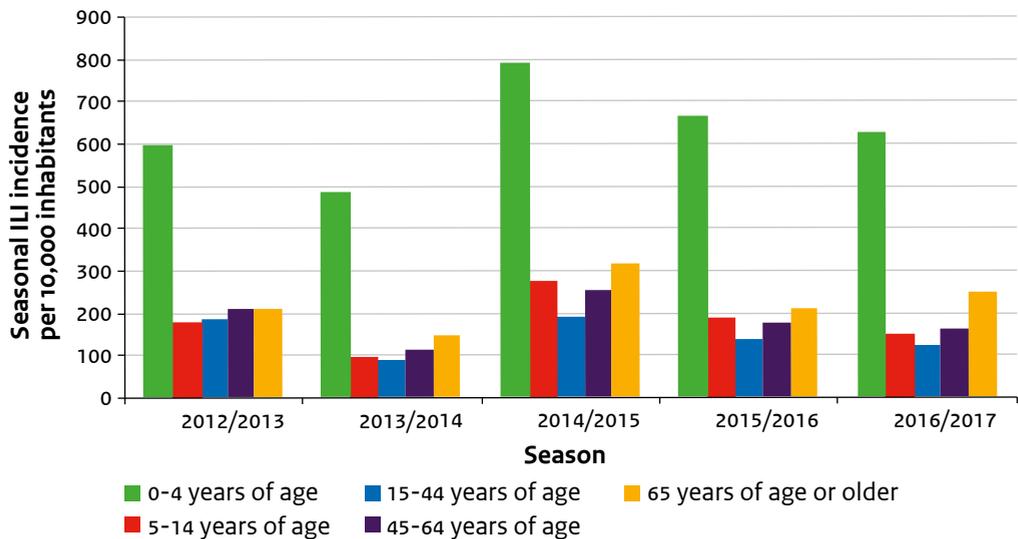
**Footnote:** ILI = influenza-like illness.

**Figure 2.6** Weekly ILI incidence during the seasons 2012/2013-2016/2017 (through week 20 of 2017) (Source: NIVEL Primary Care Database).



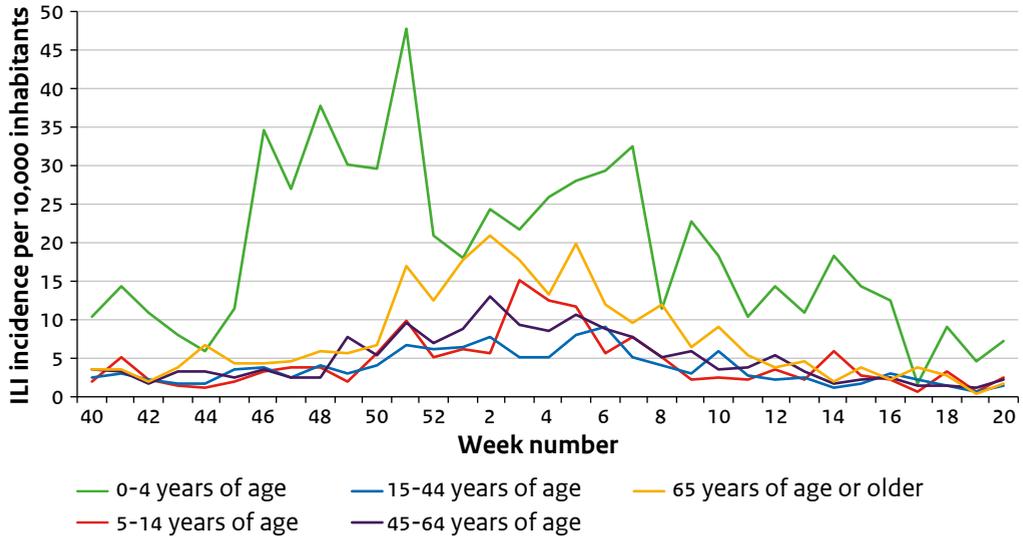
Footnote: ILI = influenza-like illness.

**Figure 2.7** Seasonal cumulative ILI incidence in the respiratory seasons (week 40 through week 20 of the next year) 2012/2013- 2016/2017 per 10,000 inhabitants, by age category (Source: NIVEL Primary Care Database).



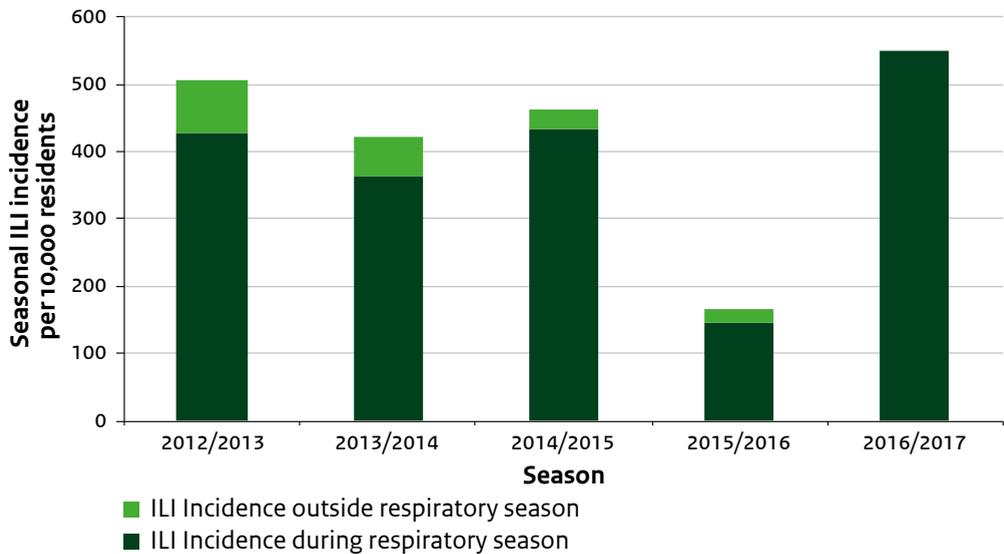
Footnote: ILI = influenza-like illness.

**Figure 2.8** Weekly ILI incidence per 10,000 inhabitants in respiratory season 2016/2017 (week 40 through week 20 of the next year) per age group (Source: NIVEL Primary Care Database).

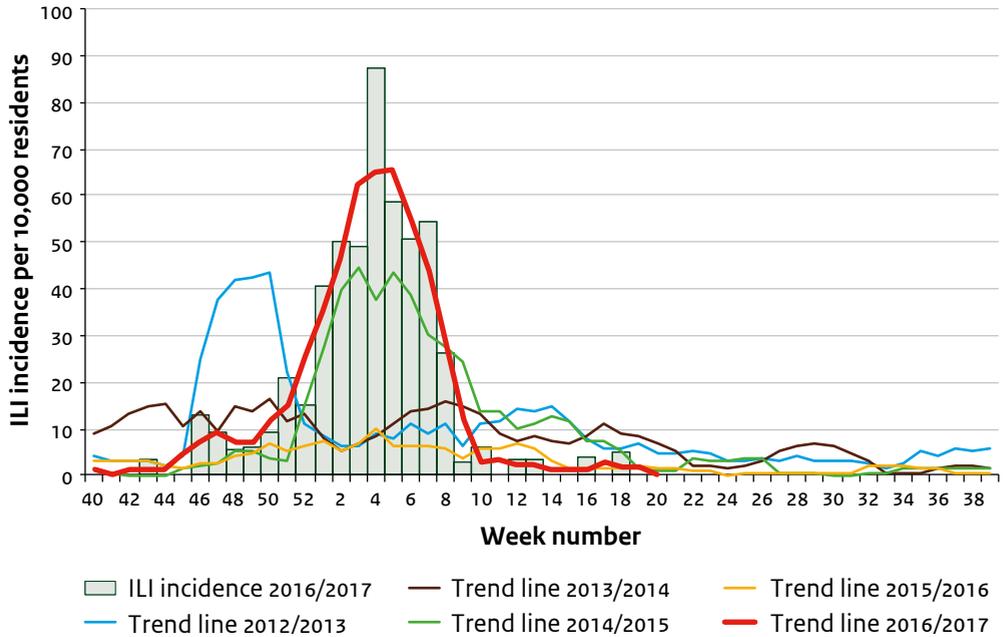


**ILI incidence: in nursing homes**

**Figure 2.9** Seasonal cumulative ILI incidence in SNIV nursing homes per 10,000 within the respiratory season (week 40 through week 20 of the next year) and outside the respiratory season (week 21 through week 39) of 2012/2013-2016/2017 (Source: SNIV, RIVM).



**Figure 2.10** Weekly ILI incidence in SNIV nursing homes per 10,000 residents in the 2016/2017 respiratory season (week 40 through week 20 2017 of the next year) and trend lines for the seasons 2012/2013-2016/2017 (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)

**Authors:** Rianne van Gageldonk-Lafeber, Mariëtte Hooiveld

**Contributor:** Linda Verhoef

### 2.2.1 Key points

- The overall seasonal cumulative pneumonia estimate (week 40 through week 20) of general practitioner (GP) consultations for 2016/2017 was 143 per 10,000 inhabitants (range 2012/2013-2015/2016: 115-172 per 10,000 inhabitants).
- The peak in weekly pneumonia GP consultations (7 per 10,000 inhabitants) was seen in week 1 of 2017 (range 2012/2013-2015/2016: week 51-week 7).
- Most pneumonia consultations were seen in people aged 65 or older, followed by children aged 4 and younger, which is in line with the four previous seasons.
- The overall seasonal cumulative incidence (week 40 through week 20) of pneumonia in SNIV nursing homes for 2016/2017 was 1,570 per 10,000 residents (range 2012/2013-2015/2016: 1,250-10,731 per 10,000 residents).
- The peak in weekly pneumonia incidence in nursing homes (109 per 10,000 residents) was seen in week 2 of 2017 (range 2012/2013-2015/2016: week 42-week 12).

### 2.2.2 Background

Pneumonia is a common clinical disorder of the lower respiratory tract with high morbidity and mortality, especially in the elderly. Typical symptoms include cough, chest pain, fever and difficulty breathing.

Many studies in the Netherlands and other countries show that *Streptococcus pneumoniae* is the predominant aetiological agent of community-acquired pneumonia (CAP), but CAP can be caused by many other microorganisms, mainly bacteria and viruses (van Gageldonk-Lafeber, Wever et al. 2013). In daily clinical care, a general practitioner (GP) diagnosis of CAP is based on clinical symptoms, often without confirming the presence of consolidations on a chest X-ray and without laboratory-confirmed diagnosis (Verheij, Hopstaken et al. 2011). Also in hospital settings, causative pathogens remain unknown in the majority of CAP patients, since microbiological tests are not routinely used and are usually limited to blood and sputum cultures for bacterial causes. Antibiotic treatment is therefore usually empirical, guided by the clinical presentation of the patient.

The pneumonia surveillance in this report includes both the registration of pneumonia by GPs (NIVEL Primary Care Database) and the registration of incidence of pneumonia in nursing homes (SNIV).

### 2.2.3 Discussion

The syndromic pneumonia surveillance in primary care supports the conclusion from the ARI and ILI surveillance that 2016/2017 was an average season. The early part of the 2016/2017 season clearly resembled the 2014/2015 season, but the decrease in the weekly number of pneumonia GP consultations occurred considerably earlier in the current season (respectively week 52 2016 vs week 8 2015). The peak in pneumonia GP consultations followed the peak in the weekly number of ARI consultations and preceded the ILI peak. Because virological

laboratory diagnostics are not included in the pneumonia surveillance, it is unclear to what extent pneumonia is associated with the circulation of influenza virus as well as RSV (respiratory syncytial virus) and rhinovirus.

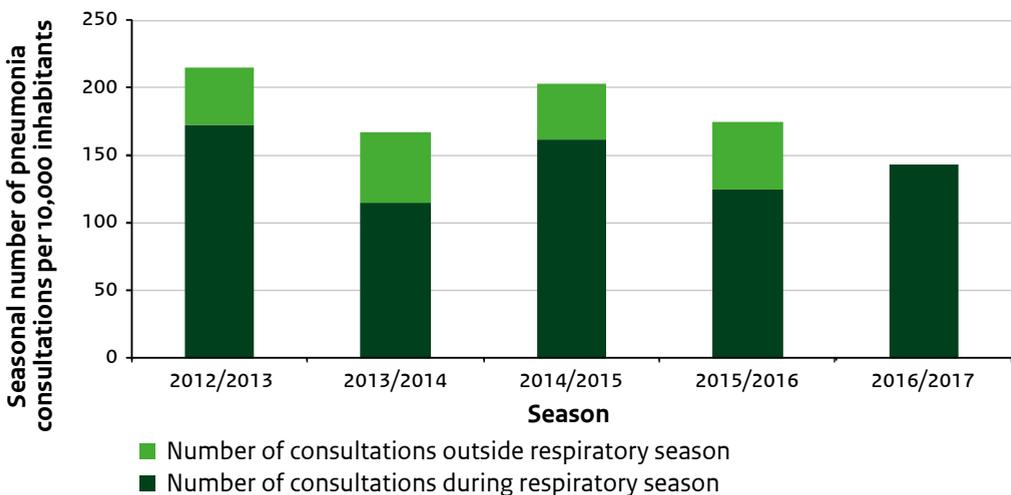
The domination of the influenza virus type A(H3N2) in the recent season might have contributed to relatively high seasonal incidence of pneumonia in nursing homes, similar to the 2014/2015 season where influenza virus type A(H3N2) also dominated.

This season the incidence of pneumonia patients in nursing homes is about 4 times higher than it is in patients aged 65 years or older in general practice, which is within the range of previous seasons (range 2012/2013-2015/2016: 3-4 times higher). This difference can largely be explained by the fact that the nursing home surveillance covers more frail elderly compared to the community dwelling elderly included in the GP surveillance. Additionally, differences in data sampling by the two surveillance systems might contribute to this difference in patient numbers, such as the active case finding in the SNIV surveillance compared with the passive surveillance within the NIVEL Primary Care Database.

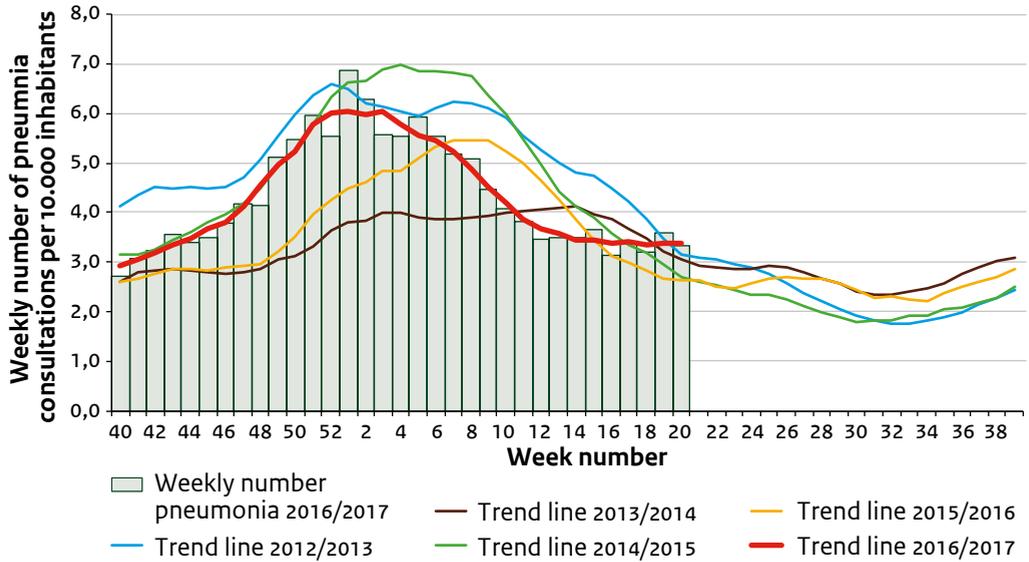
### 2.2.4 Figures

#### GP consultations because of pneumonia

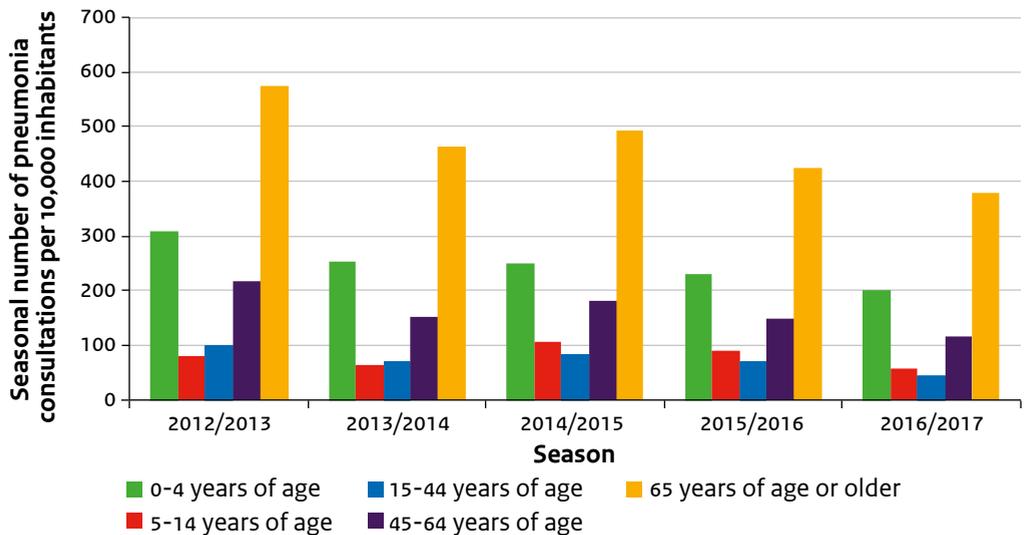
**Figure 2.11** Seasonal cumulative weekly numbers of patients consulting their GP for pneumonia per 10,000 inhabitants within the respiratory season (week 40 through week 20 of the next year) and outside the respiratory season (week 21 through week 39) of 2012/2013-2016/2017 (Source: NIVEL Primary Care Database).



**Figure 2.12** Weekly numbers of patients consulting their GP for pneumonia per 10,000 inhabitants in 2016/2017 (through week 20 of 2017) and the trend lines for 2012/2013-2016/2017 (through week 20 of 2017). Trend lines are based on a 5-week moving average (Source: NIVEL Primary Care Database).

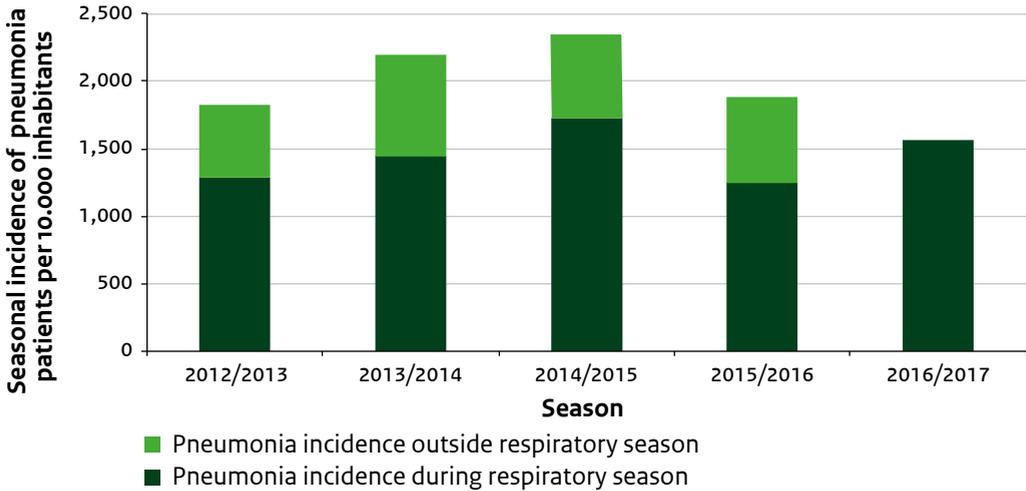


**Figure 2.13** Seasonal cumulative weekly number of GP consultations for pneumonia per 10,000 inhabitants by age group in the respiratory seasons 2012/2013-2016/2017 (week 40 through week 20 of the next year) (Source: NIVEL Primary Care Database).

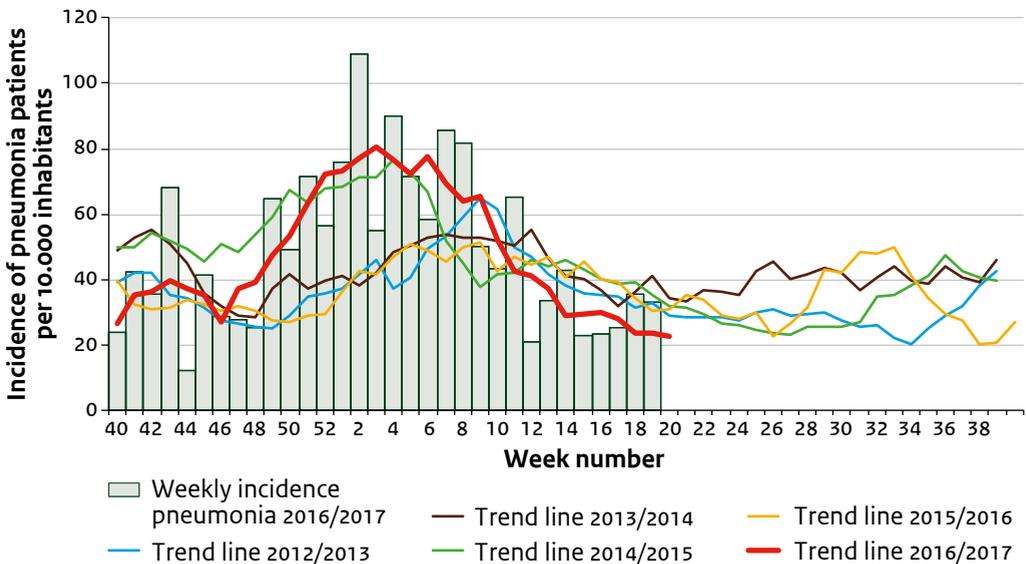


## Incidence of pneumonia (nursing homes)

**Figure 2.14** Pneumonia seasonal incidence in SNIV nursing homes per 10,000 residents within the respiratory season (week 40 through week 20 of the next year) and outside the respiratory season (week 21 through week 39) of 2012/2013-2016/2017 (Source: SNIV, RIVM).



**Figure 2.15** Weekly incidence of pneumonia patients in SNIV nursing homes per 10,000 residents in 2016/2017 (through week 20 of 2017) and trend lines for the seasons 2012/2013-2016/2017 (through week 20 of 2017). The trend lines indicate a 5-week moving average (Source: SNIV, RIVM).



## 2.3 Severe acute respiratory infections (SARI)

**Authors:** Sierk Marbus, Rianne van Gageldonk-Lafeber

**Contributors:** Peter Schneeberger, Geert Groeneveld

### 2.3.1 Key points

- The 2016/2017 SARI season showed less hospital admissions than in 2015/2016, except in those aged  $\geq 60$  years.
- A total number of 821 SARI patients were identified at Leiden University Medical Center (LUMC) during the influenza season 2016–2017. The number of admissions peaked in week 52 of 2016.
- A total number of 580 SARI patients were admitted to Jeroen Bosch Hospital (JBZ) during the influenza season 2016–2017. The number of admissions peaked in week 1 of 2017.
- In order to make SARI surveillance more sustainable, a quality of care management strategy for SARI patients is currently implemented at Jeroen Bosch Hospital.

### 2.3.2 Background

Surveillance of severe acute respiratory infections (SARI) is important to detect outbreaks in time, place and causative pathogen at hospital level in order to implement and evaluate health care interventions. After the influenza A(H1N1)pdm09 in 2009, the World Health Organization (WHO) and European Centre for Disease Prevention and Control (ECDC) advised countries to set up a SARI surveillance system to gain better insight in the severity of epidemics and detect potential pandemics earlier. SARI surveillance has been the missing link in the existing respiratory infections surveillance systems in the Netherlands. Therefore, since 2015 a pilot study started in Jeroen Bosch Hospital and Leiden University Medical Center.

### 2.3.3 Epidemiological situation, season 2016/2017

#### Leiden University Medical Center

In the Leiden–The Hague region, an automated real-time tool for detection of clusters of infectious diseases is operational (ICARES) (Groeneveld, Dalhuijsen et al. 2017). A total number of 821 SARI patients were identified by ICARES in LUMC during the influenza season 2016–2017 (week 40 of 2016 through week 20 of 2017). The intensive care unit (ICU) admitted 94/821 of these SARI patients (11%). During the influenza epidemic (week 48 of 2016 through week 10 of 2017) 453 SARI patients were identified by ICARES. In week 52 of 2016 the peak in weekly number of SARI admissions (48) was reported. Most SARI patients were aged 60 years and older (319/821; 39%), followed by 0–4 year old (293/821; 36%). Vaccination history is not part of the ICARES dataset.

### **Jeroen Bosch Hospital**

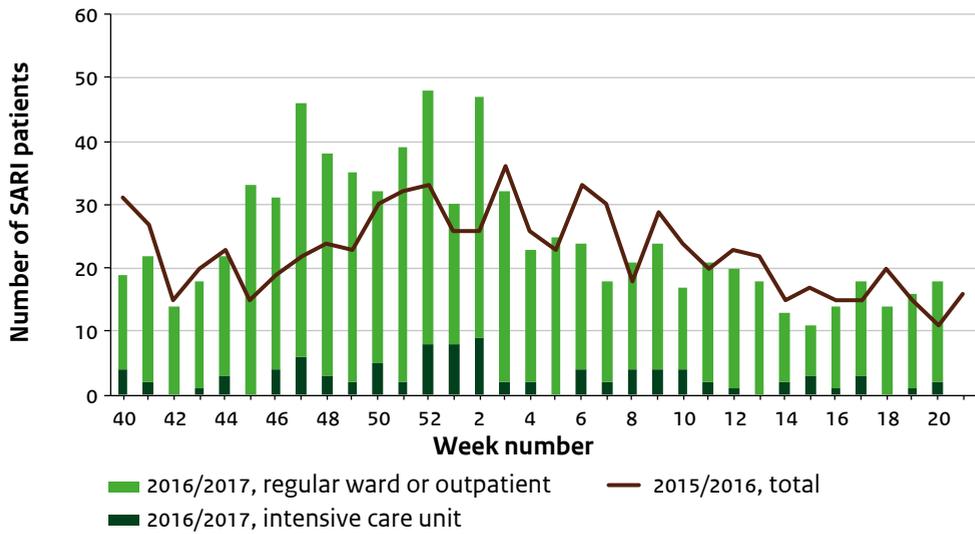
A total number of 580 SARI patients were admitted to the hospital during the influenza season 2016-2017 (week 40 of 2016 through week 20 of 2017). The peak in weekly number of SARI admissions (40) was reached in week 1 of 2017. These numbers were collected retrospectively based on a financial coding system (DBC/DOT). A total of 186 of the 580 patients (32%) were included in the SARI surveillance pilot study. Most SARI patients were aged 60 years or older (154/186; 83%). A high percentage of these SARI patients had an indication for influenza vaccination based on current guidelines (174/186; 94%). The total number of SARI patients who received an influenza vaccination was similar to the season 2015/2016 (68% and 69% respectively). During the influenza season (week 40 of 2016 through week 20 of 2017) 14/186 (8%) included SARI patients were admitted to the ICU.

### **2.3.4 Discussion**

In the 2016/2017 influenza season, the total number of SARI patients admitted to LUMC and JBZ was lower than season 2015/2016. Based on these absolute numbers, the 2016/2017 respiratory season was a less severe SARI season compared to season 2015/2016. Most SARI patients were aged 60 years and older during this influenza A(H3N2) dominated season, which is known to have a higher burden of disease in the elderly (Turbelin, Souty et al. 2013, Beaute, Zucs et al. 2015). Compared to the influenza A(H1N1)pdm09 dominated season 2015/2016 at the LUMC, there were more SARI patients aged 60 years and older and less SARI patients 0-4 year old in 2016/2017. This season, our goal was to optimize ICARES regarding data supply for four hospitals in the Leiden/The Hague region and make distinction between SARI patients requiring hospital admission and outpatients. Unfortunately, the planned improvements of ICARES have not materialised yet. In order to make SARI surveillance more sustainable in the future at JBZ, the SARI surveillance pilot study changed from a research to a quality of care management strategy in February 2017. The quality of care of SARI patients is now evaluated based on quality indicators, such as diagnostics, infection control measures, and treatment. At the same time, new diagnostic guidelines are implemented to have more uniform microbiological testing during and after the respiratory season. For example, the new JBZ diagnostic guideline recommends that all SARI patients should be tested for influenza during the influenza season. In addition to a more embedded SARI surveillance system in the current electronic patient record system (HiX), the quality of care of SARI patients is thought to improve with this new strategy. Regular feedback of the quality indicators to the clinicians by the JBZ antibiotic stewardship team is thought to improve the quality of care of SARI patients in the following years. The value of the quality of care management strategy of SARI patients at JBZ is evaluated after season 2017/2018.

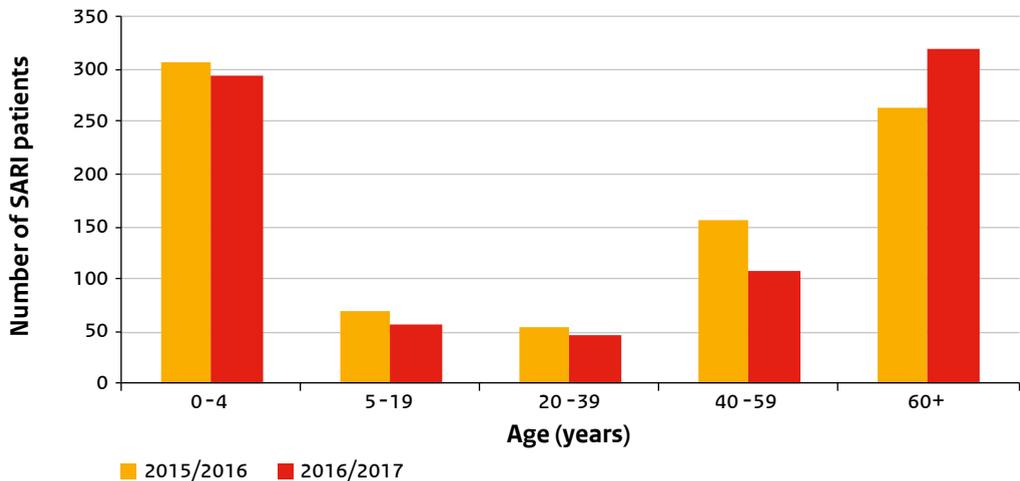
### 2.3.5 Figures

**Figure 2.16** Number of patients with a SARI during influenza season 2016/2017 (week 40 of 2016 through week 20 of 2017) and 2015/2016 in the Leiden region reported by ICARES.



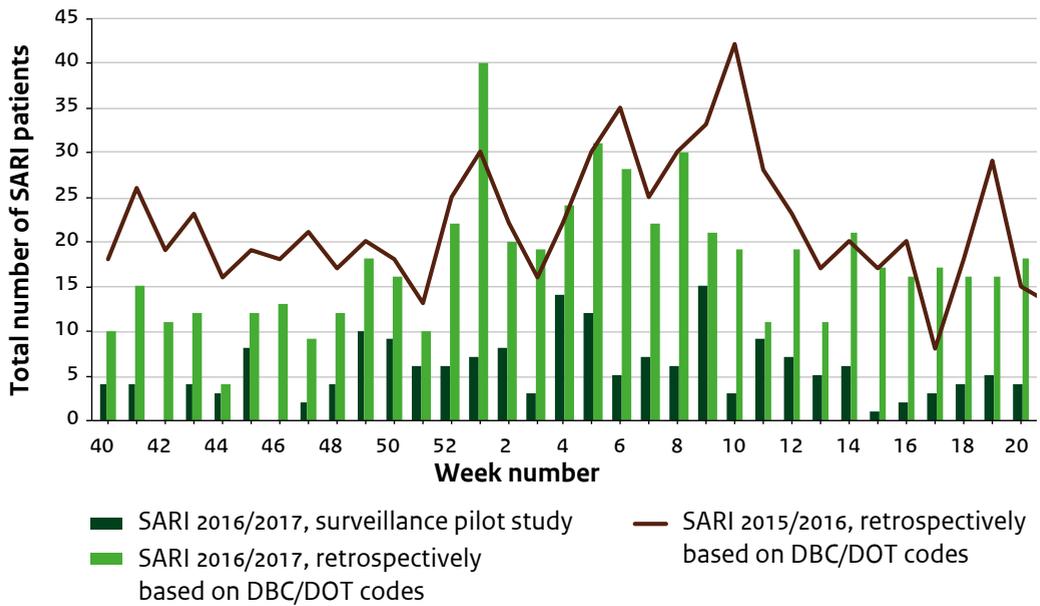
**Footnote:** SARI = severe acute respiratory infection.

**Figure 2.17** Age distribution of patients with SARI a per age category in the 2015/2016 and 2016/2017 respiratory season (week 40 through week 20) in the Leiden region reported by ICARES.



**Footnote:** SARI = severe acute respiratory infection.

**Figure 2.18** Absolute number of SARI patients admitted to the Jeroen Bosch Hospital during respiratory season 2015/2016 and 2016/2017 versus the number of SARI patients included in the SARI surveillance study during respiratory season 2016/2017.



**Footnote:** SARI = severe acute respiratory infection.

## 2.4 Severe acute respiratory infections (SARI) in paediatric intensive care units (PICU)

**Authors:** Anne Teirlinck, Gudrun Freidl

**Contributors:** Carole Brouwer, Marjan de Jong, Marjorie de Neef, Dick Markhorst, Els Roodbol, Dick Tibboel, Brigitte Timmers-Raaijmakers, Gijs Vos

### 2.4.1 Key Points

- In the 2016/2017 season, for the first time, data were available on SARI in paediatric intensive care units (PICU) for almost a full respiratory season (starting in week 42 of 2016). Six out of total eight PICUs of the Netherlands participated in the PICU SARI surveillance, covering approximately 75% of the paediatric population.
- From week 42 of 2016 through week 20 of 2017, a total of 324 SARI patients were newly admitted to one of the six PICUs.
- The number of SARI patients newly admitted to the PICUs per week ( $n=39$ ) peaked in week 49 of 2016.
- The peak prevalence was in week 50 of 2016, with 50% of the total PICU beds occupied by SARI patients during that week.
- Three patients required extracorporeal membrane oxygenation (ECMO) treatment, in week 44, 45 and week 50 of 2016.
- The majority (80%) of SARI patients admitted to PICU was below 1 year of age.
- Respiratory syncytial virus (RSV) was most often detected (68%), followed by rhino/enterovirus (25%) and influenza virus (7%). Other viruses (found in 21% of the patients) included coronavirus, adenovirus, bocavirus, parainfluenza virus (no subtype), parainfluenza virus type 2, 3 and 4, and human metapneumovirus (hMPV). In 24 of the total 162 patients with a positive RSV test result, co-infection with one or more other pathogens was detected.
- At the start of the respiratory season, RSV was clearly the dominant pathogen, accounting for 80% of the tested SARI patients from week 46 of 2016 through week 2 of 2017.

### 2.4.2 Background

While surveillance of influenza-like illness (ILI), acute respiratory infections (ARI) and pneumonia in primary care is well established in the Netherlands, there was no insight in severe acute respiratory infections (SARI). In the 2015/2016 season, ad-hoc information on SARI patients was obtained from three paediatric intensive care units (PICU) during the influenza epidemic, following media reports and anecdotal information from physicians indicating unusually high numbers of admission of relatively young patients with severe influenza virus infection. Cooperation with the PICUs had already proven successful during the 2009 influenza pandemic (Dijkstra, van 't Klooster et al. 2010). Building on that experience, all Dutch PICUs were asked to participate in a surveillance system for SARI in the paediatric population in the 2016/17 season, with the aim to develop a simple and sustainable surveillance system. In the Netherlands, eight PICUs cover the entire Dutch paediatric IC population. The PICUs fall under one organisation (in Dutch: *Sectie Intensive Care Kinderen (SICK)*).

The PICU SARI surveillance is established in addition to the SARI surveillance in two hospitals in the Netherlands (paragraph 2.3), that mainly covers adult patients and which does not provide information on virological laboratory results for children.

Collecting data on severe respiratory paediatric cases fills a crucial gap in the surveillance pyramid by providing important information on severity and burden of circulating respiratory pathogens and enabling comparison of several respiratory seasons. The PICUs provided aggregated data to the RIVM via a web-based interface. The data was used for weekly monitoring of infectious diseases by RIVM. A more comprehensive feedback report was sent to the PICUs on a monthly basis.

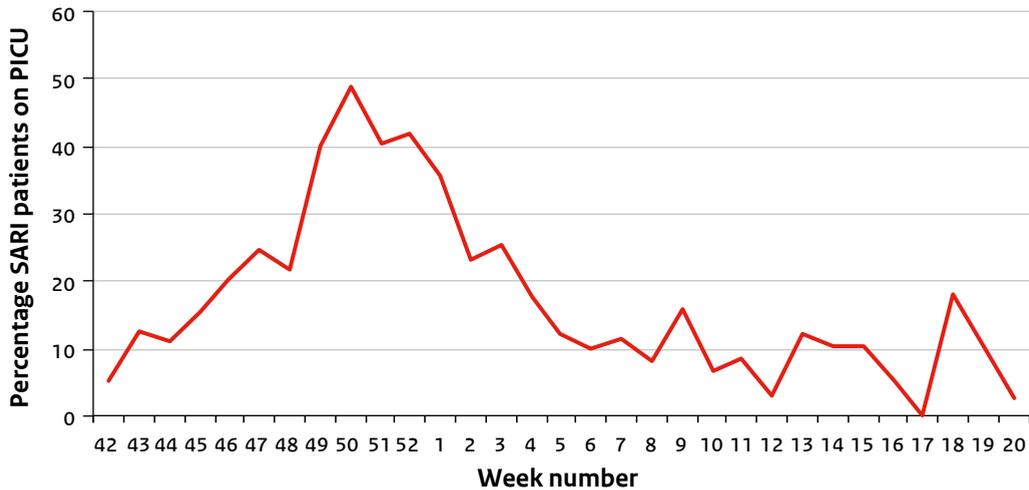
### 2.4.3 Discussion

PICU data over the 2016/2017 winter season clearly showed that most intensive care admissions for SARI were due to RSV, rather than influenza virus. The temporal pattern of SARI admissions at PICUs is consistent with the pattern among children presenting with milder ILI and ARI symptoms at the GP (see chapter 4). Because this is the first year of (almost) full respiratory SARI PICU surveillance, no trends can be explored yet. Our goal is to develop a sustainable surveillance system, which would allow for comparison of trends over multiple seasons in the future. This surveillance system was evaluated by including all relevant stakeholders (PICUs and public health professionals from RIVM). In according with the triple S guidelines (Triple S. Project 2011) the following indicators were evaluated: usefulness, costs (resources and time-investment), acceptability, simplicity and flexibility.

The usefulness of the PICU SARI surveillance to better understand SARI epidemiology was rated 3.7 on average, on a scale from 1 (not at all useful) to 5 (extremely useful). Usefulness with respect to public health action was rated 3.4 for all stakeholders combined, whereas usefulness for clinical practice scored 2, since it does not change therapy plans. The most appreciated features of this surveillance system by the PICUS were the real-time reporting and the availability of laboratory results. PICUs generally found the time investment acceptable (average score: 3.2). General user-friendliness and simplicity of the system was rated with 3.5. The evaluation identified several points for improvements which will be used to further advance the system.

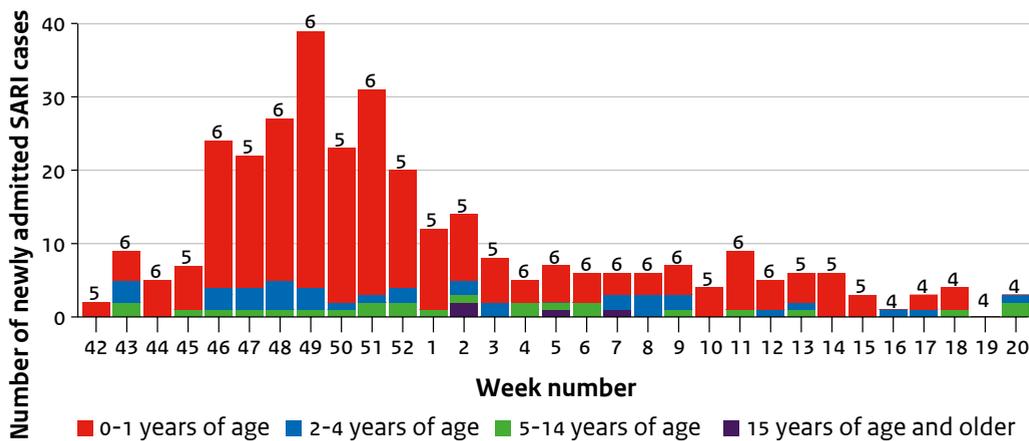
## 2.4.4 Figures

**Figure 2.19** Prevalence of SARI cases in PICUs (week 42 of 2016 through week 20 of 2017) (Source: PICU SARI surveillance).



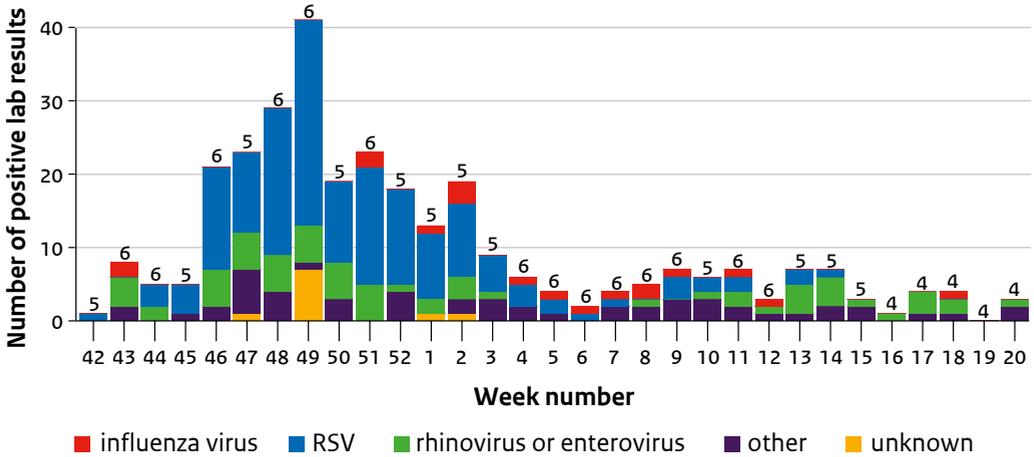
**Footnote:** The line indicates the percentage of SARI cases out of the total number of patients admitted to the PICUs at certain point of the week. SARI = severe acute respiratory infection; PICU = paediatric intensive care unit.

**Figure 2.20** Number of new SARI cases admitted to the six PICUs per age group (week 42 of 2016 through week 20 of 2017) (Source: PICU SARI surveillance).



**Footnote:** The numbers above the bars represent the number of PICUs that reported data for that week. SARI = severe acute respiratory infection; PICU = paediatric intensive care unit.

Figure 2.21 Number of positive laboratory tests in SARI cases newly admitted to the six PICUs (week 42 of 2016 through week 20 of 2017) (Source: PICU SARI surveillance).



**Footnotes:** Important for interpretation of laboratory results is that virological testing at PICUs is done to facilitate individual patient management, not for surveillance purposes. Because coinfection occurs regularly, the graph does not represent the total number of cases with a positive test result. The numbers above the bars represent the number of PICUs that reported data for that week. RSV = respiratory syncytial virus  
 SARI = severe acute respiratory infection; PICU = paediatric intensive care unit.

## 2.5 Weekly mortality monitoring

**Author:** Liselotte van Asten

**Contributors:** Ursula de Bruijn- van Leijden, Felicia Minnaard, Lenny Stoeldraijer, Marit de Lange, Anne Teirlinck

### 2.5.1 Key Points

- An average of 2,750 deaths occurred weekly in the Netherlands over the past five years (2012-2016).
- Excess mortality was estimated at 7,503 deaths occurring during the 15 weeks of the 2016/2017 influenza epidemic (week 48 of 2016 through week 10 of 2017).
- Increased mortality occurred during the entire influenza epidemic except for the first two weeks and a drop in week 52 (week 52 coinciding with the Christmas holiday).
- Excess mortality was estimated at 8,890 during the total respiratory season (week 40 of 2016 through week 20 of 2017, a total of 44 weeks).
- Excess mortality was high during the 2016/2017 15-week-long influenza epidemic. In the past 5 years, it was only higher during the 2014/2015 season, which was the longest recorded epidemic in the Netherlands.
- Excess mortality was mainly observed in persons 75 years and older.

### 2.5.2 Background

The Dutch weekly mortality monitoring system was initiated in August 2009, during the influenza A(H1N1) 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 million in 2016) 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). 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.

### 2.5.3 Epidemiological situation, season 2016/2017

In the 2016/2017 winter-season, all-cause mortality (number of deaths reported within two weeks) was significantly increased since the 3rd week of the influenza epidemic. The number of deaths were increased from week 50 of 2016 up to week 10, except for a dip in week 52. Cumulative excess mortality was estimated at 7,503 deaths occurring during the 15 weeks of the 2016/2017 influenza epidemic (week 48-10). Excess mortality was high during the 2016/2017 influenza epidemic: in the past 10 years it was only higher, during the longest 21-week influenza epidemic of 2014/2015 (estimated 8,680 deaths).

Excess mortality was primarily observed in persons 75 years and older. During several weeks of the influenza epidemic, it was also observed in younger age groups. Excess deaths were seen for three weeks in 65-74 year olds (in weeks 1, 2 and 6) with a higher peak than observed in the previous five years in week 2 (585 deaths, when 485 baseline deaths were predicted). The mortality in 15-24 year olds was slightly increased in weeks 52, 1 and 8 (but not statistically significant) with 14 weekly deaths where 7 to 8 deaths were expected as baseline. Although these numbers are much lower than in the elderly, for the total influenza epidemic, the cumulative mortality in this age group was higher than in any of the previous 5 years (43 excess deaths during the 15 influenza weeks).

### Excess Mortality in Europe

The Netherlands participates in weekly mortality monitoring at a European level in the EuroMOMO collaboration [[www.EuroMOMO.eu](http://www.EuroMOMO.eu)]. The majority of 19 participating European countries have had a marked excess in all-cause mortality, since the end of 2016; in particular among elderly aged 65 years and above. Excess mortality was primarily explained by circulation of influenza virus A(H3N2). Cold weather snaps contributed in some countries. The pattern was similar to the last major influenza A(H3N2) season in 2014/15 in Europe, although starting earlier in line with the early influenza season start (Vestergaard, Nielsen et al. 2017).

#### 2.5.4 Discussion

In terms of number of deaths during the respiratory season (weeks 40-20) and during the influenza epidemic (weeks 48-10), the 2016/2017 season in the Netherlands was more severe compared to most earlier years; in the past 5 years, it was only higher during the 2014/2015 season (which was the longest recorded epidemic in the Netherlands with 21-weeks and an estimated 8,680 excess deaths).

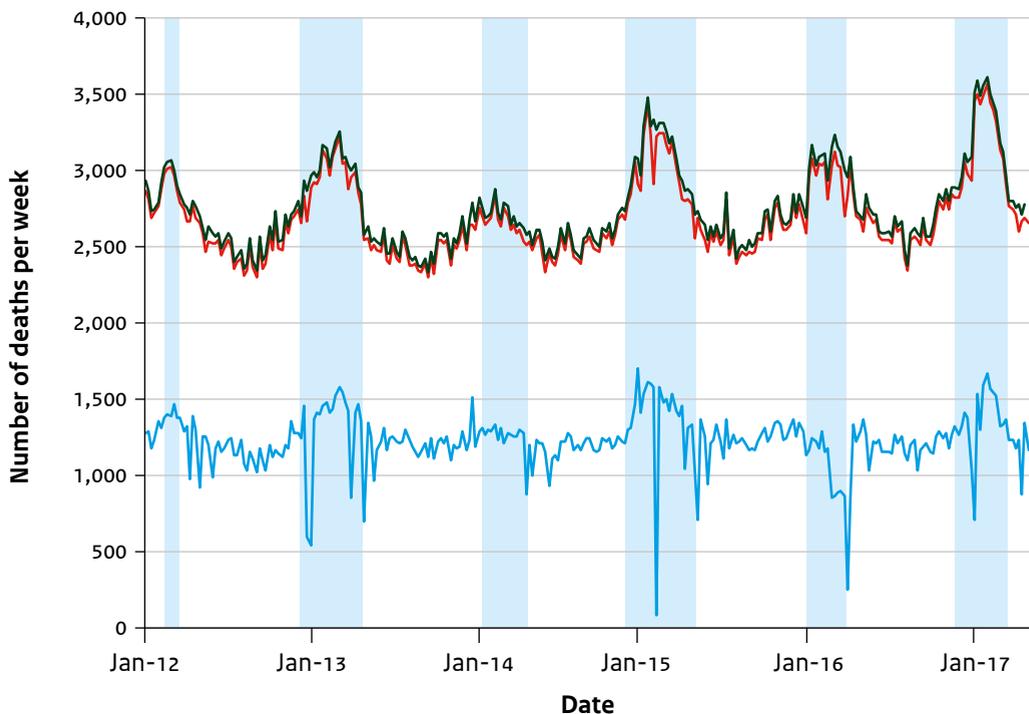
The influenza epidemic often coincides with increased mortality. It is assumed that influenza plays a role in the increased mortality observed during wintertime in the Northern Hemisphere (Molbak, Espenhain et al. 2015). Other typical winter pathogens can also play a role in increased seasonal mortality, such as RS-virus and norovirus (van Asten, van den Wijngaard et al. 2012). Cold temperatures may also play a role in increased mortality. There were 2 short cold periods during the influenza epidemic (3 days around January 17th and 4 days around February 10th) with maximum daily temperatures between -2°C and 1°C. Mortality showed a transient drop in week 52 coinciding with the Christmas holiday (perhaps signifying decreased influenza transmission due to school and work closure).

Estimates of influenza-attributable deaths have been made using statistical models. Although estimates vary hugely between seasons (due to influenza virus strain variability), an average of 1,389 deaths per year for the Netherlands were estimated to be attributable to influenza A and B infections in the 65+ age group (1999-2007) (van Asten, van den Wijngaard et al. 2012) and an average of 1,956 yearly deaths (all ages) were estimated to be attributable to influenza for 1999-2009 using influenza-like-illness data instead of influenza laboratory diagnoses (Wijngaard, Asten et al. 2012).

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

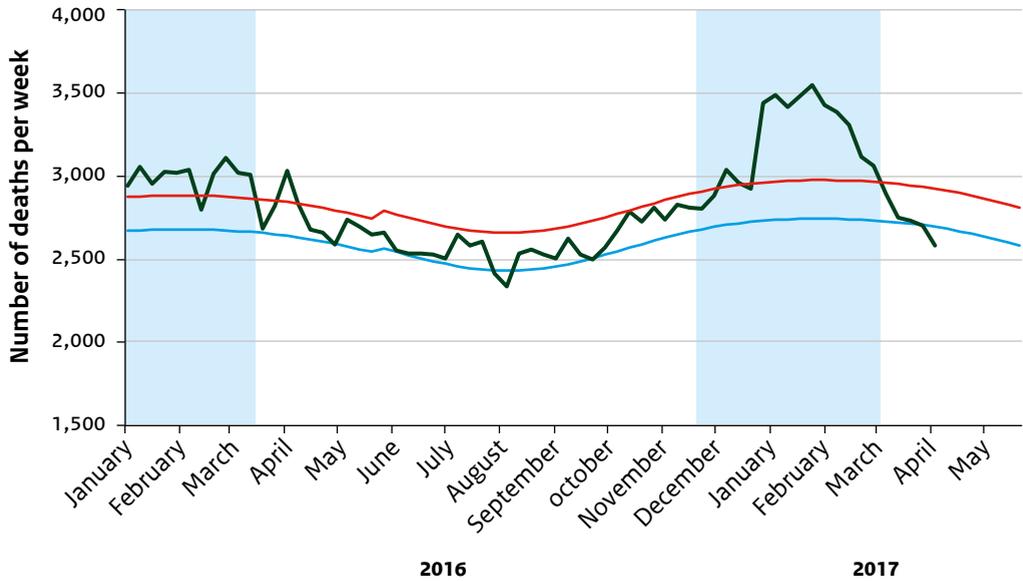
### 2.5.5 Figures

**Figure 2.22** Weekly number of deaths from 2012 to 2017 (through week 20 of 2017) by date of death at three different levels of notification delay (notified within one, two and three weeks from date of death).



**Footnote:** Bottom blue line: deaths notified within one week; red line: notified within two weeks; top green line: notified within three weeks.

**Figure 2.23** Observed and expected ('baseline') weekly number of deaths (reported within two weeks, 93% complete) from 2016 through week 20 of 2017 with the influenza epidemic weeks depicted by blue shading.



**Footnote:** Green line: number of deaths per week (reported within two weeks). Blue line: expected number of deaths (calculated using historical data in which extremes were excluded). Red line: upper prediction limit (based on the 95% confidence interval).

# Chapter 3

## Influenza

**Authors:** Marit de Lange, Gé Donker, Sierk Marbus, Adam Meijer

**Contributors:** Anne Teirlinck, Frederika Dijkstra, Pieter Overduin, Ton Marzec, Gabriel Goderski, Sharon van den Brink, Lisa Wijsman, Mariam Bagheri, Ruud van Beek, Mark Pronk, Guus Rimmelzwaan, Jan de Jong<sup>†</sup>, Linda Verhoef, Peter Schneeberger, Anne Robben, Scott McDonald

<sup>†</sup> Deceased during the reporting period.

### 3.1 Key points

- In the 2016/2017 season, the influenza epidemic lasted 15 weeks.
- Subtype A(H3N2) was the dominating influenza virus during the entire season.
- The dominant A(H3N2) virus in the Netherlands showed wide genetic diversity resulting in many amino acid substitution in antigenic determinants of the hemagglutinin.
- Antigenic characterization of A(H3N2) viruses was difficult due to lack of hemagglutination. However, those characterized worldwide with similar amino acid substitution profiles as the Dutch A(H3N2) viruses showed generally a good to moderate match with the vaccine strain.
- The estimated cumulative symptomatic influenza incidence in the 2016/2017 respiratory season was 2,920 (95% uncertainty interval (UI): 2,400-3,580) per 100,000 inhabitants. This was lower than the estimates of most four previous respiratory seasons, except for season 2013/2014. The influenza incidence was almost exclusively caused by subtype A(H3N2) and highest for the age group <5 years old.
- Except for one A(H3N2) virus all 945 viruses tested for antiviral susceptibility were sensitive for neuraminidase inhibitors.
- In the Netherlands, the vaccine effectiveness (VE) against laboratory confirmed influenza virus subtype A(H3N2) infection was estimated as 47% (95% confidence interval (CI): 15% to 67%) overall, 25% (95%CI: -56% – 64%), and 70% (95% CI: 38% – 85%) among those aged < 60 years and ≥ 60 years respectively.
- Preliminary end-of-season estimates of the European I-MOVE study, in which the Netherlands participates, shows an influenza VE of 27% [95% CI: 15% – 37%] for patients at the primary care level and 18% [95% CI: 2% – 31%] at hospital level.

## 3.2 Background

Influenza is an acute respiratory infection caused by influenza viruses. It can cause mild to severe illness. Possible symptoms are fever, cold shivers, headache, muscle pain, sore throat and cough. 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. There are several types of influenza virus, which are constantly mutating, possibly resulting in antigenic drift.

Human influenza viruses cause yearly epidemics mostly in winter. Most influenza virus infections in humans are caused by the influenza virus types A and B. Influenza type A viruses are divided into subtypes based on proteins on the surface of the virus: hemagglutinin (HA) and neuraminidase (NA). Many different combinations of HA and NA proteins are possible, for example H1N1 and H3N2. 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.

## 3.3 Epidemiological situation, season 2016/2017

### **Virological surveillance**

In the 2016/2017 respiratory season, 1,061 specimens were taken from patients with influenza-like illness (ILI) or another acute respiratory infection (ARI) by the sentinel GPs. In 197 of the 584 ILI specimens (34%) influenza viruses were detected and, in 77 of the 477 other ARI specimens (16%) influenza viruses were detected. Only eight specimens (2 ILI and 6 other ARI specimens) were taken from SNIV nursing home residents (results not shown), of which two other ARI specimens were positive for influenza virus A(H3N2). Additionally, 3,357 influenza virus-positive specimens were submitted by Dutch laboratories for further investigation. The origin of these specimens is unknown, but presumably they were more often taken from hospitalized patients than from ambulatory patients. The highest percentage of influenza viruses detected among all age groups was found in the age group of 5-14 years, both for the ILI (66%) and the other ARI (48%) specimens.

In the 2016/2017 season, there was an influenza epidemic from week 48 of 2016 through week 10 of 2017. During the entire season, influenza virus A(H3N2) virus dominated in the GP sentinel surveillance and in the influenza specimens sent in by Dutch Laboratories. A(H1N1)pdm09 and B (both Yamagata and Victoria lineage) viruses were only sporadically detected. Except for one virus, all Dutch A(H3N2) viruses belonged to clade 3C.2a, which is the same as the vaccine virus. However, most viruses belonged to subclade 3C.2a1. In addition, several clusters with distinct amino acid substitution patterns were observed. The vast majority of these amino acid substitutions in the hemagglutinin were located in antigenic determinants. Antigenic characterization of A(H3N2) viruses was difficult due to lack of hemagglutination. However, those characterized worldwide with similar amino acid substitution profiles as the Dutch A(H3N2) viruses showed generally a good to moderate match with the vaccine strain.

The B virus (Yamagata lineage) was not included in the trivalent influenza vaccine in the 2016/2017 season; however, the detected numbers were low.

The estimated influenza incidence is a useful estimate of the extent of symptomatic influenza in the population that can be compared across seasons, in which the estimated ILI incidence in the community, the GP ILI incidence, and the percentage positive specimens for influenza virus are combined. (McDonald, Presanis et al. 2014). During the 2016/2017 season, an estimated 2,920 (95% uncertainty interval (UI): 2,400-3,580) per 100,000 population had symptoms of an influenza virus infection. This was lower than the estimates for the previous four respiratory seasons, except for season 2013/2014. The highest symptomatic influenza incidence of the previous four respiratory seasons was in season 2014/2015 (4,830 (95% UI 4,050-5,740)), the lowest in season 2013/2014 (1,050 (95% UI 720-1,490)) per 100,000 population. The influenza incidence in respiratory season 2016/2017 was almost exclusively caused by subtype A(H3N2) whereas in most of the four previous seasons, co-circulation occurred. The influenza type A(H3N2) specific symptomatic influenza incidence in season 2016/2017 (3,190 per 100,000 population (95% UI 2,550-3,890)) was similar to the incidence of season 2014/2015 (3,450 per 100,000 population (95% UI 2,740-4,250)). However, in this latter season, also influenza type B (Yamagata lineage) caused a substantial number of symptomatic influenza cases (1,640 per 100,000 population (95% UI 1,150-2,220)). The estimated cumulative symptomatic influenza incidence in the 2016/2017 respiratory season was highest in children under the age of five (5,660 per 100,000 <5 years old population (95% UI 2,330-12,030)), but lower than in most four previous seasons. The incidence in people of 65 years or older (2,900 per 100,000 ≥65 years old population (95% UI 1,730-4,680)) was similar to the other age groups above 5 years old. In four previous seasons, this was however always the age group with the lowest symptomatic influenza incidence.

Except for one influenza A(H3N2) virus with oseltamivir reduced inhibition, there were no indications of reduced inhibition by the neuraminidase inhibitors oseltamivir and zanamivir among influenza A and B viruses in the 2016/2017 season. The influenza virus isolate with oseltamivir reduced inhibition had no known amino acid substitution explaining this result; other amino acid substitutions were present but that have never been associated with reduced inhibition before.

In the 2016/2017 season, the severe acute respiratory infections (SARI) surveillance pilot study started its second season at the Jeroen Bosch Hospital (JBZ). During the influenza epidemic 2016/2017, 77 respiratory specimens of 124 SARI patients were tested for influenza virus (62%). In 32 of 77 respiratory specimens, influenza virus was detected (42%). On average, 8 SARI patients per week were included in the SARI surveillance pilot study. The median age of SARI patients with a positive influenza test was 75 years (SD 15, range 18-93). Influenza A(H3N2) was the dominant strain detected in patients ≥ 18 years at the JBZ. LUMC participated in the I-MOVE+ study that aims to assess vaccine effectivity in patients ≥ 60 years and older. For this study, specimens of SARI patients in LUMC were tested for influenza at RIVM's Centre for Infectious Disease Research, Diagnostics and Screening (IDS). In these specimens, influenza A(H3N2) was also the dominant strain.

### Vaccine effectiveness

The vaccine effectiveness (VE) against laboratory confirmed influenza virus infection was estimated partly protective for the subtype A(H3N2): 47% (95% confidence interval (CI): 15% – 67%). The VE for subtype A(H3N2) was higher for people of 60 years and older (VE=70% [95% CI: 38% – 85%]), than for people below 60 years (VE=25% [95% CI: -56% – 64%]). Next to the calculations on national level, the RIVM participates in a European influenza VE network, I-MOVE. The preliminary end-of-season estimates of influenza VE against influenza type A(H3N2) at primary care level was 27% (95%CI: 15% – 37%) overall, 29% (95%CI: -8%-54%), 32% (95%CI: 16%-46%) and 14% (95%CI:-12%-33%) among those aged 0-14, 15-64 and 65+ years respectively. At hospital level, adjusted VE for influenza A(H3N2) was 18% (95% CI: 2%-31%) overall; 25% (95% CI: 2%-42%) among the 65-79 years old and 12% (95% CI: -12%-31%) among the ≥80 years (personal communication, Esther Kissling).

## 3.4 Discussion

During the 15-weeks epidemic in the 2016/2017 season, influenza virus A(H3N2) was dominant. Because of the reasonably good match between the circulating and the vaccine influenza virus A(H3N2), the same strain as the 2016/2017 season has been selected by the WHO for the trivalent vaccine for the 2017/2018 season in the northern hemisphere [[http://www.who.int/influenza/vaccines/virus/recommendations/2017\\_18\\_north/en/](http://www.who.int/influenza/vaccines/virus/recommendations/2017_18_north/en/)]. Unlike the 2014/2015 and the 2015/2016 season, where influenza virus type B became dominant in the second half of the epidemic, the virus was now only sporadically detected. Influenza virus type B (Yamagata lineage) and (Victoria lineage) were both detected at a low level. The B component in the 2017/2018 trivalent vaccine remains the same as in the 2016/2017 trivalent vaccine. In the 2016/2017 season, influenza virus A(H1N1)pdm09 was also only sporadically detected. For next season, the A(H1N1)pdm09 component will be changed in a more recent virus for the northern hemisphere 2017/2018 trivalent vaccine. This is mainly because some human post-vaccination sera had a lower reactivity with some recent circulating influenza viruses of this subtype compared to the vaccine strain, despite that those most recent circulating viruses were indistinguishable from the old vaccine strain with post-infection ferret sera in the hemagglutination inhibition assay.

The low number of specimens that is generally available from sentinel surveillance results in broad confidence intervals in VE analyses. To overcome this problem, the Netherlands participates in the I-MOVE (<65 years) and I-MOVE+ (≥65 years) studies since the 2015/2016 season, and contributes data for pooled VE analysis. A surprising finding over the 2016/2017 season is the relatively high VE in the Netherlands compared to the I-MOVE pooled estimates, but this was only true for those ≥60 years of age. In the Netherlands, people ≥60 years of age have an indication for vaccination and the vaccination coverage is relatively high, and therefore VE estimates for this age group are quite robust (small CI's). There is no clear explanation for the relatively high VE among the elderly. The circulating strains in the Netherlands might have had a better antigenic match than the strains circulating in other European countries. However, in preliminary phylogenetic analysis of sequences from the whole of Europe the Dutch sequences are found dispersed throughout the phylogenetic tree.

Definitive conclusions can only be drawn after the results from ongoing virus neutralisation experiments become available. In the 2015/2016 A(H1N1)pdm09 season, the percentage influenza positives among the non-vaccinated was 29% against 43% in the 2016/2017 A(H3N2) season. One could speculate that the vaccine is more beneficial when baseline natural immunity is relatively low, such as for A(H3N2) among the elderly. Conversely, the elderly have generally a better baseline natural immunity against A(H1N1)pdm09 and the additional benefit of vaccination could then be limited. However, this is not supported by historical analysis over the period 2003-2014, which shows a low VE in seasons that A(H3N2) dominated, with an average VE of only 38% (95% CI 14-55) (Darvishian, Dijkstra et al. 2017). The influenza VE estimates remain not optimal and are overall lower than the effectiveness of many childhood vaccinations. This can be explained as it is never known which influenza viruses will dominate in the next season. Next, the circulating influenza viruses can evolve over time and deviate from the chosen vaccine viruses.

Although the sampling instructions were changed since the 2015/2016 season, the same age groups were sampled more often (15-44 years and 45-64 years) as in 2014/2015 and 2015/2016. The new instructions included the sampling of all patients with ILI of 65 years and older. This led only to a small increase in the specimens taken of patients with ILI of 65 years and older in the 2016/2017 season, despite the domination of the A(H3N2) virus, which usually leads to a higher burden in the elderly.

In the SNIV nursing home surveillance, only eight specimens were taken from residents with ILI or another acute respiratory infection, despite that influenza virus A(H3N2) dominated this season, which caused a high ILI burden among nursing home residents in the 2016/2017 season. The consistently low number of specimens submitted by nursing homes is a reason for concern, because it remains unknown which influenza virus types and subtypes/lineages and antigenic variants are circulating in this vulnerable group, and if there are differences with the general population.

A higher number of SARI patients were included in the SARI surveillance pilot study in 2016/2017 than in the 2015/2016 influenza epidemic. This is primarily caused by a more systematic screening and inclusion method ensured by the involvement of research nurses. Based on SARI surveillance pilot study data, a smaller percentage of SARI patients were tested for influenza virus by their treating physicians at the JBZ during the 2016/2017 influenza epidemic. In the absence of national or hospital guidelines on influenza diagnostics, this finding indicates that influenza diagnostics is still primarily based on clinical judgement by the treating physician. However, in February 2017, new diagnostic guidelines during and after the influenza season were implemented at the JBZ. The new JBZ diagnostic guideline recommends that all SARI patients should be tested for influenza virus during the influenza season. At this stage, it cannot be determined whether this indeed leads to a higher percentage of SARI patients tested for influenza virus, because the new diagnostic guidelines were implemented half way the 2016/2017 influenza season. During the following influenza season 2017/2018, the awareness of the new guidelines for SARI patients will likely improve among clinicians at the JBZ and a better evaluation of the new JBZ diagnostic guidelines can be performed.

## 3.5 Tables and figures

### Virus surveillance

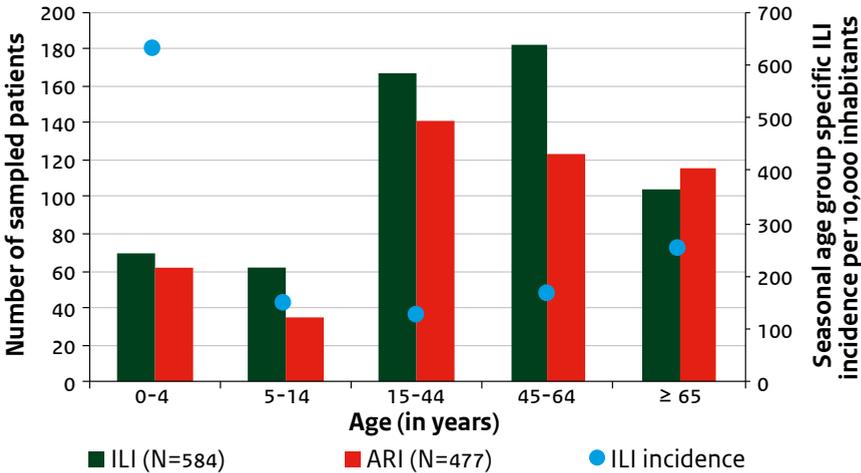
**Table 3.1** Characteristics of influenza-like illness (ILI) and other acute respiratory infections (ARI) patients, who are sampled by sentinel GPs in the 2016/2017 season (week 40 of 2016 through week 20 of 2017) (Source: NIC location RIVM).

Characteristics	ILI patients n/N (%)	Other ARI patients n/N (%)
Male gender	272/584 (47)	216/476 (45)
Vaccinated against influenza	146/584 (25)	131/477 (27)
If yes, brand was Influvac	66/140 (47)	49/129 (38)
If yes, brand was Vaxigrip	74/140 (53)	80/129 (62)
Part of target group for vaccination	237/584 (41)	209/477 (44)
• Lung disease (including asthma, COPD)	104/237 (44)	94/209 (45)
• Immune deficiency due to treatment (including chemotherapy and radiotherapy)	8/237 (3)	8/209 (4)
• Immune deficiency due to disease (including HIV)	8/237 (3)	3/209 (1)
• Cardiac disease (myocardial infarction, angina pectoris, arrhythmias, valvular heart disease, heart failure)	40/237 (17)	38/209 (18)
• Diabetes mellitus	27/237 (11)	25/209 (12)
Obesitas	58/581 (10)	53/471 (11)
Smoking:		
Yes or stopped < 1 year	77/565 (14)	66/466 (14)
No, stopped > 1 year	80/565 (14)	73/466 (16)
Never	408/565 (72)	327/466 (70)
Women:		
Pregnant	5/312 (2)	4/260 (2)
People aged 65 years and older:		
Needs assistance with showering	4/103 (4)	3/114 (3)
Needs assistance with walking	2/103 (2)	7/114 (6)
Delay in sampling, in days <sup>a</sup>	3 (2-5)	4 (2-7)

<sup>a</sup> Number of days between the first day of illness and the day of sampling (median, 1<sup>st</sup>, and 3<sup>rd</sup> quartile)

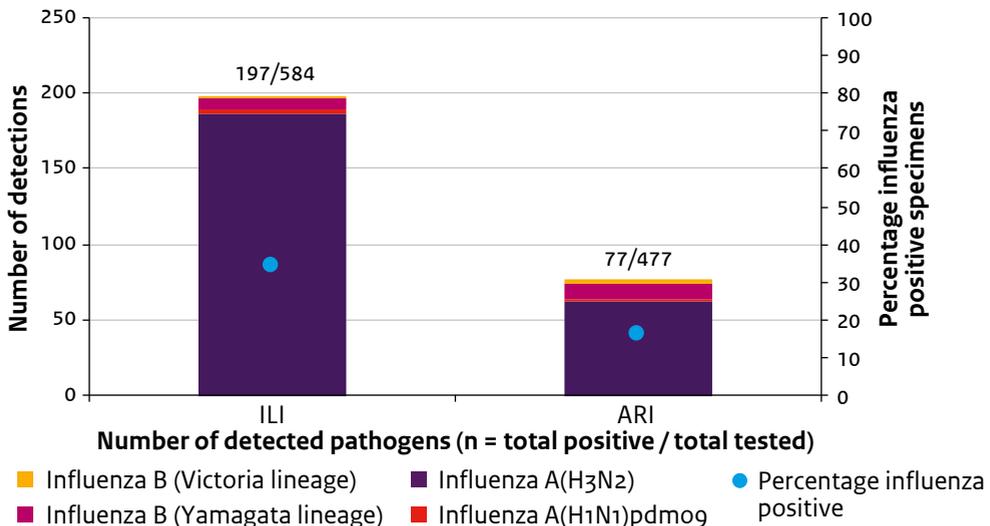
**Footnote:** n = the number in the corresponding group; N = total number of patients, for whom the information was available; GP = general practitioner; ILI = influenza-like illness; ARI = acute respiratory tract infection; COPD = chronic obstructive pulmonary disease, HIV = human immunodeficiency virus. Please note that for the virological surveillance, the ARI patients do not include the ILI patients.

**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 2016/2017 respiratory season (week 40 of 2016 through week 20 of 2017) (Source: NIVEL Primary Care Database, NIC location RIVM).



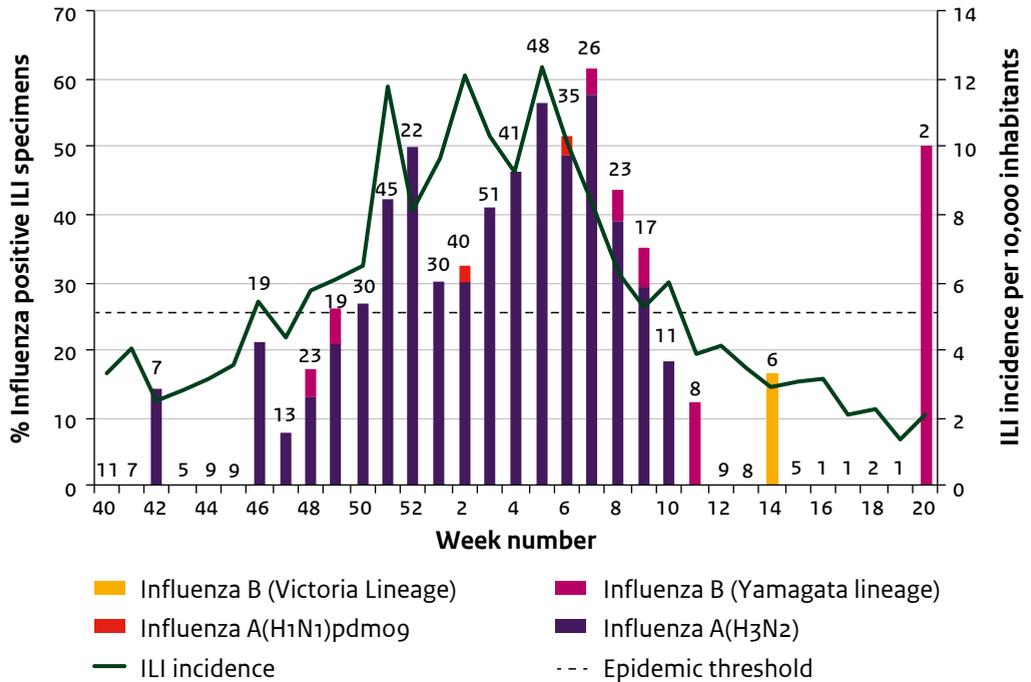
**Footnote:** ILI = influenza-like illness; ARI = other acute respiratory tract infections, GP = general practitioner. Please note that for the virological surveillance, the ARI patients do not include the ILI patients.

**Figure 3.2** Number of detected respiratory pathogens among ILI and ARI patients, who were sampled in the NIVEL GP sentinel surveillance in the 2016/2017 respiratory season (week 40 of 2016 through week 20 of 2017) (Source: NIC location RIVM).



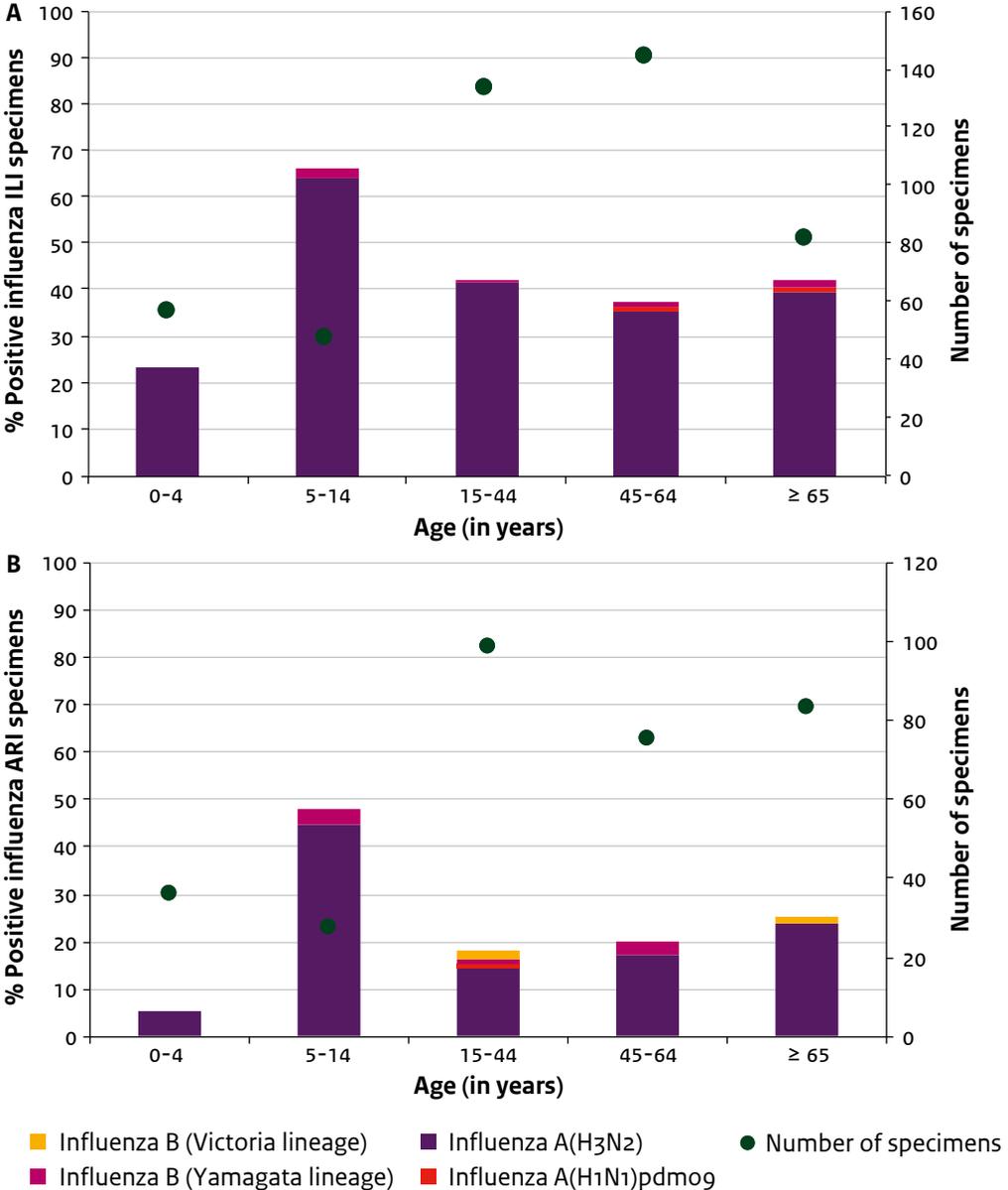
**Footnote:** ILI = influenza-like illness; ARI = other acute respiratory tract infection. Please note that for the virological surveillance, the ARI patients do not include the ILI patients.

**Figure 3.3** Percentage of ILI specimens positive for influenza virus, taken by sentinel GPs, and ILI incidence with ILI incidence epidemic threshold during the 2016/2017 respiratory season (week 40 of 2016 through week 20 of 2017), displayed by week of sampling (Source: NIVEL Primary Care Database, NIC location RIVM).



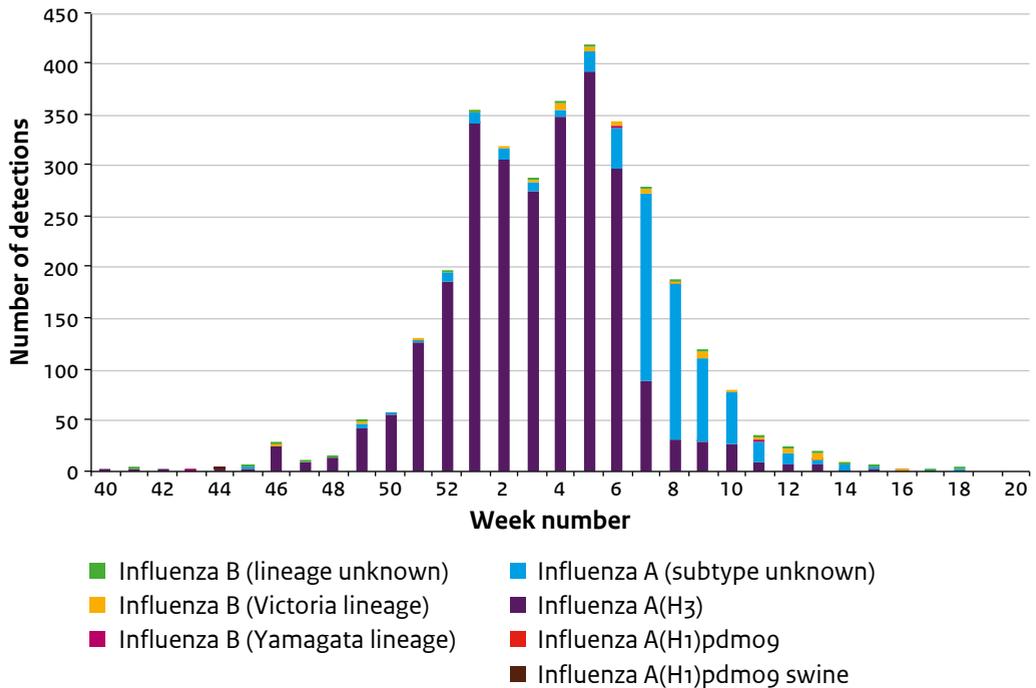
**Footnote:** ILI = influenza-like illness; GP = general practitioner  
The numbers above the bars are the total number of tested specimens.

**Figure 3.4** Percentage of influenza positive ILI (A) and ARI (B) specimens per age group, taken by sentinel GPs, during the epidemic weeks (week 48 of 2016 through 10 of 2017) of the 2016/2017 season (Source: NIC location RIVM).



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

**Figure 3.5** Subtyping of influenza viruses submitted by Dutch laboratories to the NIC location Erasmus MC during the 2016/2017 season, displayed by week of specimen collection, excluding specimens taken for sentinel GP surveillance and the SNIV nursing home surveillance (Source: NIC location Erasmus MC).



**Footnote:** GP = general practitioner

**Table 3.2** Genetic characterisation of influenza viruses, week 40 of 2016 through week 16 of 2017 (Source: NIC location RIVM, NIC location Erasmus MC)

Virus (sub)type	Clade	Antigenic match with 2016/2017 vaccine strains <sup>a</sup>	Source		
			Sentinel GP <sup>b</sup>	Hospital SARI <sup>b</sup>	Virology labs <sup>c</sup>
A(H1N1)pdm09 (n=4)	6B.1	good	2		2
A(H3N2) (n=92)	3C.2a	good to moderate <sup>d</sup>	82	1	9
	3C.2a1 <sup>e</sup>	good to moderate <sup>d</sup>	64	1	8
	3C.3a	bad	1		
B-Yamagata (n=6)	3	absent <sup>f</sup>	6		
B-Victoria (n=2)	1A	good	2		

**Footnote:** GP = general practitioner; SARI = severe acute respiratory infection

<sup>a</sup> Composition 2016/2017 vaccine: A/California/7/2009 (H1N1)pdm09; A/Hong Kong/4801/2014 (H3N2); B/Brisbane/60/2008 Victoria lineage. Antigenic match based on a limited number of Dutch viruses analysed and the WHO CC, London, interim report ([https://www.crick.ac.uk/media/358671/crick\\_nh\\_vcm\\_report\\_feb\\_2017\\_v2.pdf](https://www.crick.ac.uk/media/358671/crick_nh_vcm_report_feb_2017_v2.pdf)).

<sup>b</sup> Source NIC location RIVM

<sup>c</sup> Source NIC location Erasmus MC

<sup>d</sup> Clade 3C.2a viruses match antigenic moderately with the egg-grown vaccine strain A/HongKong/4801/2014, but match well with the cell-grown vaccine strain. Egg-grown viruses are used for vaccine production.

<sup>e</sup> Subclade of 3C.2a, therefore this number is also included in the number of clade 3C.2a viruses.

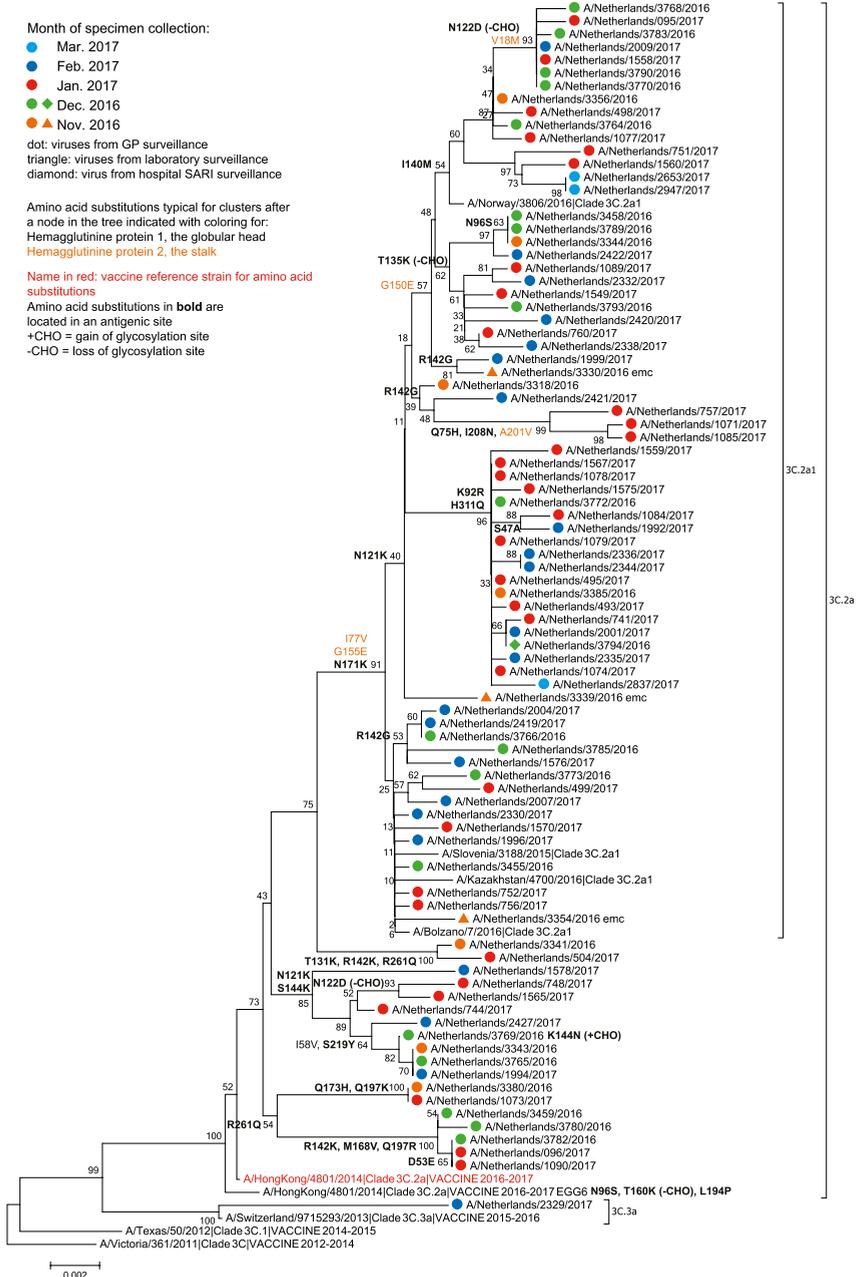
<sup>f</sup> A B-Yamagata lineage virus was not included in the trivalent influenza vaccines used in the Dutch National Programme for prevention of Influenza in the 2016/2017 season

**Table 3.3** Influenza virus diagnostics of SARI patients during the influenza epidemics in 2015/2016 and 2016/2017 at the Jeroen Bosch Hospital

Total	Influenza epidemic 2015/2016 n=80	Influenza epidemic 2016/2017 n=124
	N (%)	N (%)
Influenza test performed	59 (74)	77 (62)
Influenza virus positive	28 (47)	32 (42)
type A	22 (79)	32 (100)
H3N2	0 (0)	32 (100)
H1N1 pdm09	15 (68)	0 (0)
type B	6 (21)	0 (0)
Yamagata	0 (0)	0 (0)
Victoria	3 (50)	0 (0)
Influenza virus negative	31 (53)	45 (58)

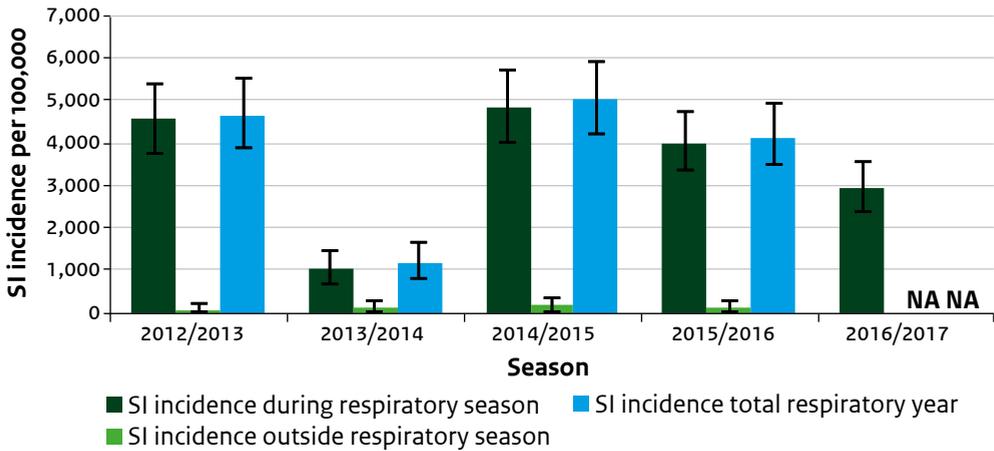
**Footnote:** SARI = severe acute respiratory infection ; n = total number of patients, for whom the information was available; N = the number in the corresponding group

**Figure 3.6** Phylogenetic analysis of the hemagglutinine gene of A(H3N2) influenza viruses sequenced directly from clinical specimens collected week 40 of 2016 through week 16 of 2017 (Source: NIC location RIVM, NIC location Erasmus MC).



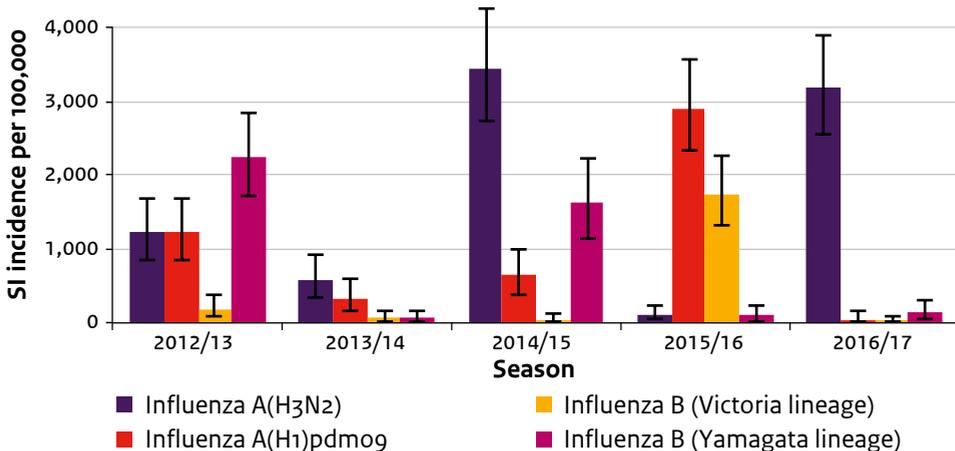
## Influenza incidence estimation

**Figure 3.7** Estimated symptomatic influenza (SI) incidence per 100,000 population during the respiratory season (week 40 through week 20 of 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) aggregating over age, for the seasons 2012/2013 through 2016/2017 (Source: NIVEL Primary Care Database, NIC location RIVM, Influenzanet).



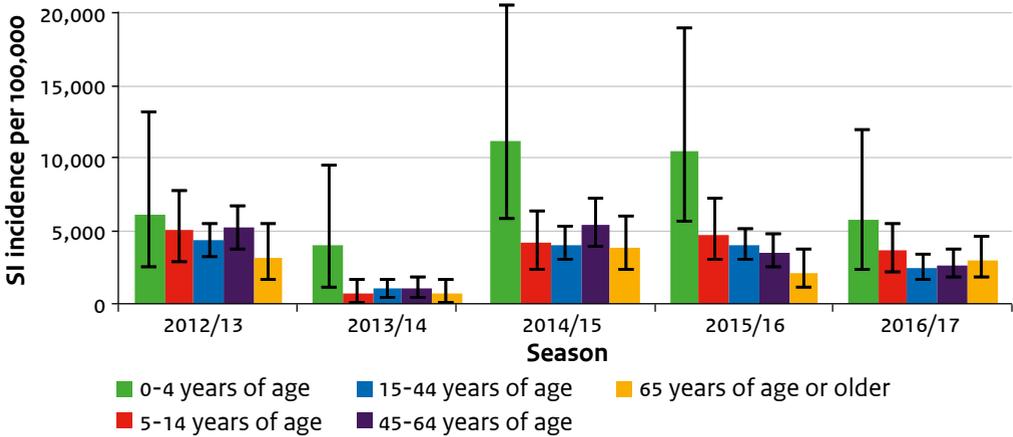
**Footnote:** NA= not applicable  
Error bars represent 95% uncertainty intervals (UI).

**Figure 3.8** Estimated symptomatic influenza (SI) incidence per 100,000 population by subtype (aggregated over age) for the respiratory seasons (week 40 through week 20 of the next year) 2012/2013 through 2016/2017 (Source: NIVEL Primary Care Database, NIC location RIVM, Influenzanet).



**Footnote:** Error bars represent 95% uncertainty intervals (UI).

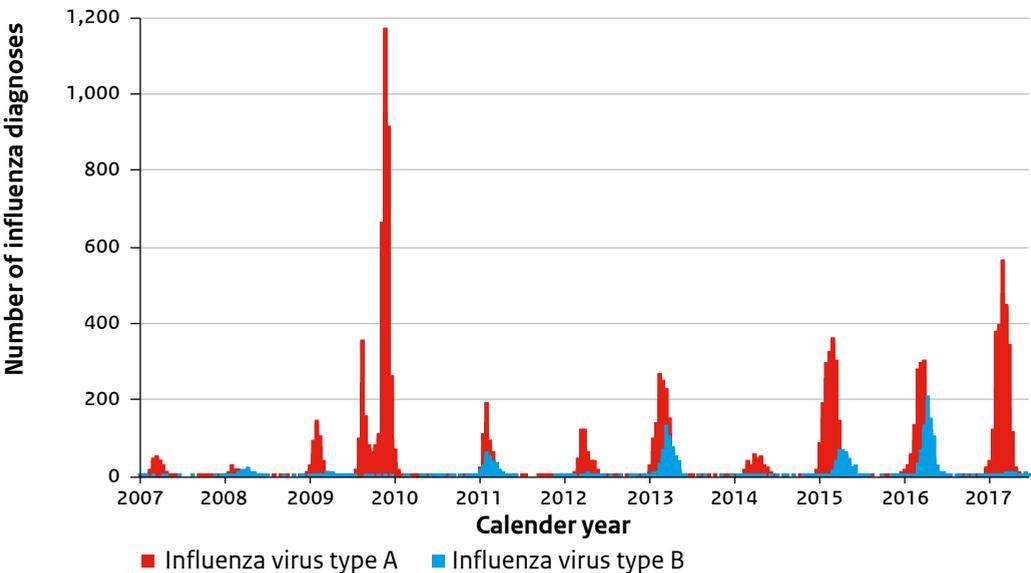
**Figure 3.9** Estimated symptomatic influenza (SI) incidence per 100,000 population by age group for the respiratory seasons (week 40 through week 20 of the next year) 2012/2013 through 2016/2017 (Source: NIVEL Primary Care Database, NIC location RIVM, Influenzanet).



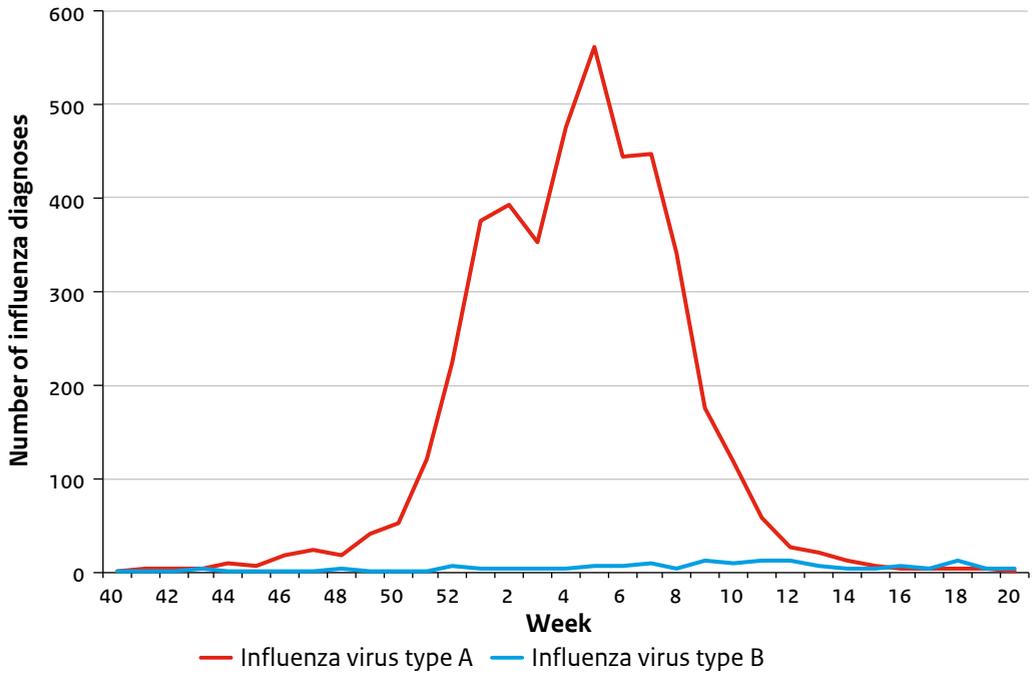
**Footnote:** Error bars represent 95% uncertainty intervals (UI).

### Influenza diagnostics in virological laboratories

**Figure 3.10** Weekly number of influenza virus type A and B diagnoses, reported by the virological laboratory surveillance in the period week 1 of 2007 through week 20 of 2017 (Source: Virological laboratory surveillance, RIVM).



**Figure 3.11** Weekly number of influenza virus type A and B diagnoses reported in the virological laboratory surveillance, for the period week 40 of 2016 through week 20 of 2017 (Source: Virological laboratory surveillance, RIVM).



## Antiviral resistance

**Table 3.4** Reduced inhibition of influenza viruses by neuraminidase inhibitors and M2 ion-channel blockers, 2014/2015-2016/2017 (Source: NIC location RIVM, NIC location Erasmus MC).<sup>a</sup>

Antiviral Influenza virus (sub)type	Viruses with reduced inhibition by season		
	2014/2015 n/N (%)	2015/2016 n/N (%)	2016/2017 n/N (%) <sup>b</sup>
<b>Neuraminidase inhibitor</b>			
A(H1N1)pdm09	1/130 (<1) <sup>c</sup>	1/1191 (<1) <sup>d</sup>	0/6 (0)
A(H3N2)	0/727 (0)	0/44 (0)	1/92 (<1) <sup>e</sup>
B	0/42 (0)	1/69 (1.5) <sup>f</sup>	0/14 (0)
<b>M2 ion-channel blocker</b>			
A(H1N1)pdm09	9/9 (100)	73/73 (100)	2/2 (100)
A(H3N2)	50/50 (100)	4/4 (100)	56/56 (100)

**Footnote:** n = the number in the corresponding group; N = total number of patients, for whom the information was available;

<sup>a</sup> Combined results obtained with phenotypic (virus isolates) and genotypic (clinical specimens) assays. Season defined as week 40 of the first year through week 39 of the following year.

<sup>b</sup> Preliminary data week 40/2016 through week 16/2017.

<sup>c</sup> One virus with highly reduced inhibition by oseltamivir due to mixture 275H/Y amino acid substitution in the neuraminidase. The patient was treated with oseltamivir prior to specimen collection.

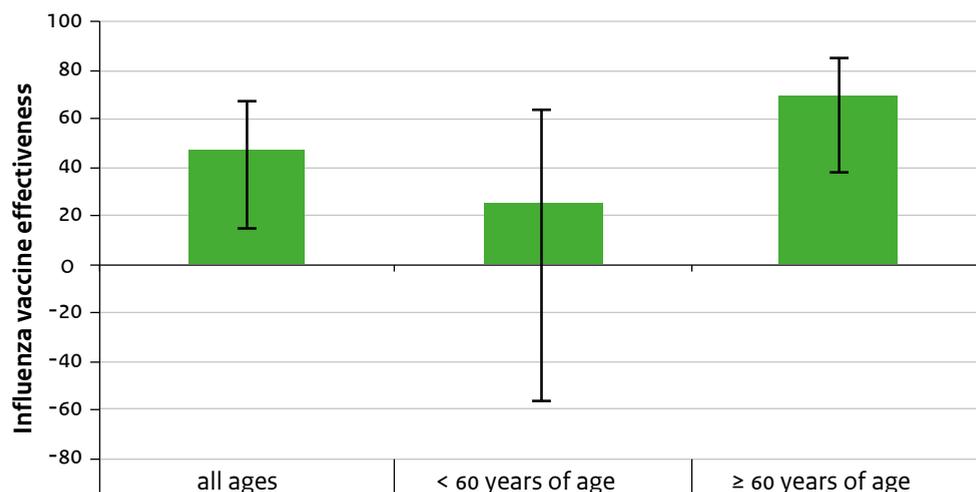
<sup>d</sup> One virus with highly reduced inhibition by oseltamivir due to mixture 275H/Y amino acid substitution in the neuraminidase. No patient characteristics or antiviral exposure data available.

<sup>e</sup> One virus with borderline reduced inhibition by zanamivir and normal inhibition by oseltamivir. No amino acid substitutions explaining this result were found in the virus in the clinical specimen or in the virus isolate.

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

## Influenza vaccine effectiveness

**Figure 3.12** Influenza vaccine effectiveness in the 2016/2017 season in the Netherlands, measured in GP sentinel surveillance, against laboratory confirmed influenza A(H3N2) virus infection (Source: NIVEL Primary Care Database).



**Footnote:** GP = general practitioner. Error bars represent 95% confidence intervals (CI).

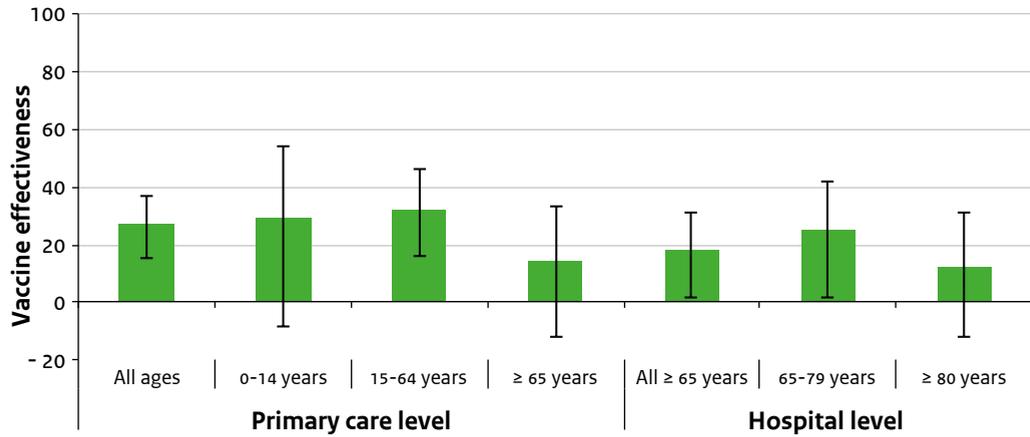
**Table 3.5** Estimation of vaccine effectiveness (VE) against laboratory confirmed influenza for all ages, based on influenza positive and influenza negative ILI and ARI specimens (test negative design), which were collected for the Dutch sentinel GP surveillance in the 2016/2017 season.

	Adjustment / stratification	Cases			Controls			Adjusted VE	95% CI
		All	Vaccinated	%	All	Vaccinated	%		
All ages	All subtypes <sup>a</sup>	248	54	21.7	571	156	27.3	48.3	17.5 to 67.5
	H3N2 <sup>a</sup>	228	53	23.2	575	149	25.9	47.1	14.8 to 67.2
< 60 years	All subtypes <sup>a</sup>	181	21	11.6	424	55	13.0	23.5	-56.9 to 62.7
	H3N2 <sup>a</sup>	165	21	12.7	431	52	12.0	24.8	-56.0 to 63.8
≥ 60 years	All subtypes <sup>b</sup>	67	33	49.3	146	100	68.5	68.1	36.0 to 84.2
	H3N2 <sup>b</sup>	63	32	50.8	143	97	67.8	69.9	37.7 to 85.4

**Footnote:** VE = vaccine effectiveness, ILI = influenza-like illness, ARI = other acute respiratory tract infection; GP = general practitioner; CI = confidence interval.

<sup>a</sup> Adjusted by age, comorbidity, period. <sup>b</sup> Adjusted by age, comorbidity, period, and gender.

**Figure 3.13** Influenza vaccine effectiveness in the 2016/2017 season in Europe, measured in, I-MOVE/I-MOVE+ multicentre case control studies, against laboratory confirmed influenza virus A(H3N2) infection, per age group (Source: I-MOVE/I-MOVE+).



**Footnote:** Error bars represent 95% confidence intervals (CI).

# Chapter 4

## RS-Virus

**Authors:** Anne Teirlinck, Gé Donker, Wim van der Hoek, Adam Meijer

**Contributors:** Marit de Lange, Pieter Overduin, Sharon van den Brink, Lisa Wijsman, Janneke Duijster

### 4.1 Key points

- The RSV (respiratory syncytial virus) season, defined as the consecutive number of weeks with at least 20 positive RSV diagnoses reported by the virological laboratory surveillance started in week 45 of 2016 and lasted 18 weeks.
- The peak number of detections in the virological laboratory surveillance (n=199) in week 52 of 2016 and the cumulative number of detections (n=1,937) was higher than in the previous three seasons.
- A total of 123 RS-viruses were detected in 1060 combined nose swabs and throat swabs of ILI and other ARI patients, collected by sentinel GPs in the 2016/2017 respiratory season.
- For ILI patients, the percentage of positive specimens peaked in week 48 of 2016 (9/23 swabs; 39%) and for other ARI patients in week 51 of 2016 (12/28 swabs; 43%).
- The percentage of RSV positive specimens taken by the GPs was highest in children under two years of age, in ILI patients: 13/37 swabs; 35%, as well as in other ARI patients: 17/39 swabs; 44%.
- On pediatric ICUs (PICUs), RSV was the most common cause (63%) of severe acute respiratory infections in children in whom laboratory diagnostics were performed (see chapter 2.4).

## 4.2 Background

Respiratory Syncytial Virus (RSV) causes a respiratory infection, and is commonly contracted by children (Hall, Weinberg et al. 2009), mostly in the winter season. During their first two years of life, most children are infected with this virus and re-infections later in life are very common. Especially in risk groups, such as newborns and preterms, infection can lead to severe illness, hospitalization and even death (Nair, Nokes et al. 2010, Diez-Domingo, Perez-Yarza et al. 2014). In addition, long term respiratory problems, such as recurrent wheezing, have been reported in children after RSV infection (Blanken, Rovers et al. 2013). Studies suggest that RSV is also a common cause for respiratory infections in the elderly (Falsey, Hennessey et al. 2005, Fleming, Taylor et al. 2015) causing outbreaks in elderly care facilities (Meijer, Overduin et al. 2013). RSV ranks third among infectious outbreaks in elderly care facilities, with a median fatality rate of 20% (range 2–20%) (Utsumi, Makimoto et al. 2010). In the Netherlands, an estimated 1,640 (range 1,315-1,925) deaths among persons aged 65 years or older are attributable to RSV per year, in comparison to 1,711 (range 206-2,777) for influenza type A (van Asten, van den Wijngaard et al. 2012). RSV is divided in two types, RSV-A and RSV-B, mainly based on the variation in the attachment protein, the G-protein. These two types can circulate simultaneously in the population. Currently, no vaccine for RSV is available, but 60 vaccine candidates are in the pipeline. Most vaccine candidates that are currently in phase 2 and phase 3 clinical trials are based on the fusion protein (F-protein) [[http://www.path.org/publications/files/CVIA\\_rsv\\_snapshot\\_final.pdf](http://www.path.org/publications/files/CVIA_rsv_snapshot_final.pdf)].

## 4.3 Epidemiological situation, season 2016/2017

The RSV season is defined as the period with at least 20 RSV-diagnoses per week reported by the virological laboratory surveillance. The RSV season lasted from week 45 of 2016 through week 10 of 2017. The total number of positive RSV diagnoses reported by 20 virological laboratories in the Netherlands (virological laboratory surveillance) in 2016/2017 (n=1,937; through week 20 of 2017) was higher than in the previous three seasons. In the 2016/2017 season (week 40 through week 20), a total of 123 RS-viruses were detected in 1060 nose swabs and throat swabs (12%) of ILI and other ARI patients, collected by sentinel GPs. Of these 123 specimens, 87 were RSV-A (71%) and 36 were RSV-B (29%). For ILI patients the peak in percentage of positive specimens was found in week 48 of 2016 (9/23 swabs (39%) and for other ARI patients in week 51 of 2016 (12/28 swabs (43%). The percentage of RSV positive specimens from the GP sentinel surveillance was highest in the 0 to 2 years old, both for ILI patients: 13/37 swabs (35%) and for other ARI patients: 17/39 swabs (44%). In the 2-4 years olds, 9/32 swabs (28%) of the ILI specimens and 3/22 swabs (14%) of the other ARI specimens were positive for RSV. The percentages were lowest in young adults, and increased again slightly with older age, starting in the 45-64 years olds (ILI patients) and 65-plus year olds (other ARI patients). Overall, more RSV-A than RSV-B was detected in specimens, which was apparent in all age groups.

## 4.4 Discussion

In the 2016/2017 respiratory season, the peak in the percentage of RSV positive specimens, taken by GPs, occurred earlier than in the four previous seasons. The total absolute number of RSV detections reported by the virological laboratory surveillance was higher than in the three previous seasons. In pediatric ICUs (PICUs), RSV was the most common cause of severe acute respiratory infections (See chapter 2.4). The early start of the epidemic of influenza-like illness in the season 2016/2017, with high ILI incidence in the age group 0-4 years old, might therefore have been driven more by RSV than by influenza virus.

At present, there is no clear case definition for RSV and the incidence and burden of RSV can therefore not be calculated directly. The need for reliable burden estimates of RSV, to identify risk groups and to build a sustainable infrastructure for surveillance has become more urgent, now that an RSV vaccine will likely become available in five to ten years time (Modjarrad, Giersing et al. 2016). Several international initiatives have recently started, in which RIVM is involved. Data that is sent to the European Center for disease prevention and control (ECDC) by 20 member states/EAA states, provides information on seasonality and trends (Meerhoff, Mosnier et al. 2009, Broberg, Waris et al. manuscript submitted). However, currently this European data collection does not include age-specific and detailed clinical and epidemiological information. Often a large part of this information is collected nationally (Mair-Jenkins et al, manuscript submitted). Surveillance would therefore need improvement and harmonization in order to obtain data that can be used as baseline data to monitor the implementation of RSV vaccines and to evaluate the effect on burden of disease. Currently, ECDC is developing a joint protocol for activities related to surveillance on RSV. RIVM works closely together with ECDC and other public health institutes, specifically SSI (Denmark) in order to strengthen international collaboration on RSV surveillance and improve the surveillance on RSV.

Furthermore, RIVM is partner in the RESCEU project (<http://resc-eu.org/>), that aims to explore the burden (clinical, economic and social) of RSV populations that are at high-risk for developing severe (complication of) RSV infection, and strengthening RSV surveillance and European/international collaboration on RSV surveillance and research.

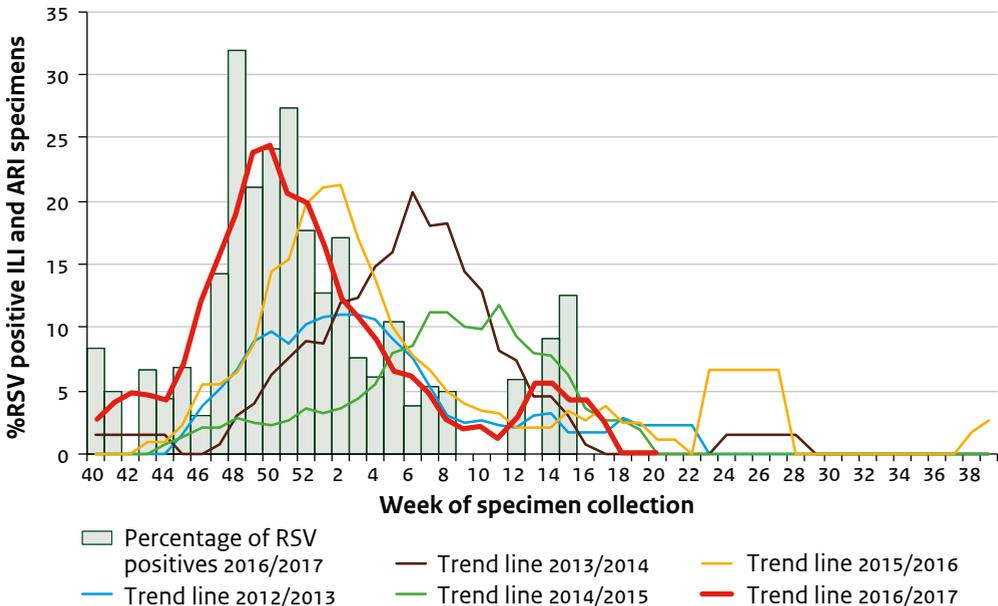
The current Dutch RSV surveillance builds on GP ILI and other ARI surveillance that was designed for influenza surveillance purposes. The sensitivity of the ILI case definition (that includes fever) for RSV is likely to be low, because RSV cases often present without fever. The vast majority of RSV cases however fit the ARI case definition (Lusing et al., manuscript in preparation), which also includes ILI cases. In the current surveillance system, GPs are instructed to sample the first two ILI patients they encounter and if no ILI patients consult the GP, to sample patients with other ARI. To be able to assess the incidence of RSV in total ARI cases (including ILI), the number of ARI patients should be combined with the percentage of RSV positivity in ARI cases. This is complicated due to two reasons. Firstly, due to oversampling of ILI patients, the percentage positive RSV specimens in total ARI cases might be skewed towards the percentage in ILI cases. Secondly, because of the focus on ILI cases, the swabbed ARI cases (other than ILI) probably do not represent a random selection of all ARI cases.

The swabbed patients with ARI are therefore likely not representative for the total group of ARI patients.

Another important real-time data source for RSV circulation is the virological laboratory surveillance, in which RSV detections are reported weekly to the RIVM by 20 virological laboratories in the Netherlands. Although background information is lacking, presumably the test results from virological laboratory surveillance are mostly from hospitalized patients, and in the case of RSV mostly from children (Heijnen 2003). The peak in RSV laboratory diagnostic reports (week 52) was somewhat later than the peak in laboratory confirmed pediatric RSV cases in the six PICU (week 49, see chapter 2.4). At least some of these PICU cases will also have been registered in the virological hospital surveillance. It should be noted that the timings of registration are different for the surveillance system: for NIVEL GP surveillance: week of specimen collection; for PICU surveillance; week of hospital admission; for virological laboratory surveillance: week of laboratory diagnostic report. This might partly explain the difference in the timing of peaks, although no more than a week delay should be expected.

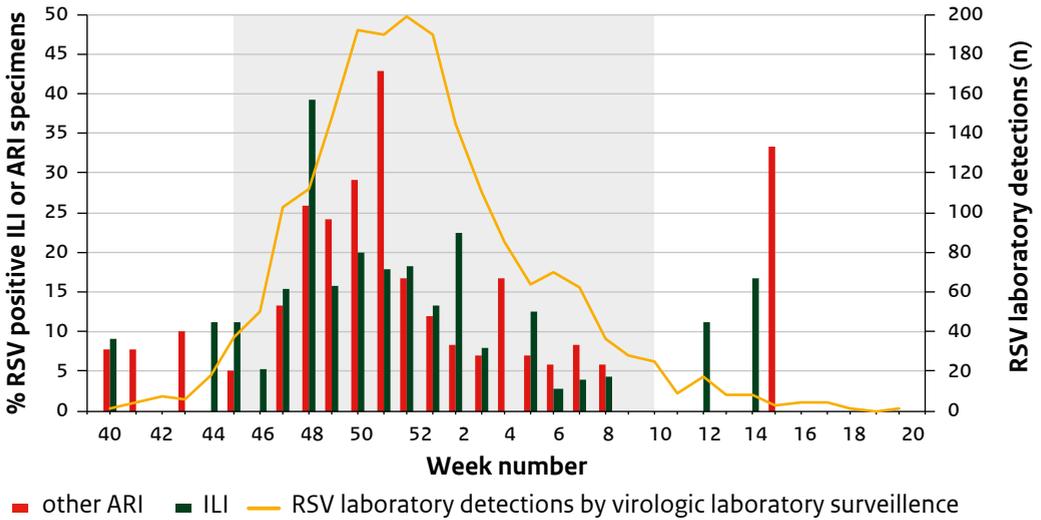
### 4.5 Tables and figures

**Figure 4.1** Percentage of RSV positive ILI and other ARI specimens, taken by sentinel GPs during the seasons 2012/2013-2016/2017 (for 2017 through week 20 only) (Source: NIVEL Primary Care Database, NIC location RIVM).



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

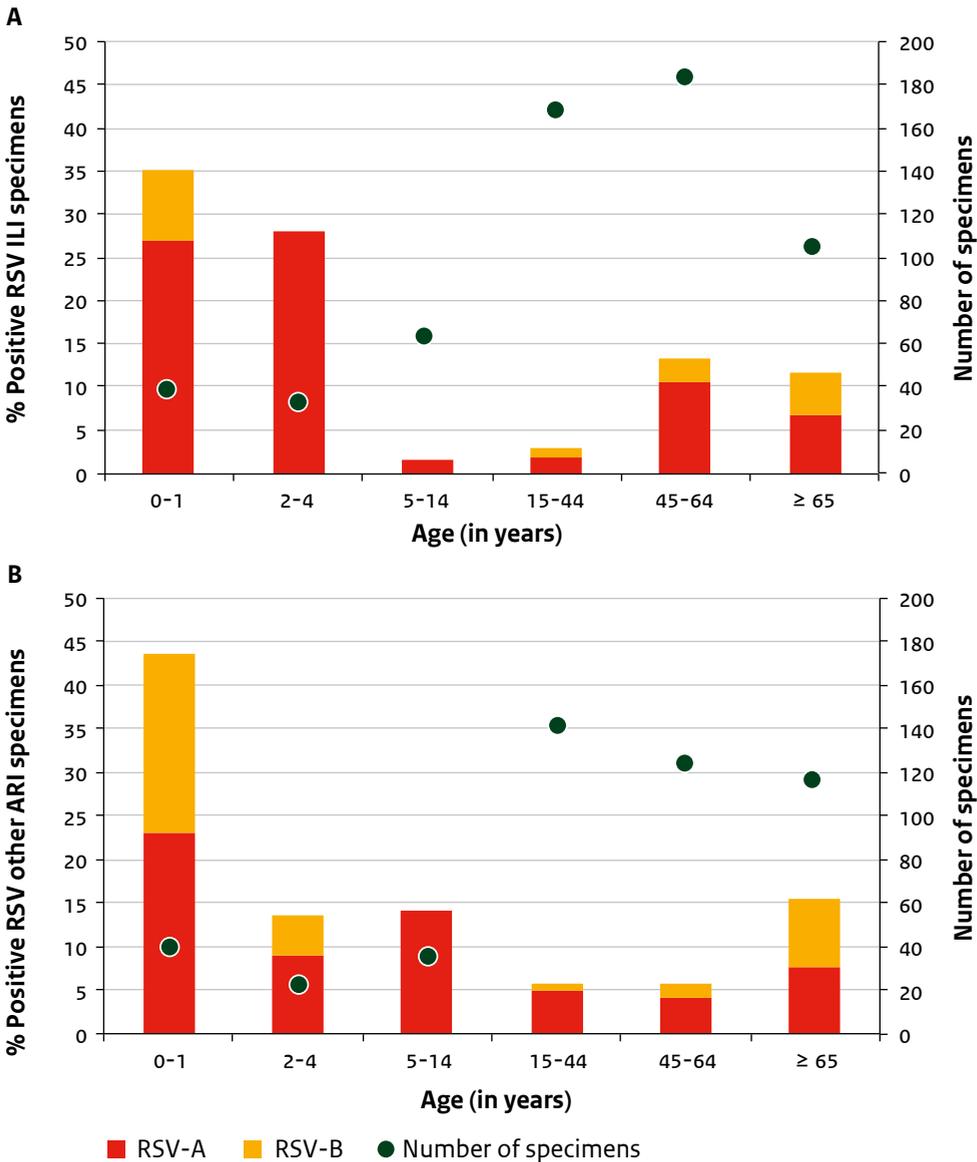
**Figure 4.2** Percentage of positive ILI and other ARI specimens, taken by sentinel GPs, and number of RSV detections as reported by the virological laboratory surveillance, during the 2016/2017 respiratory season (week 40 of 2016 through week 20 of 2017), displayed by week of sampling (Source: NIC location RIVM, virological laboratory surveillance).



**Footnote:** The grey area represents the RSV season. From week 11 of 2017 onwards, the number of collected ILI and other ARI specimen were each below 10 per week. Green bars represent specimen from ILI cases, red bars from other ARI cases.

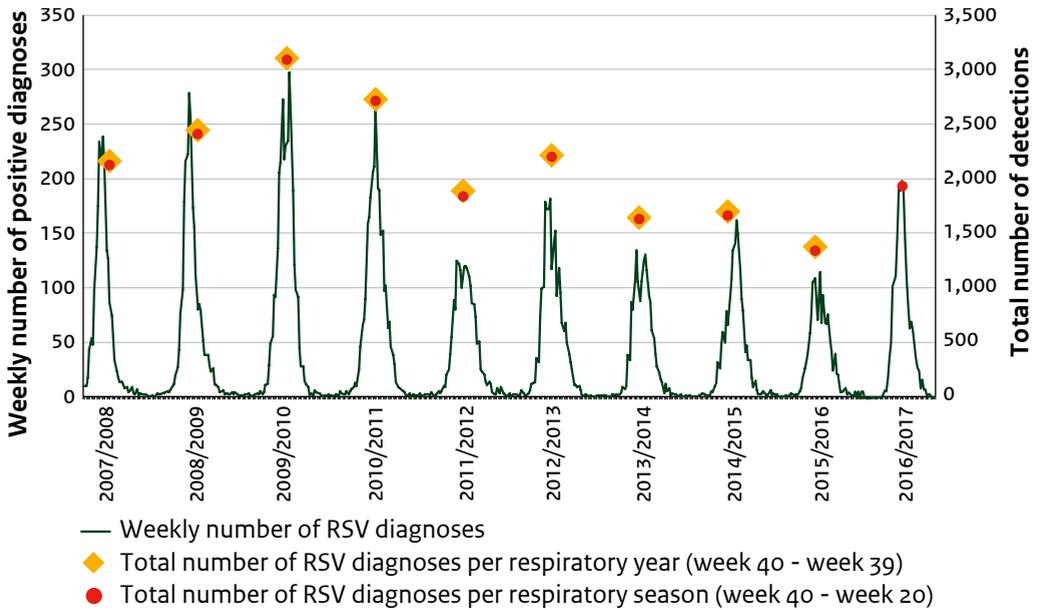
Please note that for the virological surveillance, the ARI patients do not include the ILI patients. ILI= influenza-like illness; ARI = acute respiratory infection; RSV = respiratory syncytial virus.

**Figure 4.3** Percentage of RSV-A and RSV-B positive specimens from patients with ILI (A) and other ARI (B), and the number of tested specimens, taken by sentinel GPs during the respiratory season of 2016/2017 (week 40 of 2016 through week 20 of 2017), displayed for six age categories. (Source: NIVEL Primary Care Database, NIC location RIVM).



**Footnote:** Please note that for the virological surveillance, the ARI patients do not include the ILI patients. ILI = influenza-like illness; ARI = acute respiratory infection; RSV = respiratory syncytial virus.

**Figure 4.4** Number of weekly reported RSV diagnoses (black line) and total number of RSV diagnoses in the respiratory year (red diamond) and respiratory season (red dot) in the virological laboratory surveillance for the period 2007/2008-2016/2017 (for 2017 through week 20 only) (Source: virological laboratory surveillance).



**Footnote:** RSV = respiratory syncytial virus

**Table 4.1** Number of reported respiratory syncytial virus (RSV) diagnoses in the Virological laboratory surveillance for the period 2007/2008-2016/2017 (for 2017 through week 20 only).

RSV diagnoses	weeks 40-20 (N)	weeks 21-39 (N)	weeks 40-39 (N)
2007/2008	2,128	43	2,171
2008/2009	2,416	35	2,451
2009/2010	3,075	34	3,109
2010/2011	2,702	27	2,729
2011/2012	1,838	51	1,889
2012/2013	2,197	12	2,209
2013/2014	1,629	16	1,645
2014/2015	1,661	32	1,693
2015/2016	1,348	42	1,390
2016/2017	1,937 <sup>a</sup>	- <sup>b</sup>	- <sup>b</sup>

<sup>a</sup> Data for weeks 40 of 2016 through week 20 of 2017 are preliminary. <sup>b</sup> Data for weeks 21-39 of 2017 are not yet available.

**Footnote:** RSV = respiratory syncytial virus

**Table 4.2** RSV seasonal trends in the Virological laboratory surveillance for the period 2007/2008-2016/2017 (for 2017 through week 20 only): season onset, duration and peak. Week is week of laboratory diagnosis report. Epidemic period threshold is 20 detections per week.

	Onset week (week number)	Season duration (N weeks)	Peak	
			Timing (week number-year)	RSV diagnoses (N)
2007/2008	43	17	51-2007	239
2008/2009	43	22	50-2008	278
2009/2010	45	21	4-2010	297
2010/2011	45	22	3-2011	264
2011/2012	45	23	51-2011	125
2012/2013	46	22	2-2013	182
2013/2014	48	19	6-2014	130
2014/2015	49	20	8-2015	177
2015/2016	48	20	4-2016	114
2016/2017	45	18	52-2016	199

**Footnote:** RSV = respiratory syncytial virus

# Chapter 5

## Notifiable Respiratory Diseases

### 5.1 Legionnaires' disease

**Author:** Petra Brandsema

**Contributor:** Sjoerd Euser

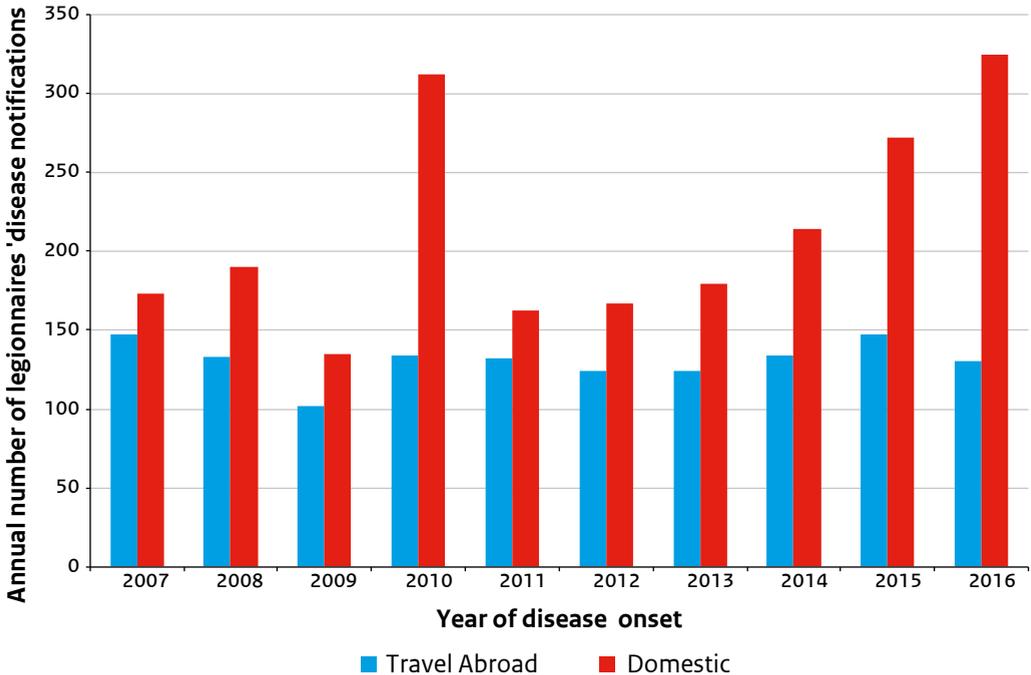
#### 5.1.1 Key points

- From 2012 to 2016, an increasing trend is observed in Legionnaires disease notified in the Netherlands. In 2016, a total of 468 notifications for legionellosis were received of which 454 were confirmed or probable cases of Legionnaires' disease (LD) in Dutch residents.
- The incidence in 2016 was 2.7 LD cases per 100,000 inhabitants, which is similar to the incidence in 2010.
- Domestic LD accounted for 71% of cases and 29% was associated with travel abroad. Most domestic cases (93%, 300 cases) were community acquired.
- The steady increase of LD since 2012 is due to an increase in domestic cases only. With 324 cases, the number of domestic cases in 2016 was the highest ever reported.
- Twenty deaths were reported, which is the highest number since 2006. The case fatality rate was 6% in domestic cases and 0% in cases with travel abroad.
- The cases of LD were spread over multiple Municipal Health Service regions and no large outbreaks were detected. However several small geographic clusters in different regions were observed, for which no common source of infection was found.
- Seasonality: In 2016 more cases than usual were observed in the winter months. This increase during winter was also observed in 2015 and may be associated with the mild and wet winters. In May and June a large number of cases was observed, following a period of extensive rainfall.

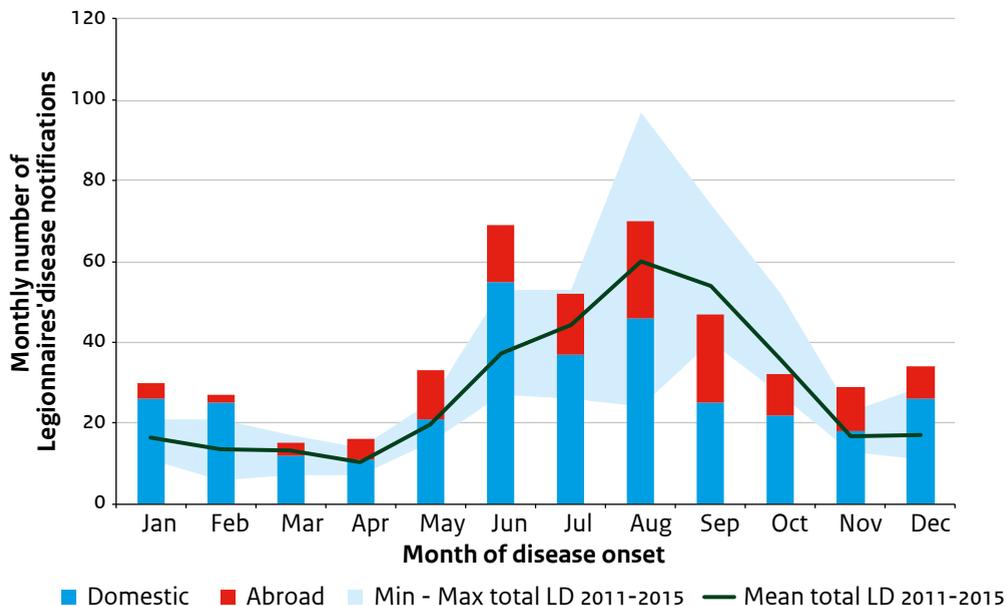
- Most cases (67%) were solely diagnosed by urine antigen test, which only reliably detects *L. pneumophila* serogroup 1. Sputum culture on *Legionella* was performed for only a minority of patients (46%), and a positive culture was available for only 19% of the 454 patients.
- A small part of the increase may be attributed to improved case detection, since the proportion of PCR identified cases increased slightly. However, improved diagnostics can only explain a small part of the increase.
- Environmental sampling was done in relation to 67 patients (15%) and *Legionella* was detected in potential sources linked to 33 of these patients (49%). There was only one genotypic match between a clinical isolate and an environmental isolate. This confirmed the showers at an industrial site as source of infection. In 2015 another LD case was also associated with the same location.
- Environmental sampling of wet cooling towers at geographic cluster locations was often hampered by the absence of (up to date) registrations of wet cooling towers.

### 5.1.2 Tables and figures

**Figure 5.1** Annual numbers of notified Legionnaires' disease, 2007 through 2016, by infection acquired abroad or domestic (within the Netherlands) (Source: Osiris).



**Figure 5.2** Notifications of Legionnaires' disease acquired abroad or acquired in The Netherlands (domestic), by month of disease onset in 2016 and the monthly average 2011-2015. (Source: Osiris).



**Table 5.1** Number of legionellosis notifications in 2012-2016, incidence, clinical and epidemiological background, mortality and diagnostics (Source: Osiris).

Year of onset disease <sup>a</sup>	2012	2013	2014	2015	2016
Number of Legionellosis notifications <sup>b</sup>	308	310	370	438	468
Excluded from analysis <sup>b</sup> :	17 <sup>b</sup>	7	22	19	14
Of which based on single high titer <sup>c</sup>	13	5	12	13	6 <sup>b</sup>
<b>Total included</b>	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>
<b>Legionnaires' disease (LD) (=100%)<sup>b</sup></b>	<b>291 (100)</b>	<b>303 (100)</b>	<b>348(100)</b>	<b>419 (100)</b>	<b>454 (100)</b>
Confirmed Legionnaires' disease <sup>d</sup>	265 (91)	288 (94)	327 (94)	393 (94)	422 (93)
Probable Legionnaires' disease <sup>d</sup>	26 (9)	15 (4)	21 (6)	26(6)	32 (7)
LD Incidence (per 100,000 residents)	1.7	1.8	2.1	2.5	2.7
Male gender	207 (71)	202 (67)	255 (73)	293 (70)	327 (72)
Median age (Q1-Q3)	62 (53-72)	63 (54-72)	61 (53-71)	62 (53-69)	63 (55-72)
Hospital admission <sup>e</sup>	287 (99)	294 (97)	342 (98)	410 (98)	449 (99)
X-thorax confirmed pneumoniae	277 (98)	285 (98)	328 (94)	401 (96)	436 (96)
Deaths <sup>e</sup>	16 (6)	17 (6)	13 (4)	13 (3)	20 (4)

Year of onset disease <sup>a</sup>	2012	2013	2014	2015	2016
<b>Setting of infection</b>					
Travel abroad <sup>f</sup>	124 (42)	124 (41)	134 (39)	145 (35)	130 (29)
Domestic (acquired in The Netherlands)	166 <sup>g</sup> (57)	179 (59)	214 (61)	273 <sup>g</sup> (65)	324 (71)
<b>Domestic categories</b>					
Domestic travel <sup>f</sup>	16 (5)	12 (4)	20 (6)	24 (6)	17 (4)
Nosocomial	1 (<1)	1 (<1)	4 (1)	2 (<1)	-
Healthcare associated	4 (1)	-	6 (2)	3 (<1)	7 (2)
Community acquired	145 (50)	166 (55)	184 (53)	244 (58)	300 (66)
No information/other <sup>g</sup>	1 <sup>g</sup> (<1)	-	-	1 <sup>g</sup> (<1)	-
<b>Diagnostics</b>					
<i>Legionella</i> cultured performed (=yes)	131 (45)	122 (40)	156 (45)	181 (43)	209 (46)
Positive culture	58 (20)	49 (16)	67 (19)	79 (19)	84 (19)
Proportion <i>L.pneumophila</i> sg1 in culture (or PCR) positives <sup>h</sup>	88%	96%	90%	87%	85%
Positive urine antigen test	256 (88)	283 (93)	314 (90)	381 (91)	404 (89)
Positive PCR	40 (14)	43 (14)	54 (16)	65 (16)	88 (19)
Significant titer rise	6 (2)	5 (2)	5 (1)	6 (1)	6 (1)
Direct immunofluorescence	2 (<1)	-	-	1 (<1)	-
Diagnostic delay in days: median( Q1-Q3)	6 (4-9)	6 (4-8)	6 (4-8)	6 (4-7)	6 (4-8)
Notification delay in days: median (90% reported )	0 (2)	0 (2)	0 (2)	0 (2)	0 (2)

<sup>a</sup> If date of onset disease was unknown, date of diagnosis minus median diagnostic delay was used to estimate onset. Analysis based on data as available on March 30, 2017, including all authorized notifications.

<sup>b</sup> Exclusion of cases in non-residents, cases without pneumonia and/or cases based on a single high titre c.

<sup>c</sup> Diagnostic confirmation only based on a single high titer with polyvalent serology on (usually *L. pneumophila* serogroup 1-6 or sg1-7, i.e. not specific for *L. pneumophila* serogroup 1) or single high titre without information on type of serology. This diagnostic method is excluded from the European case definition 2012.

<sup>d</sup> 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>).

<sup>e</sup> Percentage based on the number of patients for which this specific information was available.

<sup>f</sup> 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, unless source finding suggests a non-travel associated source. This differs from the TALD cases that are reported to the surveillance network ELDSNet which is limited to travel 2-10 days before onset. [<http://ecdc.europa.eu/en/activities/surveillance/ELDSNet/Pages/index.aspx>]. In 2016 includes were 2 cases defined as travel associated (both domestic) with travel at day 11-14 before onset.

<sup>g</sup> In 2012 and 2015 setting of infection (domestic or travel abroad) was unknown for one case.

<sup>h</sup> Proportion based on the number of patients for whom clinical specimens (culture or PCR) were available for typing at the reference lab.

## 5.2 Psittacosis

**Author:** Frederika Dijkstra

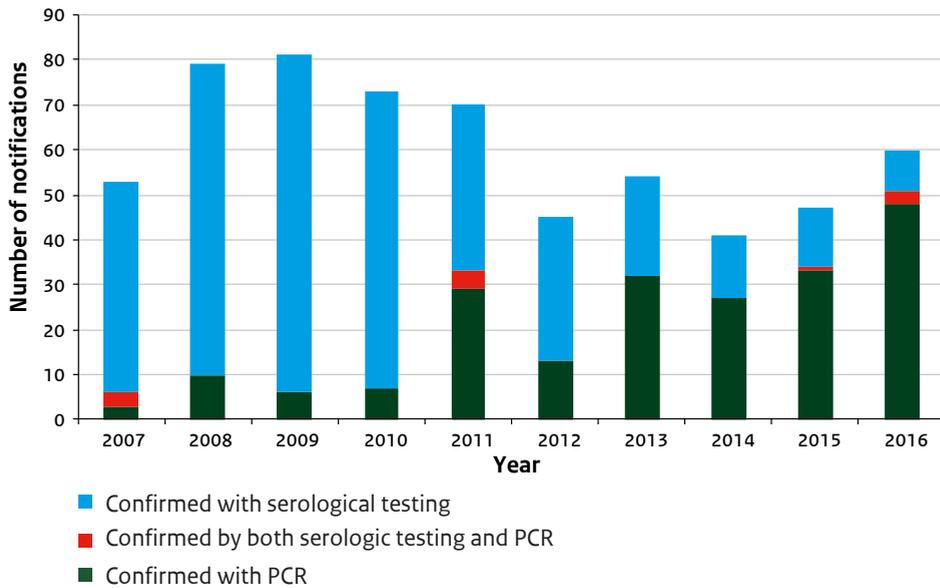
**Contributors:** Stasja Valkenburgh en Edou Heddema

### 5.2.1 Key points

- In 2016, 60 patients with psittacosis were notified. This number is somewhat higher than in the previous four years, but is in the range of the number of notifications over the years 2008 to 2011.
- The percentage of notified cases in which the diagnosis was confirmed with PCR has increased considerably to 85%.
- In July 2016, after a paper-based pilot period, the psittacosis source finding tool ('bronopsporingstool') was integrated into Osiris, aiming for a more systematic and efficient way of data exchange on source tracing between the Municipal Health Service and the Dutch Food and Consumer Product Safety Authority (NVWA). This was done in the framework of the multidisciplinary project 'Plat4m-2Bt-psittacosis' financed by ZonMW.
- As in the previous 3 years, genotype A (mainly associated with parrot-like birds) and genotype B (mainly associated with doves and pigeons) were most prevalent among patients in 2016.
- There were differences in number of genotyping outcomes reported in the psittacosis source finding tool and those reported directly by ZuyderlandMC. Probably, there is underreporting of genotypes in the source finding tool, possibly because of incomplete reporting of genotypes from peripheral laboratories to the Municipal Health Services and/or from the Municipal Health Service into the source finding tool. RIVM and ZuyderlandMC will sort out the causes of these differences in the near future.
- In 2016, a total number of 105 psittacosis notifications were received by the NVWA. These notifications can be subdivided into 50 veterinary notifications of clinical ill birds or positive laboratory test results of birds, and 55 notifications from Municipal Health Services with a request for tracing the source of a human case. The number of notifications due to the latter category was considerably higher than in previous years.
- Of 50 veterinary notifications, 45 times a location was visited and birds were sampled (cloaca and/or faecal swabs). In 24 cases (53%) *C. psittaci* DNA was detected.
- As part of human source tracing, birds were sampled on 43 locations. 22 locations (51%) tested positive for *C. psittaci* DNA.

## 5.2.2 Tables and figures

**Figure 5.3** Number of notifications of human psittacosis by year and mode of confirmation of laboratory diagnosis, 2007 through 2016 (Source: Osiris).



**Table 5.2** Demographic, clinical and diagnostic characteristics of notified patients with psittacosis and positive diagnoses in the virological laboratory surveillance, in 2012 up to 2016 (Source: Osiris and virological laboratory surveillance).

N (%), unless otherwise specified	2012	2013	2014	2015	2016
<b>Osiris notifications:</b>					
Number of notifications <sup>a</sup>	45 (100)	54 (100)	41 (100)	47 (100)	60 (100)
Incidence per 100,000 inhabitants	0.27	0.32	0.24	0.28	0.35
Median age in years (Q1-Q3)	57 (45-65)	59 (43-70)	58 (47-71)	57 (41-68)	58 (45-71)
Male gender <sup>b</sup>	28 (62)	36 (67)	32 (78)	32 (68)	48 (80)
Hospitalised <sup>b</sup>	32 (71)	41 (76)	38 (93)	37 (79)	49 (82)
Deaths <sup>b</sup>	0	0	1 (2)	1 (2)	1 (2)
Infected abroad <sup>b</sup>	1 (2)	2 (4)	1 (2)	0	4 (7)
Notification delay in days median (Q1-Q3) <sup>c</sup>	0 (0-2)	0 (0-2)	0 (0-1)	0 (0-1)	0 (0-2)
<b>Diagnostics used for notifications:</b>					
Median diagnostic delay in days (Q1-Q3) <sup>d</sup>	28 (11-45)	18 (9-29)	12 (7-21)	10 (8-14)	9 (6-14)
Mode of confirmation of laboratory diagnosis:					
PCR only	13 (29)	32 (59)	27 (66)	33 (70)	48 (80)
PCR and serological	0	0	0	1 (2)	3 (5)
Serological only	32 (71)	22 (41)	14 (34)	13 (28)	9 (15)
Number of patients eligible for genotyping <sup>e</sup>	4	33	28	36	51
Notified patients for whom diagnostic material for genotyping was received by Zuyderland MC	3 (75)	31 (94)	24 (86)	30 (83)	NA
Notified patients for whom genotyping was performed by Zuyderland MC <sup>f</sup>	NA	NA	NA	NA	24 (47) <sup>g</sup>
Typing outcomes:					
<i>C. psittaci</i> genotype A:	3 (100)	16 (52)	9 (38)	11 (37)	7 (29)
<i>C. psittaci</i> genotype B:	0	11 (36)	11 (46)	9 (30)	6 (25)
<i>C. psittaci</i> genotype C:	0	0	1 (4)	2 (7)	2 (8)
<i>C. psittaci</i> genotype E/B:	0	0	1 (4)	2 (7)	

N (%), unless otherwise specified	2012	2013	2014	2015	2016
New <i>C. psittaci</i> genotype most similar to C (93% homology)	0	0	1 (4)	0	
Unknown genotype of <i>C. psittaci</i> , with characteristics of B and E	0	0	0	1 (3)	2 (8)
Negative for any <i>C. psittaci</i> genotype	0	2 (7)	1 (4)	2 (7)	
Of which further diagnostics revealed:					
<i>C. caviae</i>	0	1 (3)	1 (4)	1 (3)	
No assessment possible	0	2 (7)	0	3 (10)	7 (29)
<b>Virological laboratory surveillance:</b>					
Number of positive diagnoses	23	23	16	18	30

- <sup>a</sup> 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.
- <sup>b</sup> Percentage based on the number of patient for whom this specific information was available.
- <sup>c</sup> Notification delay = number of days between date of laboratory confirmation and date of notification at the Municipal Health Service. Negative delays and delays of more than a year are excluded.
- <sup>d</sup> 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.
- <sup>e</sup> 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 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.
- <sup>f</sup> In 2016 we had (from the source finding tool) availability on answer on the question 'was genotyping performed'. This is different from previous years, for which we reported data on 'number of notified patients for whom diagnostic material for genotyping was received' by Zuyderland MC. In 2016, genotyping was performed in 24 of 51 patients (47%) of whom diagnostic material was available, i.e. those who were diagnosed by PCR. For 15 patients, the question 'was genotyping performed' was not filled in, for 6 patients the answer was 'no' and for 6 patients was 'unknown'.

## 5.3 Q fever

**Author:** Frederika Dijkstra

**Contributor:** Stasja Valkenburgh

### 5.3.1 Key points

- In 2016, 14 patients with acute Q fever were notified. This is the lowest annual number of cases after the epidemic that took place between the years 2007 and 2010.
- There was no geographic clustering of cases. The notified patients were from 12 different Municipal Health Services regions.
- Six of 14 patients (43%) had a date of onset of illness within the same one month period: between the end of September and the end of October. These patients were otherwise not related and two of these patients were probably infected abroad. Five other patients (36%) had a date of onset of illness in the months June, July and August, and 3 patients (21%) had a date of onset outside these periods.
- The percentage of notified cases that was confirmed for Q fever has decreased from 98% in 2012 to 64% in 2016. This might be related to the change in the case definitions of confirmed and probable cases that came into force per January 2015.
- The median diagnostic delay was considerable lower than in the previous four years (14 days in 2016 versus 25-33 days in 2012-2015).
- The percentage of hospitalised patients decreased from 75% in 2013 to 50% in 2016.
- In the virological laboratory surveillance 89 diagnoses of Q fever were reported, which is considerable higher than the number of notifications. Two thirds of the diagnoses came from one laboratory in the South of the Netherlands. The other third came from 10 other laboratories in various regions of the Netherlands. This laboratory in the South of the Netherlands also reported a high percentage of diagnoses in the previous 3 three years (44- 59%).
- Possible animal sources of infection can be sampled in the following situations:
  - *Bulk milk monitoring:*

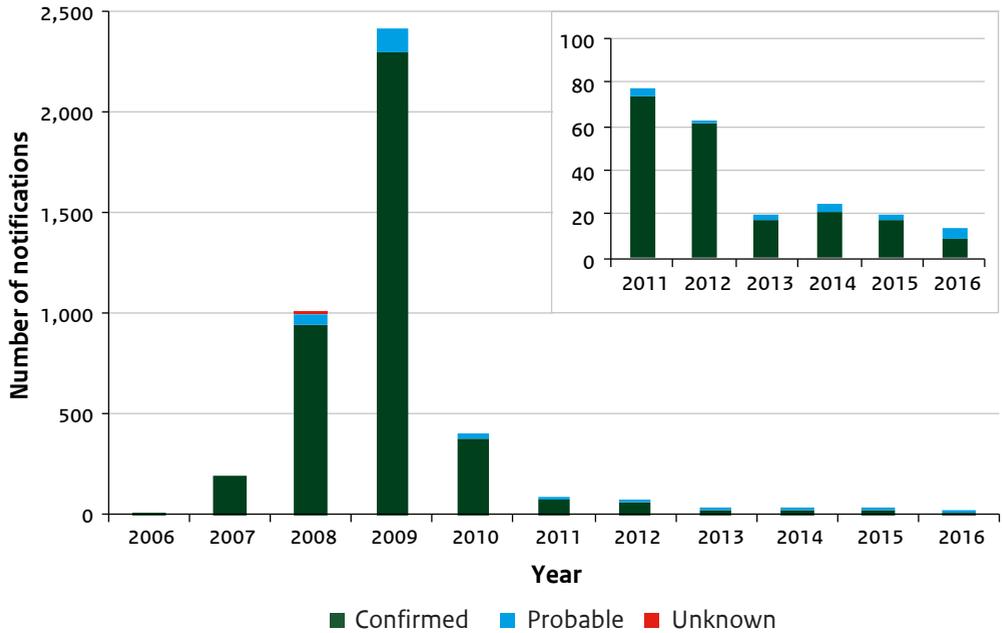
In 2016, Dutch Food and Consumer Product Safety Authority (NVWA) received two notifications of a positive sample in the bulk milk monitoring from the GD Animal Health (GD). NVWA took official samples on one of these farms, but *C. burnetii* could not be demonstrated. The restrictions on the last Q fever positive farm has been withdrawn in 2016, because bulk milk monitoring test results were negative during a period of one year.
  - *Investigation of veterinary abortion waves:*

In 2016, the NVWA received two notifications of a deviating number of abortions among sheep and/or goats. NVWA visited one of these farms and took samples, but *C. burnetii* was not demonstrated. No samples were taken on the other farm, because all goats were properly vaccinated.
  - *Source finding following human cases:*

In 2016, Municipal Health Services reported four human cases to the NVWA for source finding. Nevertheless, no locations were sampled, because of travel history abroad (n=1), various animal contacts which were not traceable for the NVWA (n=1) and lack of indications that animal contacts were infected, for example because of vaccination of these animals (n=2).

### 5.3.2 Tables and figures

**Figure 5.4** Number of notifications of acute Q fever by case classification<sup>a</sup> and year, 2006 through 2016 (Source: Osiris). The insert zooms in on the years 2011 through 2016.5.



<sup>a</sup> The distinction between confirmed and probable notifications has been made since 1 July 2008.

**Table 5.3** Demographic, clinical and diagnostic characteristics of notified acute Q fever patients and positive diagnoses in the laboratory surveillance, 2012-2016 (Source: Osiris and virological laboratory surveillance).

N (%), unless otherwise specified	2012	2013	2014	2015	2016
<b>Notifications (Osiris):</b>					
Number of notifications <sup>a</sup>	63 (100)	20 (100)	26 (100)	20 (100)	14 (100)
Confirmed <sup>b</sup>	62 (98)	18 (90)	22 (85)	17 (85)	9 (64)
Probable <sup>c</sup>	1 (2)	2 (10)	4 (15)	3 (15)	5 (36)
Incidence per 100,000 inhabitants	0.38	0.12	0.15	0.12	0.08
Median age in years (Q1-Q3)	52 (43-64)	52 (39-64)	57 (39-70)	58 (39-70)	49 (30-66)
Male gender <sup>d</sup>	48 (76)	13 (65)	21 (81)	9 (45)	11 (79)
Hospitalised <sup>d</sup>	33 (52)	15 (75)	17 (65)	12 (60)	7 (50)
<b>Deaths</b>					
Notified in Osiris <sup>d</sup>	0	0	0	1 (5)	0
Total number reported to RIVM <sup>e</sup>	1	0	0	1	0
Infected abroad <sup>d</sup>	5 (8)	3 (15)	5 (19)	2 (10)	3 (21)
Median notification delay in days (Q1-Q3) <sup>f</sup>	1 (0-5)	1 (0-2)	0.5 (0-6)	1 (0-3)	1 (0-3)
Median diagnostic delay in days (Q1-Q3) <sup>g</sup>	28 (15-47)	33 (8-52)	25 (14-48)	27 (12-44)	14 (11-31)
<b>Virological laboratory surveillance:</b>					
Number of positive diagnoses	83	89	130	125	89

<sup>a</sup> 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.

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

<sup>c</sup> Probable case = a clinical confirmed case with IgM antibodies against phase 2 of *C. burnetii*.

<sup>d</sup> Percentage based on the number of patients for whom this specific information was available.

<sup>e</sup> This includes deaths caused by Q fever that are notified in Osiris as well as deaths that are reported to RIVM/LCI outside Osiris.

<sup>f</sup> Notification delay = number of days between date of laboratory confirmation and date of notification at the Municipal Health Service. Negative delays and delays of more than a year are excluded.

<sup>g</sup> Diagnostic delay = number of days between onset of disease illness and date of laboratory confirmation. Negative delays and delays of more than a year are excluded.

## 5.4 Tuberculosis

**Authors:** Erika Slump

**Contributors:** Inger Bregman, Henriëke Schimmel, Rianne van Hunen, Gerard de Vries

### 5.4.1 Key points

- In 2016, 889 patients with tuberculosis (TB) were notified, an increase of 3% compared to 2015 (861 notifications). The steady decline in previous years, from 1995 until 2014, was interrupted in 2015 when the number of TB patients increased with 6%.
- The higher number of TB patients is mainly due to an increase of asylum seekers in the Netherlands from high-incidence countries.
- Most of the TB patients were foreign born (75%), mainly from Eritrea and Ethiopia (n=149), followed by Somalia (n=94) and Morocco (n=68).
- The incidence rate was 5.2 per 100,000 population in 2016.
- 484 TB patients (54%) had pulmonary TB and 405 (46%) had extrapulmonary TB.
- Nineteen percent of all TB patients were detected by active case-finding (20% in 2015 and 17% in 2014).
- In 2016, 15 patients with rifampicin-resistant TB were registered, including 13 patients with Multidrug-resistant (MDR) TB. Eleven of these 15 patients were foreign born.
- 554 TB patients (62%) were tested for HIV in 2016, of whom 21 (3.8%) were positive. The percentage patients with a known HIV status might increase due to an ongoing study requesting GGDs and hospitals to review their TB patient files on HIV test results.<sup>1</sup>
- In 2015, 88% of all TB patients with rifampicin-susceptible TB completed treatment successfully, which is similar to the treatment outcome for the years 2009-2014<sup>2</sup>.
- Seven of 8 patients (88%) diagnosed in 2014 with rifampicin-resistant TB completed treatment successfully.

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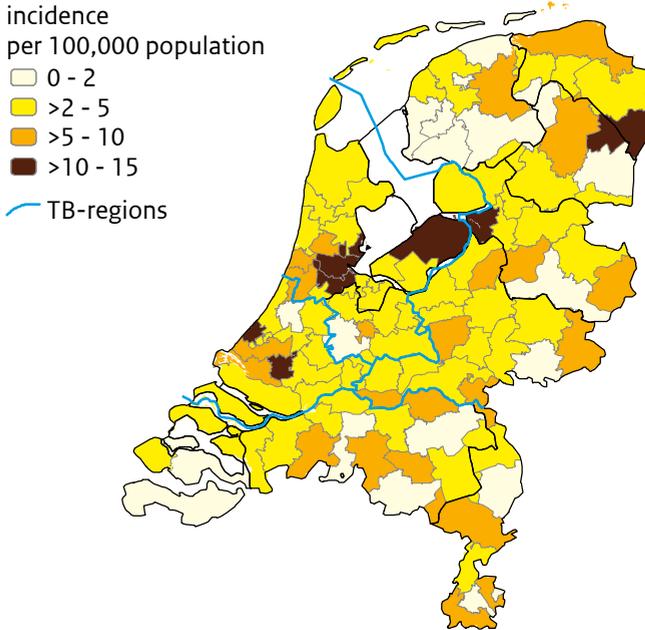
<sup>1</sup> In 2015 the proportion of TB patients with a known HIV status increased from 61% to 74%, due to this study.

<sup>2</sup> Treatment takes at least 6 months for drug-susceptible TB and often 20 months for rifampicin-resistant TB.

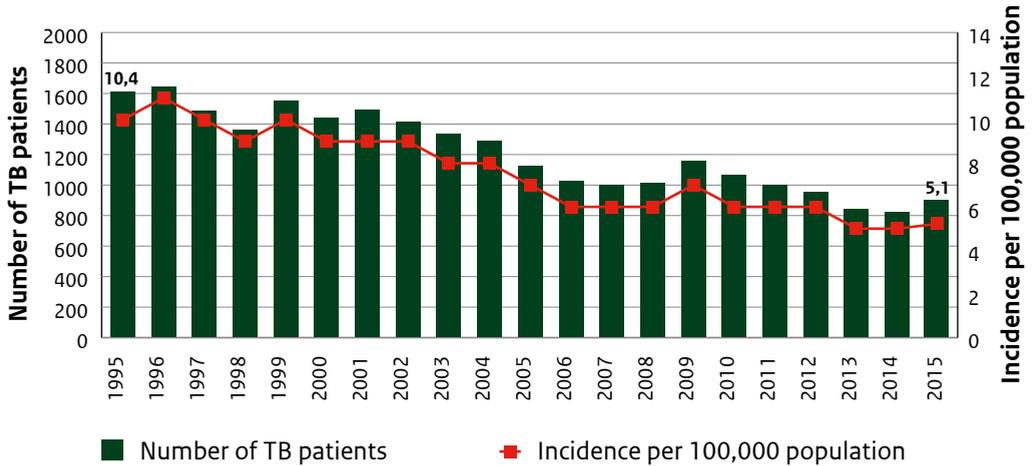
Treatment outcome of drug-susceptible TB of 2016 and rifampicin-resistant TB of 2015 have not been reported yet.

## 5.4.2 Tables and figures

**Figure 5.5** Tuberculosis incidence (per 100,000 population) in 2016 by two digit postcode area.



**Figure 5.6** Number of tuberculosis (TB) patients and incidence per 100,000 population, 1996-2016.



**Table 5.4** Summary tuberculosis data the Netherlands, 2014, 2015 and 2016.

	2014 N (%)	2015 N (%)	2016 N (%)
Incidence per 100,000 population	4.9	5.1	5.2
Mean age (years)	41	40	40
Age < 15 years	48 (5.9)	42 (4.8)	49 (5.5)
Age ≥ 65 years	125 (15)	127 (15)	133 (15)
Male to female ratio	1.6	1.5	1.4
Foreign born	601 (74)	625 (72)	669 (75)
Residence in 1 of 4 largest cities <sup>a</sup>	235 (29)	233 (27)	256 (29)
Previous episode of TB (treatment)	21 (2.6)	40 (4.6)	30 (3.4)
HIV status known	495 (61)	636 (74)	554 (62)
HIV positive	22 (2.7)	36 (4.2)	21 (2.4)
TNF-alpha inhibitors	11 (1.3)	16 (1.9)	10 (1.1)
Active case finding	137 (17)	170 (20)	172 (19)
Pulmonary tuberculosis (PTB & EPTB)	452 (56)	495 (58)	484 (54)
Sputum-positive PTB	201 (25)	216 (25)	172 (19)
Culture-confirmed TB	527 (65)	576 (67)	583 (66)
Rifampicin resistant TB (incl. MDR TB) <sup>b</sup>	8 (1.5)	11 (1.7)	15 (1.7)
Isoniazid resistance <sup>b</sup>	36 (6.8)	25 (4.3)	33 (5.7)
TB patients in risk groups	350 (43)	407 (47)	422 (48)
- TB contacts	65 (8)	87 (10)	110 (12)
- Immigrant < 2.5 yr. in the Netherlands	89 (11)	93 (11)	75 (8)
- Asylum seeker < 2.5 yr. in the Netherlands	97 (12)	149 (17)	162 (18)
Latent tuberculosis Infection	1,229	1,433	1,742

**Footnote:** TB=tuberculosis, PTB= pulmonary TB, EPTB= combination of pulmonary and extrapulmonary TB  
HIV= Human Immunodeficiency Virus, TNF = Tumor Necrose Factor, MDR = Multidrug-resistant

<sup>a</sup> Amsterdam, Rotterdam, The Hague and Utrecht

<sup>b</sup> percentage of culture-confirmed TB

More detailed information about surveillance of tuberculosis in the Netherlands and the latest surveillance report 'Tuberculose in Nederland, 2015' is available through the tuberculosis webpage of the RIVM (<http://www.rivm.nl/Onderwerpen/T/Tuberculose>), only available in Dutch). The next surveillance report 'Tuberculose in Nederland, 2016' will be published in December 2017.

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

## 5.5 Animal influenza viruses

**Authors:** Marit de Lange, Adam Meijer

### 5.5.1 Key points

- In the Netherlands, one human infection with swine influenza A(H1N1)v virus of the Eurasian avian lineage was notified in the years 2016 and 2017 (through 21 May 2017). In the same period, no other human infections with animal influenza virus were notified.
- No human infections of the avian influenza virus type A(H5N8) were notified in the Netherlands, despite that this virus caused several outbreaks among poultry (2016/2017) and was widely detected in water birds.

### 5.5.2 Background

Many different animals, including ducks, chickens and pigs, can host influenza A viruses. These viruses have the capacity to also cause infection in humans, sometimes with high morbidity and mortality. Worldwide, the WHO reports once a month an overview of the worldwide animal influenza virus infection in humans. Last years, influenza virus types A(H5N1) and A(H7N9) are most reported worldwide. In the Netherlands, human infection with an animal influenza virus is a notifiable disease in 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 Municipal 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 2016, nine commercial poultry holdings and nine hobby farms were infected with the high pathogenic avian influenza virus type A(H5N8) in the Netherlands. In 2016, four people were tested with influenza-like illness, and five in 2017 (through May 2017). For seven of them the reason for testing was that they were exposed to an animal influenza virus at an infected farm, one had wild bird droppings on themselves, and one was a contact of an exposed human. None of the nine people had an infection with an avian influenza virus. No returning travellers were tested for possible influenza virus type A(H5N1) and A(H7N9) in 2016 and 2017 (through May 2017).

Furthermore, in October 2016, a human case of infection with an influenza A(H1N1)v virus in a child was reported. The patient was admitted to a hospital with severe respiratory symptoms and received supportive treatment and oseltamivir. The patient has since recovered and been discharged from hospital. The child had entered a pigsty but had not been in direct contact with pigs. The patient was diagnosed with swine influenza A(H1N1)v virus of the Eurasian avian lineage. Pigs at the farm visited by the patient tested positive for the same swine influenza virus. Six contacts developed mild respiratory symptoms including cough, coryza and conjunctivitis during the monitoring period but all tested negative for influenza A virus (Fraaij, Wildschut et al. 2016).

#### 5.5.4 Discussion

In the Netherlands, one human infection with a swine influenza A(H1N1)v virus of the Eurasian avian lineage was notified in 2016 and 2017. No human cases of avian influenza virus were reported, despite several A(H5N8) infections among poultry were reported in the Netherlands (Van der Hoek, Meijer et al. 2017). Since early 2015, the RIVM started a new study on human infections with an avian influenza virus. In this study, we aim to investigate whether people might be exposed to and infected by avian influenza viruses in case of an outbreak in poultry farms. In addition, finger prick blood is collected for serology tests for antibodies against the outbreak virus using protein micro-array (Koopmans, de Bruin et al. 2012). This study was initiated after the notification of five poultry outbreaks caused by influenza virus type A(H5N8) at the end of 2014. So far, no human infections of the A(H5N8) virus are described and it is currently unknown whether this virus is able to infect humans. In the end of 2016 and the beginning of 2017, 22 people are included in the study. The results of this study are expected later in 2017.

In 2016 and 2017, no returning travellers were tested for influenza virus type A(H5N1) and A(H7N9) infections in the Netherlands. However, the number of influenza virus type A(H7N9) infections in China had an upsurge in the 2016/2017 winter season, as usual since its emergence, so travellers should remain aware of the risk of exposure to animal influenza viruses, especially when having contact with poultry.

## 5.6 MERS-CoV

**Authors:** Rianne van Gageldonk-Lafeber, Adam Meijer

### 5.6.1 Key points

- In the Netherlands, no MERS-CoV infections were notified in the years 2016 and 2017 (through 21 May 2016).

### 5.6.2 Key points

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 have been identified as the most probable host, however, the exact role of camels in transmission of the virus and the exact route(s) of transmission are unknown. In the Netherlands, no MERS-CoV infections were notified in the years 2016 and 2017 (through 21 May 2016).

### 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 [[http://www.rivm.nl/en/Topics/M/MERS\\_Coronavirus](http://www.rivm.nl/en/Topics/M/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 2016, a total of 21 patients with severe acute respiratory illness, returning from countries where exposure to MERS-CoV is possible, were tested for MERS-CoV as well as 2 patients in 2017 (through May 2017). None of them had an infection with MERS-CoV.

# Chapter 6

## Other respiratory infections reported in the weekly virological surveillance

**Authors:** Rianne van Gageldonk-Lafeber

**Contributors:** Adam Meijer, Janneke Duijster

### 6.1 Key points

- The total number of positive rhinovirus (N=2.589) test results in 2016 was the highest reported since five years (range 2012-2015: 1.780-2.410), because of high numbers of positive test results from week 40 2016 onwards.
- Compared to the past five years the number of positive hMPV test results was relatively high between week 47 and 52 of 2016.
- The total number of positive coronavirus (N=712) test results in 2016 was the highest reported since five years (range 2012-2015: 307-575), because of relatively high numbers of positive test results around week 6 and the last weeks of 2016.
- As in previous years, the total number of positive parainfluenza virus test results was highest for type 3. The peak of parainfluenza virus type 3 was relatively late (week 31 of 2016) compared to previous seasons where the peak was around week 19. The total number of positive tests for parainfluenza virus type 3 was higher than in the previous four seasons (N=411, range 2012-2015: 218-344).
- Also for parainfluenza virus type 2, the total number of positive tests was highest reported since 5 years (N=105; range 2012-2015: 53-74). A peak in the number of positive parainfluenza virus type 2 test results was seen in the end of 2016.
- In the past five years, the total number of positive adenovirus test results is increasing (range from 1.116 in 2012 up to 1.612 in 2016).

- The total number of positive bocavirus (N=159) test results in 2016 was higher than the past four years (range 2012-2015: 107-136).
- The numbers of positive diagnoses for parainfluenza virus type 1, parainfluenza virus type 4, *Mycoplasma pneumoniae* 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 2016, the total numbers of positive test results for rhinovirus, coronavirus, parainfluenza virus type 2, parainfluenza virus type 3, adenovirus and bocavirus were the highest reported since five years. Changes in the number of positive test results in the virological laboratory surveillance data are not necessarily caused by actual changes in the incidence of infection, but can also be caused by changes in the policy of testing and testing procedures by the physicians and/or microbiological laboratories. One such change in testing might be the increased application of respiratory panels, which can be used for detection of the causative agent of disease in patients displaying a respiratory disease syndrome. In these panels, molecular detection of the most common viruses is performed in one test. However, which viruses are included in the respiratory panels and the extent to which the panels are used, differs between laboratories and between years. Despite such potential surveillance artefacts, the virological laboratory surveillance remains a valuable source for monitoring long-term trends in the viral diagnostics assuming that testing policies remain relatively stable over the years.

### 6.3 Tables and figures

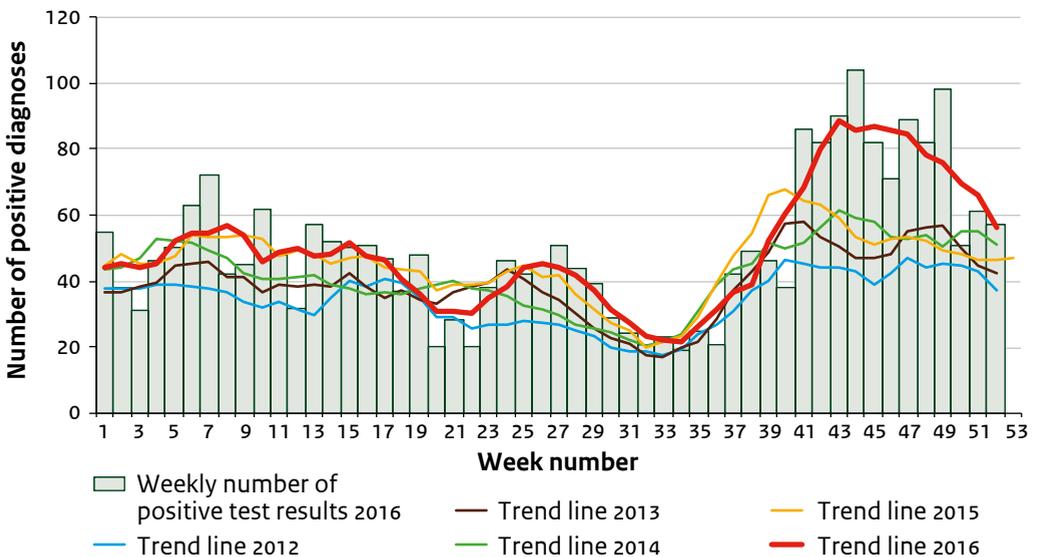
**Table 6.1** Number of reported positive tests of rhinovirus, *Mycoplasma pneumoniae*, human metapneumovirus (hMPV), coronavirus, parainfluenza virus (PIV) type 1-4, *Chlamydia pneumoniae*, adenovirus and bocavirus in the virological laboratory surveillance for the period 2012-2016.

Year	Number of positive diagnoses										
	Rhinovirus	<i>Mycoplasma pneumoniae</i>	hMPV	Coronavirus	Parainfluenza virus type 1	Parainfluenza virus type 2	Parainfluenza virus type 3	Parainfluenza virus type 4	<i>Chlamydia pneumoniae</i>	Adenovirus <sup>a</sup>	Bocavirus
2012	1,780	775	298	307	41	53	238	36	60	1,116	136
2013	2,049	325	469	377	138	74	291	76	27	1,244	111
2014	2,193	436	385	318	76	66	218	53	20	1,268	107
2015	2,410	525	651	575	149	72	344	122	31	1,322	114
2016	2,589	608	542	712	55	108	411	65	19	1,612	159

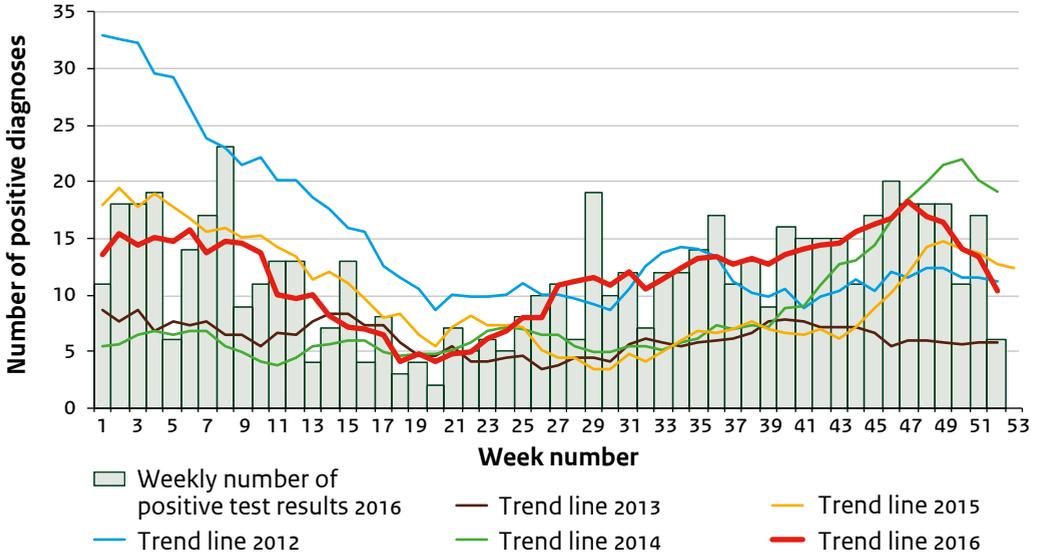
<sup>a</sup> Due to a technical error, the number of positive diagnoses for adenovirus has been displayed incorrectly in previous annual reports.

hMPV= human metapneumovirus

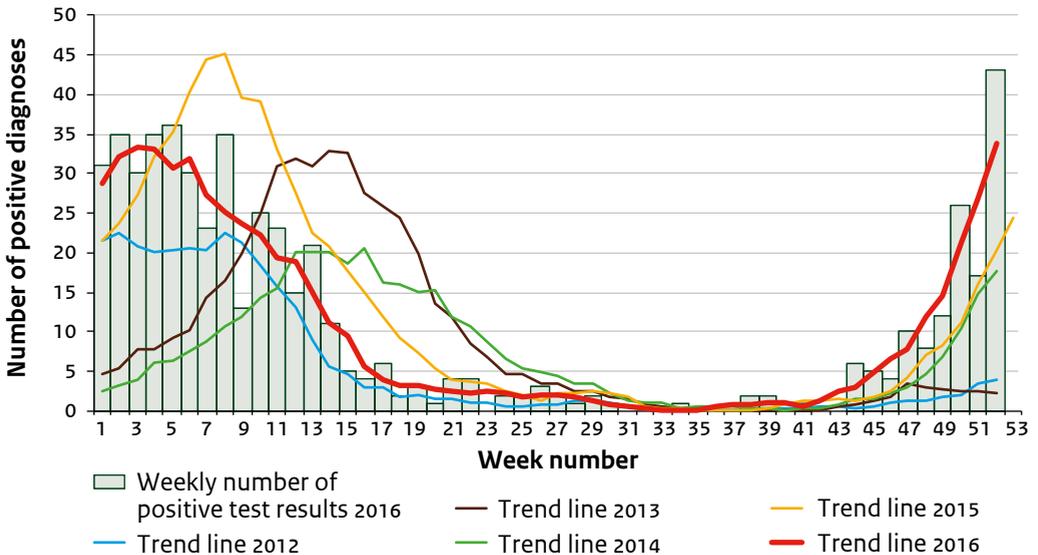
**Figure 6.1** Number of weekly reported positive test results of rhinovirus in the virological laboratory surveillance for the calendar year 2016 and the trend lines for the calendar years 2012-2016.



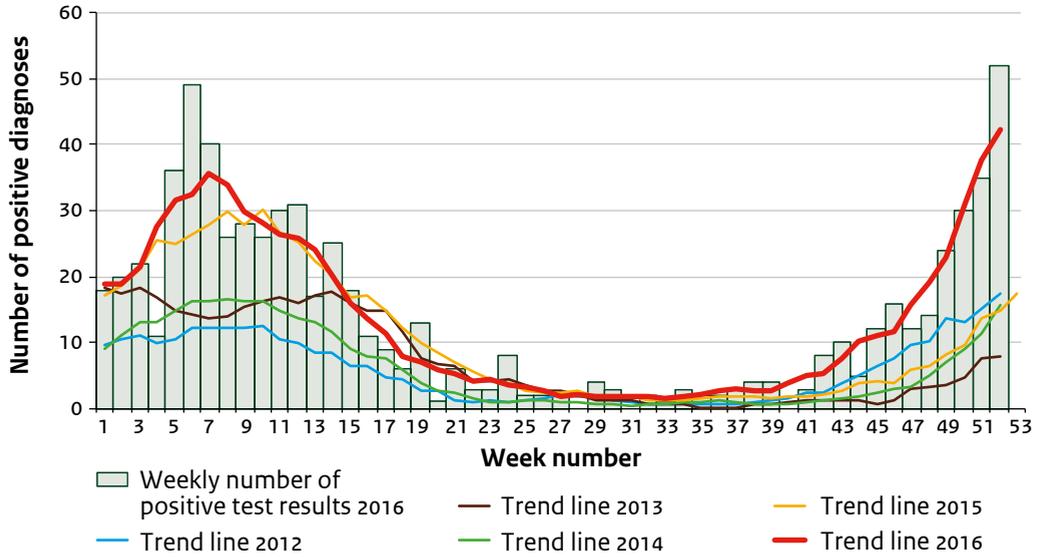
**Figure 6.2** Number of weekly reported positive tests *Mycoplasma pneumoniae* in the virological laboratory surveillance for the calendar year 2016 and the trend lines for the calendar years 2012-2016.



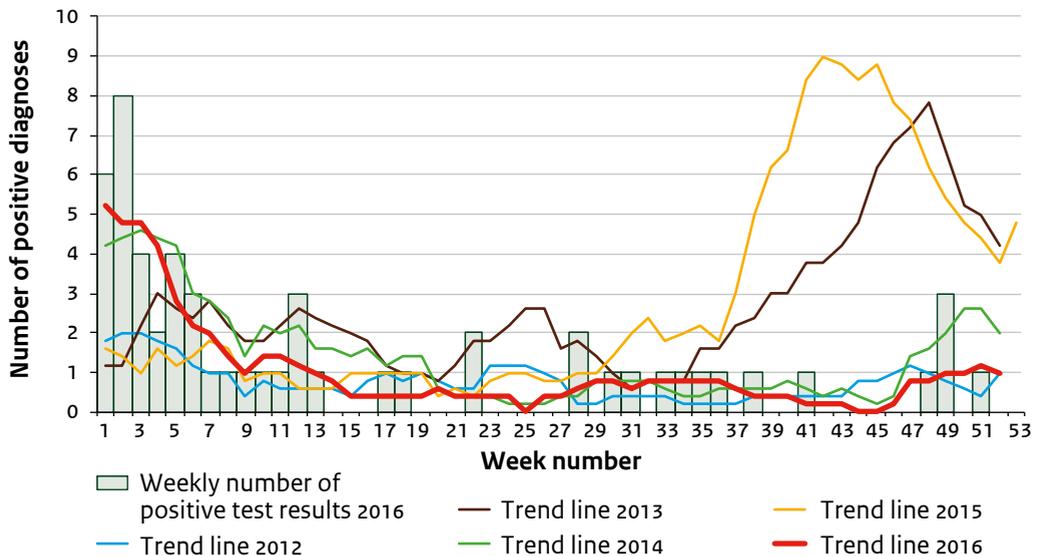
**Figure 6.3** Number of weekly reported positive tests of human metapneumovirus (hMPV) in the virological laboratory surveillance for the calendar year 2016 and the trend lines for the calendar years 2012-2016.



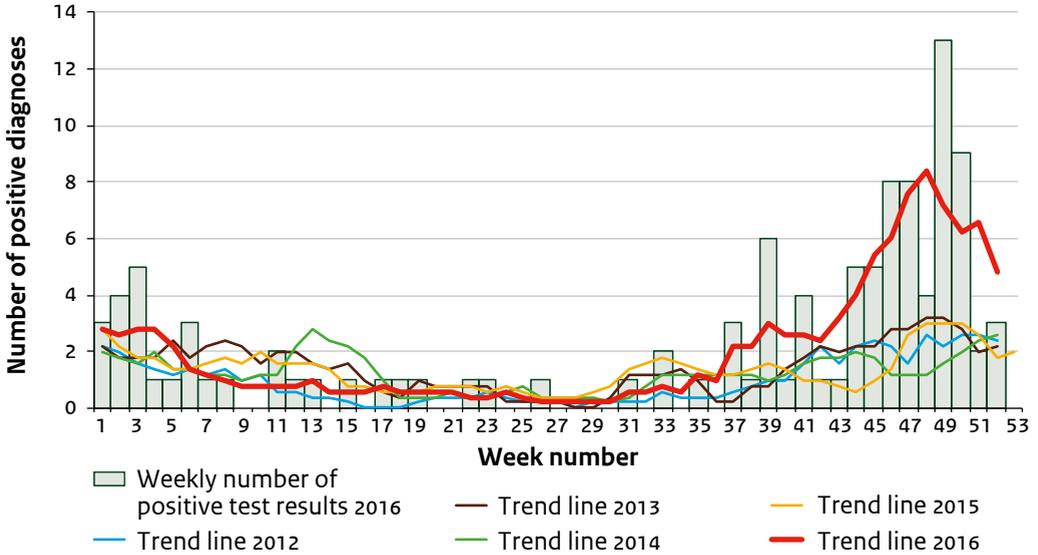
**Figure 6.4** Number of weekly reported positive tests of coronavirus in the virological laboratory surveillance for the calendar year 2016 and the trend lines for the calendar years 2012-2016.



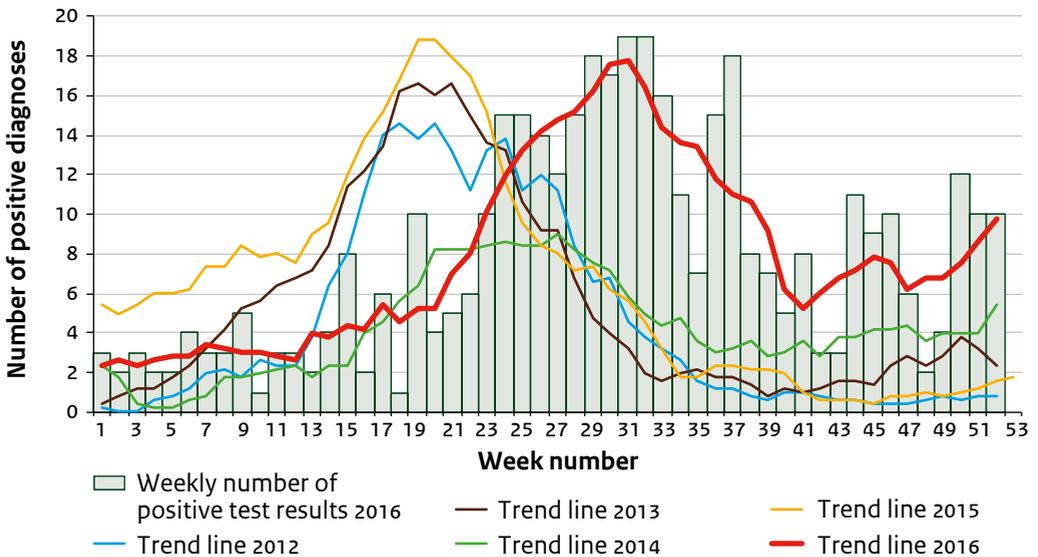
**Figure 6.5** Number of weekly reported positive tests of parainfluenza virus type 1 in the virological laboratory surveillance for the calendar year 2016 and the trend lines for the calendar years 2012-2016.



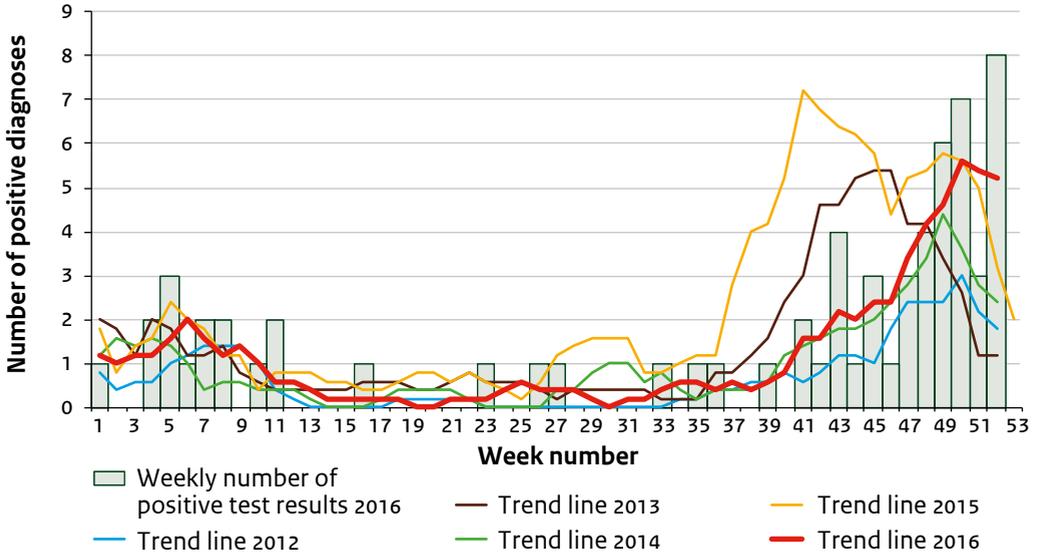
**Figure 6.6** Number of weekly reported positive tests of parainfluenza virus type 2 in the virological laboratory surveillance for the calendar year 2016 and the trend lines for the calendar years 2012-2016.



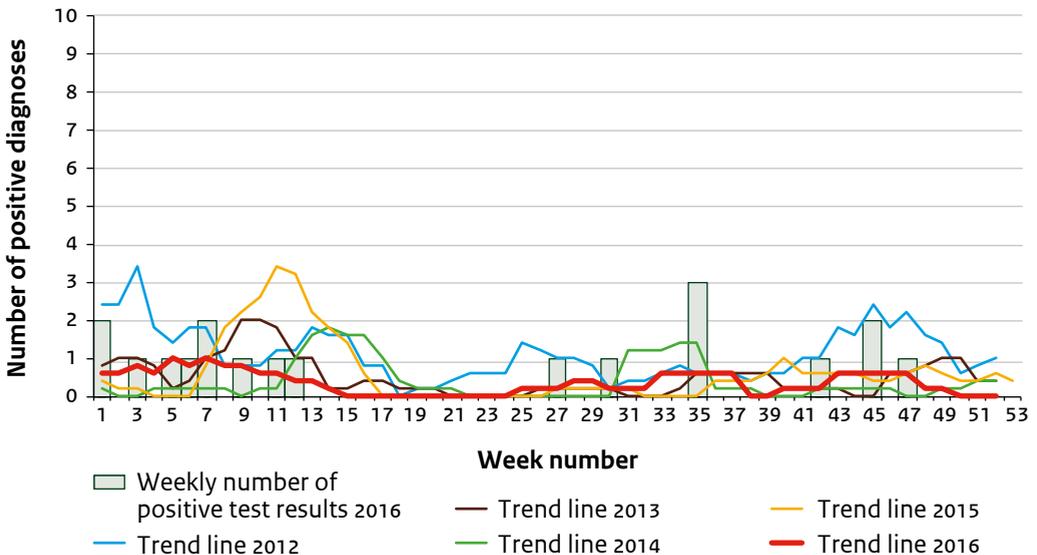
**Figure 6.7** Number of weekly reported positive tests of parainfluenza virus type 3 in the virological laboratory surveillance for the calendar year 2016 and the trend lines for the calendar years 2012-2016.



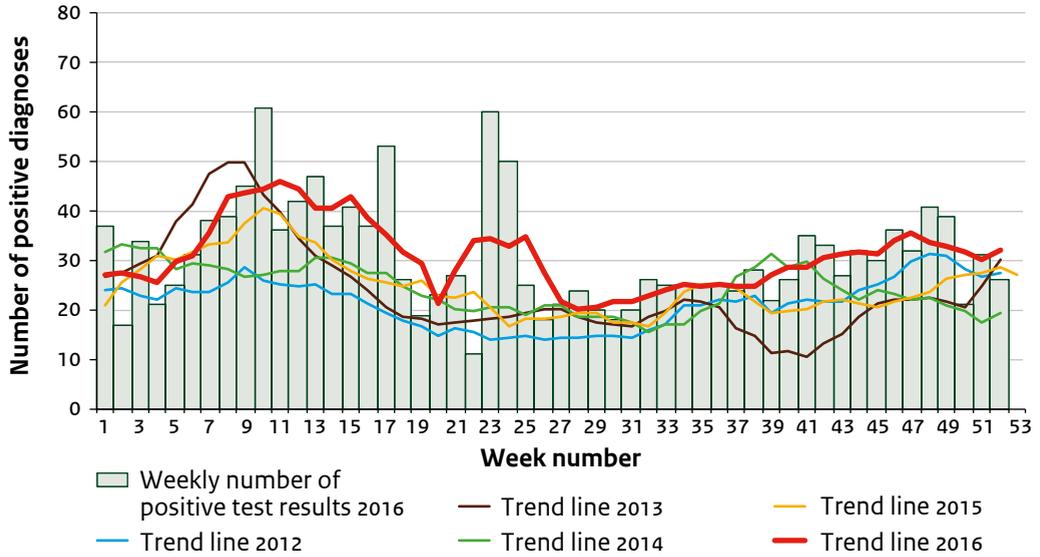
**Figure 6.8** Number of weekly reported positive tests of parainfluenza virus type 4 in the virological laboratory surveillance for the calendar year 2016 and the trend lines for the calendar years 2012-2016.



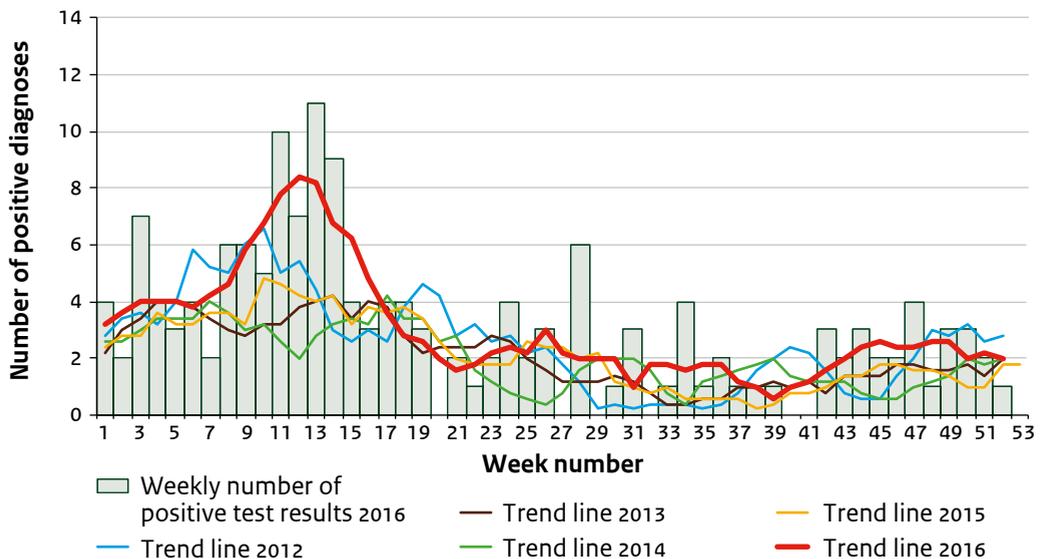
**Figure 6.9** Number of weekly reported positive tests of *Chlamydia pneumoniae* in the virological laboratory surveillance for the calendar year 2016 and the trend lines for the calendar years 2012-2016.



**Figure 6.10** Number of weekly reported positive tests of adenovirus in the virological laboratory surveillance for the calendar year 2016 and the trend lines for the calendar years 2012-2016.



**Figure 6.11** Number of weekly reported positive tests of bocavirus in the virological laboratory surveillance for the calendar year 2016 and the trend lines for the calendar years 2012-2016.



# Chapter 7

## Burden of respiratory infectious diseases in the Netherlands

**Authors:** Brechje de Gier, Anne Teirlinck

**Contributors:** Alies van Lier, Scott McDonald, Lenny Hogerwerf, Erika Slump, Petra Brandsema, Frederika Dijkstra, Marit de Lange, Adam Meijer

### 7.1 Key points

- The respiratory infectious disease with the highest estimated annual burden in 2016 was influenza: 16,316 DALYs (95% CI 15,169-17,501), followed by legionellosis: 6,503 DALY (95% CI 5806-7304), tuberculosis: 2,737 DALY/year (95% CI 2253-3255), psittacosis: 92 DALY (95% CI 70-118) and Q fever: 46 DALY/year (95% CI 36-56).
- The burden of influenza is variable through the years, while the burden caused by the other four respiratory pathogens is generally more stable. The burden of legionellosis slightly increased during the last two years and the burden of psittacosis and Q fever decreased.
- When assessing the average burden per individual case, the burden is highest for legionellosis and lowest for influenza.
- On population level, the annual burden of respiratory disease is highest in older adults, mainly because of the accumulation of burden of influenza and legionellosis in this age group and in elderly above 85, mostly due to influenza.

## 7.2 Background

Estimates of the burden of infectious diseases are used to compare health impact between different infectious diseases in the Dutch population and to follow trends in time. The burden of a disease is a combination of incidence and severity. Disease burden is expressed here in disability-adjusted life years (DALY), which indicates the number of healthy life years lost due to a disease. DALY is a 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 2012 to 2016, or the disease burden that theoretically could have been avoided by preventing infections in those years. We present an update of previous infectious disease burden estimates of influenza, tuberculosis, legionellosis, psittacosis and Q fever (Bijkerk, de Gier et al. 2016), now separated per year instead of showing aggregated data over a few years. This chapter is based on Chapter 6 in the State of Infectious Diseases in the Netherlands, 2016 (de Gier, Nijsten et al. 2017), showing the information of these five respiratory infections.

## 7.3 Burden of respiratory infectious diseases

Of the five respiratory infectious diseases of which the burden was estimated, influenza had the highest burden during the period 2012-2016, of on average 11,189 DALY/year (95% CI 10,260-12,193). This is a sum of 9,461 YLL/year (95% CI 8,689-10,298) and 1,729 YLD/year (95% CI 1,572-1,903). Influenza did not only have the highest burden of the respiratory disease compared in this chapter, but the burden was also the highest of all infectious diseases for which a burden was estimated (de Gier, Nijsten et al. 2017). Like influenza, for legionellosis (4,891 YLL/year and 514 YLD/year), tuberculosis (2,501 YLL/year and 119 YLD/year) and psittacosis (145 YLL/year and 5 YLD/year), the YLL was higher than the YLD, but not for Q fever (21 YLL/year and 69 YLD/year). The burden for Q fever declined since 2013, due to the decreasing incidence. When assessing the average annual DALY per age category, the highest burden from these five respiratory infections together is suffered by the adult age group (45-54 years old). For legionellosis, the burden is highest in the adult age groups, for tuberculosis, the burden is highest in young adults. When assessing the average burden that an individual case suffers (expressed as DALY per 100 cases), burden is highest for legionellosis and lowest for influenza.

## 7.4 Discussion

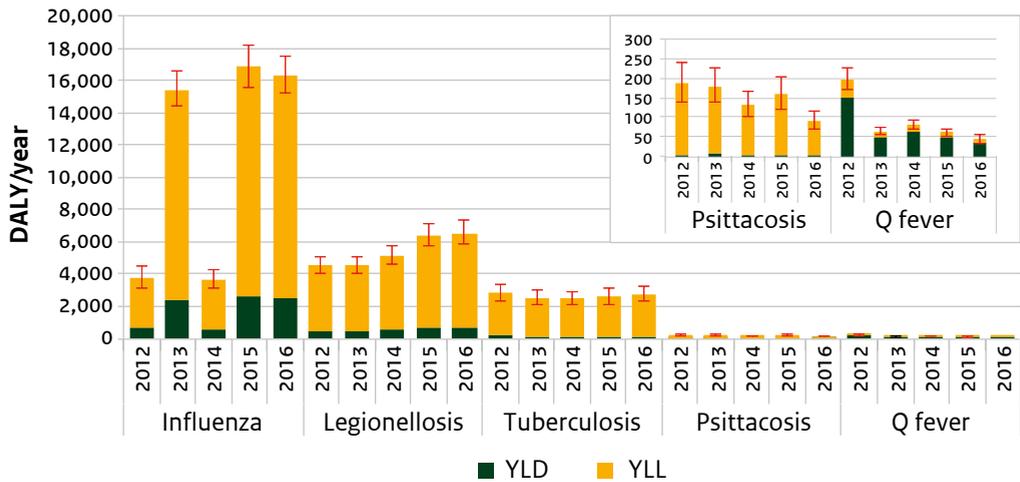
Two methodological changes have influenced the disease burden estimates compared to the report of the previous season: the application of new disability weights and the use of a different life expectancy table. In previous estimates, disability weights from different studies, derived from different methods and populations were applied. The currently used disability weights are derived from a single study among citizens of four European countries including the Netherlands. The disability weights were generally lower than disability weights previously applied. However, the application of a longer life expectancy (i.e. more recent estimates of 'optimum' remaining life expectancy) results in higher estimates for YLL and also influences the YLD of long-term sequelae. For more details, please refer to State of Infectious Diseases in the Netherlands, 2016 (de Gier, Nijsten et al. 2017).

The influenza burden estimate is based on an improved method to estimate influenza incidence; via bayesian evidence synthesis (see chapter 3 and chapter 9). Previously, influenza incidence per age group was calculated by multiplying the influenza-like illness (ILI) incidence from GP surveillance with the influenza positivity rate from sampled patients, per age. This method did not take into account the considerable uncertainty surrounding these estimates due to the limited number of specimens per age group. In the currently applied method, a model was employed to quantify this uncertainty. This has resulted in a much wider uncertainty interval (Table 7.1), compared to the interval presented last year which was based only on uncertainty for disease progression probabilities. A further change is the presentation of influenza burden per season (week 20-40) instead of per calendar year, as influenza burden is highly dependent on the specific season. We chose not to include influenza burden outside the respiratory season, as the influenza positivity rates in ILI patient swabs during this period are too low to present relevant influenza burden with any certainty. The incidence of legionellosis was higher than usual in 2015 and 2016, which is reflected in the burden estimates.

For many respiratory infectious diseases, no disease burden models are available yet. For example, substantial disease burden is expected to be caused by respiratory syncytial virus. The continuous development of both new and existing disease models is essential to produce more complete, comparable and valid disease burden estimates in the future.

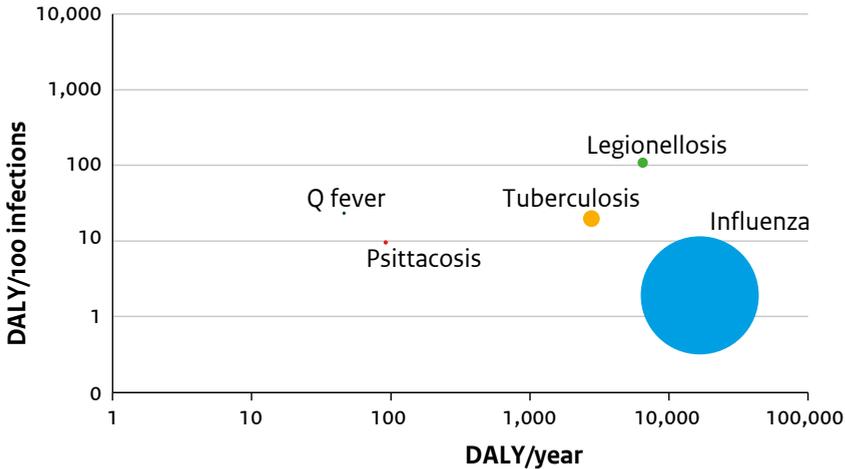
## 7.5 Figures and tables

**Figure 7.1** Average annual DALY, caused by respiratory infectious diseases in the Netherlands, split by YLL and YLD, ranked by the average disease burden caused by the annual incident cases in 2012-2016. Error bars indicate 95% confidence intervals. The insert zooms in for psittacosis and Q fever (Source: de Gier, Nijsten et al. 2017).



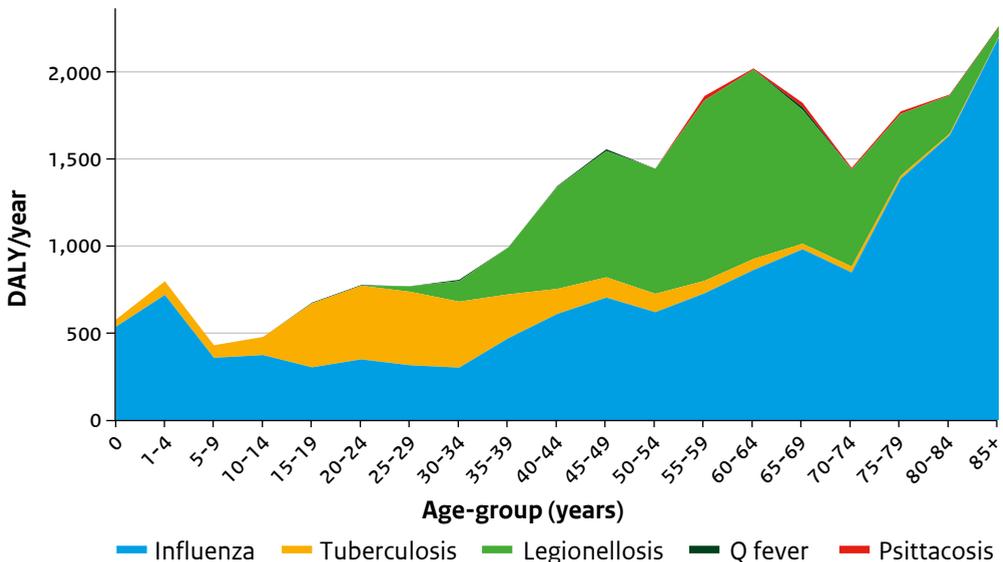
**Footnote:** DALY = disability-adjusted life years; YLL = years of life lost due to mortality ; YLD = years lived with disability.

**Figure 7.2** Ranking of respiratory diseases by estimated burden at population (DALY/year) and individual level (DALY/100 cases) in 2016 (for influenza respiratory season 2015/2016). The area of each bubble is proportional to the estimated incidence of the disease. (Source: de Gier, Nijsten et al. 2017).



**Footnote:** both axes are on a logarithmic scale. DALY = disability-adjusted life years

**Figure 7.3** DALY (population level) caused by respiratory infection events per pathogen and age category in 2016 (for influenza: respiratory season 2015/2016).



**Footnote:** The burden suffered from an infection is fully assigned to the age when the infection event occurred. DALY = disability-adjusted life years

**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 2012 to 2016 in the Netherlands in order of highest to lowest average DALY/year in 2016.

Disease	YLD/year	YLL/year	DALY/year	DALY/ 100 cases <sup>a</sup>	Annual acute infections <sup>b</sup>
<b>Influenza</b>					
2011/2012	607 (496-744)	3147 (2630-3755)	3755 (3127-4489)		187083
2012/2013	2375 (2205-2563)	13059 (12210-13984)	15435 (14417-16539)		776113
2013/2014	571 (474-687)	3035 (2573-3565)	3605 (3049-4245)		180364
2014/2015	2589 (2372-2824)	14247 (13175-15379)	16836 (15537-18193)		846704
2015/2016	2500 (2315-2698)	13816 (12858-14808)	16316 (15169-17501)	2.0 (2.0-2.0)	821081
<b>Legionellosis</b>					
2012	426 (389-471)	4085 (3619-4626)	4511 (4019-5083)		3967
2013	432 (394-474)	4042 (3597-4527)	4474 (4007-4994)		4018
2014	487 (443-537)	4661 (4141-5241)	5148 (4606-5762)		4537
2015	588 (536-647)	5801 (5141-6521)	6388 (5698-7152)		5468
2016	635 (579-699)	5868 (5201-6620)	6503 (5806-7304)	110 (102-119)	5908
<b>Tuberculosis</b>					
2012	130 (125-134)	2713 (2203-3236)	2842 (2332-3364)		14837
2013	114 (110-118)	2363 (1906-2846)	2477 (2018-2958)		13128
2014	111 (107-114)	2330 (1904-2776)	2441 (2012-2887)		12663
2015	117 (113-122)	2484 (2006-2982)	2602 (2121-3099)		13366
2016	121 (117-126)	2615 (2131-3133)	2737 (2253-3255)	20 (16-24)	13801
<b>Psittacosis</b>					
2012	5 (4-5)	182 (138-233)	187 (141-239)		1259
2013	6 (5-7)	171 (132-218)	177 (137-224)		1515
2014	4 (4-5)	127 (98-160)	131 (102-165)		1147
2015	5 (4-5)	156 (118-200)	161 (122-205)		1262
2016	3 (3-4)	89 (66-114)	92 (70-118)	9,7 (7,9-12)	950
<b>Q fever</b>					
2012	152 (132-173)	46 (40-53)	198 (172-225)		865
2013	49 (41-57)	15 (13-18)	64 (55-74)		274
2014	62 (52-71)	18 (15-21)	80 (68-92)		357
2015	48 (41-56)	14 (12-17)	62 (52-72)		275
2016	34 (27-43)	11 (9-14)	46 (36-56)	24 (19-29)	192

<sup>a</sup> for tuberculosis and 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 (or latent) acute infections per year.

<sup>b</sup> DALY/100 cases is only shown for 2016 since this is a characteristic of the disease and independent of time.

<sup>c</sup> this number includes asymptomatic (or latent) infections for Q fever and tuberculosis.

# Chapter 8

## General discussion and conclusion

**Authors:** Anne Teirlinck, Wim van der Hoek

The influenza epidemic in the 2016/2017 season lasted 15 weeks, which is longer than the average nine week duration of the past 20 years. As the epidemic period is mainly defined by the incidence of medically-attended influenza-like illness (ILI) in primary care, a longer duration as well as a higher peak of an epidemic can either be caused by a real increase in ILI, or by changes in healthcare-seeking behaviour. Media attention, for example, could make people seek medical care for respiratory symptoms for which they may previously not have visited their general practitioner (GP). However, there are no indications that this played a role in the 2016/2017 season.

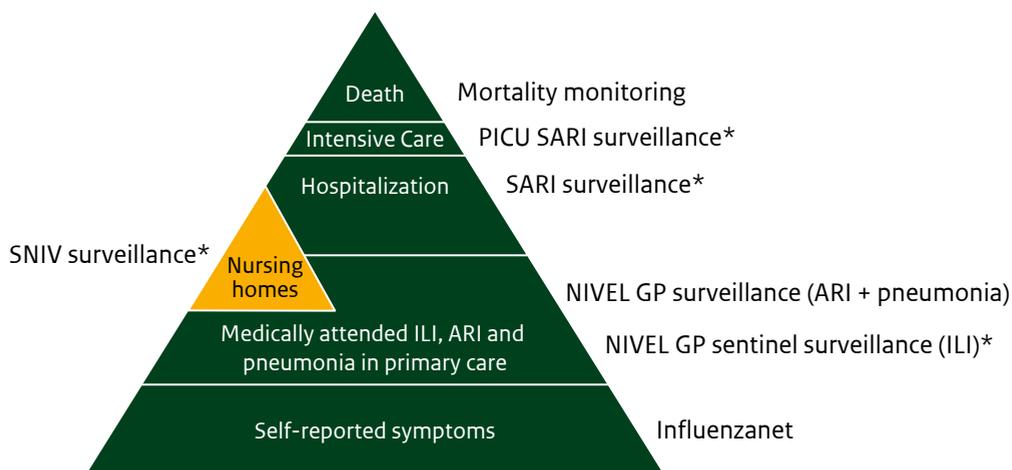
The early part of the 2016/2017 epidemic clearly resembled the epidemic of season 2014/2015. The incidence of ILI, other acute respiratory infections (ARI) and pneumonia at GP level were quite similar, both seasons had a comparable ILI incidence in nursing homes and, in both seasons, the dominant virus was the influenza virus A(H3N2). This year's epidemic, however, ended much earlier (week 10) than in 2015 (week 17), which is at least partly due to the influenza B (Yamagata lineage) circulation at the end of the season in 2015, while only a few influenza B circulated at the end of the 2017 influenza epidemic.

The 2016 epidemic also started earlier than those of previous seasons, in week 48. Even though the criteria for an influenza epidemic (an ILI incidence rate of above 5.1 per 10,000 people for more than two weeks plus evidence that the influenza virus is circulating) were fulfilled in that week, the early onset of the epidemic was probably driven by respiratory viruses other than influenza, such as respiratory syncytial virus (RSV) and rhinovirus. The ILI incidence among the 0-4 year olds was high and made an important contribution to the overall ILI incidence, while the influenza virus was detected in these children much less frequently than RSV and rhinovirus. This was the case for ILI and ARI cases visiting the GP, as

well as for children with severe acute respiratory infection (SARI) who had to be admitted to a paediatric intensive care unit (PICU).

The surveillance pyramid of influenza and other respiratory infections is displayed in Figure 8.1. The dominance of influenza virus A(H3N2) is reflected in this pyramid. Influenza virus A(H3N2) is known to cause most of the infections and disease in older people born before 1957, who are typically better protected against influenza A(H1N1) viruses because of a background natural immunity created by having the first exposure to A(H1N1) in their life. Indeed the ILI incidence in this age group over the previous five seasons was highest in the two seasons in which influenza A(H3N2) was dominant. Also the ILI incidence in nursing homes was higher than the previous four seasons and the pneumonia prevalence in nursing homes was somewhat higher in the two A(H3N2) seasons than it was in the other three seasons. The SARI incidence among people older than 60 was higher than respiratory season (2015/2016) and the excess mortality (generally mostly observed in the 75+ age group) was also higher than in most other seasons.

**Figure 8.1** The respiratory infections surveillance pyramid in the Netherlands



**Footnote:** Systems with \* also include virological surveillance

This is the first annual report in which we present the estimated annual incidence of symptomatic influenza virus infection for the entire Dutch population, based on sentinel GP influenza surveillance data and self-reported data from Influenzanet. This outcome is derived using a statistical modelling approach which combines multiple sources of evidence and, therefore, provides a useful estimate of symptomatic influenza incidence in the population that can be compared across seasons (McDonald, Presanis et al. 2014). This method also enables a direct comparison of influenza incidence to be made between age groups, and the burden attributable to the various strains across seasons in the population. In comparison with the younger age groups, the symptomatic influenza incidence in people older than 65 years is

not as high as one would expect based on GP data only. The main reason for this is that a correction for under-ascertainment is made, so that all symptomatic influenza cases are estimated, not only those patients who visit a GP. As healthcare-seeking behaviour varies between age-groups, and elderly people visit their GP more frequently than younger adults, a smaller under-ascertainment adjustment was made for the elderly than for the younger adults. Of note, for the ILI incidence and virological sampling, only the community-dwelling population was considered, as GPs do not provide medical care for nursing home residents. Because many elderly people, especially the more frail, live in nursing homes, influenza incidence in this group will be higher than estimated. Unfortunately, the number of specimens obtained from ILI patients in nursing homes was too small to assess the virus circulation.

In the 2016/2017 respiratory season, the dominant influenza strain A(H3N2) had a good to moderate match with the A(H3N2) vaccine strain. Data from 12 European countries, including the Netherlands, show a vaccine effectiveness (VE) against A(H3N2) of only 27% (95% CI: 15-37%). Surprisingly, this estimate from the European I-MOVE (Influenza Monitoring Vaccine Effectiveness) network, which includes the Dutch data, was lower than the Dutch VE estimate against A(H3N2) (47% (95% CI: 15-67%). There is no clear explanation for this. For the 2017/2018 season, the World Health Organization (WHO) has selected the same influenza A(H3N2) virus as the one that was used for the 2016/2017 vaccine. It is impossible to predict which virus(es) will dominate in seasons to come, but the A(H3N2) viruses circulating in 2016/2017 had a wide diversity of antigenic determinants and a mismatch in vaccine and circulating A(H3N2) viruses might occur for next season. It will, therefore, be very important to have early VE estimates available in the 2017/2018 influenza season as well as early characterisation of the circulating viruses, in order to inform clinicians and policy makers.

In addition to the SARI surveillance in two Dutch hospitals which was started last year and mainly covers adult patients, the PICU SARI surveillance complements information on SARI epidemiology by targeting children. Because of the high clinical relevance, previous positive experience, and their clear structure, cooperation was sought with the eight PICUs in the Netherlands, six of which agreed, which results in a coverage of about 75% of the total PICU population. Although each PICU has its own specialisations and SARI patients are, therefore, not equally distributed over the different PICUs, the PICU SARI surveillance provided important insight into the incidence, aetiology and burden of SARI among the paediatric population.

Notifiable infectious diseases which present as pneumonia are under-reported because, in most cases of community-acquired pneumonia (CAP) that are managed in primary care, no specific diagnostic laboratory tests are performed. In the virological laboratory surveillance 89 diagnoses of *C. burnetii* were reported which is considerably higher than the number (n=14) of Q fever notifications. The most likely explanation for this discrepancy is that notification only includes acute cases of Q fever, whereas the virological surveillance also includes positive laboratory results, suggesting past infection in patients who were tested to exclude chronic Q fever. Hence, an increased number of reported *C. burnetii* diagnoses in the virological surveillance after the Q fever epidemic is not unexpected. Two-thirds of the diagnoses came from just one laboratory in the south of the Netherlands which covered the part of the region

which had the most cases during the epidemic. The other third came from 10 other laboratories in various regions of the Netherlands.

For a few years, the notifications for acute Q fever have been back to the levels that they were in the period before the large 2007-2010 Q fever epidemic. However, there are still considerable numbers of patients suffering from long-term sequelae, especially chronic Q fever and Q fever fatigue syndrome (QFS). Chronic Q fever and QFS are not notifiable, but for chronic Q fever, a national database is maintained at the University Medical Centre Utrecht containing information on 439 chronic Q fever patients. Fuelled by a public debate about the need for population screening to detect any people who might be chronically infected without knowing it, RIVM-EPI is currently coordinating a cost-effectiveness analysis of such a population screening programme.

After a steady decline for many years, this is the second year in a row which shows a slight increase in the number of notified tuberculosis cases. This can be explained entirely by the increase in asylum seekers from countries which have a high tuberculosis incidence, especially those from the Horn of Africa. DNA fingerprinting of all *Mycobacterium tuberculosis* complex isolates plays an essential role in epidemiological investigations and helps Municipal Health Services in contact-tracing and in their other tuberculosis control activities. In an ongoing research project, the prevailing method of DNA fingerprinting is being compared to 'whole genome sequencing' (WGS). There are strong indications that WGS analysis is a more accurate tool than currently used DNA-typing methods.

An increasing trend in the incidence of Legionnaires' disease (LD) was observed in domestic cases from 2012 to 2016. Part of the increase in 2016 may be explained by weather conditions. Studies have shown an association between the Dutch LD incidence and extensive rainfall after warm weather. (Brandsema, Euser et al. 2014, Beaute, Sandin et al. 2016). In 2016 the high number of cases in June was associated with heavy rainfall in the preceding weeks. Additional questionnaires were used to explore the type of exposure to possible sources during this wet period. One factor that seems relevant in cases with an onset in June is exposure to flooding in the direct environment or during travel. More LD cases were also observed during the mild winter months. In scenarios of climate change and an aging population, a further increase in the incidence of Legionnaires' disease may be expected in future years. Further research is required to identify the environmental sources of this weather-driven transmission of Legionnaires' disease. In 2016, several geographic clusters were observed that could not be explained by heavy rainfall or other weather conditions. Source investigations and, when possible, sampling of environmental sources were performed for each of these clusters but the source of infection was not found for any of them. Genotyping results of the clinical isolates indicate that there may be a common source for some of the clusters. A possible explanation could be a mobile source of infection. This option should be included in the source finding investigations of any new clusters.

As wet cooling towers are shown to be the most frequent source of infection in outbreaks, the Municipal Health Services were also asked for the locations of cooling towers in the vicinity of the clusters. However, this information was often not available, incomplete or not up-to-date, and timely sampling of cooling towers in the area was not possible. The incomplete registration of cooling towers is a cause for serious concern. Worldwide there are several cooling tower-related LD outbreaks every year, including outbreaks in countries with a similar climate to the Netherlands. A cooling tower outbreak in the Netherlands is, therefore, a plausible scenario. The current legislation for the registration of wet cooling towers is not very effective and it is estimated that only a third of all wet cooling towers are currently registered. If an outbreak occurs, it could therefore take a long time to find the contaminated cooling tower. This may lead to unnecessary cases of illness and deaths.

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



# Chapter 9

## Methods of respiratory surveillance

### 9.1 Respiratory season, respiratory year and calendar year

The aim of this annual report is to describe the surveillance of influenza and other respiratory infections in the Netherlands. Since influenza, influenza-like-illness (ILI), acute respiratory infections (ARI), pneumonia, respiratory syncytial virus (RSV) infection, and all-cause mortality mainly occur in winter, data is usually presented for the respiratory season or the respiratory year. A respiratory season is defined as the period from week 40 through week 20 of the next year and the respiratory year is defined as the period from week 40 through week 39 of the next year. In this report, data on the respiratory year 2016/2017 is limited to the respiratory season to allow a timely reporting. These respiratory infections may occur outside this winter period to a limited extent. 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 2016 calendar year (weeks 1-52).

### 9.2 Data sources

#### **NIVEL Primary Care Database**

In 2012, NIVEL Netherlands institute for health services research, initiated the integral monitoring and information services for primary care, called 'NIVEL Primary Care Database' (Verheij and Koppes 2013). The NIVEL Primary Care Database holds longitudinal data registered by general practitioners (GPs) and other primary health care providers. For the surveillance of respiratory infectious diseases, the following data of NIVEL is used:

- Near real-time (weekly) surveillance data concerning pneumonia and acute respiratory infections, based on consultation data in electronic medical records from about 400

participating general practices [<http://www.nivel.nl/NZR/wekelijkse-surveillance-gezondheidsproblemen>]. In the 2016/2017 respiratory year, the coverage was about 1.1 million persons (7% of the Dutch population). These GPs do not actively report patients and do not take laboratory specimens for surveillance purposes but make their electronic patient information systems available for automatic, anonymised, data extraction (Hooiveld, ten Veen et al. 2013).

- A proportion of the GPs participating in NIVEL-Primary Care Database take part in ‘sentinel surveillance’. These GPs actively report on the number of patients who consult them for ILI. From a subset of patients they collect a throat swab and nose swab and send it to RIVM for virological laboratory diagnostics and further characterisation of detected viruses. The population of these 40 sentinel practices covers approximately 0.7% of the Dutch population and is nationally representative for age, sex, regional distribution and population density (Donker 2016).

### **National sentinel surveillance network for infectious diseases in nursing homes (SNIV)**

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

### **Surveillance of severe acute respiratory infections (SARI) on paediatric intensive care units (PICU)**

A web-based surveillance was set up, in which six out of the eight PICUs participated: Emma Children’s hospital/Academic Medical Center, Amsterdam (EKZ/AMC); VU Medical Center (VUMC); Amsterdam; Leiden University Medical Center (LUMC), Maastricht University Medical Center (MUMC+), Erasmus MC-Sophia, Rotterdam and UMCU Wilhelmina children’s hospital, Utrecht. All PICUs were requested to fill out a weekly form on the online platform Questback. Reported data comprised total number of patients admitted to PICU, total number of SARI cases, number of SARI cases with extracorporeal membrane oxygenation (ECMO) treatment and number of newly admitted SARI cases per age group. If laboratory diagnostics were performed for newly admitted SARI cases, we additionally asked for the laboratory results for respiratory viruses. What is important to mention for correct interpretation of laboratory results is that virological testing at PICUs was performed to facilitate individual patient management, and not for surveillance purposes.

### **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, 43% (median) is received by CBS within 1 week after the date of death, 93% within 2 weeks after date of death and 99% within 3 weeks of date of death.

### **Virological laboratory surveillance**

On a weekly basis, about 20 virological laboratories, all members of the Working Group for Clinical Virology of the Dutch Society for Medical Microbiology (NVMM), report the number of diagnoses of several viral pathogens and certain obligatory intracellular (i.e. only growing within a cell) bacteria to RIVM. Data are reported by week of laboratory diagnosis. No distinction can be made between specimens originating from primary care or hospital care, or between the used diagnostic methods, such as culture, molecular diagnostic, serology or rapid tests. Data are therefore reported in an aggregated format. Although no background information concerning patient status, clinical data and type of diagnostic method is available, the weekly laboratory surveillance can be used as an additional source to follow trends of respiratory infections over a prolonged period because of their relative robust reporting history.

### **Osiris**

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

### **New respiratory virus infections**

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

## 9.3 Data analysis

### **Influenza-like-illness (ILI)**

ILI incidence is calculated using two data sources: 1) NIVEL Primary Care Database - sentinel GP practices and 2) SNIV nursing homes. These two data sources all 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 2016). The influenza epidemic threshold is set at an ILI incidence of 5.1 per 10,000 persons per week, based on historical data (Vega Alonso, Lozano Alonso et al. 2004). An influenza epidemic is defined as a period of at least two consecutive weeks with ILI incidence above the influenza epidemic threshold, during which influenza virus is detected in nose swabs and throat swabs of ILI patients.

The ILI incidence in SNIV nursing homes is calculated using the number of residents with ILI as numerator, and the number of observed resident weeks as denominator. The case definition of ILI used by SNIV surveillances is according to the ECDC case definition for ILI and is as follows:

- Sudden onset of symptoms
- And at least one of the following four systemic symptoms:

- Fever or feverishness
- Malaise
- Headache
- Myalgia

And at least one of the following three respiratory symptoms:

- Cough
- Sore throat
- Shortness of breath

### **Acute respiratory infections (ARI)**

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

### **Pneumonia**

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

### **Severe acute respiratory infections (SARI)**

An active surveillance system is implemented at Jeroen Bosch Hospital (JBH) versus a passive surveillance system at the Leiden University Medical Center (LUMC). 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 by the WHO is:

An acute respiratory infection with:

- history of fever or measured fever of  $\geq 38\text{ C}^\circ$ ;
- and cough;
- with onset within the last 10 days;
- and requires hospitalization.

#### *Leiden University Medical Center*

The passive SARI surveillance is embedded in an automated cluster detection system “Integrated Crisis Alert and Response System (ICARES)”, which was implemented in the region of Leiden in 2013. General practitioners (GPs), general practitioner out-of-hours services and hospitals including ICU departments send a minimal dataset from patients with a respiratory tract infection using a routinely used Dutch coding system. The data are presented on a dashboard available for the research team and public health care authorities in the Leiden-The Hague region. The dashboard is updated daily in order to have real-time insight in occurrence of respiratory tract infection. DBC/DOT (Diagnose Behandel Combinatie Op weg naar Transparantie) is the routinely used coding system dictated by the national Dutch

Healthcare Authority (NZa). The accompanying minimal dataset supplied by the hospitals consists of age cohort, gender, four digit postal code, ICU admission, date of consultation GP and an encrypted patient ID code. However, it has to be noted that ICARES not only reports absolute numbers of SARI patients admitted to the regular ward or ICU, but also outpatients discharged from the emergency ward with an acute respiratory infection. An historic cohort (8 years) is available for epidemiological and mathematical modelling.

#### *Jeroen Bosch Hospital*

In February 2017, the SARI surveillance pilot study changed from research to a quality of care management strategy. The quality of care of SARI patients is now evaluated based on quality indicators, such as diagnostics, infection control measures, and treatment. The included SARI patient had to answer a short online questionnaire about symptoms, influenza and pneumococcal vaccination status, comorbidities and several risk factors. In addition, routinely collected urine- and respiratory specimens were used for influenza virus (sub)typing and a pneumococcal urinary antigen test. If influenza virus diagnostics were not requested by the treating physician, influenza (sub)typing and lineage determination were performed in research setting at RIVM's Centre for Infectious Disease Research, Diagnostics and Screening (IDS). No outpatients are included in the SARI surveillance at the Jeroen Bosch Hospital.

#### **Surveillance of severe acute respiratory infections (SARI) on paediatric intensive care units (PICU)**

We used a modified WHO case definition for SARI [[http://www.who.int/influenza/surveillance\\_monitoring/ili\\_sari\\_surveillance\\_case\\_definition/en/](http://www.who.int/influenza/surveillance_monitoring/ili_sari_surveillance_case_definition/en/)]:

- A child (0- 18 year) attended to the PICU
- BECAUSE of acute respiratory complaints
- AND onset of symptoms within the past 7 days
- AND doctor's judgment that the complaints are caused by an infection

#### **Determining excess mortality**

Every Thursday the number of reported deaths, as provided by Statistics Netherlands (CBS), is checked 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 (43% of all deaths) and deaths reported within 2 weeks after date of death (93% of all deaths). The baselines and prediction limits are calculated using a Serfling type algorithm on historical mortality data from the 5 previous years. In the historical data, any weeks with extreme underreporting were removed (the 7.5% most underreported values, often coinciding with public holidays). Also periods with high excess mortality in winter and summer were removed so as not to influence the calculated baseline with time-periods with previous excess mortality. When the observed number of deaths exceeds the upper limit of the prediction interval mortality is considered to be significantly increased (excess deaths calculated as the number of deaths above the baseline).

## Influenza virus, RS-virus and other respiratory viruses

### *Surveillance of circulating viruses*

At the National Influenza Centre (NIC) location RIVM the respiratory specimens are analysed that are taken for the influenza virus surveillance at the GP sentinel practices and the SNIV sentinel nursing homes. Additionally, Dutch laboratories submit all or a subset of their influenza virus positive clinical specimens to the NIC location Erasmus MC, for further subtyping, lineage determination, antigenic characterization and antiviral susceptibility testing.

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 participation, the instructions for the GPs to swab ILI patients are changed. The reason for the change is to obtain the data as systematically as possible. The instructions are changed into:

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

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

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

### *Influenza virus antigenic and genetic characterization*

Antigenic characterization of a subset of influenza viruses and influenza virus positive clinical specimens, submitted by peripheral laboratories and from the sentinel GP surveillance, is performed by NIC location Erasmus MC in Rotterdam. This provides an indication of the degree of antigenic match between the circulating influenza viruses and the vaccine virus. Furthermore, a subset of influenza viruses are characterized genetically by sequence analysis of the haemagglutinin genome segment at both NIC locations. At NIC location RIVM this is done on a systematic sample of the dominant influenza virus subtype and on all sporadically detected types and subtypes from the GP sentinel surveillance. This phylogenetic and amino acid substitution analysis gives information about the evolution of influenza viruses and changes that might lead to the emergence of potential antigenic variants. In addition, this type of information complements the antigenic analysis, especially when antigenic characterization is cumbersome, as was the case with the sporadic A(H<sub>3</sub>N<sub>2</sub>) viruses that could be antigenically characterised during the 2016/2017 season.

### *Antiviral susceptibility of influenza viruses*

Infection with an influenza virus with a reduced susceptibility for an antiviral agent can lead to a reduced effectiveness of treatment. The antiviral susceptibility of influenza viruses is systematically monitored. Of the influenza virus isolates obtained in the NIVEL and SNIV influenza surveillance, the phenotypic antiviral susceptibility for neuraminidase inhibitors (oseltamivir and zanamivir) is determined by NIC location RIVM. For a subset of virus isolates derived from specimens sent to NIC location Erasmus MC, the phenotypic antiviral susceptibility for neuraminidase inhibitors is determined at that location. Of viruses that appear reduced susceptible, the neuraminidase genome segment is sequenced to determine the amino acid substitution that explains the reduced susceptible phenotype. In addition, the virus in the clinical specimen is sequenced to exclude the reduced inhibited amino acid substitution is caused by the virus isolation procedure. Molecular markers for resistance to adamantanes (M<sub>2</sub> ion channel blockers: amantadine and rimantadine) are assessed in a subset of influenza virus type A positive clinical specimens by sequencing at NIC location RIVM. For all influenza virus type A positive specimens, the most important molecular markers for reduced sensitivity for neuraminidase-inhibitors are determined by a rapid molecular test at both NIC locations. From a systematic sample of influenza virus positive clinical specimens the whole genome is sequenced at the NIC location RIVM in order to screen for other and new molecular markers for reduced sensitivity for antivirals. In case of mutations with previously unknown impact on antiviral susceptibility, the phenotypical neuraminidase inhibition test is the final proof for the degree of inhibition. This is done at both locations of the NIC for their own set of viruses. Data from viruses analysed at location RIVM and data from viruses analysed at location Erasmus MC are combined on a weekly basis to achieve one overall picture of the current situation.

### **Influenza vaccine effectiveness**

The influenza vaccine effectiveness (VE) for the 2016/2017 season is calculated using data from patients of the NIVEL sentinel surveillance, using the test-negative (case control) design (Jackson and Nelson 2013). Cases are defined as influenza virus positive patients with ILI or another acute respiratory infection, controls as influenza virus negative ILI or ARI patients. Only specimens taken within 7 days after day of onset were included in the analysis. Using this method, the odds of being vaccinated as a case is divided by the odds of being vaccinated as a control. With logistic regression this odds ratio (OR) is adjusted for confounding factors. The VE is calculated as  $(1-OR) \times 100\%$ . As there was one very dominant virus subtype, A(H3N2), circulating during the 2016/2017 season, detailed stratification of VE by virus type, subtype or lineage was not possible. The analysis is restricted to the period that influenza virus was circulating in the Netherlands (for any subtype: week 42 in 2016 to week 20 in 2017, for A(H3N2): week 42 of 2016 to week 16 of 2017). 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 10 weeks each), age group (penalized spline with two degrees of freedom), gender, smoking (classified as 'yes, or quit smoking <1 year ago', 'quit smoking >1 year ago' and 'never smoked'), obesity, pregnancy, chronic medical condition, hospitalization in previous 12 months for a chronic disease that is listed as an indication for flu vaccination, number of GP appointments in the last 12 months (<5 visits or ≥5 visits) and several proxy variables for frailty (hospitalisation in the previous 12 months, number of GP consultations (0-4, 5 or more) need for assistance with showering, need for assistance with walking, and stay in an elderly care home). The association between the potential confounders and influenza virus positivity was analysed with univariate logistic regression. Variables with a p-value of <0.20 were considered in the multivariable analysis. Variables that changed the OR by at least 5% were included in the final multivariable logistic regression model for any influenza subtype (forward selection). Age and comorbidity were chosen a priori as potential confounders. Therefore, they were both kept into the model, since these variables are associated with increased susceptibility to influenza (Madjid, Aboshady et al. 2004, Kurai, Saraya et al. 2013, Sansonetti, Sali et al. 2014, McElhaney, Garneau et al. 2015, Bahadoran, Lee et al. 2016).

### **Estimating influenza incidence**

We extended previously published methods for estimating the incidence of symptomatic influenza by combining all relevant data sources in a statistically principled way, via Bayesian evidence synthesis (McDonald, Presanis et al. 2014). This estimation procedure can be viewed as the 'multiplier method', 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) (from NIVEL Primary Care Database; see chapter 2.1); (ii) underascertainment: age-group specific number of respondents reporting ILI and number of respondents reporting ILI and who contacted their GP; both averaged over the 3-season period 2004/5, 2005/6 and 2005/7 (from the Grote Griep Meting; (Friesema, Koppeschaar et al. 2009)), (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 on the previous method, we estimated incidence for each season through specification of an evidence synthesis model that recognized that ILI incidence over multiple seasons should not be considered to be independent data. To show variation in influenza incidence by subtype across seasons, we also fitted a model in which data were stratified by subtype A(H1N1)pdm09 and A(H3N2) and lineage (B Victoria, B Yamagata) rather than age-group.

### **Virological laboratory surveillance**

To describe trends over time in adenovirus, bocavirus, coronavirus, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, para-influenza virus, rhinovirus and human metapneumovirus (hMPV), we use the weekly number of positive diagnoses reported in the virological laboratory surveillance. Trends are reported for the 2016 calendar year. Number of diagnoses of psittacosis, Q fever, influenza and RSV as reported in virological laboratory surveillance are given in their dedicated chapters.

### **Burden of disease**

To estimate disease burden in DALY, an incidence- and pathogen-based approach was applied to quantify the burden due to illness, disability and premature mortality associated with all short and long-term consequences of infection. The underlying outcome trees, disease progression probabilities and the used models were described previously (Mangen, Plass et al. 2013, Bijkerk, van Lier et al. 2014, de Gier, Nijsten et al. 2017). DALY estimates incorporate both years of life lost (YLL) due to premature mortality and years lived with disability (YLD) (Murray and Lopez 2013). YLD were calculated by multiplying the number of acute cases, duration of a health state and the disability weight of the health state. The disability weight is a value between 0 (perfect health) and 1 (death). In contrast to the disease burden estimates presented in previous editions of this report, we used the newly available European disability weights by Haagsma et al. (Haagsma, Maertens de Noordhout et al. 2015). These disability weights were derived from a survey of over 30,000 European citizens, using a systematic developed for the Global Burden of Disease (GBD) study 2010. These disability weights are incorporated in the BCoDE toolkit (Colzani, Cassini et al. 2017). The selection of the disability weights per health state was discussed with disease and burden experts at RIVM. For acute infections that comprise a range of separate health states (e.g. acute measles with health states pneumonia, diarrhea, encephalitis, otitis media) a syndromic approach was taken to obtain an average disability weight for this acute syndrome. In the same spirit, one duration was applied to all health states belonging to an acute infection. A full overview of the disability weights and durations that we used in the disease models can be found in the State of infectious diseases, 2016 (de Gier, Nijsten et al. 2017).

Another difference in methodology compared to the previous edition of this report is the use of the life expectancy table as determined for the GBD 2010 study (WHO 2013) (note, the previously used table was from the GBD 1990 study). This is the projected frontier remaining life expectancy in 2050 per age group. Equal life expectancies are assumed for men and women.

### *Incidence*

The multiplication factor applied to psittacosis notifications was updated to 22.7 (95% CI 12.2 – 64.8) (De Gier, Hogerwerf et al. 2017). For all other diseases, models as first described in the State of Infectious Diseases 2013 and model modifications as reported in State of Infectious Diseases 2015 were maintained for the current estimations (Bijkerk, van Lier et al. 2014, Bijkerk, de Gier et al. 2016). We extended previously published methods for estimating the incidence of seasonal influenza by combining all relevant data sources via Bayesian evidence synthesis (McDonald, Presanis et al. 2014). As an improvement on the method, we estimated incidence for each season through specification of an evidence synthesis model that recognized that ILI incidence over multiple seasons should be considered as dependent data. We estimated disease burden ascribed to infections occurring in 2012, 2013, 2014, 2015 and 2016 separately. No time discounting was applied. We estimated the burden of seasonal influenza for respiratory seasons (week 40 to week 20) of 2011-2012 to 2015-2016.



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## Abbreviations

ARDS	Acute Respiratory Distress Syndrome
ARI	acute respiratory infection
BEL	Legionella Source Identification Unit (NL: Bronopsporingseenheid legionellapneumonie)
CALD	community-acquired Legionnaires' disease
CAP	community-acquired pneumonia
CBR	complement binding reaction
CBS	Statistics Netherlands (NL: Centraal Bureau voor de Statistiek)
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)
DBC/DOT	NL: Diagnose Behandel Combinatie Op weg naar Transparantie
ECDC	European Centre for Disease Prevention and Control
ECMO	extracorporeal membrane oxygenation
EISN	European Influenza Surveillance Network
ELDSNet	European Legionnaires Disease Surveillance Network
EPTB	combination of pulmonary and extrapulmonary TB
ETB	extrapulmonary tuberculosis
EV-D68	human enterovirus D68
GGD	Municipal 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
JBZ	Jeroen Bosch Hospital
LD	Legionnaires' Disease
LTBI	latent tuberculosis infection
LUMC	Leiden University Medical Center
MDR-TB	Multi Drug Resistant tuberculosis
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
NIC	National Influenza Centre
NIVEL	Netherlands institute for health services research (NL: Nederlands instituut voor onderzoek van de gezondheidszorg)

NTR	Dutch Tuberculosis Registry
NVMM	Dutch Society for Medical Microbiology
NVWA	Netherlands Food and Consumer Product Safety Authority (NL: Nederlandse Voedsel- en Warenautoriteit: NVWA)
NZa	Dutch Healthcare Authority
PCR	Polymerase Chain Reaction
PTB	pulmonary tuberculosis
PICU	paediatric intensive care unit
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
VE	vaccine effectiveness
WHO	World Health Organization

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