



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

Annual report Surveillance of influenza and other respiratory infections in the Netherlands: *winter 2015/2016*



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Netherlands institute for health services research (NIVEL)

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Synopsis

Surveillance of influenza and other respiratory infections in the Netherlands: winter 2015/2016

During the 2015/2016 winter season, the influenza epidemic in the Netherlands took place in the first eleven weeks of 2016. With approximately 200,000 general practitioner (GP) visits for influenza-like symptoms, 96,000 GP visits for pneumonia, and 3,900 more deaths than the expected number of deaths in this 11-week period, the duration and severity of the epidemic was moderate compared with previous years. During the first weeks of the influenza epidemic, the influenza virus type A(H1N1)pdm09 predominated, while later influenza virus type B (Victoria lineage) started to become more prevalent.

The effectiveness of the influenza vaccine (44 per cent) was better than last season although the trivalent influenza vaccine for the 2015/2016 season contained the B Yamagata lineage and not the B Victoria lineage. For next year's trivalent vaccine, the WHO has therefore recommended replacing the Yamagata lineage with the Victoria lineage. The dominating influenza virus type A(H1N1)pdm09 had a good match with the vaccine strain.

For the first time, during the 2015/2016 season, limited insight into the occurrence of severe acute respiratory infections (SARI) was obtained through a pilot SARI surveillance system in two Dutch hospitals. Media reports and anecdotal information from hospital physicians reported unusually high numbers of relatively young patients being admitted with severe influenza virus infections. This could not be quantified with the pilot SARI surveillance data and therefore the further development of SARI surveillance remains a priority topic for the coming years.

There were more notifications of the notifiable respiratory infectious diseases tuberculosis (867 notifications) and legionellosis (419 notifications) in the 2015 calendar year than in previous years. For tuberculosis, this is mainly due to an increase of asylum seekers in the Netherlands in 2014 and 2015 from high incidence countries. For legionellosis, the increase may be associated with the warm and wet weather conditions in 2015. The number of notifications for psittacosis (47 notifications) and Q fever (20 notifications) was comparable to previous years. However, notifiable infectious diseases presented as pneumonia are notoriously underreported because most cases of community-acquired pneumonia are managed in primary care without specific diagnostic laboratory tests.

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 2015/2016

In de winter 2015/2016 was er een griep epidemie in de eerste elf weken van 2016. Dit griepseizoen week niet sterk af van een gemiddeld griepseizoen, met naar schatting ruim 200 duizend huisartsbezoeken voor griepachtige klachten, 96 duizend huisartsbezoeken voor longontstekingen en 3900 doden bovenop het verwachte aantal doden gedurende de elf weken van de epidemie. In de eerste weken van de epidemie werd vooral het influenzavirus A(H1N1)pdm09 aangetroffen. Later was dat vooral het influenzavirus B (Victoria-lijn).

De effectiviteit van het griepvaccin (44 procent) leek beter dan vorig jaar, hoewel het influenzavirus B van de Victoria-lijn er niet in was opgenomen. Daar was voor gekozen omdat in voorgaande jaren vooral een ander influenzavirus B (Yamagata-lijn) circuleerde. De Wereldgezondheidsorganisatie heeft geadviseerd om volgend jaar de Victoria-lijn te gebruiken in plaats van de Yamagata-lijn. Het influenzavirus A(H1N1)pdm09 had wel een goede match met het vaccin van dit jaar.

Het RIVM heeft dit jaar voor het eerst in twee ziekenhuizen geregistreerd hoeveel mensen zijn opgenomen vanwege complicaties van de griep. Vanuit andere ziekenhuizen is via de media vernomen dat een ongewoon hoog aantal relatief jonge patiënten was opgenomen met ernstige luchtwegklachten. Dit was niet terug te zien in de RIVM-data, maar onderstreept het belang van een uitgebreidere surveillance in ziekenhuizen.

Van de meldingsplichtige luchtweginfectieziekten kwam in 2015 zowel tuberculose (867 meldingen) als legionellose (419 meldingen) meer voor dan voorgaande jaren. Bij tuberculose heeft dit vooral te maken met het toegenomen aantal asielzoekers. Bij legionellose komt dit waarschijnlijk door het warme en natte weer. Het aantal meldingen van psittacose (47) en Q-koorts (20) was niet opvallend. Dit aantal is echter een onderschatting van het werkelijke aantal, omdat bij longontsteking vaak de oorzaak niet wordt vastgesteld.

Kernwoorden: luchtweginfecties, griep, influenza, RS-virus, longontsteking, pneumonie, legionellose, papegaaizenziekte, psittacose, Q-koorts, tuberculose

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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 public 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.

The structure of this report is slightly different compared with previous years in order to provide a more coherent picture of surveillance activities at the Department for Respiratory Infections. 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 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. 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) and at NIC, location Erasmus Medical Centre. 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, as 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 2015/2016 respiratory winter season, i.e. week 40 of 2015 through week 20 of 2016.

Chapter 5 describes the summary of the results of the surveillance of the notifiable respiratory infectious diseases legionellosis, tuberculosis, Q fever and psittacosis for the 2015 calendar year. These results are described in greater detail in separate reports. 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 2015 calendar year. Chapter 7 describes the international developments with respect to the emergence of new respiratory pathogens as part of preparedness for threats that are relevant for the Netherlands. This year, a new topic has been added to this report in Chapter 8, describing 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, 2015' (Bijkerk, de Gier et al. 2016). In Chapter 9, the main findings of this report are discussed and put into perspective. Finally, Chapter 10 describes the data sources and methods used for surveillance of the different diseases or pathogens.

1.2 Collaborations: national and international

For the surveillance of respiratory infectious diseases, the Centre for Infectious Disease Control 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; Influenzanet; KNCV Tuberculosis Foundation; the Regional Public Health Laboratory Kennemerland, Haarlem (national reference laboratory for legionellosis); and Statistics Netherlands (CBS).

The collaboration with the Public Health Services (in Dutch: GGD) is the basis for the surveillance of notifiable infectious diseases. For zoonoses (psittacosis and Q fever), collaboration with the Netherlands Food and Consumer Product Safety Authority (NVWA) is in place and, for psittacosis, 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). A part of the data in this report is also reported internationally. The notifiable infectious diseases legionellosis, Q fever and tuberculosis are reported annually to the European Centre for Disease Prevention and Control (ECDC). Travel-related legionellosis is reported daily to the European Legionnaires Disease Surveillance Network (ELDSNet) of the ECDC. Moreover, the RIVM (Cib/IDS and Cib/EPI) participates together with NIVEL and Erasmus MC in the European

Influenza Surveillance Network (EISN) of ECDC, in FluNet and FLUID of the WHO (World Health Organization) in Geneva, and in EUROFLU of WHO-EURO in Copenhagen. 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. SARI surveillance is a new programme that was implemented on a pilot basis during the 2015/2016 season in two hospitals: the Jeroen Bosch hospital and LUMC. Late in the season the UMCU also joined this pilot project. 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 ILI and ARI

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

Contributors: Anne Teirlinck, Carl Koppeschaar, Ronald Smalenburg, Linda Verhoef

2.1.1 Key points

- In the 2015/2016 season, the influenza epidemic lasted for 11 weeks (weeks 1–11 of 2016) (measured as GP-attended influenza-like illness incidence above the epidemic threshold, combined with circulating influenza virus, see Chapter 3).
- GP-attended ILI incidence peaked at 15 per 10,000 inhabitants in week 7 of 2016. The cumulative seasonal incidence (weeks 40 through 20) was 201 per 10,000 inhabitants. Both are within the range of the four previous seasons.
- The GP-attended ILI incidence was highest in the 0–4 year olds, followed by people aged 65 or older.
- The peak in self-reported ILI in Influenzanet in the 2015/2016 season was 93 per 10,000 participants in week 6. In the four previous seasons, only a higher peak was observed in the 2012/2013 season.
- The ILI incidence in nursing home residents was lower than in the four previous years.
- There were fewer consultations in primary care for acute respiratory infections (ARI) compared with the four previous seasons, except for 2013/2014.
- The ARI consultations peaked at 38 per 10,000 inhabitants in week 7 of 2016. The cumulative seasonal incidence (weeks 40 through 20) was 888 per 10,000 inhabitants. Both are within the range of the four previous seasons.
- The number of ARI consultations was (similar to ILI) highest in the 0–4 year olds, followed by people aged 65 or older.

2.1.2 Background

Acute respiratory infections (ARI) are infections involving the respiratory tract and can be caused by bacteria and viruses. ARI include upper and lower respiratory infections.

An influenza-like illness (ILI) is a specific sub diagnosis of ARI. There are several case definitions of ILI (see Chapter 10). In the Netherlands, the 'Pel criteria' (Pel 1965) are mainly used, defining ILI as: 1) sudden onset of symptoms, 2) fever and 3) at least one of the following symptoms: cough, rhinorrhoea, sore throat, frontal headache, retrosternal pain or myalgia. The trends of the ILI and ARI syndromes are described in this chapter. For the surveillance of ARI and ILI, two types of data sources from the NIVEL Primary Care Database are used. First, near real-time (weekly) surveillance data concerning ARI, based on consultation data in electronic medical records from general practices (excluding pneumonia, and including acute/chronic sinusitis, acute laryngitis/tracheitis, acute bronchitis/bronchiolitis, and influenza). In the 2015/2016 respiratory season, the coverage increased to about 1.3 million persons (7.8% 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, anonymized data extraction. Secondly, a proportion of the GPs in the NIVEL Primary Care Database participate in 'sentinel surveillance'. These GPs actively report on the number of patients who consult them for ILI. From a random subset of ILI and/or other acute respiratory infection patients, they systematically collect a throat swab and nose swab and send it to RIVM for virological laboratory diagnostics. The population for these sentinel practices covers approximately 0.7% of the Dutch population and is representative for age, sex, regional distribution and population density (Donker 2016).

In the Netherlands, two additional systems register the ILI incidence in other populations. First, the RIVM measures the ILI incidence in institutionalized elderly [www.rivm.nl/sniv/]. From a subset of patients, a throat swab and nose swab are analysed at RIVM for respiratory viruses. Secondly, Influenzanet [www.grotegriepmeting.nl and www.influenzanet.eu] measures the self-reported ILI incidence in the general population. No specimens are taken from people who report ILI to influenzanet.

2.1.3 Epidemiological situation, season 2015/2016

Influenza-like illness (ILI)

For 11 weeks, from week 1 of 2016 through week 11 of 2016, the ILI incidence, measured by the sentinel GPs, was above the epidemic threshold. In week 7 of 2016, the peak of weekly ILI incidence as reported by sentinel GPs was 15/10,000. The cumulative incidence (weeks 40 through 20) in the 2015/2016 season was 201/10,000. Both the peak incidence and cumulative incidence are higher than in the 2011/2012 and the 2013/2014 seasons, but lower compared with the 2012/2013 and the 2014/2015 seasons. The ILI incidence was highest among small children (4 years of age and younger), followed by the elderly (65 and older), which is in line with the four previous seasons. The ILI incidence in the general population measured by Influenzanet using self-reported symptoms showed the same trend as the incidence of medically attended ILI measured by the sentinel GPs. The peak of self-reported ILI incidence of 93 per 10,000 participants was one week earlier (week 6), compared with the GP sentinel surveillance. This peak was relatively high, exceeded in the last five seasons only by the

2012/2013 season (peak of 124 per 10,000 participants). Among nursing home residents, the ILI incidence was lower than the four previous seasons.

Acute respiratory infections (ARI)

Like ILI, the weekly number of patients that consulted a GP participating in the NIVEL Primary Care Database for an ARI (including ILI) peaked in week 7 of 2016 (38 per 10,000 inhabitants) and was relatively low compared with the four previous seasons. The weekly number of ARI consultations was highest for small children 4 years old and younger, which is in line with the four previous seasons.

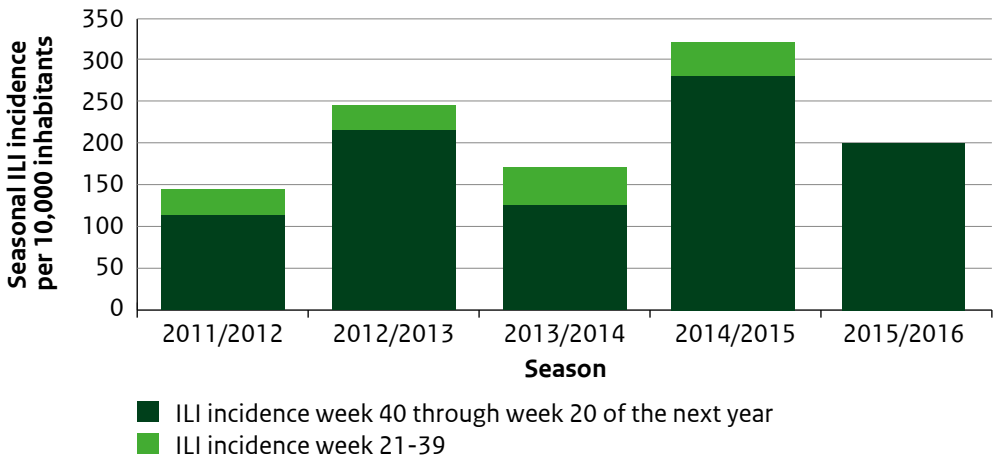
2.1.4 Discussion

The 2015/2016 season was an average season with respect to ILI incidence and weekly numbers of ARI, compared with the four previous seasons. Both ILI incidences, measured by the sentinel GPs and by Influenzanet in the general population, followed the same trend in the 2015/2016 season. The peak ILI incidence measured by Influenzanet was six times higher than the ILI incidence measured by the sentinel GPs. This multiplication factor is within the range of the four previous seasons (range 5-9 times). Influenzanet also captures people with ILI that do not seek medical care, while the more severe cases are expected to visit their GP. Therefore, these systems contain information about other groups of patients. Although the trend of ILI incidence, measured by the sentinel GPs, and the trend in weekly ARI numbers were the same, the seasonal number (weeks 40 through 20) of ARI was about four times higher than the ILI incidence measured by the sentinel GPs. In the seasons 2011/12 and 2013/2014 this ratio was higher, 11 and 7 respectively (range 4-11 seasons 2011-2012 through 2015/2016). A possible explanation for this difference is that the seasonal ILI incidence was higher in 2015/2016 season than it was in the 2011/2012 and 2013/2014 seasons. Differences between ARI numbers and ILI incidence occur because of the contribution of viruses other than influenza is higher in ARI than in ILI. Interestingly, in contrast to the general population, the ILI incidence among nursing home residents was low in the 2015/2016 season. This may be partly explained by the domination of the influenza virus type A(H1N1)pdm09 and type B (Victoria lineage) in the recent season, instead of the subtype A(H3N2). It is known that subtype A(H3N2) leads to more infections in the elderly.

2.1.5 Tables and figures

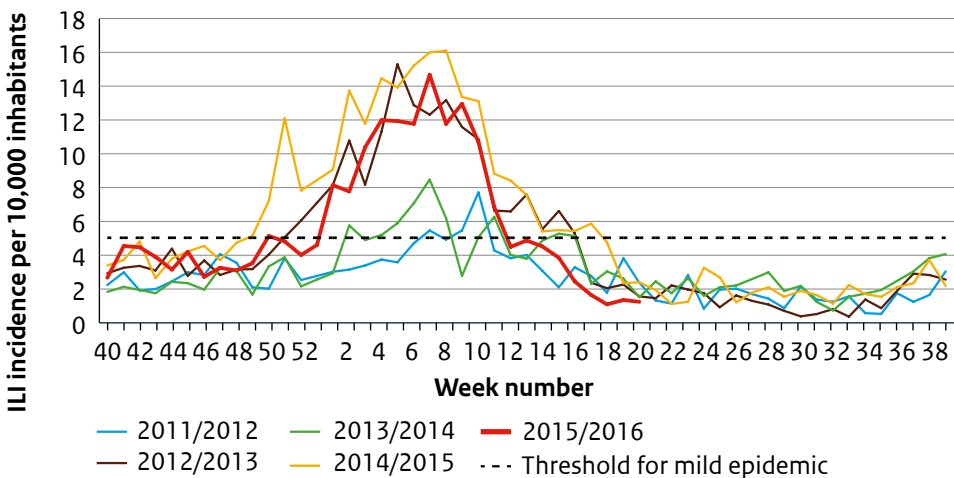
ILI incidence: sentinel GP practices

Figure 2.1 Seasonal cumulative ILI incidence in the respiratory seasons 2011/2012 - 2015/2016 (through week 20 of 2016) (Source: NIVEL Primary Care Database).



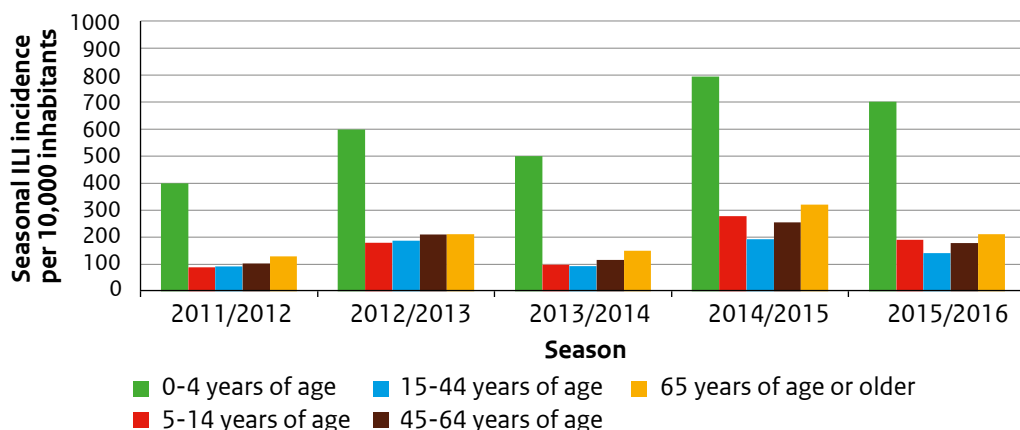
Footnote: ILI = influenza-like illness. For the years without a week 53, the average of weeks 52 and 1 was used.

Figure 2.2 Weekly ILI incidence during the respiratory seasons 2011/2012 - 2015/2016 (through week 20 of 2016) (Source: NIVEL Primary Care Database).



Footnote: ILI = influenza-like illness. The year 2015 had 53 weeks. For the years without a week 53, the average of weeks 52 and 1 was used.

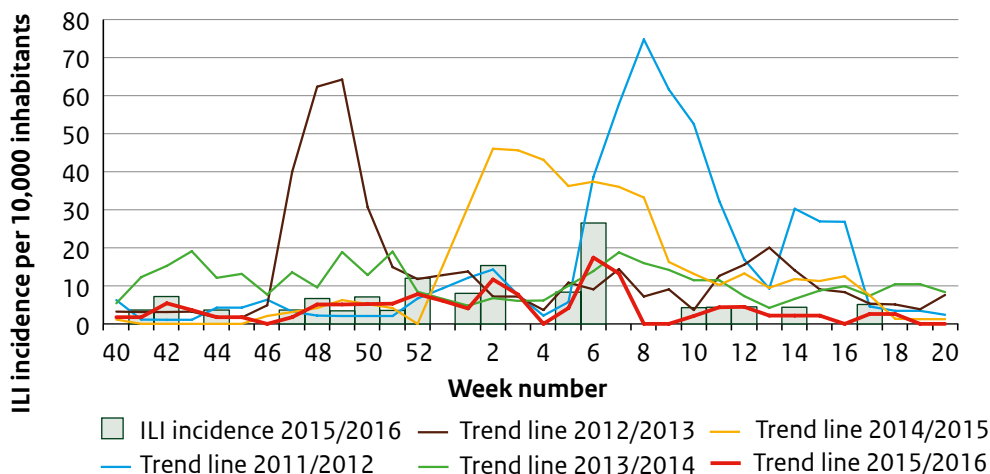
Figure 2.3 Seasonal cumulative ILI incidence per season (weeks 40 through 20) per 10,000 inhabitants, per age category, of the seasons 2011/2012 through 2015/2016 (Source: NIVEL Primary Care Database).



Footnote: ILI = influenza-like illness.

ILI incidence: in nursing homes

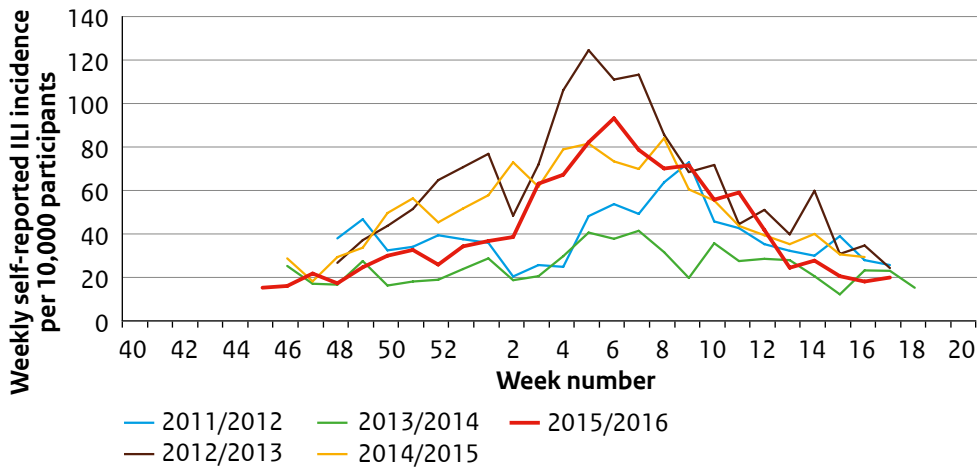
Figure 2.4 Weekly ILI incidence in SNIV nursing homes in the 2015/2016 respiratory season (through week 20 of 2016) and trend lines for the respiratory seasons 2011/2012 through 2015/2016 (Source: SNIV, RIVM).



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. The year 2015 had 53 weeks. For the years without a week 53, the average of weeks 52 and 1 was used.

ILI incidence: self-reported in Influenzanet

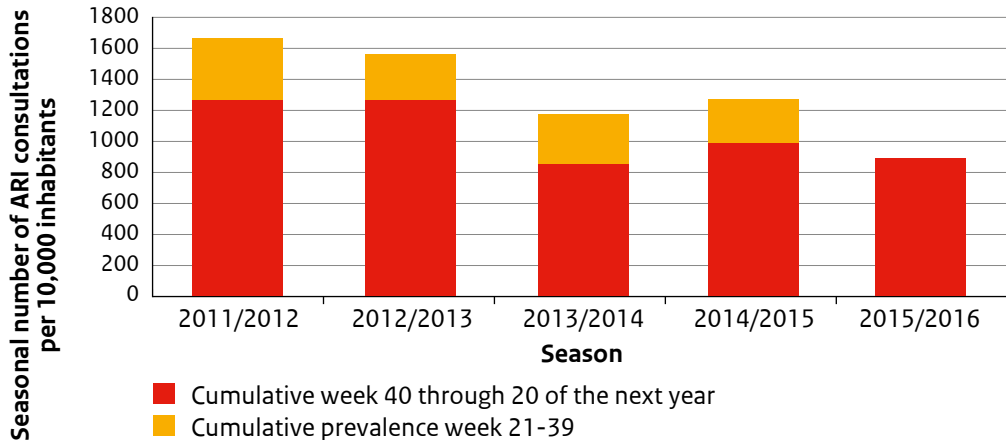
Figure 2.5 Self-reported weekly ILI incidence, seasons 2011/2012 through 2015/2016 (through week 20 of 2016) (Source: Influenzanet, the Netherlands: <http://www.degrotegriepmeting.nl>).



Footnote: ILI = influenza-like illness. The year 2015 had 53 weeks. For the years without a week 53, the average of weeks 52 and 1 was used.

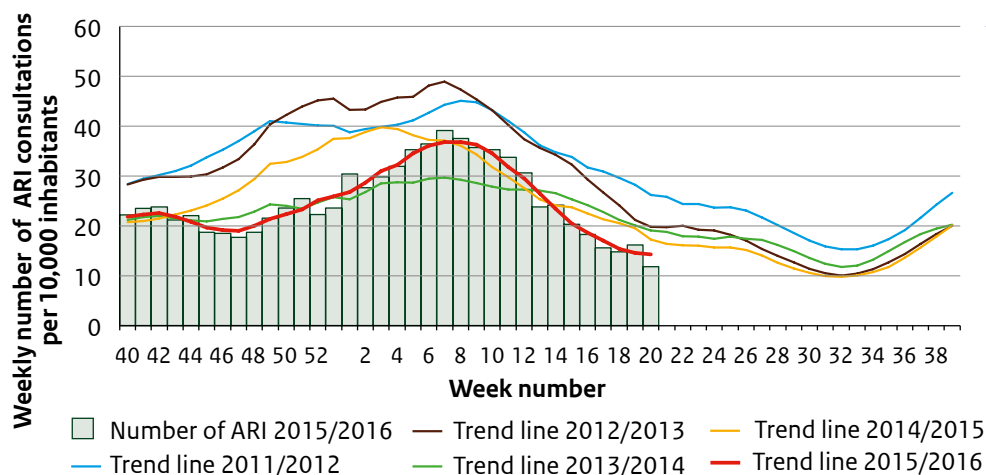
GP consultations for ARI

Figure 2.6 Seasonal cumulative weekly numbers of patients consulting a GP because of ARI in the respiratory seasons 2011/2012 - 2015/2016 (through week 20) (Source: NIVEL Primary Care Database).



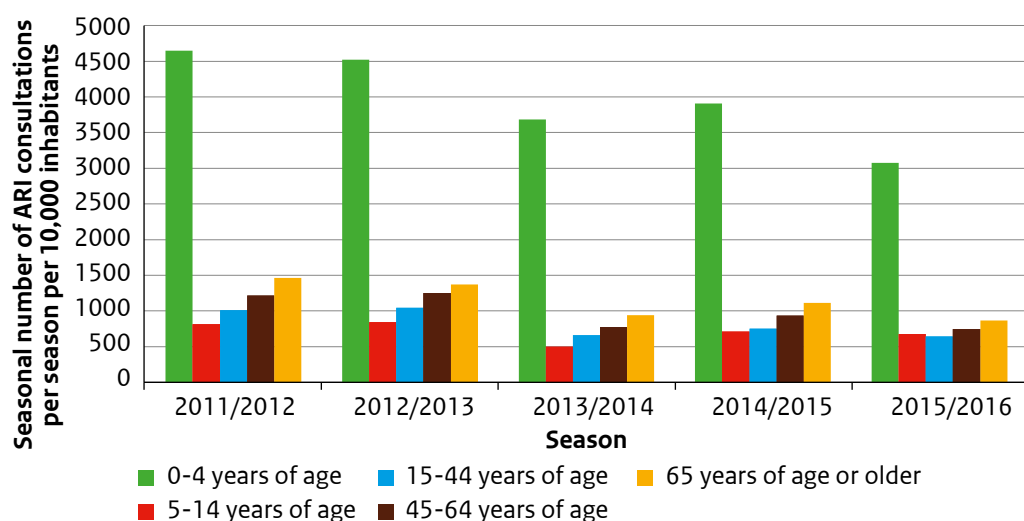
Footnote: ARI = acute respiratory infections, including influenza-like illness; GP = general practitioner. The year 2015 had 53 weeks. For the years without a week 53, the average of weeks 52 and 1 was used.

Figure 2.7 Weekly number of patients consulting a GP because of ARI per 10,000 inhabitants in 2015/2016 (through week 20 of 2016) and the trend lines for 2011/2012 - 2015/2016 (through week 20) (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. For the years without a week 53, the average of weeks 52 and 1 was used.

Figure 2.8 Seasonal cumulative weekly number of patients consulting a GP because of ARI per season (weeks 40 through 20) per 10,000 inhabitants, per age category, of the seasons 2011/2012 through 2015/2016 (Source: NIVEL Primary Care Database).



Footnote: ARI = acute respiratory infection, including influenza-like illness; GP = general practitioner. For the years without a week 53, the average of weeks 52 and 1 was used.

2.2 Community-acquired pneumonia

Authors: Rianne van Gageldonk-Lafeber, Mariëtte Hooiveld

Contributor: Linda Verhoef

2.2.1 Key points

- The overall seasonal cumulative pneumonia estimate of GP consultations for 2015/2016 (through week 20; 133 per 10,000 inhabitants) was within the range of the previous 4 seasons (range: 114–199 per 10,000 inhabitants).
- The peak in pneumonia weekly GP consultations was seen in week 7 of 2016 (6 per 10,000 inhabitants).
- The pneumonia consultation was highest in people aged 65 or older, followed by children aged 4 and younger, which is in line with the four previous seasons.
- The cumulative incidence of pneumonia in SNIV nursing homes (through week 19; 1,248 per 10,000 residents) was within the range of incidence figures reported since the 2011/2012 season (through week 20; range: 1,215–1,798 per 10,000 residents).
- Nursing home pneumonia incidence peaked relatively late in week 14 of 2016 (66 per 10,000 residents).
- A pilot study on the aetiology of community-acquired pneumonia in primary care suggests it is not useful to implement routine diagnostics using urinary antigen tests for *Streptococcus pneumoniae* and *Legionella pneumophila* in primary care, since none of the 52 collected specimens tested positive.

2.2.2 Background

Pneumonia is a common clinical disorder of the lower respiratory tract with high morbidity and mortality, especially in the elderly. Pneumonia is an inflammatory condition of the lungs affecting primarily the microscopic air sacs known as alveoli. Typical symptoms include a cough, chest pain, fever and difficulty breathing.

Infection with microorganisms, mainly bacteria and viruses, is the most common cause of community-acquired pneumonia (CAP). Many studies in the Netherlands and other countries show that *Streptococcus pneumoniae* is the predominant aetiological agent of CAP (van Gageldonk-Lafeber, Wever et al. 2013).

In daily clinical care, a general practitioner (GP) diagnosis of CAP is based on clinical symptoms, usually 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 pneumonia in nursing homes (SNIV).

2.2.3 Epidemiological situation, season 2015/2016

The highest number of weekly GP pneumonia consultations (5.8 per 10,000 inhabitants) was reported in week 7 of 2016. This timing of the peak coincided with the peak in ILI incidence. The seasonal cumulative weekly number of pneumonia consultations in 2015/2016 (week 40 of 2015 through week 20 of 2016; 133 per 10,000 inhabitants) was within the range of the last four respiratory seasons (range: 114-199 per 10,000 inhabitants). As in previous seasons, the cumulative weekly number of pneumonia consultations was the highest in the elderly aged 65 and older.

In the SNIV-nursing homes, the cumulative incidence of pneumonia in 2015/2016 (weeks 40 through 19; 1,248 per 10,000 residents) was at the lower end of the range that has been reported since 2011/2012 (range: 1,215-1,798 per 10,000 residents). Nursing home pneumonia incidence peaked in week 14 of 2016 (66 per 10,000 residents). Compared with earlier respiratory seasons since 2011/2012, this peak was relatively late (range: week 42 in 2013 - week 8 in both 2012 and 2013).

In 2015 a pilot study was performed in the sentinel GPs (proportion of the GPs participating in NIVEL-Primary Care Database) in which aetiology of community-acquired pneumonia in patients aged 65 and older was assessed through urinary antigen tests for *Streptococcus pneumoniae* and *Legionella pneumophila*. A total of 52 specimens were collected, but none of these urine samples tested positive. The median age of the sampled patients was 70.

2.2.4 Discussion

In 2015/2016, both the seasonal cumulative weekly number of pneumonia GP consultations and the cumulative incidence of pneumonia in nursing homes were lower than in the previous season but within the range of respiratory seasons since 2011/2012. This is in line with the conclusion that the current ILI season was an average season, compared with the four previous seasons. Moreover, the highest number reported for pneumonia was for GP consultations and in nursing homes within the range of the four earlier respiratory seasons. The peak in nursing homes was relatively late, both compared with previous seasons and with the peak in GP consultations.

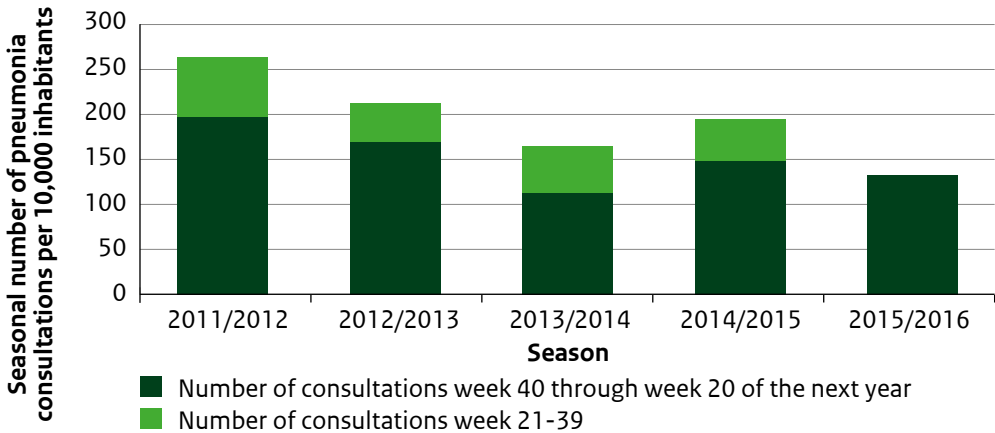
Like previous seasons, the incidence of pneumonia patients in nursing homes is between 6 and 13 times higher than it is in general practice. This can largely be explained by the high rate of comorbidity and the high average age of nursing home residents compared with the population of GP patients. Additionally, 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.

Based on the results of the pilot study conducted on the aetiology of pneumonia, a decision was made in the end not to implement routine diagnostics for community-acquired pneumonia in primary care using urine antigen tests.

2.2.5 Figures

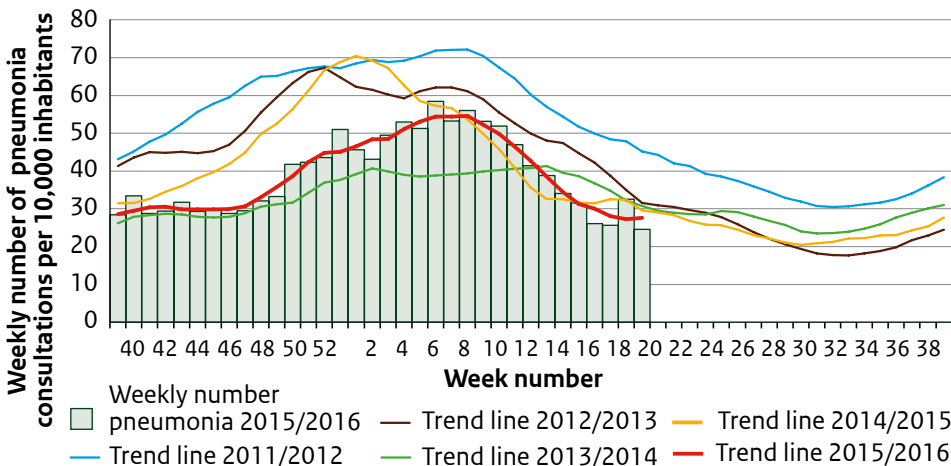
GP consultations because of pneumonia

Figure 2.9 Seasonal cumulative weekly numbers of patients consulting their GP for pneumonia per 10,000 inhabitants in the seasons 2011/2012 - 2015/2016 (through week 20) (Source: NIVEL Primary Care Database).



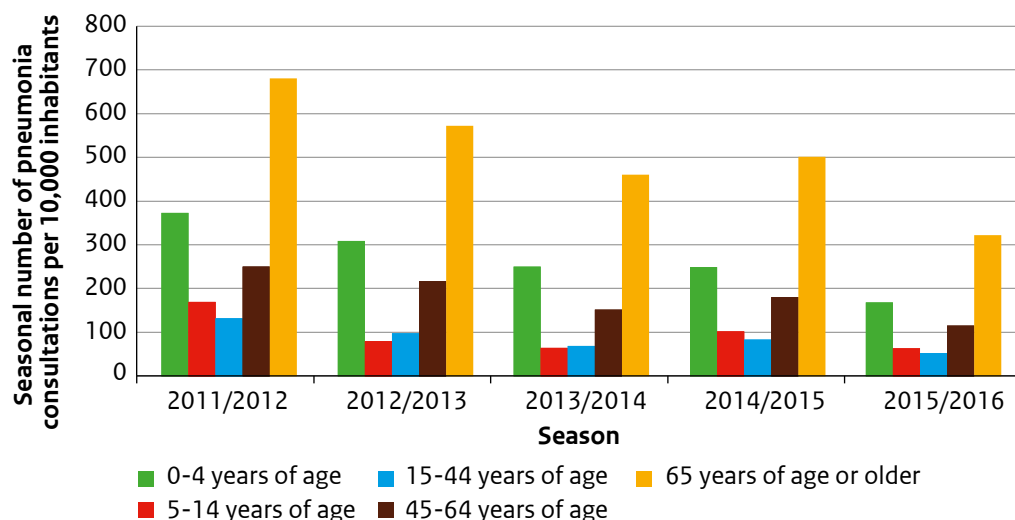
Footnote: The year 2015 had 53 weeks. For the years without a week 53, the average of weeks 52 and 1 was used.

Figure 2.10 Weekly numbers of patients consulting their GP for pneumonia per 10,000 inhabitants in 2015/2016 (through week 20) and the trend lines for 2011/2012 - 2015/2016 (through week 20). Trend lines are based on a 5-week moving average (Source: NIVEL Primary Care Database).



Footnote: The year 2015 had 53 weeks. For the years without a week 53, the average of weeks 52 and 1 was used.

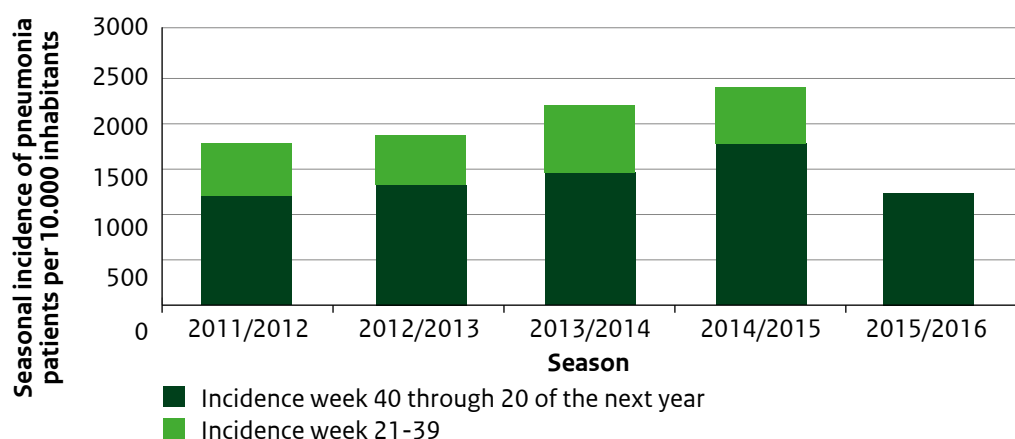
Figure 2.11 Seasonal cumulative weekly number of GP consultations for pneumonia per 10,000 inhabitants by age group in the seasons 2011/2012 - 2015/2016 (through week 20) (Source: NIVEL Primary Care Database).



Footnote: The year 2015 had 53 weeks. For the years without a week 53, the average of weeks 52 and 1 was used.

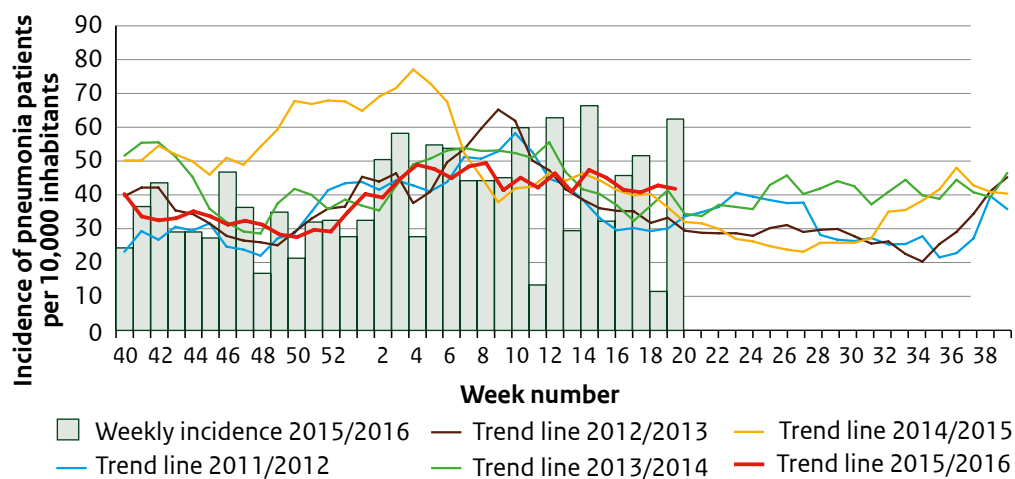
Incidence of pneumonia (nursing homes)

Figure 2.12 Pneumonia seasonal incidence in SNIV nursing homes per 10,000 residents in the seasons 2011/2012 - 2015/2016 (through week 19) (Source: SNIV, RIVM).



Footnote: The year 2015 had 53 weeks. For the years without a week 53, the average of weeks 52 and 1 was used. Data for week 20 of 2016 was not available.

Figure 2.13 Weekly incidence of pneumonia patients in SNIV nursing homes per 10,000 residents in 2015/2016 (through week 19) and trend lines for the seasons 2011/2012 - 2015/2016 (through week 19). The trend lines indicate a 5-week moving average (Source: SNIV, RIVM).



Footnote: The year 2015 had 53 weeks. For the years without a week 53, the average of weeks 52 and 1 was used. Data for week 20 of 2016 was not available.

2.3 Severe acute respiratory infections (SARI)

Authors: Sierk Marbus, Rianne van Gageldonk-Lafeber

Contributors: Peter Schneeberger, Geert Groeneveld

2.3.1 Key points

- For the first time in the Netherlands, a weekly SARI surveillance was operational during the 2015/2016 influenza season in two hospitals.
- The SARI admissions at the Jeroen Bosch Hospital peaked in week 9.
- The number of patients with an acute respiratory infection at Leiden University Medical Center peaked in week 2.

2.3.2 Background

Surveillance in patients with severe acute respiratory infections (SARI) that require hospital admission is important to gain a full view of influenza and other respiratory infections. A sustained SARI surveillance system might detect outbreaks in time, place, causative pathogen and person in order to implement and evaluate health care interventions. Several other countries have already implemented an operative SARI surveillance system as advised by the World Health Organization (WHO). In the Netherlands from October 2015 onwards, a pilot study started at the Jeroen Bosch Hospital and Leiden University Medical Center. The main objective is to set up a sentinel surveillance system for SARI patients in the Netherlands consisting of syndrome surveillance. However, adding laboratory diagnostic results is crucially important and should result in a sustained integrated respiratory surveillance system in the future.

2.3.3 Epidemiological situation, season 2015/2016

Leiden University Medical Center

A total number of 288 SARI patients were reported by ICARES during the influenza epidemic of 2015-2016 (weeks 1 through 11 of 2016). The intensive care unit (ICU) admitted 40/288 patients (14%). The peak of 36 SARI admissions was reached in week 2 of 2016. Most SARI patients were found in the age group 0-4 years (109/288; 38%), followed by the 60 years and older (93/288; 32%).

Jeroen Bosch Hospital

A total number of 702 SARI patients were admitted to hospital during the influenza season of 2015-2016 (weeks 42 through 20 of 2016). In week 9 of 2016, the peak of 42 SARI patients per week was reached. These numbers were collected retrospectively based on DBC/DOT codes. A total of 138 of the 702 admitted SARI patients (20%) were included in the SARI surveillance study. The majority of these SARI patients were 60 and older (96/138; 70%). Almost two-thirds of these patients received an influenza vaccination (86/138; 64%). The gross majority of these SARI patients belonged to the indication group for influenza vaccination (120/138, 87%). During the influenza epidemic (weeks 1 through 11 of 2016) 20/101 included SARI patients (20%) were admitted to ICU.

2.3.4 Discussion

The 2015/2016 influenza season lasted 11 weeks, from the 4th of January until the 20th of March, based on ILI surveillance data. Since this is only the first season of SARI surveillance in the Netherlands, it is unclear what the time lag is between hospital-based SARI surveillance and ILI and ARI surveillance in primary care. We aim to have a better understanding of this relationship at the end of the study.

ICARES is currently operational in four hospitals in the Leiden/The Hague region. However, the data is incomplete for three hospitals in the Leiden/The Hague region during the 2015/2016 influenza season due to information and communication technology (ICT) implementing difficulties. This has led to an inconsistent data supply from these three hospitals. As a result, only data from one hospital with a complete dataset is described in this report. We aim to include all four hospitals in the analysis during the next influenza season. In addition, during the next season a distinction should be made between SARI patients requiring hospital admission and outpatients with an acute respiratory infection that were discharged and sent home from the Emergency Department. Our future goal is to analyze the 8-year ICARES historical data and make comparisons with ARI, ILI and crude mortality surveillance data. The SARI surveillance study population of the Jeroen Bosch Hospital only reflects a sample of the total population of SARI patients admitted to the Jeroen Bosch Hospital. The screening and inclusion of SARI patients is presumably suboptimal, because of the increased workload of the attending physicians who are responsible for the inclusion. For this reason, a research nurse was appointed in week 8 of 2016 in order to achieve a more systematic screening and better inclusion.

2.3.5 Figures

Figure 2.14 Number of patients with a severe acute respiratory infection (SARI) during the 2015/2016 influenza season (week 40 of 2015 through week 20 of 2016) in the Leiden region reported by ICARES.

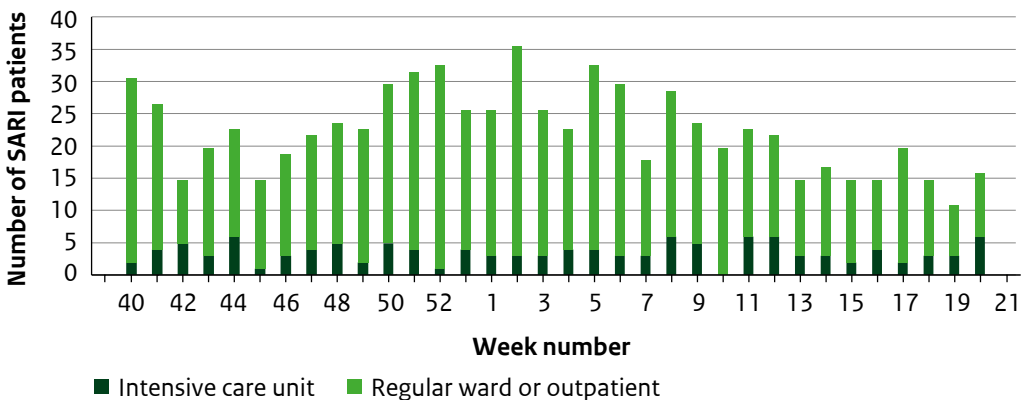
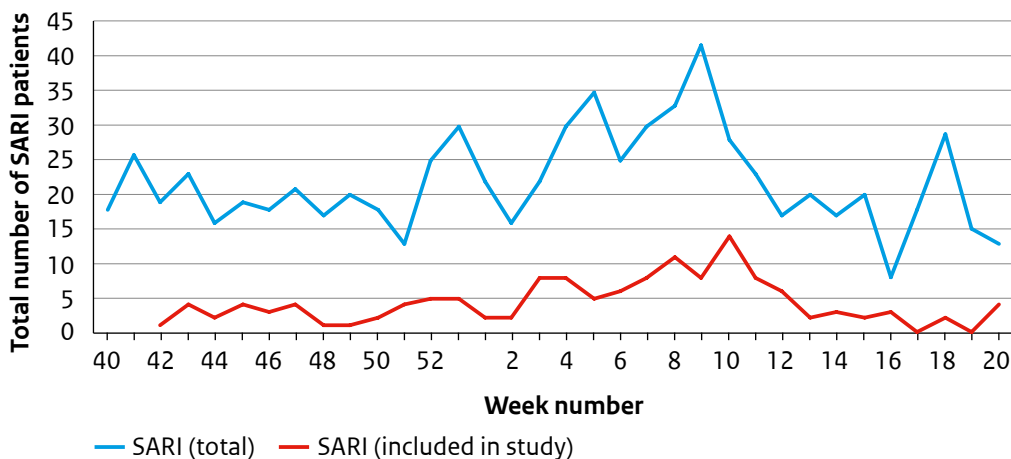


Figure 2.15 Absolute number of SARI patients admitted to the Jeroen Bosch Hospital versus the number of SARI patients included in the SARI surveillance study.



Footnote: The blue line represents syndrome surveillance based on DBC/DOT codes. The red line represents the SARI patients included in the SARI surveillance study.

2.4 Weekly mortality monitoring

Author: Liselotte van Asten

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

2.4.1 Key Points

- An average of 2,700 deaths occurred weekly in the Netherlands over the past five years (2011-2015).
- Excess mortality was estimated at 3,900 deaths occurring during the 11 weeks of the 2015/2016 influenza epidemic.
- Increased mortality occurred during the entire influenza epidemic and up to three weeks thereafter (weeks 1-14), except for a drop in week 7.
- Excess mortality was estimated at 6,085 during the total winter season (44 weeks running from week 40 up to week 20).
- Excess mortality during the 2015/2016 winter period (weeks 40-20) was average compared with the previous five winters and was similar to the 2011/2012 winter.
- Excess mortality was observed in the 75-plus age group. In some weeks of the influenza epidemic, increases were also observed in 65-74 year age group, with a higher peak than in previous years.

2.4.2 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 16.9 million in 2015) 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 and cold snaps and seasonal influenza epidemics, for which the morbidity and mortality burden varies due to variations in the circulation of influenza types and strains.

2.4.3 Epidemiological situation, season 2015/2016

In the 2015/2016 winter-season, all-cause mortality (number of deaths reported within three weeks) was significantly increased during and up to three weeks after the influenza epidemic. The number of deaths were increased from week 1 of 2016 up to week 14, except for a dip in week 7. Excess mortality was primarily observed in persons 75 or older. But 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 4 to 6, with a higher peak than observed in the previous five years in week 4 (with 564 deaths, when 468 baseline deaths were predicted). Also in week 4, the mortality in the 25-34 year-old age group was significantly

increased (25 deaths, though 14 were expected as baseline). In this age group, mortality was also increased earlier in the season (long before the influenza epidemic); in week 40 of 2015, numbering 26 deaths. There were no cold snaps in the 2015/2016 winter season. While the previous (2014/2015) influenza season was of long duration and coincided with high excess deaths and the 2013/2014 season was very mild with no excess deaths, the 2015/2016 season seems to have been of roughly average severity. The estimated cumulative total excess mortality was 3,900 deaths observed above the expected baseline. This is lower than the cumulative excess mortality in two (2012/2013 and 2014/2015) of the five previous influenza epidemics. In total, the excess deaths for the entire winter season from week 40 to week 20 in the current 2015/2016 season (6,085 excess deaths) seems comparable to the 2011/2012 winter season (5,843 excess deaths), although the influenza epidemic was very short in that season (with an estimated 758 excess deaths during the two weeks it lasted).

Excess Mortality in Europe

The Netherlands participates in weekly mortality monitoring at a European level in the EuroMOMO collaboration [www.EuroMOMO.eu].

Pooled analysis of 16-19 countries showed a continued pattern of an excess in all-cause mortality among the 15-64 age group. This pattern appeared at the end of 2015 and is at the same level that was observed in the 2012/13 and 2014/15 winter seasons. The mortality among children under 15 and among the elderly was within the expected levels for the season [www.euromomo.eu].

2.4.4 Discussion

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). 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).

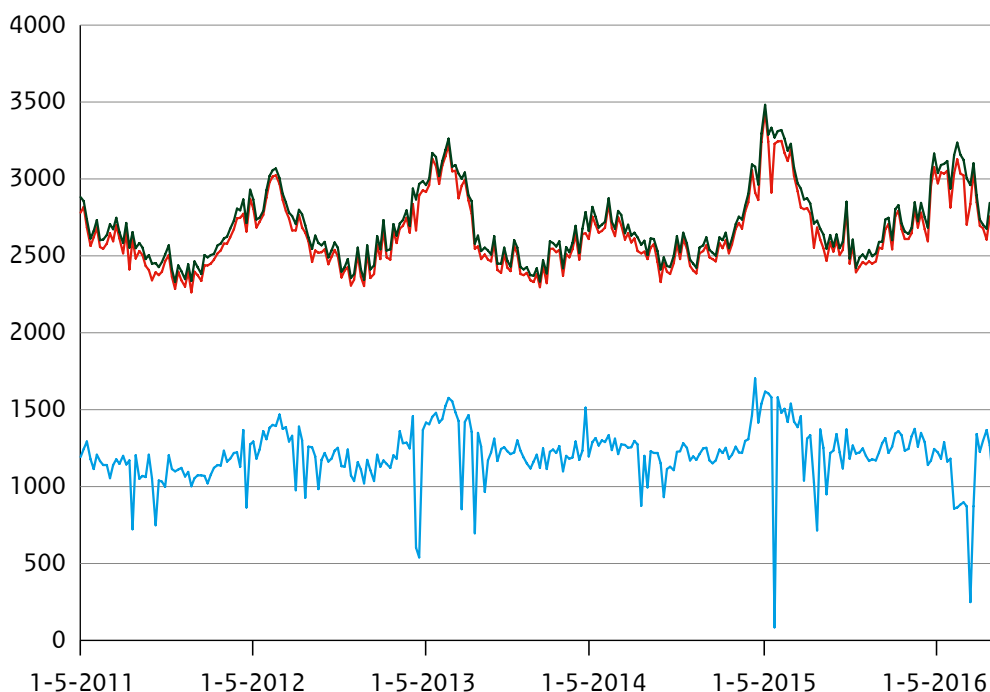
In terms of number of deaths during the winter season (weeks 40-20) and during the influenza epidemic (weeks 1-11), the 2015/2016 season in the Netherlands seems moderately severe compared with the previous five years. Notable was the short three-week time span with a higher peak in mortality in 65-74 year olds than has been observed in recent years. Although the influenza epidemic reached its peak in week 7, the mortality data showed a dip in week 7. The reason for the temporary decrease is unknown. The only known coinciding event was a partial overlap with southern and central school holidays in week 8 (partial as weekly mortality was summed from Thursday to Wednesday instead of from Monday to Sunday), but the causality is not known.

Mortality trends in the elderly in the Netherlands seems comparable to the overall mortality trend in Europe (pooled across 16-19 countries). Yet, as in many countries, the number of deaths in younger age groups is small in the Netherlands. When pooled, the European data also revealed continued increased mortality in 15-65 year olds (not further specified to smaller age groups) [www.EuroMOMO.eu].

Weekly mortality monitoring is currently performed using unspecified mortality data. Using cause-specific death reports to estimate the impact of influenza circulation on mortality is currently not an option as 1) deaths caused by influenza reflect only a small part of the mortality attributable to influenza, since 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 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.

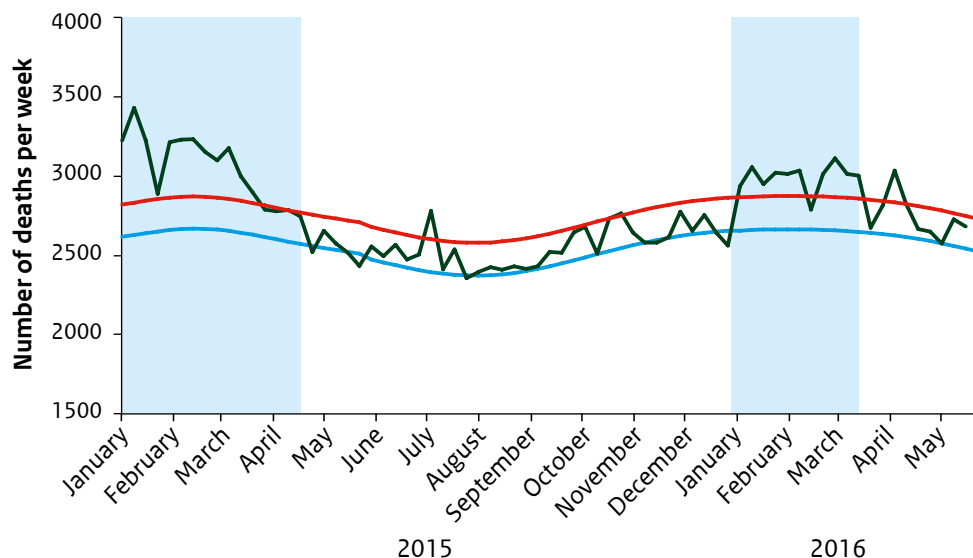
2.4.5 Figures

Figure 2.16 Weekly number of deaths from 2011 to 2016 (through week 20 of 2016) 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 dark green line: notified within three weeks.

Figure 2.17 Observed and expected ('baseline') weekly number of deaths (reported within two weeks, 93% complete) from 2015 to week 20 of 2016 with the influenza epidemic weeks depicted by blue shading.



Footnote: Dark 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

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Contributors: Anne Teirlinck, Frederika Dijkstra, Pieter Overduin, Ton Marzec, Gabriel Goderski, Sharon van den Brink, Lisa Wijsman, Mariam Bagheri, Carl Koppeschaar, Ronald Smalenburg, Ruud van Beek, Mark Pronk, Guus Rimmelzwaan, Jan de Jong, Linda Verhoef, Peter Schneeberger, Anne Robben

3.1 Key points

- In the 2015/2016 season, the influenza epidemic lasted 11 weeks.
- Subtype A(H1N1)pdm09 was the dominating influenza virus in the beginning of the 2015/2016 epidemic.
- In the second half of the epidemic, the influenza virus type B (Victoria lineage) increased in proportion and became dominant in the last weeks of the epidemic.
- The number of influenza B diagnoses in the virological laboratory surveillance in the 2015/2016 season was higher than in the previous ten seasons.
- The detected A(H1N1)pdm09 viruses were antigenically similar to the A(H1N1)pdm09 component of the vaccine.
- The dominant B virus (Victoria lineage) was not included in the trivalent influenza vaccine of the season.
- The vaccine effectiveness (VE) against laboratory confirmed influenza virus infection was estimated as protective for both the subtype A(H1N1)pdm09 and type B (Victoria lineage), respectively 42% (95% CI: -40% to 76%) and 53% (95% CI: -61% to 86%) with wide 95% confidence intervals.
- A small protective effect of the influenza vaccination on a self-reported influenza-like illness (ILI) in Influenzanet could be demonstrated (VE=18% [95% CI: -11 % to 41%]).
- In general, there is little evidence of reduced inhibition of influenza A and B viruses by neuraminidase inhibitors oseltamivir and zanamivir.

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 condition. There are several types of influenza virus, which are constantly changing and mutating (antigenic drift). Sometimes two or more different strains of influenza virus combine to form a new subtype (antigenic shift). Since humans have no or low pre-existing immunity against such a new virus type, this can lead to a worldwide pandemic, such as the 2009 pandemic.

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. In contrast, influenza type B viruses are divided into lineages based on their HA only. Currently circulating influenza B viruses belong to the lineage B/Yamagata/16/88 or B/Victoria/2/87.

Since the 2015/2016 season, RIVM and NIVEL have been participating in the European I-MOVE and I-MOVE+ studies. These studies aim to estimate the influenza vaccine effectiveness in all age groups (I-MOVE) and in persons that are 65 or older (I-MOVE+) by pooling data from several European countries.

To collect the data as systematically as possible, participation in the I-MOVE projects was the reason for changing the sampling instruction for influenza-like illness (ILI) and other acute respiratory infections (ARI) in patients. Before week 40 of 2015, the sampling instruction was to sample two ILI patients per week. If no ILI patients presented to the general practitioner (GP), two ARI patients should be sampled. Of the sampled patients, one person should be younger than ten years of age.

Since week 40 of 2015, the instruction has been changed into:

- Swab the first two ILI patients on Monday through Wednesday;
- When no ILI patients younger than 65 present to the GP on Monday through Wednesday, swab the first two ILI patients or ARI patients who are younger than 65 on Thursday through Sunday;
- Swab all ILI and ARI patients aged 65 and older throughout the week.

3.3 Epidemiological situation, season 2015/2016

Viral surveillance

In the 2015/2016 respiratory season, 1,238 ILI and ARI specimens were taken by the sentinel GPs. In the 729 ILI specimens, 345 influenza viruses were detected (47%) and, in the 509 ARI specimens, 83 influenza viruses were detected (16%). Only two specimens were taken from SNIV nursing home residents (results not shown) and both were negative for influenza virus. Additionally, 2,954 positive influenza 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. In the sentinel GP surveillance, specimens from ILI patients were more often influenza virus positive than were specimens taken from ARI patients (weeks 40 through 20). Most specimens were taken in patients aged 15-44 years and 45-64 years. The highest percentage of influenza virus was found in the age group of 5-14 years, both for the ILI (74%) and the ARI (48%) specimens; this was especially the case for the percentage of influenza B (Victoria lineage) specimens.

In the 2015/2016 season, there was an influenza epidemic from week 1 through week 11 of 2016. During the season, influenza virus type A(H3N2), type A(H1N1)pdm09 and type B Victoria lineage circulated both in GP and hospital. Type A(H3N2) and B (Yamagata lineage) viruses were sporadically detected. Type A(H1N1)pdm09 predominated at the beginning of the season, but increasing proportions of type B viruses (Victoria lineage) were detected in the last weeks of the epidemic. The number of influenza B diagnoses in the virological laboratory surveillance in the 2015/2016 season was higher than in the previous ten seasons. The detected A(H1N1)pdm09 viruses were antigenically similar to the A(H1N1)pdm09 component of the vaccine; all viruses that were sequenced belonged to genetic clade 6B.1. The B virus (Victoria lineage) was not included in the trivalent influenza vaccine in the 2015/2016 season. All B (Victoria lineage) viruses that were sequenced belonged to genetic clade 1A.

Except for one influenza A(H1N1)pdm09 virus with oseltamivir reduced inhibition, there were no indications of reduced inhibition of influenza A and B viruses by the neuraminidase inhibitors oseltamivir and zanamivir in the 2015/2016 season.

In the 2015/2016 season, severe acute respiratory infection (SARI) surveillance with virological testing started at the Jeroen Bosch Hospital. The results of the 2015/2016 season were compared with a retrospective study, which was performed to determine the number of hospital admissions for SARI during the influenza epidemic of 2014/2015. During the influenza epidemic of 2015/2016, 59 respiratory specimens were tested for influenza virus (74%). In 28 respiratory specimens, influenza virus was detected (47%). The median age of the SARI patients testing positive for influenza virus was 62, \pm 12 years. Influenza virus type A(H1N1)pdm09 was dominant in SARI patients during the 2015/2016 influenza epidemic. The detected influenza viruses type B belonged to the Victoria lineage.

Vaccine effectiveness

The vaccine effectiveness against laboratory confirmed influenza virus infection was estimated protective for the subtype A(H1N1)pdm09: 42% and for type B (Victoria lineage): 53%. However, the 95% confidence intervals were broad, respectively (95% CI: -40% to 76%) and (95% CI: -61% to 86%). The small number of specimens does not allow for stratification of VE by age or risk group. The incidence of self-reported ILI in Influenzanet was higher in the non-vaccinated participants than the vaccinated participants. Therefore, a protective effect of influenza vaccination could be expected, although the VE was low and not significant (VE=18% [95% CI: -11 % to 41%]). The highest VE was found in participants of 60 years or older with no chronic illness (VE=67% [95% CI: -41% to 92%]). In participants of 60 years or older with chronic illness the VE was significant above zero (VE=54% [95% CI: 6% to 77%]). No protection of the vaccine could be shown in participants younger than 60 years with a chronic illness (VE=-8% [95% CI: -69% to 30%]). However, the 95% confidence intervals in the stratified analysis were broad.

3.4 Discussion

In the beginning of the 11-weeks epidemic in the 2015/2016 season, influenza virus type A(H1N1)pdm09 was dominant. Because of the good match between the circulating and the vaccine influenza virus type A(H1N1)pdm09, the same strain as the 2015/2016 season was selected by the WHO for the trivalent vaccine for the 2016/2017 season in the northern hemisphere [http://www.who.int/influenza/vaccines/virus/recommendations/201602_recommendation.pdf?ua=1]. Towards the end of the epidemic, influenza virus type B (Victoria lineage) dominated. Because of the circulation of this B lineage in the 2015/2016 season rather than the B (Yamagata lineage), which was included in the 2015/2016 vaccine, no vaccine effectiveness for the B (Victoria lineage) strain was expected. Although type B (Victoria lineage) was not included in the vaccine, the point estimate of the vaccine effectiveness against this virus was quite high, albeit with wide 95% confidence interval. Cross-protection of the B/ Yamagata lineage for the Victoria lineage cannot be expected, as was shown in human serology studies (see WHO website mentioned above). Because of the circulation of the Victoria lineage in this season, the recommendation for vaccine composition is to include a type B virus of the B/Victoria lineage in trivalent vaccines for the 2016/2017 season in the northern hemisphere. In addition, a more recent A(H3N2) virus that raises cross-reactive antibodies against the three major subclades of A(H3N2) virus is recommended for inclusion in the trivalent vaccines for the 2016/2017 season in the northern hemisphere. The low number of specimens for VE analysis resulted in broad confidence intervals in the VE analysis. To overcome this problem, the Netherlands participates in the I-MOVE and I-MOVE+ studies since the 2015/2016 season, to estimate a pooled VE for several European countries. Preliminary (unpublished) data from the I-MOVE pooled analysis showed an influenza VE for influenza virus type A(H1N1)pdm09 of 32% (95% CI: 15% to 46%); the 95% CI of this pooled VE included the Dutch point estimated of the VE for this subtype (42%, 95% CI: -40% to 76%, as presented above). In the I-MOVE study there was considerable heterogeneity in the adjusted VE

estimates against influenza B among all ages by study site. Therefore, pooled estimates for influenza B were not presented.

The vaccine effectiveness against self-reported ILI seemed to be higher than the VE against laboratory confirmed influenza. This is unexpected, as not all ILI is caused by influenza virus infection. However, the confidence intervals are very broad for all estimates, so no definite conclusions can be drawn. Additionally, the vaccine effectiveness against self-reported ILI was highest for the elderly. The preliminary I-MOVE pooled analysis however, showed a lower crude VE among the elderly (≥ 65 years) than among the 15-64 years age group. However, the sample size was too low to calculate adjusted VE estimates for the eldest age group.

Based on clinical presentation only, it is difficult to diagnose influenza. However, the percentage ARI cases positive for influenza virus is considerably lower than the percentage ILI cases positive for influenza virus, thereby illustrating that GP's can identify influenza patients to some extent based on clinical presentation only.

Despite the change in sampling instructions for the 2015/2016 season, the same age groups were oversampled (15-44 years and 45-64 years) as in the 2014/2015 season. The new instructions included the sampling of all people of 65 years and older. This did not lead to a higher number of specimens than in the 2014/2015 season. However, this may be partly explained by the domination of the influenza virus type A(H1N1)pdm09 and type B (Victoria lineage) in the recent season, instead of the subtype A(H3N2). It is known that subtype A(H3N2) leads to more infections in the elderly. This example shows that when comparing influenza trends over the years, dominance of types and subtypes of circulating influenza viruses should always be taken into account.

In the SNIV nursing home surveillance, only two specimens were taken from residents with ILI or another acute respiratory infection. This could be partly due to the influenza virus type A(H1N1)pdm09 and type B (Victoria lineage) dominated season. However, the consistently low number of specimens submitted by nursing homes is a reason for concern.

Hospital admissions of severe acute respiratory infections (SARI) were much higher during the 2014/2015 than the 2015/2016 influenza epidemic at the JBZ. This is primarily explained by differences in data collection. The 2014/2015 data are collected retrospectively by reviewing electronic patient records (EPR). The 2015/2016 data reflect only patients that were actively recruited in the SARI surveillance study. During the influenza epidemic 2015/2016, the influenza virus type A(H1N1)pdm09 was predominant at hospital level, like in primary care. Since the introduction of SARI surveillance at the Jeroen Bosch Hospital, these results show an increase of number of influenza tests ordered by the clinicians as well as influenza-positive detected cases. Ultimately, better influenza diagnostics should improve infection control measures and the adequate prescription of antiviral medication against influenza in hospitals. This would lead to an important improvement in the quality of care of SARI patients.

3.5 Tables and figures

Virus surveillance

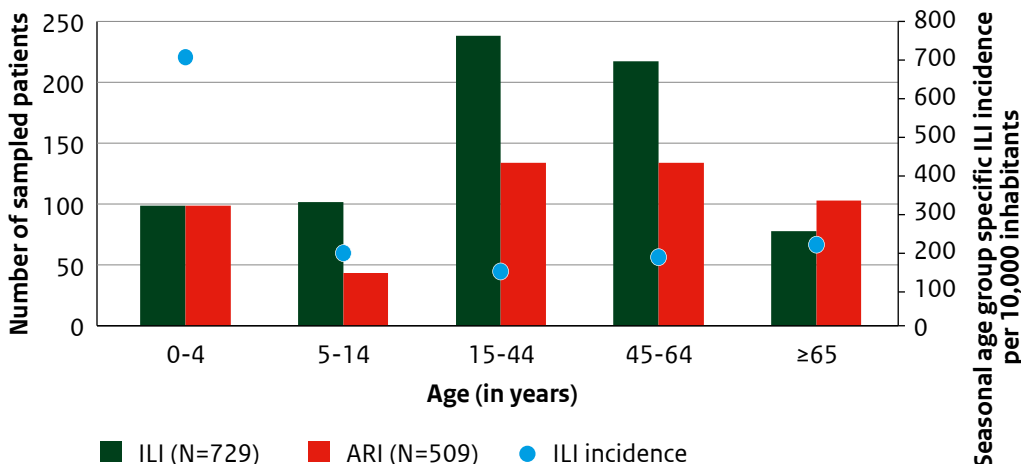
Table 3.1 Characteristics of influenza-like illness (ILI) and other acute respiratory infections (ARI) patients, who are sampled by sentinel GPs in the 2015/2016 season (through week 20 of 2016) (Source: NIC location RIVM).

| Characteristics | ILI patients n/N (%) | ARI patients n/N (%) |
|--|-------------------------|-------------------------|
| Male gender | 319/729 (44) | 228/509 (45) |
| Vaccinated against influenza | 131/727 (18) | 111/506 (22) |
| If yes, brand was Influvac | 55/120 (46) | 41/102 (40) |
| If yes, brand was Vaxigrip | 65/120 (54) | 61/102 (60) |
| Vaccinated against pneumococci | 54/674 (8) | 37/454 (8) |
| Part of target group for vaccination | 217/729 (30) | 190/508 (37) |
| • Lung disease (including asthma, COPD) | 85/216 (39) | 66/189 (35) |
| • Immune deficiency due to treatment (like chemotherapy or radiation, or else) | 11/215 (5) | 12/187 (6) |
| • Immune deficiency due to disease (like immune disease, HIV, or else) | 8/215 (4) | 5/187 (3) |
| • Cardiac disease (myocardial infarction, angina pectoris, arrhythmias, valvular heart disease, heart failure) | 31/212 (15) | 40/183 (22) |
| • Diabetes mellitus | 33/212 (16) | 32/186 (17) |
| Obesity | 60/698 (9) | 56/474 (12) |
| Smoking: | | |
| Yes or stopped < 1 year | 107/638 (16) | 50/459 (11) |
| No (or stopped > 1 year) | 56/638 (8) | 62/459 (14) |
| Women: | | |
| Pregnant | 7/394 (2) | 2/268 (1) |
| People aged 65 years and older: | | |
| Needs assistance with showering | 1/75 (1) | 3/94 (3) |
| Needs assistance with walking | 1/75 (1) | 2/94 (3) |
| Delay in sampling, in days ^a | 4 (2-6) | 4 (2-7) |

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

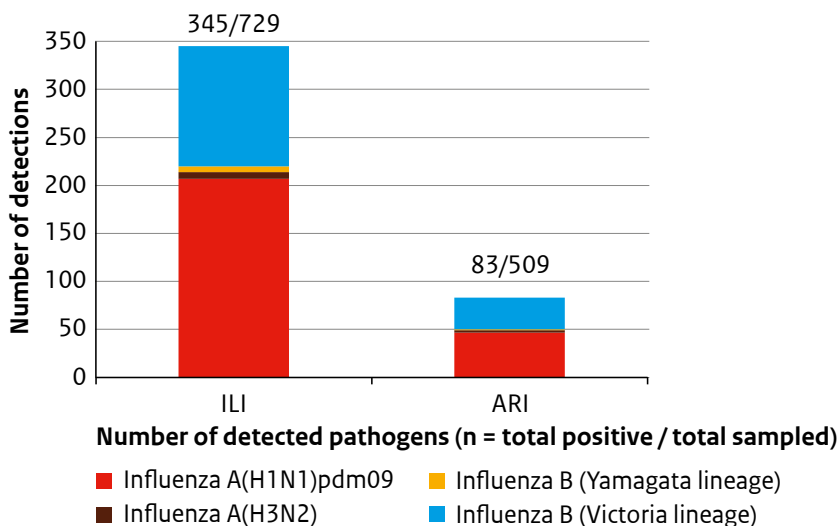
Footnote: n = the number in the corresponding group; N = total number of patients, for whom the information was available; ILI = influenza-like illness; ARI = other acute respiratory tract infection.

Figure 3.1 Age distribution of ILI and ARI patients, sampled by NIVEL sentinel GPs, and the ILI cumulative seasonal incidence per age category in the 2015/2016 respiratory season (through week 20 of 2016) (Source: NIVEL Primary Care Database, NIC location RIVM).



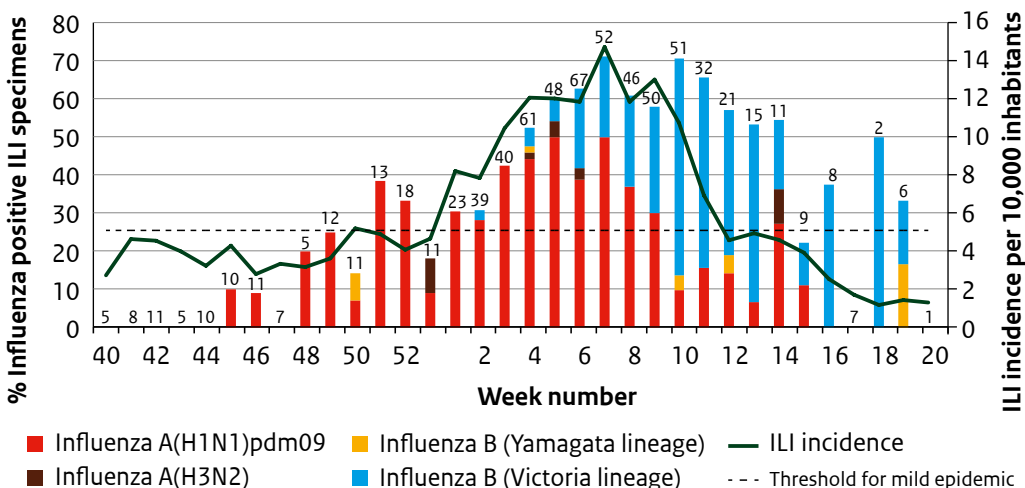
Footnote: ILI = influenza-like illness; ARI = other acute respiratory tract infections, GP = general practitioner.

Figure 3.2 Number of detected respiratory pathogens among ILI and ARI patients, who were sampled in the NIVEL GP sentinel surveillance in the 2015/2016 respiratory season (through week 20 of 2016) (Source: NIC location RIVM).



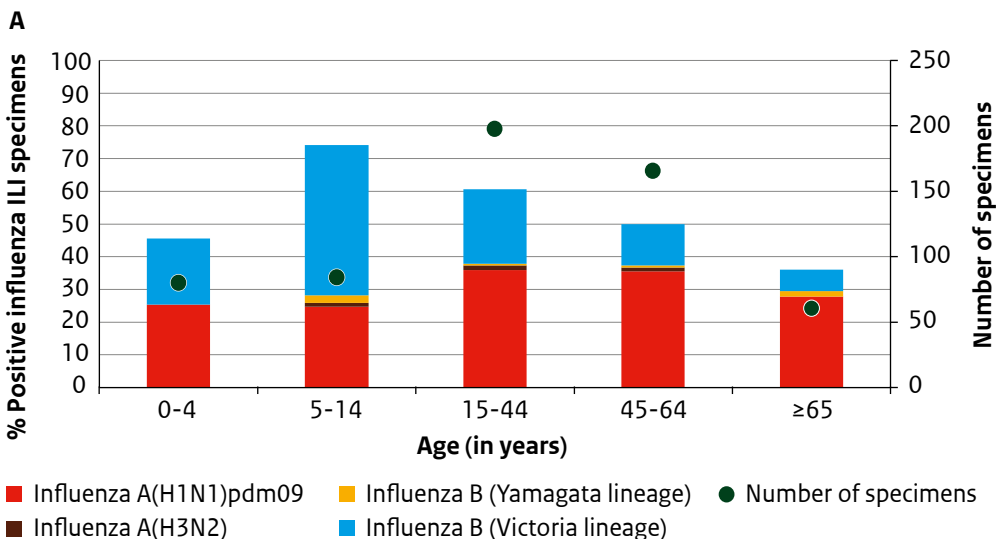
Footnote: ILI = influenza-like illness; ARI = other acute respiratory tract infection.

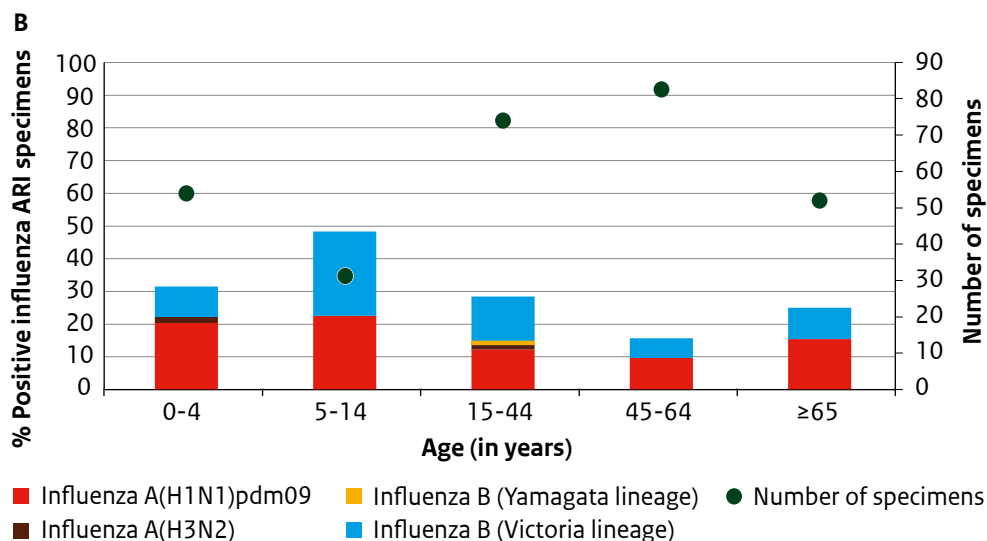
Figure 3.3 Percentage of positive ILI specimens, taken by sentinel GPs, and ILI incidence with epidemic threshold during the 2015/2016 respiratory season (through week 20 of 2016), displayed by week of sampling (Source: NIVEL Primary Care Database, NIC location RIVM).



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 1 through 11 2016) of the 2015/2016 season (through week 20 of 2016) (Source: NIC location RIVM).





Footnote: ARI = other acute respiratory tract infection, ILI = influenza-like illness

Figure 3.5 Subtyping of influenza viruses submitted by Dutch laboratories to the NIC location Erasmus MC during the 2015/2016 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).

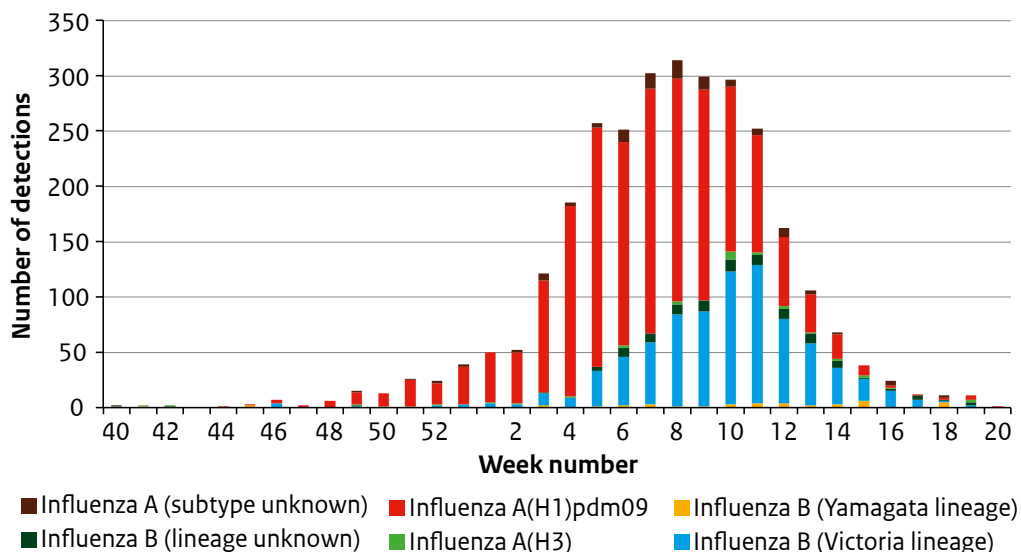


Table 3.2 Genetic characterisation of influenza viruses, week 40 of 2015 through week 20 of 2016. (Source: NIC-RIVM Clb/IDS)

| Virus (sub)type | Clade | Antigenic match with 2015/2016 vaccine strains ^a | Source | | | | |
|---------------------|-------|---|--------------------------|----------------------------|--------------------|----------------------------|------------------------------------|
| | | | Sentinel GP ^b | Virology labs ^c | Aruba ^b | Hadi pilgrims ^b | Nursing home outbreak ^b |
| A(H1N1)pdm09 (n=86) | 6B.1 | Good | 40 | 27 | 15 | 1 | 3 |
| A(H3N2) (n=4) | 3C.2a | Good | 1 | | | 1 | |
| | 3C.3b | Less good | 2 | | | | |
| B-Victoria (n=11) | 1A | Not in vaccine | 10 | | | | 1 |

^a Composition 2015/2016 vaccine: A/California/7/2009 (H1N1)pdm09; A/Switzerland/9715293/2013 (H3N2, Clade 3C.3a); B/Phuket/3073/2013 Yamagata lineage.

^b Source NIC location RIVM

^c Source NIC location Erasmus MC

Footnote: GP = General Practitioner

Table 3.3 Influenza virus diagnostics of SARI patients; comparison influenza epidemic 2014/2015 and 2015/2016 at the Jeroen Bosch Hospital

| Total | Influenza epidemic 2014/2015 n=679 | Influenza epidemic 2015/2016 n=80 |
|--------------------------|---------------------------------------|--------------------------------------|
| | N (%) | N (%) |
| Influenza test performed | 276 (41) | 59 (74) |
| Influenza virus positive | 109 (39) | 28 (47) |
| type A | 89 (82) | 22 (79) |
| type B | 20 (18) | 6 (21) |
| Influenza virus negative | 167 (61) | 31 (53) |

Footnote: SARI = severe acute respiratory infection

Influenza diagnostics in virological laboratories

Figure 3.6 Weekly number of influenza virus type A and B diagnoses, reported by the virological laboratory surveillance in the period week 1 of 2006 through week 20 of 2016 (Source: Virological laboratory surveillance, RIVM).

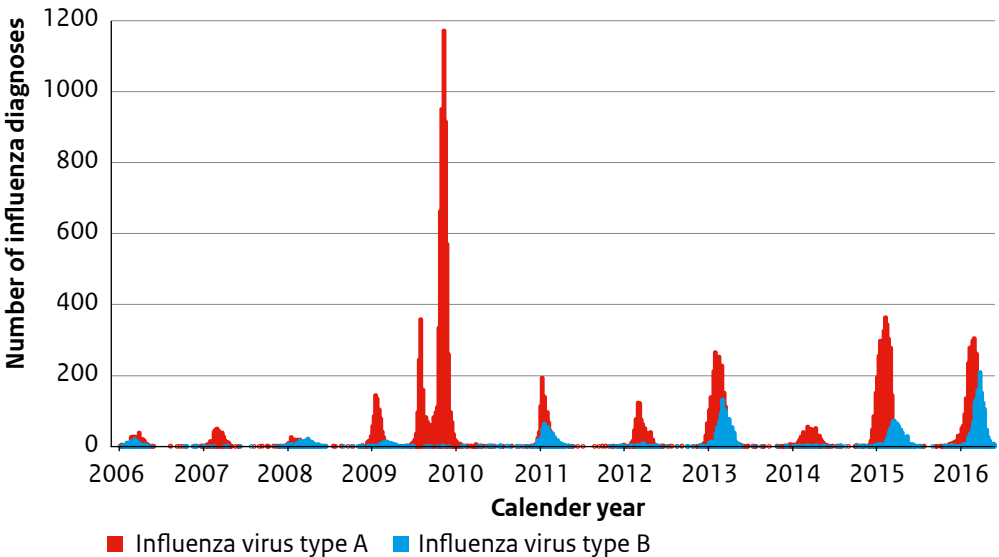
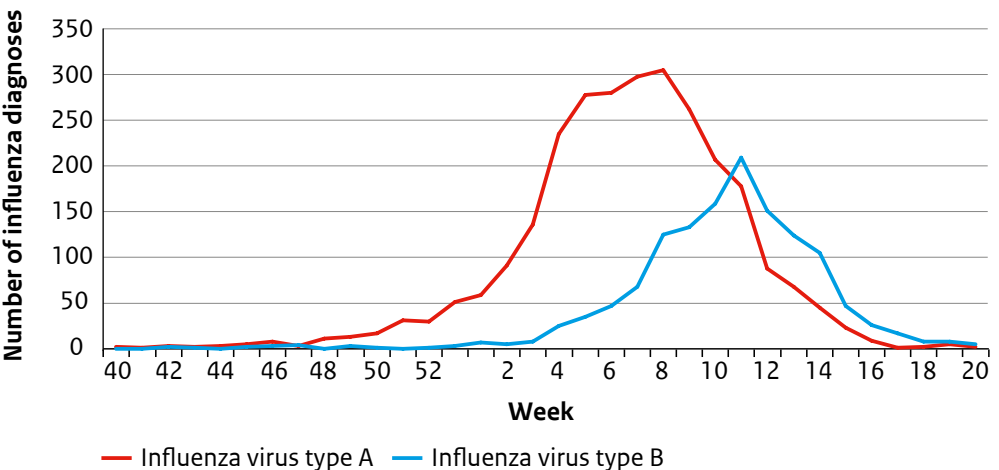


Figure 3.7 Weekly number of influenza virus type A and B diagnoses reported in the virological laboratory surveillance, for the period week 40 of 2015 through week 20 of 2016 (Source: Virological laboratory surveillance, RIVM).



Antiviral resistance

Table 3.4 Reduced inhibition of influenza viruses by neuraminidase inhibitors and M2 ion-channel blockers, 2013/2014 - 2015/2016 (Source: NIC location RIVM, NIC location Erasmus MC).^a

| | 2013/2014 n/N (%) | 2014/2015 n/N (%) | 2015/2016 n/N (%) ^b |
|-----------------------------------|-------------------------|-------------------------|-----------------------------------|
| Neuraminidase inhibitor | | | |
| Influenza virus type A(H1N1)pdm09 | 1/150 (<1) ^c | 1/130 (<1) ^d | 1/1208 (<1) ^e |
| Influenza virus type A(H3N2) | 2/220 (<1) ^f | 0/727 (0) | 0/35 (0) |
| Influenza virus type B | 0/4 (0) | 0/42 (0) | 0/38 (0) |
| M2 ion-channel blocker | | | |
| Influenza virus type A(H1N1)pdm09 | 20/20 (100) | 9/9 (100) | 55/55 (100) |
| Influenza virus type A(H3N2) | 31/31 (100) | 50/50 (100) | 3/3 (100) |

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

^b Preliminary data.

^c One virus with highly reduced inhibition by oseltamivir due to the H275Y amino acid substitution. No patient characteristics or viral exposure data available.

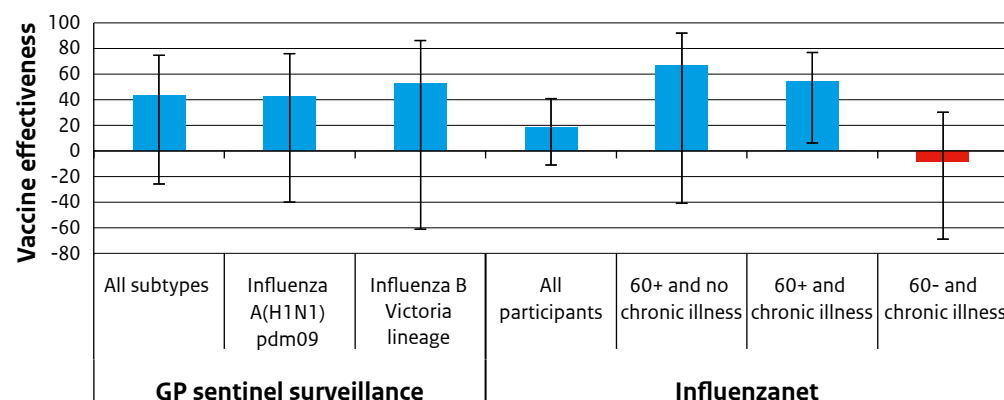
^d One virus with highly reduced inhibition by oseltamivir due to mixture 275H/Y amino acid substitution. The patient was treated with oseltamivir prior to specimen collection.

^e One virus with highly reduced inhibition by oseltamivir due to H275Y amino acid substitution.

^f Two clinical specimens from two patients with mixture of 292R and 292K amino acid composition; R292K is associated with highly reduced inhibition for oseltamivir and zanamivir. No patient characteristics or viral exposure data available.

Influenza vaccine effectiveness

Figure 3.8 Overview of influenza vaccine effectiveness in the 2015/2016 season, measured in GP sentinel surveillance (against laboratory confirmed influenza virus infection) and in Influenzanet (against not-laboratory confirmed ILI) (Source: NIVEL Primary Care Database, Influenzanet).



Footnote: Blue box indicate a point estimate of the VE above zero, red box indicate a point estimate of the VE below zero.

Table 3.5 Estimation of vaccine effectiveness 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 sentinel GP surveillance in the 2015/2016 season.

| | Number of used observations | Vaccine effectiveness % (95% CI) ^a |
|---|-----------------------------|---|
| All influenza virus subtypes | 821 | 44% (-26% – 75%) |
| Influenza virus type A(H1N1)pdm09 | 678 | 42% (-40% – 76%) |
| Influenza virus type B (Victoria lineage) | 602 | 53% (-61% – 86%) |

^a Corrected for period in the season (7 categories), age (5 categories), ≥5 GP consultations in 12 months, vaccination received 2 seasons ago.

Footnote: ILI = influenza-like illness; ARI = other acute respiratory tract infection; GP = general practitioner; CI = confidence interval

Table 3.6 Estimation of vaccine effectiveness against ILI for all participants, and stratified for participants 60 years or older, and chronic ill patients based on self-reported ILI to Influenzanet (the Netherlands) in the 2015/2016 season.

| | Number of used observations | Vaccine effectiveness % (95% CI) |
|----------------------------|-----------------------------|----------------------------------|
| All participants | 6044 | 18% (-11% to 41%) |
| 60+ and no chronic illness | 1519 | 67% (-41% to 92%) |
| 60+ and chronic illness | 2969 | 54% (6% to 77%) |
| 60- and chronic illness | 1556 | -8% (-69% to 30%) |

Footnote: ILI = influenza-like illness; CI = confidence interval
VE's significantly higher than zero are displayed in bold.

Chapter 4

RSV

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4.1 Keypoints

- In the 2015/2016 respiratory season (week 40 of 2015 through week 20 of 2016), a total of 107 RS-viruses were detected in 1,238 nose swabs and throat swabs of ILI and ARI patients, collected by sentinel GPs.
- For ILI patients the peak in percentage of positive specimens was found in week 2 2016 (9/39 swabs; 23%) and for ARI patients in week 52 2015 (9/19 swabs; 47%).
- RSV-B is more frequently detected than RSV-A (5.7% versus 3% of total specimens) except in 0-4 year old ILI patients (6% RSV-B versus 12% RSV-A of total specimens in this age group).
- The percentage of RSV positive specimens taken by the GP was highest in the children below two years of age; both in ILI patients (12/43 swabs; 28%) and in ARI patients (25/60 swabs; 42%).
- The RSV season, defined as the period of consecutive weeks with at least 20 positive RSV diagnoses, reported by the virological laboratory surveillance, started in week 48 of 2015 and lasted for a total of 20 weeks.
- The number of RSV diagnoses by the virological laboratory surveillance (n=1348; through week 20) was lower than in earlier seasons (range: 1629-3075 in 2005/2006-2014/2015; week 40 through week 20). It is unclear whether this reflects a lower incidence or a change in testing practices. The policy of restricting diagnostic tests for budgetary reasons in many hospitals might explain this decrease.

4.2 Background

Respiratory Syncytial Virus (RSV) causes a respiratory infection that is commonly acquired 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). Also 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). Approximately 10,000 deaths in persons aged 65 and older are attributable to RSV each year in the United States (Thompson, Shay et al. 2003). In the Netherlands, this estimate is 1,685 per winter season, in comparison to 2,110 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. All vaccine candidates that are currently in phase 2 and phase 3 clinical trials are based on the fusion protein, the F-protein (Higgins, Trujillo et al. 2016).

The current RSV surveillance is primarily based on the influenza GP surveillance of ILI and ARI patients. As the GPs do not follow the case definitions for ILI and ARI exactly, but also incorporate their clinical experience and judgment to diagnose a patient with ILI or ARI and sample these patients, a wider definition of the two syndromes is monitored, e.g. also patients without fever and with wheezing (shortness of breath). Although this is not systematically done, RSV is therefore also detected by this surveillance system. Another important real-time data source for RSV circulation in the population is the virological laboratory surveillance where RSV detections are weekly reported 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.

4.3 Epidemiological situation, season 2015/2016

In the 2015/2016 season (week 40 through week 20), a total of 107 RS-viruses were detected in 1,238 nose swabs and throat swabs (8.6%) of ILI and ARI patients, collected by sentinel GPs. Of these 107 specimens, 37 were RSV-A (35%) and 70 were RSV-B (65%). The highest percentage of positive specimens in ILI and ARI patients combined was 35% (13/37 swabs) in week 52 of 2015. For ILI patients the peak in percentage of positive specimens was found in week 2 2016 (9/39 swabs (23%)) and for ARI patients in week 52 2015 (9/19 swabs (47%)). The percentage of positive specimens from the GP sentinel surveillance was highest in the 0 to 2 years old, both in the ILI specimen (28% positive, 12/43 swabs) and in the ARI specimen (42% positive, 25/60 swabs). In the 2–4 years olds, 11% (6/55 swabs) of the ILI specimens and

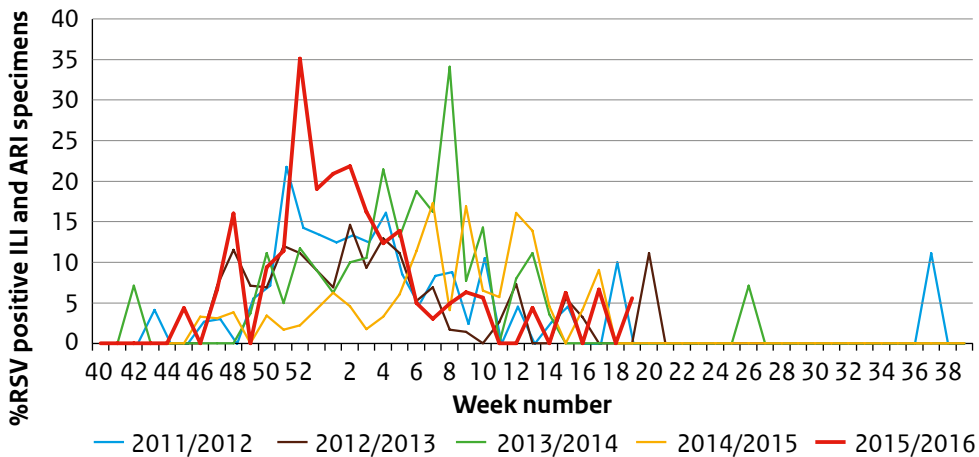
16% (6/38 swabs) of the ARI specimens were positive for RSV. The percentages were lower in older children and young adults, and seemed to increase again with older age, starting in the 45-64 years olds (ARI patients) and 65-plus year olds (ILI patients). Overall, more RSV-B than RSV-A was detected in specimens, except in the youngest ILI patients (0-4 years old), where the number of RSV-A detections was higher than the number of RSV-B detections. The total number of positive RSV diagnoses reported by 20 virological laboratories in the Netherlands (virological laboratory surveillance) in 2015/2016 (n=1,348; through week 20) was lower than the earlier seasons. Since the respiratory season 2011/2012, a clear drop can be observed in the number of detections compared with the previous years. The RSV season is defined as the period in which the number of RSV-diagnoses as reported by the virological laboratory surveillance is over 20 per week. In the winter 2015/2016, this period lasted from week 48 of 2015 through week 14 of 2016.

4.4 Discussion

In the 2015/2016 respiratory season, the peak in the percentage of RSV positive specimens, taken by GPs, occurred earlier than in the two previous seasons. However, RSV was still detected in considerable numbers at the time that the ILI incidence was increasing, even in weeks when a very high proportion of specimens tested positive for influenza virus. At present, there is no clear case definition for RSV and the incidence of RSV can therefore not directly be calculated. However, a provisional estimate of incidence of RSV virus infection in the community can be obtained by multiplying the proportion of ILI patients testing positive for RSV with the ILI incidence. This is a conservative estimate as RSV can present without fever and sensitivity of the ILI case definition if applied to RSV is likely to be very low. ARI incidence is also available, but is obtained from a larger group of GPs, most of whom are not involved in swabbing patients for virological analysis. Multiplying this ARI incidence with percentage swabs positive for RSV would provide an upper limit for the range of RSV incidence. These data will be important in the future to calculate burden estimates for RSV, as is now already implemented for influenza (Chapter 8). Another potential surveillance system where RSV specimens can be sampled is the SARI surveillance that is currently being piloted. Other than for influenza virus, the percentages of RSV positive specimens are not higher for ILI patients than for ARI patients. On the contrary, in 16 out of 21 weeks in which RSV was detected, the percentage of RSV is higher in ARI than in ILI specimen. The lower percentage of RSV in ILI specimens later in the season may not necessarily represent a lower absolute number of RSV cases in the population, but may be due to the many influenza cases contributing to an increase of ILI cases, thereby lowering the relative contribution of RSV. Calculating the RSV incidence as described above might provide more insight into this. Another explanation for the lower detection of RSV in ILI patients during the influenza epidemic is that GPs might successfully identify influenza patients for sampling during the epidemic. The peak of the weekly virological laboratory surveillance was indeed somewhat later, in week 4, indicating that RSV was still clearly circulating in the beginning of 2016.

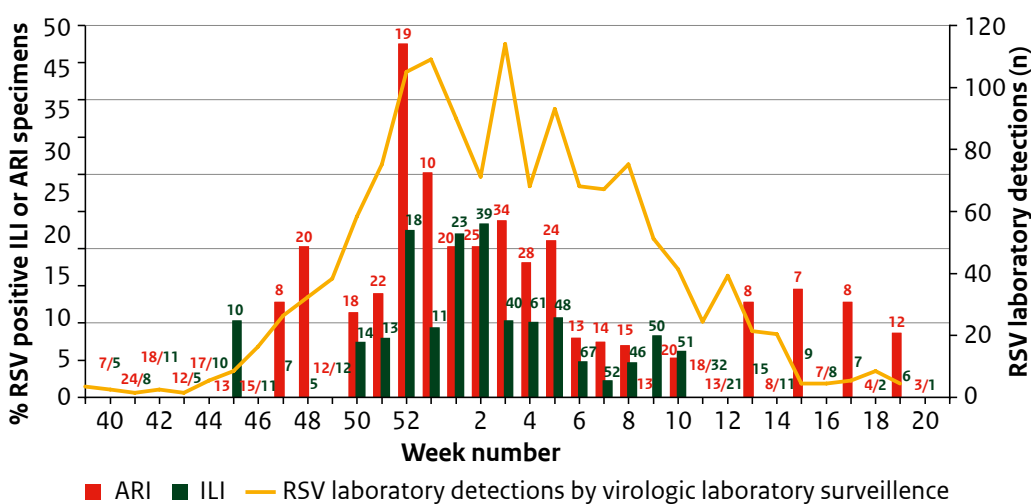
4.5 Tables and figures

Figure 4.1 Percentage of RSV positive ILI and ARI specimens, taken by sentinel GPs during the respiratory seasons 2011/2012 - 2015/2016 (week 40 through week 20 of 2016)
(Source: NIVEL Primary Care Database, NIC location RIVM).



Footnote: The year 2015 had 53 weeks. For the years without a week 53, the average of weeks 52 and 1 was used.

Figure 4.2 Percentage of positive ILI (green bars) and ARI (red bars) specimens, taken by sentinel GPs, and number of RSV detections as reported by the virological laboratory surveillance, during the 2015/2016 respiratory season (through week 20 of 2016), displayed by week of sampling (Source: NIC location RIVM, virological laboratory surveillance).



Footnote: the numbers above the bars are the total number of tested specimens (red font for ARI and dark green font for ILI).

Figure 4.3 Percentage of RSV-A and RSV-B positive ILI specimens (A) and ARI specimens (B), and the number of tested specimens, taken by sentinel GPs during the respiratory season of 2015/2016 (week 40 of 2015 - week 20 of 2016), displayed for six age categories. (Source: NIVEL Primary Care Database, NIC location RIVM).

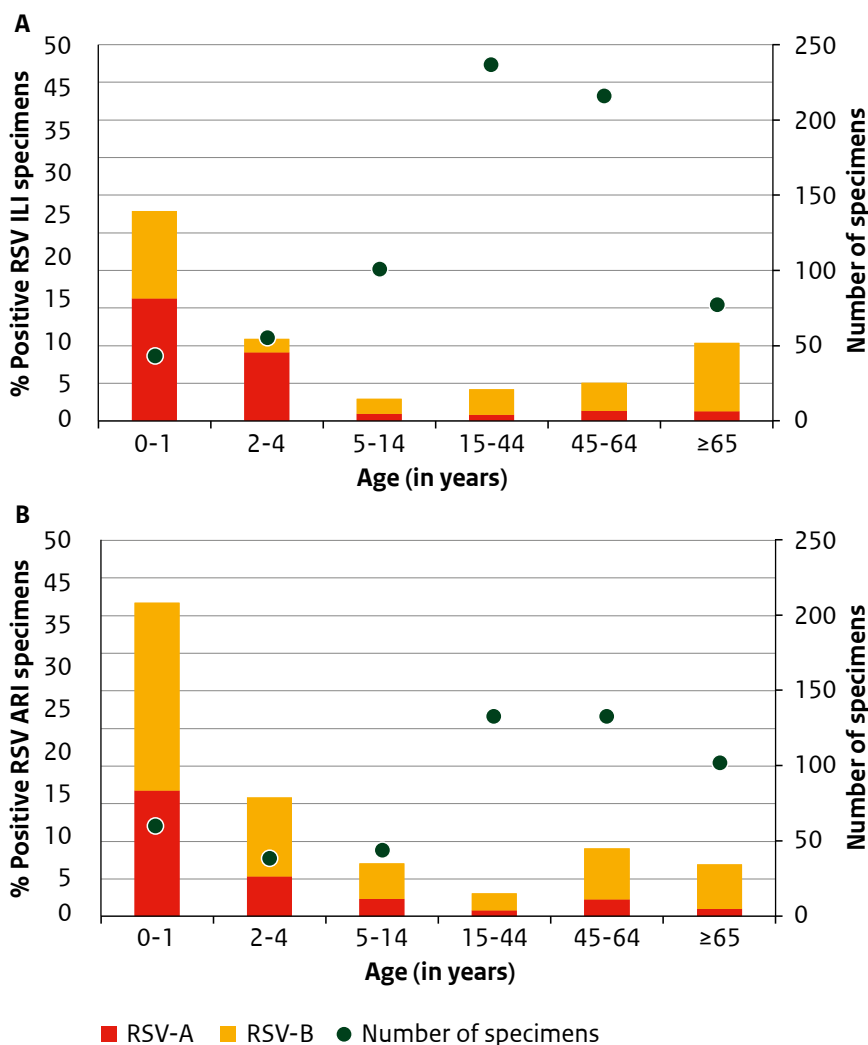


Figure 4.4 Number of weekly reported positive diagnoses (black line) and total number of positive diagnoses in the respiratory year (orange diamond) and respiratory season (red dot) of respiratory syncytial virus (RSV) in the virological laboratory surveillance for the period 2006/2007-2015/2016 (until week 20).(source: virological laboratory surveillance).

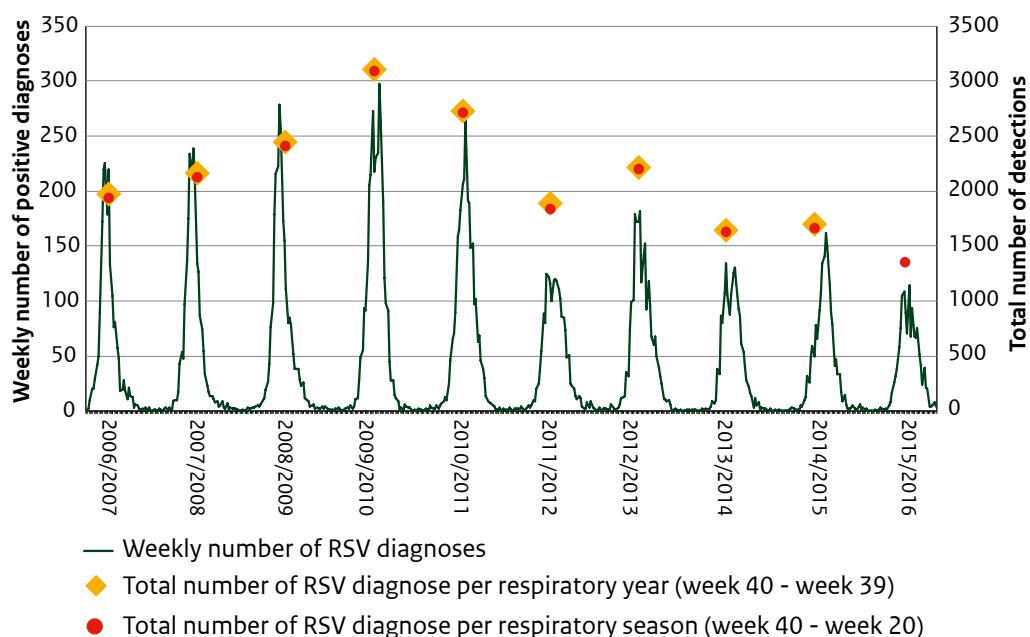


Table 4.1 Number of reported positive diagnoses of respiratory syncytial virus (RSV) in the Virological laboratory surveillance for the period 2006/2007-2015/2016 (through week 20).

| | Positive diagnoses weeks 40-20 (N) | Positive diagnoses weeks 21-39 (N) | Positive diagnoses weeks 40-39 (N) |
|-----------|------------------------------------|------------------------------------|------------------------------------|
| 2006/2007 | 1939 | 32 | 1971 |
| 2007/2008 | 2128 | 43 | 2171 |
| 2008/2009 | 2416 | 35 | 2451 |
| 2009/2010 | 3075 | 34 | 3109 |
| 2010/2011 | 2702 | 27 | 2729 |
| 2011/2012 | 1838 | 51 | 1889 |
| 2012/2013 | 2199 | 12 | 2211 |
| 2013/2014 | 1629 | 16 | 1645 |
| 2014/2015 | 1670 | 32 | 1702 |
| 2015/2016 | 1348 ^a | - ^b | - ^b |

^a Data for weeks 40 of 2015 through week 20 of 2016 are preliminary.

^b Data for weeks 21-39 of 2016 are not yet available.

Table 4.2 RSV seasonal trends in the Virological laboratory surveillance for the period 2006/2007-2015/2016 (through week 20): season onset, duration and peak.

| | Onset week (week number) | Season duration (N weeks) | Peak | |
|-----------|-----------------------------|---------------------------------|----------------------------------|------------------------------|
| | | | Timing (week number- year) | Positive diagnoses (N) |
| 2006/2007 | 43 | 17 | 51-2006 | 225 |
| 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 |

Chapter 5

Notifiable Respiratory Diseases

5.1 Legionnaires' disease

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Contributor: Sjoerd Euser

5.1.1 Key points

- In 2015, 438 notifications for legionellosis were received, of which 419 cases were confirmed or probable Legionnaires' disease (LD) in Dutch residents. The incidence was 2.5 LD cases per 100,000 inhabitants, which was substantially higher than the incidence in previous years (1.8-2.1 per 100.000 in 2011-2014).
- In 65% of cases, LD was acquired in the Netherlands (domestic) and 35% was associated with travel abroad (TALD).
- Domestic cases accounted for the largest increase: 47% increase compared with 2011-2014. Most domestic cases (244 of 273 cases) were community acquired (CALD).
- Seasonality: as usual, most cases were diagnosed in summer. In 2015, a mild increase was seen in the winter months (January-March), but the large increase in domestic cases occurred from July to October.
- The higher incidence was spread over multiple regions. No large clusters or outbreaks were detected that could explain the rise in domestic cases. The weather conditions in 2015 may explain the rise in cases. After a mild winter and a heatwave in July 2015, August was warm with days of heavy rainfall. Previous studies have shown an association between the LD incidence in the Netherlands and warm and wet weather conditions. There was a cluster with 11 cases of legionellosis associated with a campsite in Croatia, involving five Dutch families. Legionnaires' disease was confirmed in one adult and one child. Pontiac fever (with positive serology) was seen in nine other family members, of which eight involved children. The probable source of infection was a jacuzzi.

- Environmental sampling of potential sources within the Netherlands was done for 32 of 419 patients. For 21 patients a clinical isolate was available and environmental sources were sampled. This resulted in a genotypic match between the clinical and environmental isolate in four of 21 patients (19%). These matches identified respectively a jacuzzi in a club, an apnea machine, a wet cooling tower of a hospital, and a hospital ward as source of infection.
- Most cases (75%) 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 (43%), and a positive culture was available for only 19% of the 419 patients. The proportion PCR positive cases was also low (16%). This could mean that pneumonia caused by non-*L. pneumophila* serogroup 1 may still remain undetected.

5.1.2 Tables and figures

Figure 5.1 Annual numbers of notifications of Legionnaires' disease, 2005 through 2015 by setting of infection (Source: Osiris).

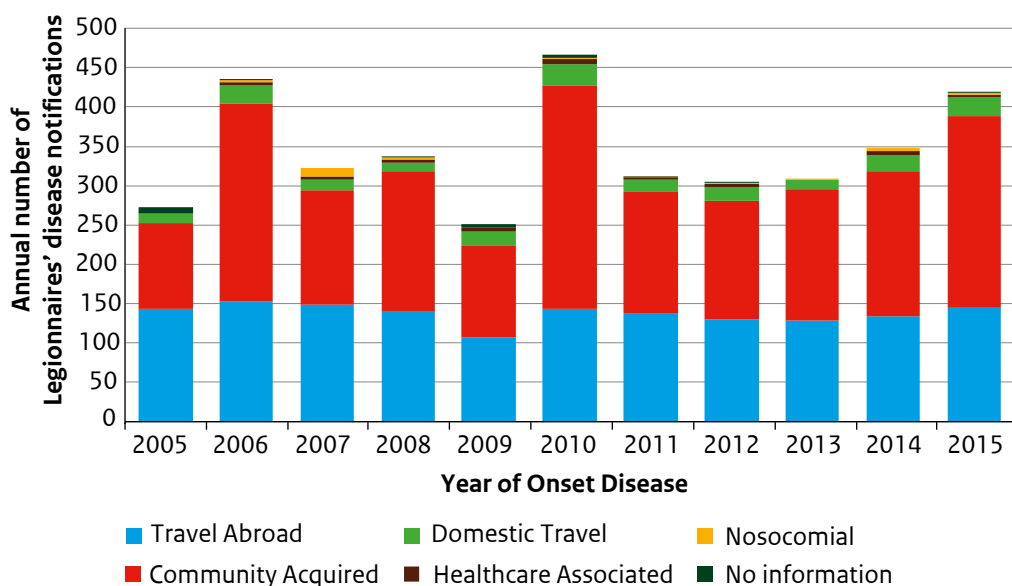


Figure 5.2 Notifications of Legionnaires' disease acquired abroad or acquired in The Netherlands (domestic), by month of disease onset in 2015 and the monthly average 2011-2014 (Source: Osiris).

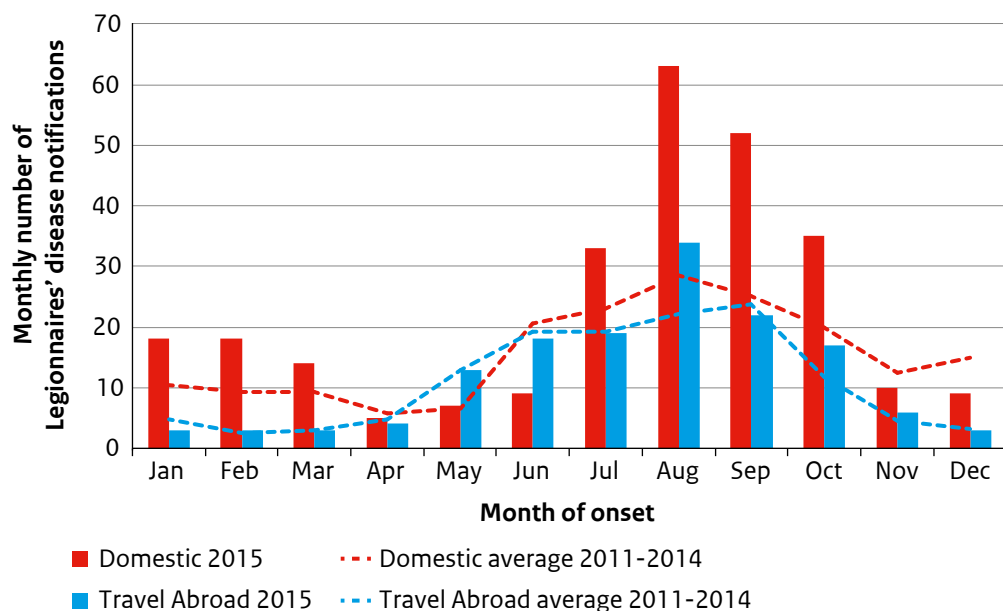


Table 5.1 Number of legionellosis notifications in 2011-2015, incidence, clinical and epidemiological background, mortality and diagnostics (Source: Osiris).

| Year of onset disease ^a | 2011 | 2012 | 2013 | 2014 | 2015 |
|---|----------------|-----------------------|----------------|---------------------------------|---------------------------------|
| Number of Legionellosis notifications ^b | 314 | 308 | 310 | 370 | 438 |
| Excluded from analysis: no pneumonia, non-resident or single high titre (in 2014-2015) ^{b,c} | 2 ^b | 4 ^b | 2 ^b | 22 ^{b,c} | 19 ^{b,c} |
| Total included: | n (%) | n (%) | n (%) | n (%) | n (%) |
| Legionnaires' disease (LD) (=100%) ^b | 312 | 304 | 308 | 348 | 419 |
| Confirmed Legionnaires' disease ^d | 266 (85) | 265 (87) | 288 (94) | 327 (94) | 393 (94) |
| Probable Legionnaires' disease ^d | 27 (9) | 25 (8) | 13 (4) | 21 (6) | 26 (6) |
| Pontiac fever or possible LD (single High titre) ^c | 19 (6) | 14 (5) | 7 (2) | 12 (-) excluded ^c | 13 (-) excluded ^c |
| LD Incidence (per 100,000 residents) | 1.9 | 1.8 | 1.8 | 2.1 | 2.5 |
| Male gender | 218 (70) | 214 (70) | 203 (66) | 255 (73) | 293 (70) |
| Median age (Q1-Q3) | 62 (54-69) | 62 (53-72) | 63 (54-72) | 61 (53-71) | 62 (53-69) |
| Hospital admission ^e | 300 (97) | 294 (97) | 299 (97) | 342 (98) | 410 (98) |
| X-thorax confirmed pneumonia ^e | 293 (97) | 287 (98) | 290 (99) | 328 (94) | 401 (96) |
| Deaths ^e | 18 (6) | 16 (5) | 17 (6) | 13 (4) | 13 (3) |
| Setting of infection: | | | | | |
| Travel abroad ^f | 138 (44) | 130 (43) | 128 (42) | 134 (39) | 145 (35) |
| Domestic (acquired in The Netherlands) | 174 (56) | 173 ^g (57) | 180 (58) | 214 (61) | 273 ^g (65) |
| Domestic categories: | | | | | |
| Domestic travel ^f | 15 (5) | 17 (6) | 12 (4) | 20 (6) | 24 (6) |
| Nosocomial | 1 (<1) | 1 (<1) | 1 (<1) | 4 (1) | 2 (<1) |
| Healthcare Associated | 2 (<1) | 4 (1) | - | 6 (2) | 3 (<1) |
| Community Acquired | 155 (50) | 151 (50) | 167 (54) | 184 (53) | 244 (58) |
| No information/ other ^g | 1 (<1) | 1 ^g (<1) | - | - | 1 ^g (<1) |

| Year of onset disease ^a | 2011 | 2012 | 2013 | 2014 | 2015 |
|--|----------|----------|----------|----------|----------|
| Diagnostics | | | | | |
| <i>Legionella</i> cultured performed (=yes) | 134 (42) | 133 (44) | 124 (40) | 156 (45) | 181 (43) |
| Positive culture | 71 (23) | 59 (19) | 49 (16) | 67 (19) | 79 (19) |
| Proportion <i>L.pneumophila</i> sg1 in culture (or PCR) positives ^h | 86% | 85% | 96% | 90% | 87% |
| Positive urine antigen test | 253 (81) | 257 (85) | 283 (92) | 314 (90) | 381 (91) |
| Positive PCR | 45 (14) | 40 (13) | 43 (14) | 54 (16) | 65 (16) |
| Significant titer rise | 12 (4) | 6 (2) | 5 (2) | 5 (1) | 6 (1) |
| Direct immunofluorescence | 1 (<1) | 2 (<1) | - | - | 1 (<1) |
| Diagnostic delay in days: median(Q1-Q3) | 6 (4-9) | 6 (4-9) | 6 (4-8) | 6 (4-8) | 6 (4-7) |
| Notification delay in days: median (90% reported) | 0 (3) | 0 (3) | 0 (3) | 0 (2) | 0 (2) |

^a 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, 2016, including all authorized notifications.

^b Legionellosis according to Dutch notification criteria, which differs from the European criteria for Legionnaires' Disease (LD). The European case definition for LD is limited to cases with pneumonia and only allow a single high titre as diagnostic method if this is specific against *L. pneumophila* serogroup1 (monovalent).

^c Single high titre (polyvalent, i.e. not specific for *L. pneumophila* serogroup1) as diagnostic confirmation. Excluded from analyses since 2014.

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

^e Percentage based on the number of patients for which this specific information was available.

^f Travel Associated Legionnaires Disease (TALD) is defined as travel (including at least 1 overnight stay) in the period of 2-14 days before disease onset. This differs from the TALD cases that are reported to the surveillance network ELDSNet [<http://ecdc.europa.eu/en/activities/surveillance/ELDSNet/Pages/index.aspx>] which is limited to travel 2-10 days before onset. In 2015 includes were 5 cases with travel at day 11-14 before onset.

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

^h Proportion based on the number of patients for whom clinical specimens (culture of PCR) were available for typing at the reference lab.

5.2 Psittacosis

Author: Frederika Dijkstra

Contributors: Mauro De Rosa, Edou Heddema

5.2.1 Key points

- In 2015, 47 patients with psittacosis were notified. This number is in the range of the previous three years, but lower than the years 2008 to 2011.
- Six patients were part of an outbreak related to one avian refugee center.
- 79% of notified patients was hospitalised, which is in line with the years 2011-2013, but a lower than 2014, when this percentage was 93%.
- The percentage of notified cases in which the diagnosis was confirmed with PCR has increased to 70%.
- Genotyping of the *C. psittaci* strain has been performed for the majority of eligible cases (83%).
- Like in 2013 and 2014, genotype A (mainly, but not exclusively associated with parrot-like birds), and genotype B (mainly associated with doves and pigeons) were most prevalent among patients in 2015.
- The genotyping and supplementary diagnostics also revealed less common (geno)types: two cases of *C. psittaci* genotype E/B, a previously unknown genotype of *C. psittaci* with characteristics of B and E and, like the previous year, a case of *C. caviae* infection (a closely related *Chlamydia* species).
- In 2015, the Netherlands Food and Consumer Product Safety Authority (NVWA) was contacted by a municipal health service for source tracing 34 times. As a result of that, the NVWA took samples at 29 possible source locations. Twelve locations tested positive for *C. psittaci*.

5.2.2 Discussion

The annual number of psittacosis notifications is relative stable since 2012. The annual incidence of notified psittacosis is 0.2-0.3 per 100,000 (for 2012-2015). Although this incidence is low, the number of notifications should be seen as only a small portion of the real number of cases. A recent study performed in 2 Dutch hospitals in the years from 2007 to 2010, in which PCR for *C. psittaci* was performed in all CAP patients, showed that 4,8% of CAP patients were positive for *C. psittaci* (Spoorenberg, Bos et al. 2016). With a total number of hospital admissions for CAP of more than 48,000 per year it was estimated that more than 300 patients are hospitalised with CAP caused by psittacosis every year (unpublished data). Because incidence of psittacosis varies by time and place, further studies on this topic are needed. Laboratories and municipal health services make use of the *C. psittaci* genotyping service available in the Zuyderland MC (Sittard, the Netherlands) in the vast majority of eligible cases. Besides the common genotypes A and B, the genotyping also revealed some less common (geno)types, which provides more insight in *C. psittaci* and *Chlamydia species* and possibly also in sources of human infection. In the ongoing multidisciplinary project 'Plat4m-2Bt-psittacosis' financed by ZonMW, data from various organisations involved in psittacosis surveillance and source tracing, about patients, animal samples and genotyping, will be linked, so that more insight will be gained in incidence and prevalence of *C. psittaci* in animals and in sources of human infection.

5.2.3 Tables and figures

Figure 5.3 Number of notifications of human psittacosis by year and mode of confirmation of laboratory diagnosis, 2006 through 2015 (Source: Osiris).

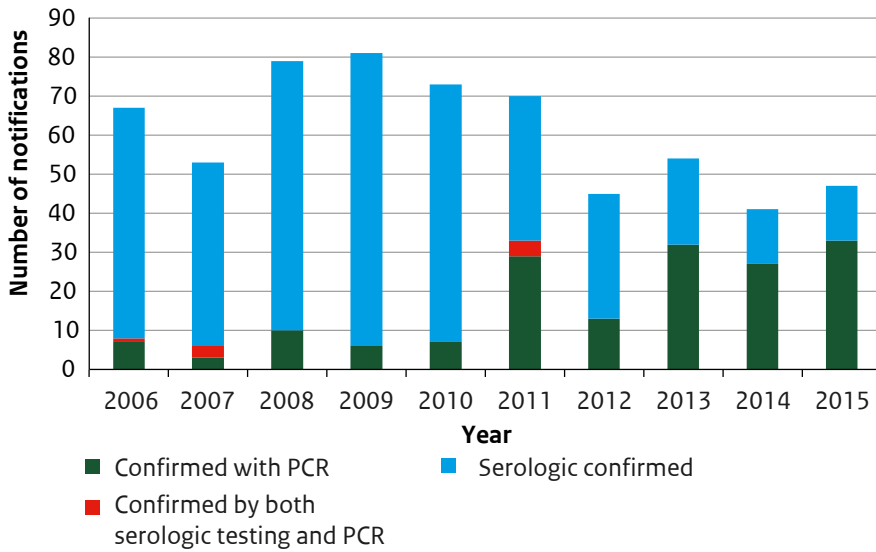


Table 5.2 Demographical, clinical and diagnostic characteristics of notified patients with psittacosis and positive diagnoses in the virological laboratory surveillance, in 2011 up to 2015 (Source: Osiris and virological laboratory surveillance).

| N (%), unless otherwise specified | 2011 | 2012 | 2013 | 2014 | 2015 |
|---|------------|------------|------------|------------|------------|
| Osiris (notifications): | | | | | |
| Number of notifications ^a | 70 (100) | 45 (100) | 54 (100) | 41 (100) | 47 (100) |
| Incidence (per 100,000 inhabitants) | 0.42 | 0.27 | 0.32 | 0.24 | 0.28 |
| Median age in years (Q1-Q3) | 59 (51-70) | 57 (45-65) | 59 (43-70) | 58 (47-71) | 57 (41-68) |
| Male gender ^b | 49 (70) | 28 (62) | 36 (67) | 32 (78) | 32 (68) |
| Hospitalised ^b | 52 (74) | 32 (71) | 41 (76) | 38 (93) | 37 (79) |
| Deaths ^b | 2 (3) | 0 | 0 | 1 (2) | 1 (2) |
| Infected abroad ^b | 0 | 1 (2) | 2 (4) | 1 (2) | 0 |
| Notification delay in days median (Q1-Q3) ^c | 1 (0-3) | 0 (0-2) | 0 (0-2) | 0 (0-1) | 0 (0-1) |
| Diagnostics used for notifications: | | | | | |
| Diagnostic delay in days median (Q1-Q3) ^d | 19 (11-41) | 28 (11-45) | 18 (9-29) | 12 (7-21) | 10 (8-14) |
| Mode of confirmation of laboratory diagnosis: | | | | | |
| Serological | 37 (53) | 32 (71) | 22 (41) | 14 (34) | 14 (30) |
| 'Demonstrating pathogen' (PCR) | 29 (41) | 13 (29) | 32 (59) | 27 (66) | 33 (70) |
| Serological and 'demonstrating pathogen' (PCR) | 4 (6) | 0 | 0 | 0 | 0 |
| Number of patients eligible for genotyping ^e | n.a. | 4 | 33 | 28 | 36 |
| Notified patients for whom diagnostic material for genotyping was received by Zuyderland MC | n.a. | 3 (75) | 31 (94) | 24 (86) | 30 (83) |
| Typing outcomes: | | | | | |
| <i>C. psittaci</i> genotype A: | | 3 (100) | 16 (52) | 9 (38) | 11 (37) |
| <i>C. psittaci</i> genotype B: | | 0 | 11 (36) | 11 (46) | 9 (30) |
| <i>C. psittaci</i> genotype C: | | 0 | 0 | 1 (4) | 2 (7) |
| <i>C. psittaci</i> genotype E/B: | | 0 | 0 | 1 (4) | 2 (7) |
| New <i>C. psittaci</i> genotype most similar to C (93% homology) | | 0 | 0 | 1 (4) | 0 |

| N (%), unless otherwise specified | 2011 | 2012 | 2013 | 2014 | 2015 |
|--|------|------|-------|-------|--------|
| Unknown genotype of <i>C. psittaci</i> , with characteristics of B and E | | 0 | 0 | 0 | 1 (3) |
| 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) |
| Virological laboratory surveillance: | | | | | |
| Number of positive diagnoses | 37 | 23 | 23 | 16 | 18 |

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

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

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

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

^e Genotyping of notified patients was started as a pilot project on 27 Augustus 2012. In this project, *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 (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) is used as denominator to calculate the percentage.

5.3 Q fever

Author: Frederika Dijkstra

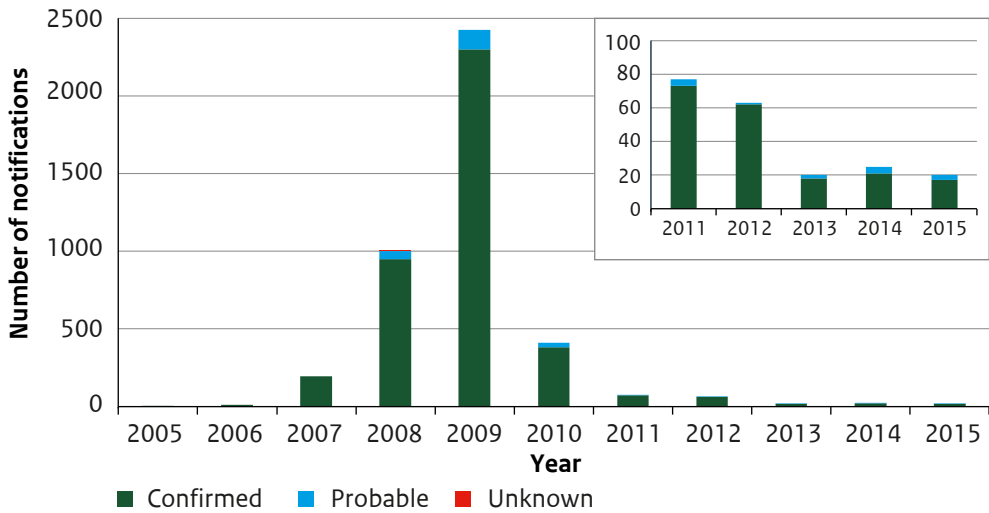
Contributor: Mauro De Rosa

5.3.1 Key points

- In 2015, 20 patients with acute Q fever were notified. This number is in line with to the number of notifications in 2013 and 2014 and with the years before the outbreak that took place between the years 2007 and 2010.
- The percentage of hospitalised patients decreased from 75% in 2013 to 60% in 2015.
- As in previous years, the number of diagnoses of Q fever reported in the laboratory surveillance was considerable higher than the number of notifications. The reason is unknown, but it is likely that many patients with positive serological test do not fulfill the clinical notification criteria.
- Possible animal sources of infection can be sampled within the framework of the mandatory bulk milk monitoring, investigation of veterinary abortion waves or source finding following human cases.
 - *Bulk milk monitoring:*
In 2015, no new farms were found positive in the bulk milk monitoring by the Netherlands Food and Consumer Product Safety Authority (NVWA).
 - *Veterinary abortion waves:*
In 2015, two sheep and/or goat farms were sampled by the NVWA. On these farms, 20 samples were taken, of which none were positive, but one result was not conclusive.
 - *Source finding following human cases:*
In 2015, five sheep and/or goat farms were sampled by the NVWA. On these farms, 68 samples were taken, of which four were positive and nine not conclusive.

5.3.2 Tables and figures

Figure 5.4 Number of notifications of acute Q fever by case classification^a and year, 2005 through 2015 (Source: Osiris). The insert zooms in on the years 2011 through 2015.



^a 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, 2011-2015 (Source: Osiris and virological laboratory surveillance).

| N (%), unless otherwise specified | 2011 | 2012 | 2013 | 2014 | 2015 |
|--|------------|------------|------------|------------|------------|
| Osiris (notifications): | | | | | |
| Number of notifications ^a | 77 (100) | 63 (100) | 20 (100) | 26 (100) | 20 (100) |
| Of which confirmed ^b | 73 (95) | 62 (98) | 18 (90) | 22 (85) | 17 (85) |
| Of which probable ^c | 4 (5) | 1 (2) | 2 (10) | 4 (15) | 3 (15) |
| Incidence (per 100,000 inhabitants) | 0.46 | 0.38 | 0.12 | 0.15 | 0.12 |
| Median age in years (Q1-Q3) | 50 (40-64) | 52 (43-64) | 52 (39-64) | 57 (39-70) | 58 (39-70) |
| Male gender ^d | 49 (64) | 48 (76) | 13 (65) | 21 (81) | 9 (45) |
| Hospitalised ^d | 42 (55) | 33 (52) | 15 (75) | 17 (65) | 12 (60) |
| Deaths | | | | | |
| Notified in Osiris ^d | 1 (1.3) | 0 | 0 | 0 | 1 (5) |
| Total number reported to RIVM ^e | 5 | 1 | 0 | 0 | 1 |
| Infected abroad ^d | 6 (8) | 5 (8) | 3 (15) | 5 (19) | 2 (10) |
| Notification delay in days median (Q1-Q3) ^f | 1 (0-6) | 1 (0-5) | 1 (0-2) | 0.5 (0-6) | 1 (0-3) |
| Diagnostic delay in days median (Q1-Q3) ^g | 23 (15-39) | 28 (15-47) | 33 (8-52) | 25 (14-48) | 27 (12-44) |
| Virological laboratory surveillance: | | | | | |
| Number of positive diagnoses | 136 | 83 | 89 | 130 | 125 |

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

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

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

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

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

^f. 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.

^g. 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

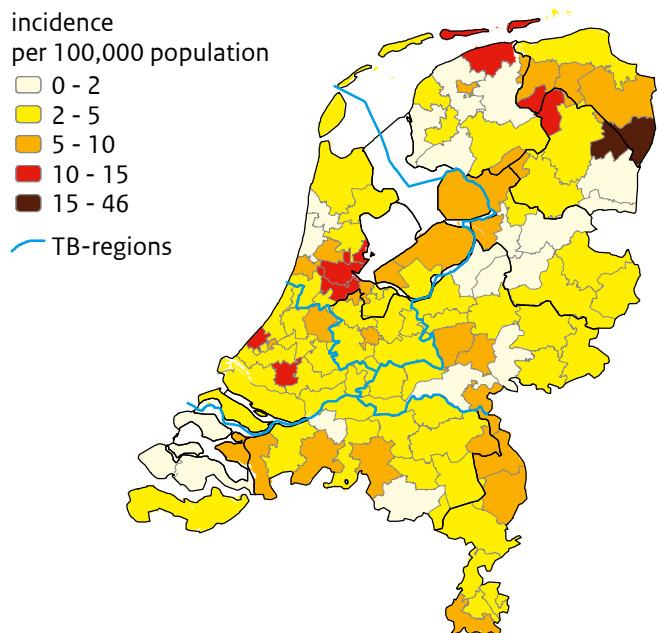
Contributors: Henrieke Schimmel, Connie Erkens, Rianne van Hunen

5.4.1 Key points

- In 2015 more patients with tuberculosis were reported in the Netherlands than last year: 867 in 2015, compared with 814 in 2014, while in previous years, from 1995 onwards, the number of TB patients had declined steadily.
- The incidence rate was 5.1 per 100,000 population, which was slightly higher than in 2014 (4.9 per 100,000). The increase of the number of TB patients is mainly due to an increase of asylum seekers in the Netherlands coming from high incidence countries.
- 501 TB patients (58%) had pulmonary TB in 2015.
- In 2015, the majority of TB patients was foreign born (72%).
- The largest group of foreign born TB patients came from Eritrea (n=94), followed by Somalia (n=90) and Morocco (n=63).
- The proportion of TB-patients belonging to risk groups was 45% in 2015 (43% in 2014, 37% in 2013). Especially the number of asylum seekers living in the Netherlands for less than 2.5 years diagnosed with TB was higher: 149 in 2015, 97 in 2014, and 44 in 2013.
- Twenty per cent of all TB patients in 2015 were detected by active case-finding (17% in 2014 and 15% in 2013).
- In 2015, 12 patients with rifampicin resistant tuberculosis (RR-TB, including 10 patients with Multi Drug Resistant-TB) were registered; all were foreign born.
- The proportion TB patients tested for HIV was 61% in 2015 (preliminary data). The proportion tested in 2014 was 60%. The HIV test was positive for 36 TB patients: 4.2% of all TB patients and 6.9% of TB patients tested for HIV.
- In 2014, 84% of all TB patients with rifampicin susceptible tuberculosis completed treatment successfully (91% in 2013).
- Of 22 patients with rifampicin resistant tuberculosis, diagnosed in 2013, 19 patients (86%) completed treatment successfully.

5.4.2 Tables and figures

Figure 5.5 Tuberculosis incidence (per 100,000 population) in 2015 by two digital postcode area.



Footnote: From January 2015, TB control in the Netherlands consists of four TB regions: Noord-Oost, Noord-West, Zuid-Holland and Zuid.

Figure 5.6 Number of TB patients and incidence per 100.000 population, 1995-2015.

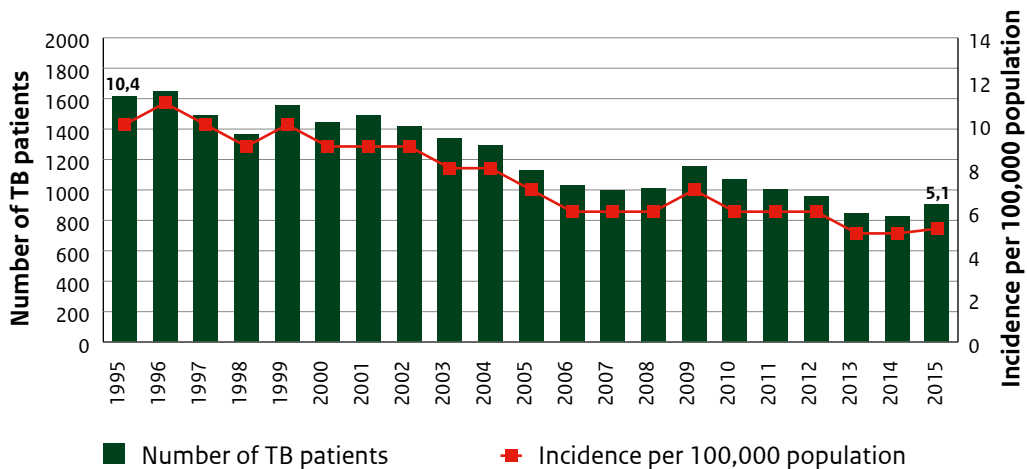


Table 5.4 Summary tuberculosis data the Netherlands, 2013, 2014 and 2015.

| | 2013 | 2014 | 2015 |
|---|----------|----------|----------|
| | N (%) | N (%) | N (%) |
| Number TB patients notified | 845 | 814 | 867 |
| Incidence per 100,000 population | 5.0 | 4.9 | 5.1 |
| Mean age (years) | 41 | 41 | 40 |
| Age <15 years | 33 (3.9) | 48 (5.9) | 42 (4.8) |
| Age >65 years | 132 (16) | 125 (15) | 127 (15) |
| Male to female ratio | 1.5 | 1.6 | 1.5 |
| Foreign born | 623 (74) | 601 (74) | 625 (72) |
| Residence in 1 of 4 largest cities | 270 (32) | 234 (29) | 236 (27) |
| Previous episode of TB (treatment) | 44 (5.2) | 21 (2.6) | 41 (4.7) |
| HIV status known | 481 (57) | 491 (60) | 525 (61) |
| HIV positive | 17 (2.0) | 22 (2.7) | 36 (4.2) |
| Active case finding | 128 (15) | 136 (17) | 170 (20) |
| Pulmonary tuberculosis (PTB & EPTB) | 458 (54) | 451 (55) | 501 (58) |
| Sputum positive PTB ^a | 197 (23) | 201 (25) | 217 (25) |
| Culture confirmed TB | 607 (72) | 526 (65) | 577 (67) |
| RR-TB (incl. MDR TB) ^{bc} | 18 (3.0) | 8 (1.5) | 12 (1.8) |
| Isoniazid resistance ^c | 32 (5.3) | 36 (6.8) | 23 (4.0) |
| TB patients in risk groups | 313 (37) | 350 (43) | 394 (45) |
| - TB contacts | 68 (8) | 68 (8) | 86 (10) |
| - Immigrant <2,5 yr. in the Netherlands | 76 (9) | 89 (11) | 91 (11) |
| - Asylum seeker <2,5 yr. in the Netherlands | 44 (5) | 97 (12) | 149 (17) |
| Latent tuberculosis Infection | 1,350 | 1,229 | 1,433 |

^a PTB= pulmonary TB, EPTB= combination of pulmonary and extrapulmonary TB

^b RR-TB (incl. MDR TB) = rifampicin resistant TB (incl. Multi Drug Resistant TB)

^c percentage of culture confirmed TB

More detailed information about surveillance of tuberculosis in the Netherlands and the latest surveillance report 'Tuberculose in Nederland, 2014' is available through the tuberculosis website of the RIVM (<http://www.rivm.nl/Onderwerpen/T/Tuberculose>), only available in Dutch). The next surveillance report 'Tuberculose in Nederland, 2015' will be published in December 2016.

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.

Chapter 6

Other respiratory infections reported in the weekly virological surveillance

Authors: Rianne van Gageldonk-Lafeber, Marit de Lange

Contributors: Adam Meijer, Pieter Overduin, Sharon van den Brink, Lisa Wijsman, Gé Donker, Janneke Duijster

6.1 Key points

- As in previous years rhinovirus and adenovirus were the most frequently reported positive test results in the virological laboratory surveillance
- The total number of positive coronavirus (N=575) and human metapneumovirus (hMPV; N=651) test results in 2015 was higher than the past five years (range 288-429 and 298-469, respectively). Especially in the first quarter of 2015 relatively high numbers of positive test results were reported.
- The total numbers of positive rhinovirus (N=2410) and parainfluenza virus (N=715) were higher than in the past five years (range 1780-2194 and 432-633, respectively), because of peaks in the number of positive test results around week 40-2015.
- The trend of rhinovirus and enterovirus positive specimens, taken by sentinel GPs, in 2015 was in line with previous four years, ranging from 0% through 57% for rhinovirus, and from 0% through 25% for enterovirus in 2015.
- In the past five years, the highest percentages of rhinovirus and enterovirus positive specimens in samples taken by sentinel GP's were found in the period outside the respiratory season.

6.2 Epidemiological situation, 2015

A relatively high number of positive coronavirus and hMPV diagnoses was seen in the first quarter of 2015. Peaks in the number of both positive rhinovirus and parainfluenza virus diagnoses were seen around week 40 in 2015. The numbers of positive diagnoses for *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, bocavirus and adenovirus were within the range of previous years.

6.3 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. It is likely that patient population and disease severity in primary care and hospitals are different. Therefore, the trends from the virological laboratory surveillance can differ from those in the sentinel practices of the NIVEL Primary Care Database.

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 by the physicians and/or microbiological laboratories. Virological laboratory surveillance remains a valuable source for monitoring long-term trends in the viral diagnostics as long as testing policies remain relatively stable over the years. The fact that the highest percentages of rhinovirus and enterovirus positive specimens in samples taken by sentinel GP's were found in the period outside the respiratory season is mainly because of the lower detections of influenza and RSV in this period, increasing the relative contribution of rhinovirus and enterovirus to ILI and ARI.

6.4 Tables and figures

Table 6.1 Number of reported positive test results of parainfluenza virus, rhinovirus, *Mycoplasma pneumoniae*, coronavirus, human metapneumovirus (hMPV) and *Chlamydia pneumoniae*, bocavirus and adenovirus in the virological laboratory surveillance for the period 2006-2015.

| Year | Number of positive test results | | | | | | | |
|------|---------------------------------|------------|------------------------------|-------------|------|-----------------------------|------------------------|------------|
| | Parainfluenza virus | Rhinovirus | <i>Mycoplasma pneumoniae</i> | Coronavirus | hMPV | <i>Chlamydia pneumoniae</i> | Bocavirus ^a | Adenovirus |
| 2006 | 298 | 665 | 588 | 82 | 87 | 40 | - | 1,072 |
| 2007 | 412 | 770 | 626 | 133 | 127 | 40 | - | 1,058 |
| 2008 | 272 | 899 | 458 | 200 | 205 | 30 | - | 1,028 |
| 2009 | 772 | 1,994 | 414 | 192 | 221 | 64 | - | 1,325 |
| 2010 | 528 | 1,906 | 541 | 429 | 419 | 35 | - | 1,513 |
| 2011 | 605 | 1,987 | 917 | 288 | 389 | 43 | 107 | 1,121 |
| 2012 | 438 | 1,780 | 775 | 307 | 298 | 60 | 136 | 1,060 |
| 2013 | 632 | 2,045 | 324 | 376 | 467 | 27 | 111 | 1,209 |
| 2014 | 431 | 2,190 | 435 | 318 | 385 | 20 | 107 | 1,141 |
| 2015 | 715 | 2,410 | 525 | 575 | 651 | 31 | 114 | 1,053 |

^a Bocavirus is registered since 2011.

Figure 6.1 Number of weekly reported positive test results of rhinovirus in the virological laboratory surveillance for the calendar years 2011-2015.

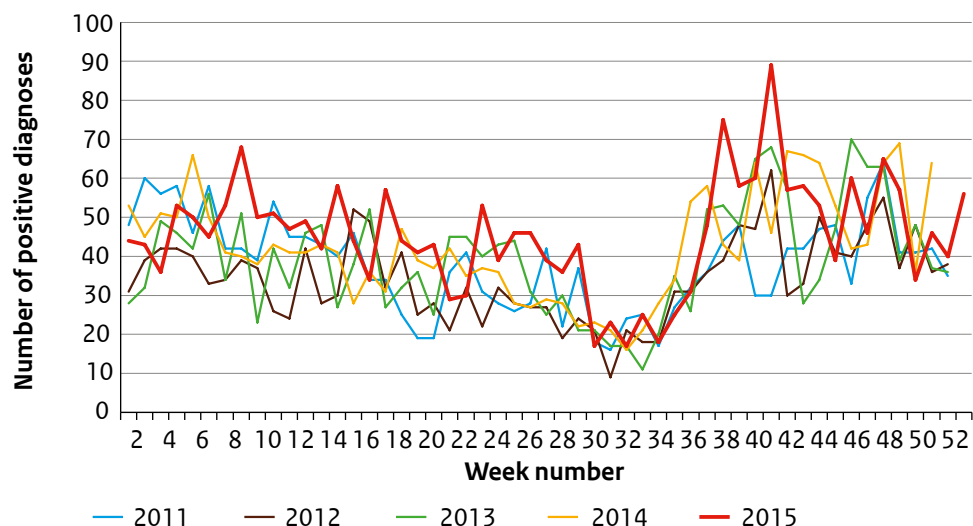
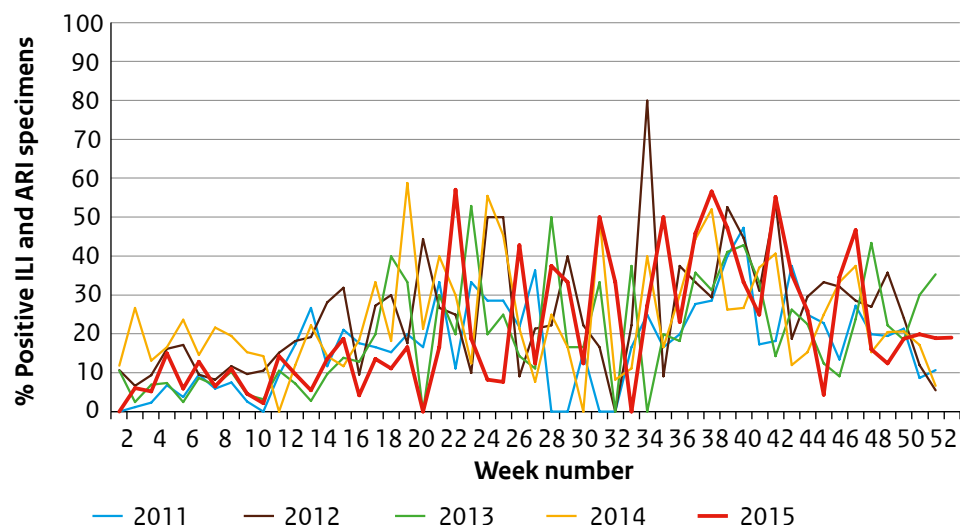


Figure 6.2 Percentage of rhinovirus positive ILI and ARI specimens, taken by sentinel GPs, displayed by week of sampling (Source: NIC location RIVM).



Footnote: ILI = influenza-like illness, ARI = other acute respiratory tract infection, GP = general practitioner

Figure 6.3 Number of weekly reported positive test results of *Mycoplasma pneumoniae* in the virological laboratory surveillance for the calendar years 2011-2015.

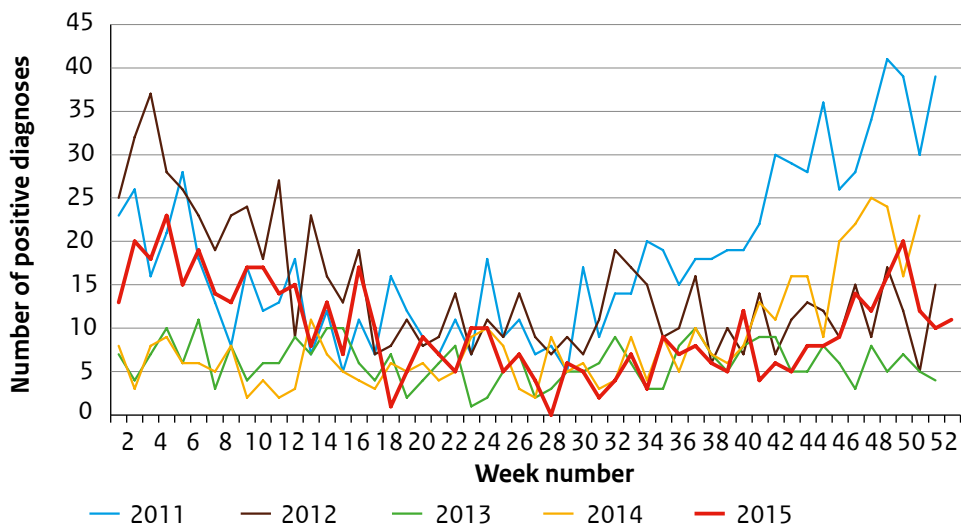


Figure 6.4 Number of weekly reported positive test results of human metapneumovirus (hMPV) in the virological laboratory surveillance for the calendar years 2011-2015.

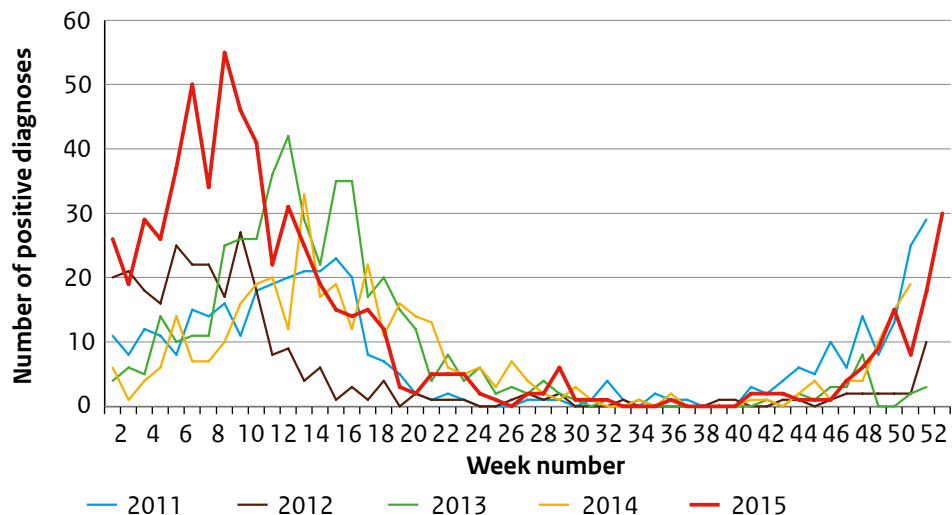


Figure 6.5 Number of weekly reported positive test results of coronavirus in the virological laboratory surveillance for the calendar years 2011-2015.

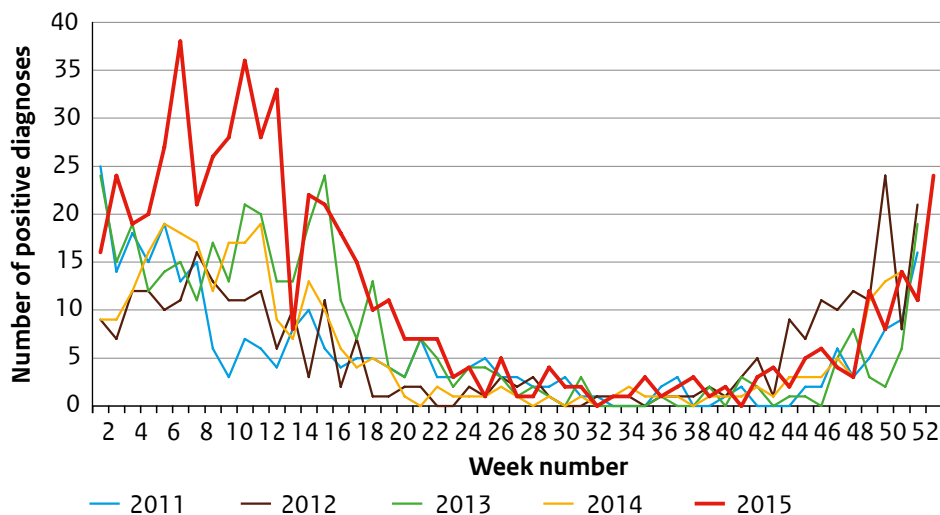


Figure 6.6 Number of weekly reported positive test results of parainfluenza virus in the virological laboratory surveillance for the calendar years 2011-2015.

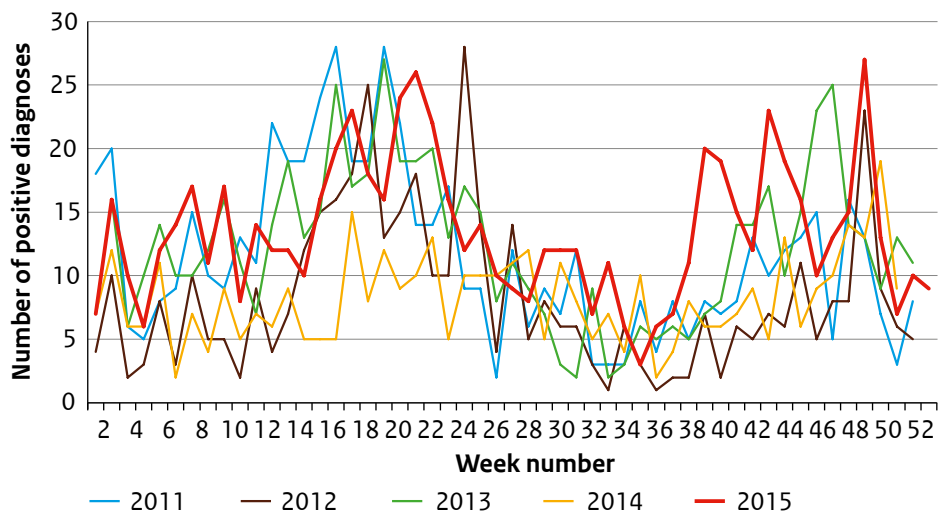


Figure 6.7 Number of weekly reported positive test results of *Chlamydia pneumoniae* in the virological laboratory surveillance for the calendar years 2011-2015.

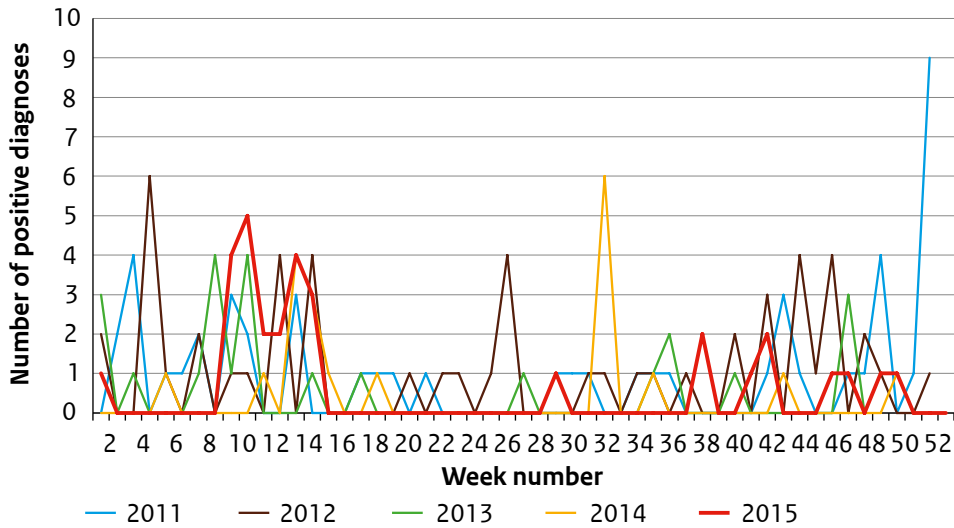


Figure 6.8 Number of weekly reported positive test results of adenovirus in the virological laboratory surveillance for the calendar years 2011-2015.

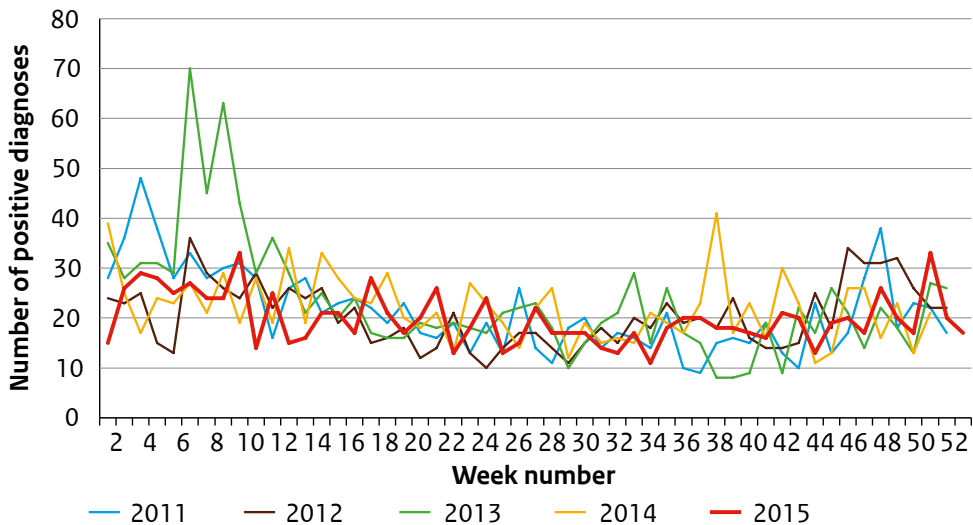


Figure 6.9 Number of weekly reported positive test results of bocavirus in the virological laboratory surveillance for the calendar years 2011-2015 (Source: NIC location RIVM).

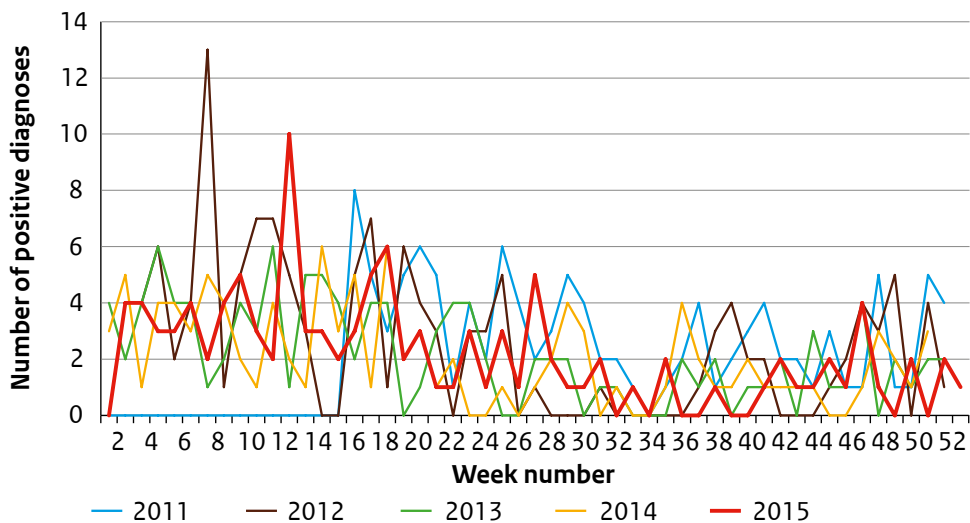
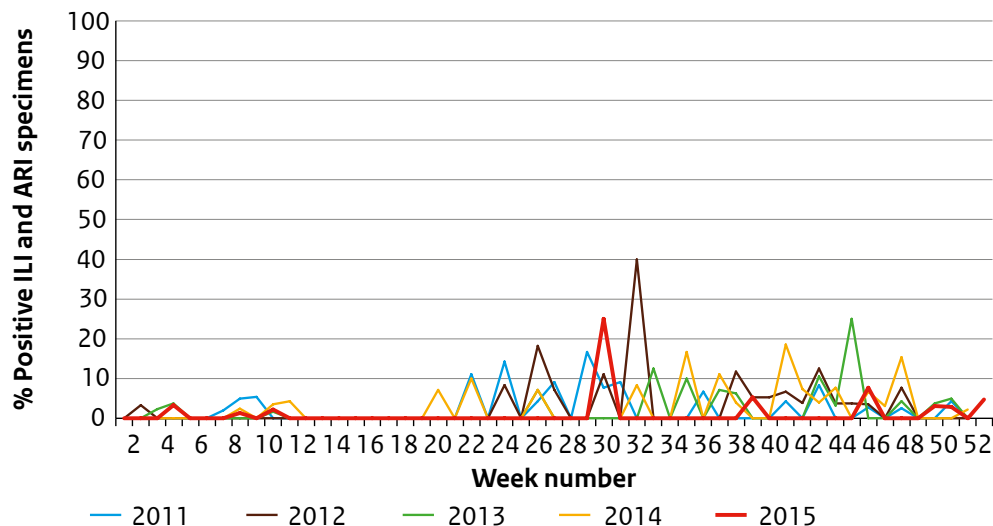


Figure 6.10 Percentage of enterovirus positive ILI and ARI specimens, taken by sentinel GPs, displayed by week of sampling (Source: NIC location RIVM).



Footnote: ILI = influenza-like illness, ARI = other acute respiratory tract infection, GP = general practitioner

Chapter 7

Emerging infections

Authors: Rianne van Gageldonk-Lafeber, Marit de Lange

Contributors: Adam Meijer

7.1 Key points

- In the Netherlands, no human infections with animal influenza virus were notified in the years 2015 and 2016 (through 22 May 2016)
- Worldwide, the animal influenza viruses type A(H5N1) and A(H7N9) caused most human infections and pose a possible threat for Dutch travellers
- In the Netherlands, no MERS-CoV infections were notified in the years 2015 and 2016 (through 22 May 2016).
- Worldwide, 27 countries have reported cases of MERS-CoV since September 2012. WHO has been notified of 1,733 laboratory-confirmed cases of infection with MERS-CoV, including 628 deaths.

7.2 Animal influenza viruses

7.2.1 Background

Influenza A viruses are found in many different animals, including ducks, chickens and pigs. These viruses have the capacity to cause infection in humans, sometimes with high morbidity and mortality. 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 Public Health Service within 24 hours. This allows the 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 National Influenza Centre (NIC) location RIVM with confirmation by NIC location ErasmusMC.

7.2.2 Epidemiological situation

Worldwide

Most human cases with animal influenza in 2015 and 2016, were caused by either A(H5N1) or A(H7N9). Additionally, sporadic human infections with swine influenza viruses, like A(H1N1)v, A(H1N2)v, and A(H3N2)v were reported to the WHO in 2015 and 2016. Next, sporadic human infections with avian influenza viruses, like A(H5N6) and A(H9N2), were reported in these years to the WHO.

Influenza A(H5N1)

High pathogenic avian influenza A(H5N1) virus is very contagious and potentially deadly to birds. Infections in birds with this avian flu virus occurred most in the South-East Asia region. Though relatively rare, sporadic human infections with this virus have occurred and caused serious illness and death, mostly in the South-East Asia region, Middle East region and in the African region. From 2003 onwards, 850 human cases and 449 deaths have been reported in humans, most of whom had contact with poultry or visited poultry markets. In Egypt, the number of laboratory-confirmed human cases of avian influenza A(H5N1) virus infection sharply increased from December 2014 through May 2015. Thereafter, only sporadic human A(H5N1) cases were reported [http://www.who.int/influenza/human_animal_interface/HAI_Risk_Assessment/en/]. No evidence of sustained person-to-person spread of A(H5N1) has been found.

Influenza A(H7N9)

The influenza virus A(H7N9) is low pathogenic for poultry but can also cause infections in humans. Human infections with avian influenza A(H7N9) virus were first reported in China in March 2013. Since then through 22 May 2016, 781 influenza A(H7N9) infections and 310 deaths were reported to the WHO by authorities in mainland China, Hong Kong, Taiwan, Malaysia, and Canada. Most human infections occurred in Eastern China [<http://www.who.int/csr/don/en/>]. No evidence of sustained person-to-person spread of A(H7N9) has been found.

Situation in the Netherlands

In the context of returning travellers from countries where possible exposure to animal influenza viruses occurred, no patients with respiratory illness were tested in 2015 and 2016 (through 22 May 2016) for avian influenza virus infection.

7.2.3 Discussion

In the Netherlands, no human infections with an animal influenza virus were notified in 2015 and 2016. However, travellers should be aware of the risk of animal influenza viruses, especially when having contact with poultry in countries where those viruses circulate. Since early 2015, the RIVM started a new study about 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. This study was initiated after the notification of five poultry outbreaks caused by influenza virus type A(H5N8) at the end of

2014. It is currently unknown whether this virus is able to infect humans. However, since the end of 2014, no new poultry outbreaks of H5N8 were reported in the Netherlands, and through 22 May 2016, no humans were included in this study yet.

7.3 MERS-CoV

7.3.1 Background

In 2012, a new type of coronavirus was discovered in the Kingdom of Saudi Arabia (KSA): the Middle East respiratory syndrome corona-virus (MERS-CoV). This virus can cause Acute Respiratory Distress Syndrome (ARDS). Most common symptoms are fever, cough and shortness of breath. There is no evidence of sustained human-to-human transmission. 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.

7.3.2 Epidemiological situation

Worldwide

Between September 2012 and 22 May 2016, 1,733 laboratory-confirmed cases of Middle East Respiratory Syndrome coronavirus (MERS-CoV) including at least 628 related deaths have been reported [WHO 16 May 2016: <http://www.who.int/csr/don/16-may-2016-mers-saudi-arabia/en/>]. Most MERS-CoV infections occur in Middle East countries, but travel-related cases have been reported in Europe, Asia and the United States. Since September 2012, 26 countries have reported cases of MERS-CoV.

Situation in the Netherlands

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]. 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 RIVM (CIb/IDS), with confirmation by ErasmusMC. In 2015 a total of 30 patients with severe acute respiratory illness, returning from countries where exposure to MERS-CoV is possible, were tested for MERS-CoV as well as 5 patients in 2016. None of them had an infection with MERS-CoV. Since 2016 MERS-CoV diagnostics are only performed at ErasmusMC.

7.4 Table

Table 7.1 Worldwide summary of the total number of human infections with Middle East Respiratory Syndrome coronavirus (MERS-CoV) and animal influenza viruses A(H5N1), and (H7N9) in 2013, 2014, 2015, and 2016 (through to week 20 of 2016).

| Infectious disease | Total number of human infections (deaths) ^{a,b} | | | | |
|--------------------------------|--|-----------|-----------|----------|--------------------|
| | 2013 | 2014 | 2015 | 2016 | Total ^e |
| MERS-CoV ^c | 172 (72) | 773 (275) | 682 (238) | 110 (40) | 1733 (625) |
| Influenza A(H5N1) ^d | 39 (25) | 52 (22) | 145 (42) | 0 (0) | 85 (449) |
| Influenza A(H7N9) ^d | 157 (46) | 337 (119) | 207 (116) | 80 (29) | 781 (310) |

^a Where the date of onset is unknown, the date of reporting has been used.

^b The number of deaths might be higher, as not all deaths might be reported retrospectively.

^c Reported through 22 May 2016 (source: <http://www.who.int/csr/don/en/>)

^d Reported through 22 May 2016 (source: <http://www.who.int/csr/don/en/> and http://www.who.int/influenza/human_animal_interface/HA1_Risk_Assessment/en/)

^e Total number is calculated by including the numbers before 2013.

Chapter 8

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

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Contributors: Alies van Lier, Scott McDonald, Lenny Hogerwerf, Erika Slump, Petra Brandsema, Frederika Dijkstra, Marit de Lange, Loes Soetens

8.1 Keypoints

- The respiratory infectious disease with the highest annual burden in 2012-2014 was influenza: 8653 DALY/year (95% CI 8466-8832), followed by legionellosis: 3874 DALY/year (95% CI 3463-4339), tuberculosis: 2262 DALY/year (95% CI 1848-2689), psittacosis: 187 DALY/year (95% CI 173-202) and Q fever: 91 DALY/year (95% CI 80-102).
- The burden of Q fever has decreased most (91 DALY/year in 2012-2014 versus 2143 DALY/year in 2007-2011) due to reduced incidence.
- When assessing the burden that an individual case suffers (DALY per 100 cases), burden is highest for legionellosis and lowest for influenza.
- The annual burden of respiratory disease on population level is highest in the adult age groups, mainly because of the accumulation of burden of influenza and legionellosis in this age group.

8.2 Background

Estimates of the burden of infectious diseases are needed 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 2012-2014, or the disease burden that theoretically could have been avoided by preventing infections in those years. We present an update of previous infectious disease burden estimates of influenza, tuberculosis, legionellosis and Q fever (Bijkerk, van Lier et al. 2014) and include a new estimate for psittacosis (Hogerwerf, De Gier et al., manuscript in preparation). This chapter is based on Chapter 5 in the State of Infectious Diseases in the Netherlands, 2015 (Bijkerk, de Gier et al. 2016), showing the information of these five respiratory infections.

8.3 Burden of respiratory infectious diseases, 2012-2014

Of the five respiratory infectious diseases of which the burden was estimated, influenza had the highest burden of 8653 DALY/year (95% CI 8466-8832). This is a sum of 6133 YLL/year (95% CI 5999-6258) and 2521 YLD/year (95% CI 2464-2574). This was not only the case comparing respiratory infectious diseases; influenza also had the highest burden of all infectious diseases of which a burden was estimated (Bijkerk, de Gier et al. 2016). Like influenza, for legionellosis (3504 YLL/year and 370 YLD/year), tuberculosis (2158 YLL/year and 104 YLD/year) and psittacosis (178 YLL/year and 9,8 YLD/year), the YLL was higher than the YLD, but not for Q fever (22 YLL/year and 68 YLD/year). The burden for Q fever of 2012-2014 was much lower than the burden of 2007-2011 (91 versus 2143). 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 burden that an individual case suffers (expressed as DALY per 100 cases), burden is highest for legionellosis and lowest for influenza.

8.4 Discussion

Since the initial estimates in the State of Infectious Diseases 2013 (Bijkerk, van Lier et al. 2014), the influenza model was further improved and a disease model for psittacosis was newly developed.

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

For influenza, tuberculosis and legionellosis, most estimates have not changed importantly since the previous calculations of 2007-2011. However, while the currently estimated DALY attributed to influenza is very similar to the estimate for 2007-2011, it is based on a higher incidence, most notably in older age categories. The increased incidence in older adults (age 65 and older) where influenza-associated mortality is estimated the highest, resulted in a higher YLL estimate. On the other hand, we reduced the duration of uncomplicated influenza episodes in the model from two weeks to five days (Turner, Wailoo et al. 2003), which resulted in lower YLD estimates. The much lower burden estimation of Q fever is due to reduced incidence (see Chapter 5 of this report).

While extending the disease burden estimations to psittacosis, the presented overview is still far from complete. 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.

8.5 Figures and tables

Figure 8.1 Average annual DALY, caused by respiratory infectious diseases in the Netherlands, split by YLL (years of life lost due to mortality) and YLD (years lived with disability), ranked by the average disease burden caused by the annual incident cases in 2012-2014. Red error bars indicate 95% confidence intervals (Source: Bijkerk, de Gier et al. 2016).

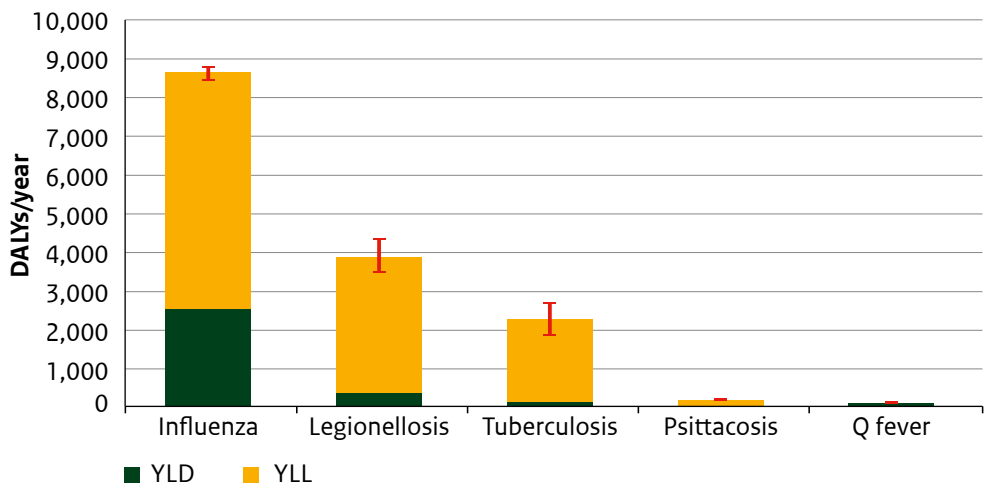
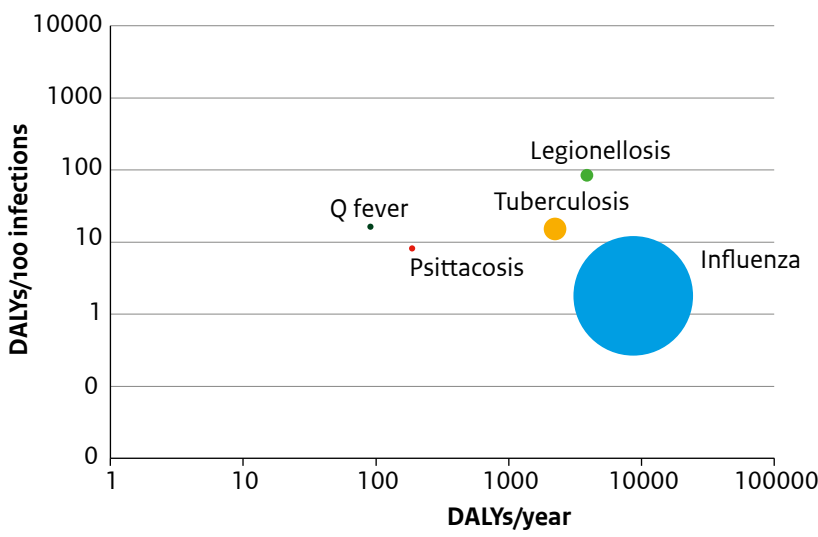
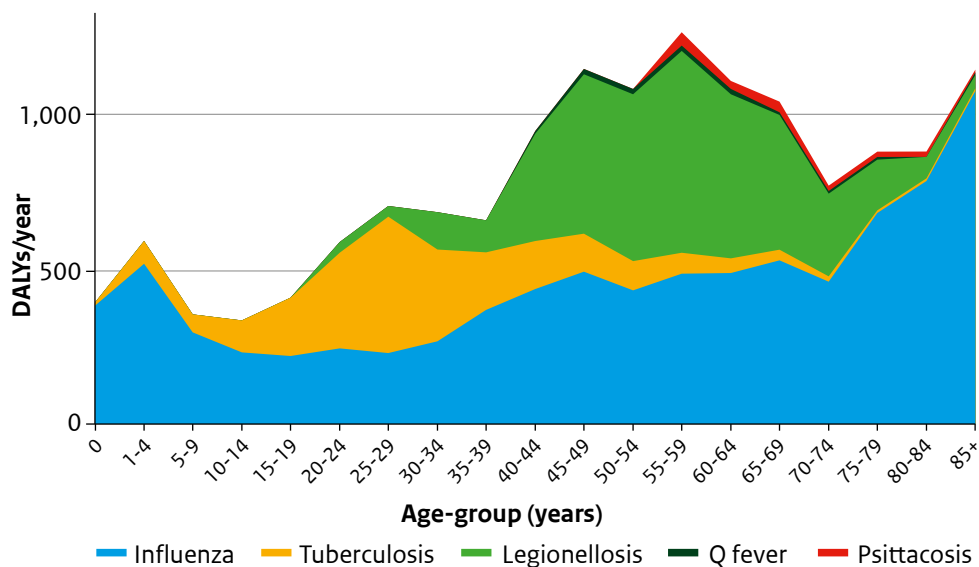


Figure 8.2 Ranking of respiratory diseases by estimated burden at population (DALYs/year) and individual level (DALYs/100 cases) in the period 2012-2014. The area of each bubble is proportional to the estimated incidence of the disease (Source: Bijkerk, de Gier et al. 2016).



Footnote: both axes are on a logarithmic scale.

Figure 8.3 Average annual DALY (population level) caused by respiratory infections per pathogen and age category, 2012-2014.



Note: The burden suffered from an infection is fully assigned to the age when the infection event occurred.

Table 1 Estimated average 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 period 2007-2011 and 2012-2014 in the Netherlands in order of highest to lowest DALY/year in 2012-2014.

| Disease | YLD/year | YLL/year | DALY/year | DALY/ 100 cases ^a | Annual acute infections ^b |
|----------------------|---------------------|---------------------|---------------------|------------------------------|--------------------------------------|
| Influenza | | | | | |
| 2007-2011 | 4090 (3993-4187) | 4580 (4474-4687) | 8670 (8468-8874) | 2.6 (2.6-2.6) | 331,995 |
| 2012-2014 | 2521 (2464-2574) | 6133 (5999-6258) | 8653 (8466-8832) | 2.0 (2.0-2.0) | 444,162 |
| Legionellosis | | | | | |
| 2007-2011 | 391 (351-435) | 3892 (3447-4389) | 4283 (3819-4805) | 97 (90-105) | 4,407 |
| 2012-2014 | 370 (334-407) | 3504 (3115-3944) | 3874 (3463-4339) | 93 (86-100) | 4,165 |

| Disease | YLD/ year | YLL/ year | DALY/ year | DALY/ 100 cases ^a | Annual acute infections ^b |
|---------------------|---------------------|---------------------|---------------------|------------------------------|--------------------------------------|
| Tuberculosis | | | | | |
| 2007-2011 | 126 (121-130) | 2615 (2117-3138) | 2741 (2241-3264) | 17 (14-20) | 16,295 |
| 2012-2014 | 104 (101-109) | 2158 (1742-2583) | 2262 (1848-2689) | 17 (14-20) | 13,575 |
| Psittacosis | | | | | |
| 2007-2011 | N/a | N/a | N/a | N/a | N/a |
| 2012-2014 | 9.8 (9.2-10.5) | 178 (164-192) | 187 (173-202) | 9.0 (8.5-9.5) | 833 |
| Q fever | | | | | |
| 2007-2011 | 1568 (1386-1755) | 574 (508-642) | 2143 (1897-2395) | 19 (17-21) | 11,271 |
| 2012-2014 | 68 (60-77) | 22 (20-25) | 91 (80-102) | 18 (16-20) | 499 |

^a 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.

^b This number includes asymptomatic (or latent) infections for Q fever and tuberculosis.

Chapter 9

General discussion and conclusion

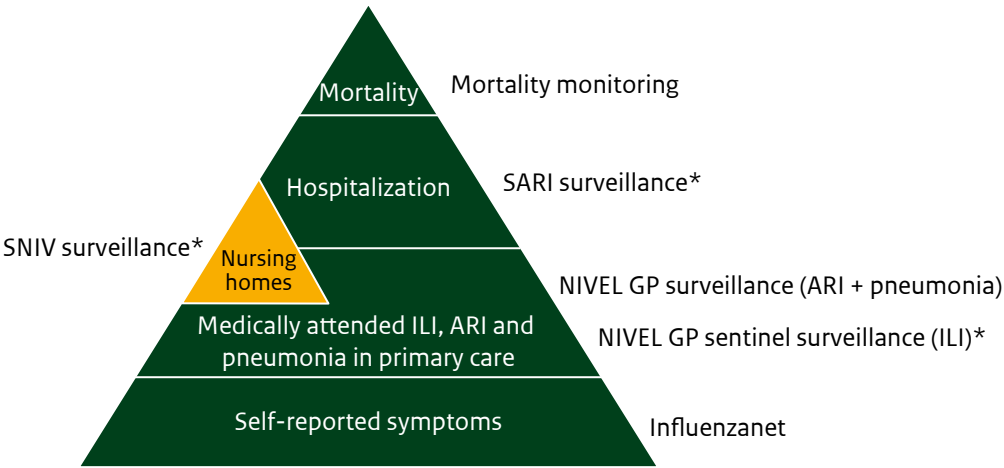
Authors: Anne Teirlinck, Wim van der Hoek

After the exceptionally long influenza epidemic in the 2014/2015 season that lasted 21 weeks, the duration of the epidemic of 2015/2016 was moderate with a total length of 11 weeks. The incidence of influenza-like illness (ILI) as reported by sentinel general practitioners (GPs) was above the epidemic threshold of 5.1 per 10,000 inhabitants from week 1 to week 11 of 2016. During this 11-week period, influenza virus was detected in nose swabs and throat swabs taken from ILI patients. The first weeks of the influenza epidemic were predominated by influenza virus type A(H1N1)pdm09 while later influenza type B (Victoria lineage) started to become more prevalent. The Victoria lineage was not included in the trivalent influenza vaccine for the 2015/2016 season. There were only a few detections of influenza type B (Yamagata lineage) which was included in the vaccine. For next year's trivalent vaccine, the WHO has recommended to replace the Yamagata lineage by the Victoria lineage.

For many years, the GP sentinel surveillance system has proven to be a robust and reliable system to monitor the trends of ILI and influenza virus circulation in primary care. In contrast, hospital-based surveillance of severe influenza infections has been lacking. For the first time, during the 2015/2016 season, limited insight into the occurrence of severe acute respiratory infections (SARI) was obtained through a pilot SARI surveillance system in two Dutch hospitals. From other hospitals, media reports and anecdotal information from physicians indicated unusual high numbers of admission of relatively young patients with severe influenza virus infections, some requiring intensive care. Severe cases of influenza, mostly related to influenza type A(H1N1)pdm09 were also reported in other countries in Europe (<https://flunewseurope.org>). In the Netherlands, this could not be substantiated with our routine surveillance data and therefore the further development of SARI surveillance, including intensive care unit surveillance, remains a priority topic for the coming years. Another approach that we piloted this season was SARI surveillance in paediatric intensive care units (PICU). This will be followed up and hopefully extended in the next season.

The surveillance pyramid of influenza and other respiratory infections is displayed in figure 9.1. An important part of this surveillance is the so-called syndromic surveillance. This surveillance is based on clinical signs without laboratory confirmation of the causative pathogen. At the bottom of the pyramid the self-reported symptoms by participants of the Influenzanet web-based surveillance system provide an estimate of ILI incidence in the general population, including people that do not seek medical care. Both the self-reported ILI incidence and the ILI incidence measured by the GP sentinel system, were moderate and within the range of the previous seasons. Also, the number of pneumonia cases that consulted the GP was within the range of the past five seasons. However, for syndromes specifically in the elderly, in the 2015/2016 season, both the number of ILI and pneumonia cases reported in nursing homes was lower than the four previous seasons. Likely, the predominance of influenza virus type A(H1N1)pdm09 partly explains these results; older people are generally better protected against this virus type that circulated extensively between 1918 and 1957 (Kilbourne 2006). However, reporting by nursing homes is still inconsistent and very few patients are swabbed for virological confirmation of influenza virus infection. Overall (all-cause) mortality was moderate compared with previous seasons. As usual, excess mortality was mostly observed in the 75+ age group. Short periods with slight increases in mortality in the 65-74 year olds are not uncommon but were higher in the 2015/2016 season than in previous seasons. While all-cause mortality monitoring has proven to be very useful for estimating the impact of influenza virus infection, cause-specific mortality figures for influenza and notifiable respiratory diseases are not available or not reliable. 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.

Figure 9.1. The respiratory infections surveillance pyramid in the Netherlands.



Footnote: Systems with * also include virological surveillance

In the 2015/2016 respiratory season, the dominating influenza strain was A(H1N1)pdm09, which had a good match with the vaccine strain. The vaccine effectiveness (VE) against all influenza virus subtypes (44%) was better than the previous seasons. However, all VE estimates have a very wide confidence interval, because the number of specimens from sentinel surveillance is too low to obtain robust estimates of VE specific for the Netherlands. Increasing the number of specimens from ILI patients in sentinel surveillance would be costly and not essential for the primary objective of monitoring the circulation of influenza viruses in the general population, and obtaining virus isolates for genetic and antigenic characterization. For the purpose of estimating VE as early in the season as possible, RIVM and NIVEL therefore participate in the European I-MOVE (influenza monitoring vaccine effectiveness) network so that results from individual countries can be pooled and robust estimates can be obtained (Valenciano, Ciancio et al. 2012, Kissling, Valenciano et al. 2014, Valenciano, Kissling et al. 2016), also allowing for more in depth research than what would be possible by individual countries (Kissling, Nunes et al. 2016). From this season onwards, special attention is given to estimations of VE in the elderly, in the additional I-MOVE+ study. In an interim analysis of the VE against medically-attended laboratory-confirmed influenza from week 41 of 2015 to week 3 of 2016 by I-MOVE, a VE of 46.3% (95% CI: 4.9-69.7%) for any influenza and 44.2% (95% CI: -3.1-69.8%) for influenza A(H1N1)pdm09 was reported, for all ages (Kissling and Valenciano 2016).

Unlike for influenza, there is no established European and global surveillance system for RSV. However, since 2003 RSV can be reported to EISN, and methods for surveillance are more or less standardized between member states (Meerhoff, Mosnier et al. 2009). RSV surveillance and estimating the burden of disease from RSV have recently been listed as priority topics by WHO and ECDC. This is because vaccines are expected to become available in the coming years and establishing an epidemiological and virological baseline will be essential for monitoring the impact of the new RSV vaccine. Currently, ECDC is developing a joint protocol for activities related to burden of RSV disease. In the Netherlands, the surveillance for RSV is partly based on the influenza surveillance, where nose swabs and throat swabs are not only collected from patients with ILI but also from patients with ARI. Specimens are collected by the GPs of the NIVEL Primary Care Database sentinel surveillance and are in addition to influenza virus, also tested for RSV, rhinovirus and enterovirus since 1996. This provides an indication of the circulation of RSV in the population and can be a good basis for future RSV surveillance.

Notifiable infectious diseases presenting as pneumonia are underreported because in most cases of community-acquired pneumonia that are managed in primary care, no specific diagnostic laboratory tests are performed. As in previous years, the number of diagnoses of Q fever reported in the virological laboratory surveillance was considerably higher than the number of notifications. In the virological laboratory surveillance no clinical and patient information is available. Therefore, it is unknown what the reason for this difference is. Probably, many cases with a positive laboratory diagnosis do not fulfil the notification criteria and are therefore not notified in Osiris as acute Q fever cases. Interestingly, for psittacosis the situation is opposite; more than 2.5 times more cases were notified in Osiris than laboratory notifications by the virological laboratory surveillance. Whether this is because only a subset of

laboratories report to the virological laboratory surveillance or because of a discrepancy between criteria for a positive laboratory diagnosis and for notification needs further investigation.

Patients with cardiac valvulopathy have a high risk to develop chronic Q fever presenting as endocarditis, after experiencing an acute infection. However, patients with valvulopathy were not routinely screened for Q fever during and after the Q fever epidemic from 2007 through 2009. The Jeroen Bosch Hospital in 's-Hertogensbosch and Bernhoven Hospital in Uden have set up a study, in collaboration with the RIVM and with financial support of Q-Support, to investigate how many chronic Q fever patients can be identified, by routinely screening patients with valvulopathy. This study should establish whether the policy of not routinely screening should be adapted. The study is ongoing and final results of this study are expected in 2017.

The Netherlands is one of the countries with the lowest tuberculosis incidence (less than 10 TB patients per 100.000 inhabitants) in Europe. The major objective of tuberculosis control in the Netherlands is elimination, defined as less than one TB patient per million inhabitants. According to the WHO's new global 'End TB' strategy and its 'Framework towards tuberculosis elimination in low-incidence countries', the incidence rate should be reduced by 90% in 2035 compared with 2015. In the Netherlands, the interim-objectives were therefore set to reduce tuberculosis transmission and case numbers in the Netherlands with 25 per cent in 2020 (de Vries and Riesmeijer 2016). Unfortunately, for the first time since six years, the number of reported tuberculosis cases slightly increased in 2015. The TB incidence in the Netherlands is strongly influenced by the influx of immigrants and asylum seekers. This increase in 2015 was mainly due to an increase of asylum seekers in the Netherlands in 2014 and 2015 coming from high incidence countries mainly in sub-Saharan Africa. In order to achieve a decrease in the number of TB cases, systematic testing and treatment of Latent Tuberculosis Infection (LTBI), among other interventions, will be gradually introduced in at-risk populations. Also the nature of tuberculosis surveillance might have to be slightly modified, focusing more on risk groups thereby enabling timely and focussed interventions (de Vries and Riesmeijer 2016).

For the third year in row, there was a substantial increase in the incidence of Legionnaires' disease, specifically of domestic cases. This may be associated with the warm and wet weather conditions in 2015 (Brandsema, Euser et al. 2014). The aging population and the climate change with more mild winters and more extensive rainfall in summer could facilitate higher incidence of Legionellosis in the years to come. During the periods of increased incidence, source finding investigations are not very successful, and it is not yet clear which environmental sources and transmission routes attribute to the weather associated increase of Legionnaires' disease. Further research is required examining the contribution of wet cooling towers, flooding, soil, and other possible environmental sources.

Swabs from sentinel GPs are analysed for influenza virus, RSV, rhinovirus and enterovirus. For other respiratory pathogens, the only information available is the weekly number of positive tests in a number of virological laboratories. The drop in RSV detections in the

virological laboratory surveillance, observed since the respiratory season 2011/2012 might be due to changes in diagnostic testing policies for RSV because of budgetary reasons. This shows the vulnerability of using data derived from systems that are not primarily built for surveillance purposes.

Despite this and the fact that clinical and patient information is lacking, these weekly reports are an important component of respiratory surveillance and have been used extensively in studies that require data on circulating respiratory pathogens (van Asten, van den Wijngaard et al. 2012). Some of the laboratories have started reporting the number of laboratory tests performed. This provides a denominator for the positive test results, thereby greatly increasing the value for surveillance. Hopefully, this additional information is substantial enough to be used for the 2016/2017 surveillance report.

An overall objective of RIVM is to make as much surveillance information as possible publicly available. 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 this is under development. Up to date information on the incidence of legionellosis, psittacosis and Q fever is also available at the RIVM website [<https://www.atlasinfectieziekten.nl/>].

Chapter 10

Methods of respiratory surveillance

10.1 Respiratory season or 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 year. A 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 2015/2016 is limited to the winter period only (week 40 of 2015 through week 20 of 2016), to allow a timely reporting. These respiratory infections may occur outside this winter period to a limited extend. Because the notifiable diseases legionellosis, tuberculosis, Q fever and psittacosis as well as the majority of pathogens monitored in the virological laboratory surveillance occur without typical winter seasonality, the results of these diseases refer to the 2015 calendar year (weeks 1-53).

10.2 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 L.L.J. 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 2015/2016 respiratory season, the coverage increased to about 1.3 million persons (7.8% 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. The population of these 37 sentinel practices covers approximately 0.7% of the Dutch population and is representative for age, sex, regional distribution and population density (Donker 2016).

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

The nursing homes participating in this network serve as sentinels for the national surveillance of infectious diseases in nursing homes. 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.

Influenzanet

Influenzanet (in Dutch: De Grote GriepMeting) is a system to monitor the incidence of ILI based on self-reported symptoms by volunteers via the internet. Since 2003, yearly press releases have encouraged people from the Dutch general population to fill in a web-based baseline questionnaire asking for demographical, medical and lifestyle data. Participants receive a weekly e-mail with a link to a short questionnaire asking about ILI symptoms experienced since their previous visit to the website. The incidence of ILI is determined on the basis of a uniform case definition. Influenzanet is operational in several other European countries, including Belgium, Portugal, Italy and the United Kingdom. In this report, we only use the data of the Dutch participants (on average 10,300 active participants every day in the 2015/2016 respiratory season).

Death notification data, Statistics Netherlands (CBS)

In the Netherlands, deaths are notified to municipalities and then reported to 'Statistics Netherlands' (In Dutch: Centraal Bureau voor de Statistiek: CBS), which collects and monitors all Dutch vital statistics. Weekly, RIVM receives data and analyses updated data that includes date of death, report-delay, age-group and region. The report-delay is the number of days between the date of death and the date that the death notification was received by CBS. Of all death notifications, 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 samples originating from primary care or hospital care, or between the used diagnostic methods, such as culture, molecular diagnostic, serology or rapid tests. Data are therefore reported in an aggregated format. Although no background information concerning patient status, clinical data and type of diagnostic method is available, the weekly laboratory surveillance can be used as an additional source to follow trends of respiratory infections over a prolonged period because of their relative robust reporting history.

Osiris

According to Dutch legislation, legionellosis, psittacosis, Q fever, tuberculosis, Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and human infections with an animal influenza virus are notifiable diseases. Medical doctors and medical-microbiological laboratories notify cases to the Public Health Services, who subsequently report these to the RIVM via the online registration program Osiris. Tuberculosis is reported to the Dutch Tuberculosis Registry (NTR), which is integrated in Osiris. Furthermore, latent tuberculosis infections (LTBI) are reported voluntarily by the Public Health Services and registered in Osiris-NTR. Osiris is a dynamic system and due to corrections and additions of the Public Health Services, small differences may exist between the data reported here and earlier or elsewhere reported data. Osiris notifications consist of anonymous patient data, date of disease onset, diagnostic information (dates, diagnostic methods, 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 were performed by the RIVM (CIb/IDS) and ErasmusMC simultaneously, but were relocated to ErasmusMC only for primary diagnostics in 2015. In case of an outbreak the RIVM (CIb/IDS) will do the testing. Both human infection with animal influenza and MERS-CoV are notifiable in the Netherlands.

Alerts concerning respiratory infectious disease outbreaks that occur outside the Netherlands but that can pose a potential hazard to the Netherlands, are monitored using website sources like those of the World Health Organization [WHO, Geneva: <http://www.who.int/csr/don/en/>], ECDC, Stockholm: http://ecdc.europa.eu/en/publications/surveillance_reports/Communicable-Disease-Threats-Report/Pages/default.aspx and international alerting systems (e.g. ProMed mail, EWRS, IHR).

10.3 Data analysis

Influenza-like-illness (ILI)

ILI incidence is calculated using three data sources: 1) NIVEL Primary Care Database – sentinel GP practices; 2) SNIV nursing homes; and 3) Influenzanet. These three 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

The case definition of ILI measured by Influenzanet is as follows:

- Fever (measured temperature at least 38 °C)
- Sudden onset of symptoms or fever

At least one of the systemic symptoms:

- Headache
- Myalgia

And at least one of the two respiratory symptoms:

- Cough
- Sore throat

The weekly ILI incidence of the general population, measured by Influenzanet, is defined as the number of participants who reported the onset of ILI in that week, divided by the number of participant-weeks. A participant who has been active during the full week is counted as one person-week. A participant who either registered during the week, or who completed his/her last symptoms' questionnaire during the week, is counted as a fraction. Data is downloaded from the website [<http://www.degrotegriepmeting.nl>].

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 $\geq 38^{\circ}\text{C}$;
- 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 (Marbus, Oost et al. 2016).

Jeroen Bosch Hospital

The SARI surveillance study started in week 42 in 2015 at the Jeroen Bosch Hospital. The attending physician or research nurse obtained an informed consent for inclusion in the study. The included SARI patient had to answer a short questionnaire about symptoms, influenza and pneumococcal vaccination status, comorbidities and several risk factors. In addition, routinely collected urine- and respiratory samples were used for influenza virus (sub) typing and a pneumococcal urinary antigen test. A research nurse assisted with the inclusion of SARI patients from week 8 onwards. No outpatients are included in the SARI surveillance at the Jeroen Bosch Hospital (Marbus, Oost et al. 2016).

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 a subset of their influenza virus isolates or clinical specimens that are positive for influenza virus to the NIC location Erasmus MC, for further subtyping, lineage determination and antigenic characterization.

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, then 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. This phylogenetic analysis gives information about the evolution of influenza viruses and changes that might lead to the emergence of potential antigenic variants. In addition, this type of information complements the antigenic analysis, especially when antigenic characterization is cumbersome, as was the case with the sporadic A(H3N2) viruses detected during the 2015/2016 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 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. Molecular markers for resistance to adamantanes (M2 ion channel blockers: amantadine and rimantadine) are assessed in a subset of influenza virus type A positive clinical specimens with a high viral load 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 the influenza virus clinical specimens with a high viral load, the neuraminidase gene is sequenced in order to screen for new molecular markers for reduced sensitivity for neuraminidase inhibitors. 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 2015/2016 season is calculated using data from patients of the NIVEL sentinel surveillance. For this goal, the test-negative (case control) design is used (Jackson and Nelson, 2013). Cases are defined as influenza virus positive patients with ILI or another acute respiratory infection, controls as influenza virus negative patients.

Only specimens taken within 6 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 vaccine effectiveness is calculated as $(1 - \text{OR}) \times 100\%$. The vaccine effectiveness is calculated per influenza virus type, and per subtype or lineage.

The analysis is restricted to the period that influenza virus was circulating in the Netherlands (2 November 2015 - 15 May 2016). Patients are excluded if it is unknown whether or not 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 (7 categories of 4 week each), age group (0-4, 5-14, 15-44, 45-64, 65 year and older), gender, smoking, obesity, pregnancy, pneumococcal vaccination, influenza vaccination received in previous season, influenza vaccination received 2 seasons ago, chronic medical condition 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 (any subtype) was analysed with univariate logistic regression. Variables with $p < 0.20$ were considered in the multivariable analysis. Variables that changed the OR by at least 5% are included in the final multivariable logistic regression model for any influenza subtype (forward selection). The final model build for any influenza subtype is also applied for the subtype or lineage specific analyses.

VE is also calculated against ILI, without laboratory tests, for the 2015/2016 season using data from participants of Influenzanet. For this purpose, the cohort method is used. When participants met the Influenzanet case definition, they were considered as cases; participants who did not meet the case definition were considered as controls. Not everyone who met the case definition will have experienced an influenza virus infection. Therefore, a seasonal baseline [baseline = $275 + 75 \cos ((\text{week number} - 2) / 52) \times 360$] incidence for non-epidemic ILI is determined. Only the cases above the baseline are included in the analysis, in the weeks that the ILI is above the Influenzanet threshold. The relative risk (RR) is calculated by the formula $[A / (A+B)] / [C / (C+D)]$. In this formula A is the number of participants that are vaccinated against influenza and did develop ILI symptoms; B is the number of participants that are vaccinated against influenza and did not develop ILI symptoms; C is the number of

participants that did not receive the influenza vaccination and did develop ILI symptoms; and D is the number of participants that did not receive influenza vaccination and did not develop ILI symptoms. The 95% confidence intervals are calculated with the LaMorte Biostatistics tool (Source: medlib.bu.edu/busm/LaMorte.xls). The VE is calculated as $(1-RR) \times 100\%$. The analysis was performed for all Dutch participants. In addition, the analysis is stratified for participants of 60 years and older and for participants with a chronic illness.

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 2015 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

Disease burden was calculated using BCoDE version 0.94 as described in the State of Infectious Diseases in the Netherlands 2013 (Bijkerk, van Lier et al. 2014), Model parameters and multiplication factors were set as described before (Bijkerk, van Lier et al. 2014), except for the duration of an uncomplicated acute influenza episode which was changed from two weeks to five days (Turner, Wailoo et al. 2003). Averages of population age distributions for 2012-2014 were calculated. Life expectancy table West level 26 was applied (Bijkerk, van Lier et al. 2014).

Incidence of influenza was calculated per age category as the incidence of ILI per 10.000 inhabitants multiplied by the proportion of influenza-positive specimens (Chapter 3) among ILI patients (Chapter 2) from sentinel surveillance and extrapolated to the whole Dutch population. Incidences of tuberculosis, legionellosis, Q fever and psittacosis were calculated by applying a multiplication factor for underestimation to the disease notifications.

For psittacosis a new model was built. Three types of symptomatic infection were defined: nonspecific febrile illness, pneumonia and invasive illness. Proportions of these clinical presentations were estimated using random effects meta-analysis for proportions, based on three published studies (Yung and Grayson 1988, Heddema, van Hannen et al. 2006, Laroucau, Aaziz et al. 2015). Aside from mortality, no long-term sequelae were included. Case fatality was set at 1% for patients above the age of 55 only for symptomatic infection, based on a study on mortality related to acute Q fever (Kampschreur, Wegdam-Blans et al. 2010). We assumed 30% of all infections to be asymptomatic (Heddema, van Hannen et al. 2006). The multiplication factor used on the notified cases of psittacosis was 35.58 (with a Pert distribution between 24.51 and 46.64), based on a meta-analysis estimating the proportion of community-acquired pneumonia hospitalizations (CAP) caused by *C. psittaci*, applied to national incidence of CAP in hospitals. These calculations and underlying assumptions are further described elsewhere (Hogerwerf, De Gier et al, manuscript in preparation).

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Abbreviations

| | |
|----------|---|
| ARDS | Acute Respiratory Distress Syndrome |
| ARI | acute respiratory infections |
| 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) |
| ECDC | European Centre for Disease Prevention and Control |
| EISN | European Influenza Surveillance Network |
| ELDSNet | European Legionnaires Disease Surveillance Network |
| EPTB | combination of pulmonary and extrapulmonary TB |
| ETB | extrapulmonary tuberculosis |
| EV-D68 | Human enterovirus D68 |
| GGD | Public Health Services (NL: Gemeentelijke Gezondheidsdienst) |
| GP | general practitioner |
| HIV | Human Immunodeficiency Virus |
| MPV | human metapneumovirus |
| ILI | influenza-like illness |
| LD | Legionnaires' Disease |
| LTBI | latent tuberculosis infection |
| MDR-TB | Multi Drug Resistant tuberculosis |
| MERS-CoV | Middle East Respiratory Syndrome Coronavirus |
| NFCPSA | the Netherlands Food and Consumer Product Safety Authority (NL: Nederlandse Voedsel- en Waren Autoriteit: NVWA) |
| 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 |
| PCR | Polymerase Chain Reaction |
| PTB | pulmonary tuberculosis |
| 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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