National Institute for Public Health
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Annual report Surveillance of COVID-19, influenza and other respiratory infections in the Netherlands: *winter 2020/2021*

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Colophon

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Synopsis

Surveillance of COVID-19, influenza and other respiratory infections: *Winter 2020/2021*

Each year, RIVM presents an overview of how many persons in the Netherlands got influenza and other respiratory infections. This year, the overview is dominated by the outbreak of the coronavirus SARS-CoV-2. The coronavirus dominated events in 2020 and 2021. As a result, in combination with the measures taken to prevent the spread of the virus, the number of persons who got other respiratory infections greatly decreased.

COVID-19
During the summer of 2020, from May through September, very few people tested positive for SARS-CoV-2. After the summer, the second period of infections began, which was characterised by two peaks: in October and at the end of December. This period started among the younger age groups (10 to 29 years old). Subsequently, increasing numbers of persons between the ages of 40 and 50 tested positive for SARS-CoV-2, followed by persons 70 years or older. The third period began in February 2021. At that time, the number of infections increased primarily due to the rise of the alpha variant, also known as the British variant. Between the beginning of February and the end of May 2021, this variant was the most frequently reported variant of the coronavirus.
Between 18 May 2020 and 23 May 2021, 1,584,237 persons tested positive for SARS-CoV-2, of whom 53,175 were admitted to the hospital and 9,649 were admitted to intensive care. 11,640 persons are known to have died as a result of COVID-19. During the second and third period, 14,739 more persons died in comparison to the average number of deaths during the same period over the last five years. This "excess mortality" is most probably related to the outbreak of the coronavirus.

Flu epidemic
During the flu season, hardly any persons were registered with influenza virus (2). There was therefore no flu epidemic this winter. This was probably due to the corona measures, which also help to prevent the spread of other viruses such as the influenza virus.

Notifiable respiratory infections
Some respiratory infections have to be reported to the Municipal Public Health Services. The Municipal Public Health Services can then intensively monitor infections and, if necessary, quickly take action to prevent their further spread. The number of reported cases of psittacosis (parrot fever) increased slightly in 2020 to 94, the highest number reported since 2010. In contrast, the numbers of reported cases of legionella (461), tuberculosis (623), and Q fever (7) have decreased in 2020. The decrease in number of legionella cases was probably due to reduced international travel in 2020. Q fever, psittacosis and legionella generally manifest themselves in the form of pneumonia. Persons with pneumonia are often not tested, so the causative pathogen remains unknown. The actual numbers are therefore higher than the reported numbers.

Key words: respiratory infections, flu, influenza, RS virus, pneumonia, SARS-CoV-2, COVID-19, coronavirus, legionella, parrot fever, psittacosis, Q fever, tuberculosis

Publiekssamenvatting

Surveillance van COVID-19, griep en andere luchtweginfecties: *winter 2020/2021*

Het RIVM brengt elk jaar in kaart hoeveel mensen in Nederland griep en andere luchtweginfecties hebben. Dit keer staat het overzicht in het teken van de uitbraak van het coronavirus SARS-CoV-2. Dit virus overheerste in 2020 en 2021. In combinatie met de maatregelen om de verspreiding van het virus tegen te gaan, hadden hierdoor veel minder mensen andere luchtweginfecties.

COVID-19

Tijdens de zomer van 2020, van mei tot en met september, hadden heel weinig mensen COVID-19, de ziekte die het coronavirus veroorzaakt. Na de zomer begon de tweede golf, die twee pieken had: in oktober en eind december. Deze golf begon onder de jongere leeftijdsgroepen (10 tot 29 jaar). Daarna kregen steeds meer mensen tussen 40 en 50 jaar COVID-19, gevolgd door mensen van 70 jaar of ouder. De derde golf begon in februari 2021. Het aantal besmettingen nam toen vooral toe door de opkomst van de Alfavariant (de Britse variant). Deze variant was tussen begin februari en eind mei 2021 de meest gemelde variant van het coronavirus.
Tussen 18 mei 2020 en 23 mei 2021 zijn 1.584.237 mensen positief getest op corona. Van hen zijn 53.175 mensen opgenomen in het ziekenhuis, en 9.649 op de intensive care. Van 11.640 mensen is bekend dat ze zijn overleden. Tijdens de tweede en derde golf stierven er 14.739 mensen meer dan de afgelopen 5 jaren in dezelfde periode. Deze 'oversterfte' hangt naar verwachting samen met de uitbraak van dit virus.

Griepepidemie

Tijdens het griepseizoen zijn er nauwelijks mensen geregistreerd met de griep (2). Er was daarom deze winter geen griepepidemie. Dit komt waarschijnlijk door de coronamaatregelen, die ook helpen om de verspreiding van andere virussen te voorkomen, zoals de griep.

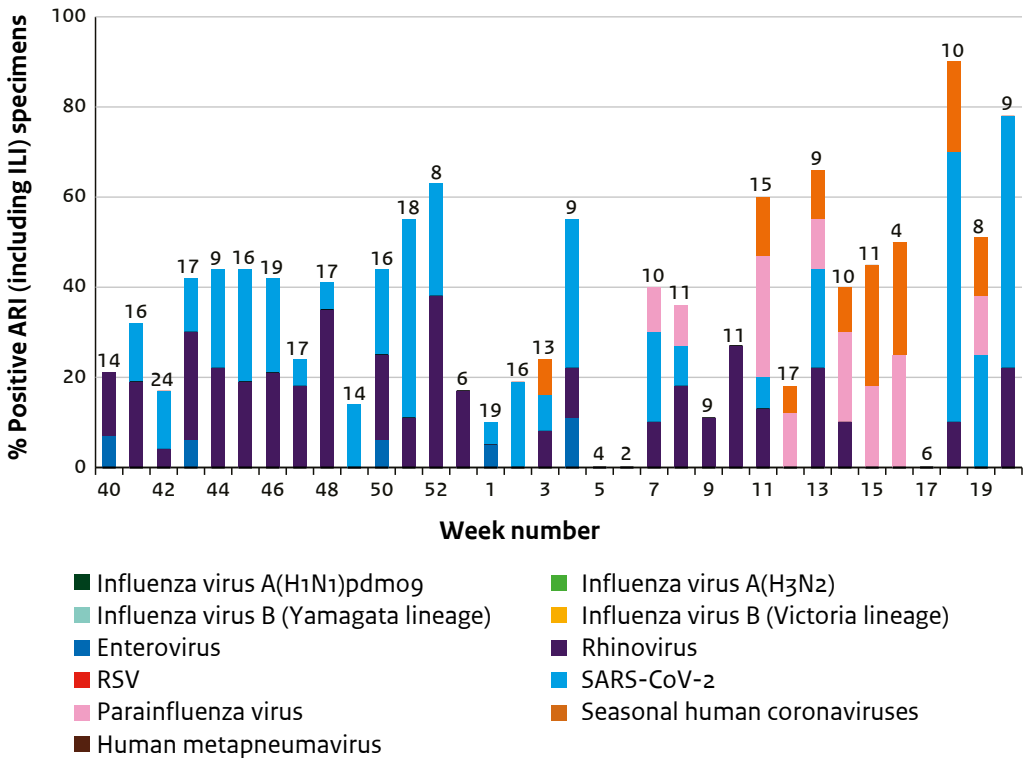
Meldingsplichtige luchtweginfecties

Sommige luchtweginfecties moeten bij de GGD worden gemeld. De GGD kan besmettingen dan intensief volgen en zo nodig snel actie nemen om te voorkomen dat ze zich verder verspreiden.
Het aantal meldingen van psittacose (papegaaienziekte) is in 2020 licht gestegen naar 94, het hoogste aantal sinds 2010. Het aantal meldingen in 2020 van legionella (461), tuberculose (623) en Q-koorts (7) nam juist sterk af. *Legionella* kwam waarschijnlijk minder vaak voor, omdat er minder internationale reizen zijn gemaakt in 2020. Q-koorts, psittacose en legionella uiten zich meestal in de vorm van longontstekingen, maar de oorzaak daarvan wordt vaak niet onderzocht. De werkelijke aantallen liggen daardoor hoger dan de gemelde aantallen.

Kernwoorden: luchtweginfecties, griep, influenza, RS-virus, longontsteking, pneumonie, SARS-CoV-2, COVID-19, coronavirus, legionella, papegaaienziekte, psittacose, Q-koorts, tuberculose

Influenza like-illness surveillance at a glance

Figure 1 Percentage of specimens from patients with influenza-like illness and other acute respiratory infections positive for influenza virus, RSV, rhinovirus, enterovirus, SARS-CoV-2 during the 2020/2021 respiratory season (week 40 of 2020 through week 20 of 2021) and since week 1 of 2021 for parainfluenza viruses, human metapneumovirus or human seasonal corona viruses taken by sentinel GPs (source: RIVM; Nivel Primary Care Database).



Footnote: ILI = influenza-like illness; GP = general practitioner; RSV = respiratory syncytial virus; SARS-CoV-2 = severe acute respiratory coronavirus 2.
The numbers above the bars are the total number of tested specimens. Since the beginning of January 2021, laboratory testing was extended with parainfluenza viruses types 1-3, human metapneumovirus and human seasonal coronaviruses.

Contents

Chapter 1
Introduction

1.1 Aim and focus of this report

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

In Chapter 2, results of the surveillance of a new notifiable respiratory infectious disease, COVID-19, are reported for a period of one full year; from week 21 2020 up to and including week 20 2021, the end of the 2020/2021 respiratory season. Since the respiratory syndromes as well as influenza virus and RS-virus infections show winter seasonality, data in the Chapters 3-5 are reported for the 2020/2021 respiratory season. Chapter 3 describes the different syndromic surveillance systems used and its findings for the 2020/2021 respiratory season: influenza-like illness (ILI), acute respiratory infections (ARI), pneumonia and mortality. The term 'influenza-like illness' is based on the notion that this clinical syndrome may be caused by influenza virus, but also by a range of other pathogens. The causative pathogen remains unknown in the majority of patients with respiratory infections, because most infections are not laboratory-confirmed but based on clinical diagnosis only. This surveillance is important because of the high burden of disease in terms of patient numbers, mortality and the impact on the health care system. The surveillance of ILI, ARI and pneumonia is currently mainly based on the registration of consultations by general practitioners (GPs) participating in Nivel Primary Care Database (in Dutch: Nivel Zorgregistraties eerste lijn). Elderly care physicians provide data within the context of the national sentinel surveillance network for infectious diseases in nursing homes (SNIV). Laboratory-confirmed influenza in the Nivel Primary Care Database is assessed by the National Influenza Centre (NIC), location RIVM (at the Centre for Infectious

Disease Research, Diagnostics and Laboratory Surveillance(IDS) of CIb). Laboratory-confirmed influenza cases reported by hospital and peripheral laboratories are monitored at NIC, location Erasmus Medical Centre. As real-time, cause-specific data on deaths are not available, mortality surveillance is based on all-cause mortality, using weekly data from Statistics Netherlands (CBS). Chapters 4 and 5 show the surveillance data for influenza virus infection and respiratory syncytial virus (RSV) infection.

Chapter 6 provides results of the surveillance of the notifiable respiratory infectious diseases legionellosis, psittacosis, Q fever, tuberculosis, animal influenza virus infections and MERS-CoV infections for the 2020 calendar year. Q fever and psittacosis will be described in greater detail in the report 'State of Zoonotic Diseases 2020' (report in preparation). More details on tuberculosis will be described in the next surveillance report on tuberculosis, 'Tuberculose in Nederland, 2020' that will be published in December 2021. Other notifiable respiratory diseases that are targeted by the National Immunization Programme, such as pertussis and invasive pneumococcal disease, are described in the annual RIVM publication 'The National Immunization Programme in the Netherlands' and are not reported here.

Chapter 7 describes diagnoses of respiratory infections reported in the virological laboratory surveillance for the 2020 calendar year. Chapter 8 provides an update on the burden of disease from six respiratory diseases: COVID-19, influenza, legionellosis, tuberculosis, Q fever and psittacosis. 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 CIb collaborates with many partners: Nivel (Netherlands institute for health services research), including the network of sentinel general practices; the surveillance network in nursing homes (SNIV); the National Influenza Centre (NIC), location Erasmus MC; the Regional Public Health Laboratory Kennemerland, Haarlem (national reference laboratory for legionellosis); and Statistics Netherlands (CBS). The National Intensive Care Evaluation (in Dutch: stichting NICE) provides data on COVID-19 intensive care admissions. The collaboration with the Public Health Services (PHS, in Dutch: GGD) is the basis for the surveillance of notifiable infectious diseases. For zoonoses (psittacosis and Q fever), collaboration with the Netherlands Food and Consumer Product Safety Authority (NVWA) is in place and for psittacosis with the Zuyderland Medical Centre in Sittard. The laboratories that report the data for the virological laboratory surveillance are all members of the Working Group for Clinical Virology of the Dutch Society for Medical Microbiology (NVMM).

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. COVID-19 is

reported weekly to the ECDC. Moreover, the RIVM (CIb/IDS and CIb/EPI) participates together with Nivel and Erasmus MC in the European Influenza Surveillance Network (EISN) of ECDC. The Dutch data are reported weekly in the joint ECDC/WHO regional office for Europe FluNews Europe Bulletin, and in FluNet and FLuID of the WHO (World Health Organization) headquarters in Geneva. All-cause mortality is reported weekly to EuroMoMo, a European consortium that weekly publishes the mortality data of 19 European countries. For the purpose of estimating influenza vaccine effectiveness at a European level, RIVM and Nivel participate in the European I-MOVE (influenza monitoring vaccine effectiveness) network.

Chapter 2
COVID-19

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Contributors: Agnetha Hofhuis, Anne Teirlinck, Eveline Geubbels, Daphne Reukers, Rianne van Gageldonk-Lafeber

2.1 Key points

- From week 21 2020 up to week 20 in 2021 a total of 1,584,237 cases positive for SARS-CoV-2 were notified in the Netherlands, resulting in a cumulative incidence of 9,100 per 100,000 inhabitants (based on the population of 2020). A total of 53,175 patients positive for SARS-CoV-2 were hospitalised of whom 9,649 were admitted to the Intensive Care Unit (ICU). Mortality was reported for 11,640 of the notified patients.
- During the course of the COVID-19 pandemic, the testing policies and types of non-pharmaceutical interventions have changed considerably. In January 2021, vaccination against SARS-CoV-2 has started.
- In February 2021, VOC Alpha became the dominant and most prevalent variant in the Netherlands and replaced the earlier circulating variants called "the wild type".

2.2 Background

Emergence of a new infectious disease

At the end of December 2019, public health authorities in Wuhan, China reported a cluster of patients with unexplained pneumonia. On January 9th 2020, the causative pathogen was isolated and later named 'severe acute respiratory syndrome coronavirus 2' (SARS-CoV-2). SARS-CoV-2 spread more rapidly to other countries compared to previous severe outbreaks caused by coronaviruses (SARS-CoV in 2003 and MERS-CoV in 2012). On January 30, 2020 the WHO declared it a public health emergency of international concern (PHEIC) (WHO 2020). In the Netherlands, laboratory-confirmed COVID-19, the disease caused by SARS-CoV-2, became a group A notifiable disease in the Netherlands on January 28, 2020.

The first period

The first case of COVID-19 in the Netherlands was reported on February 27 2020. By mid-March 2020 it became clear that there had been unnoticed community transmission in the provinces of Noord Brabant and Limburg, most likely initiated by multiple introductions by Dutch tourists returning from northern Italy and Austria (Reusken, Buiting et al. 2020). This was amplified by the annual carnival celebrations lasting for three days, mostly in the south of the Netherlands, characterised by large social indoor and outdoor gatherings. In response, the national Outbreak Management Team (OMT) recommended a range of control measures, including social distancing and hygiene measures.

Policies for testing, tracing and isolation

The trends in notifications and numbers of tests performed at PHS test locations are biased by the prevailing testing policies and influenced by transmission prevention measures such as non-pharmaceutical interventions (NPI), lockdowns and vaccination.
During the COVID-19 pandemic, the testing policies have changed considerably. In the first weeks of the pandemic, due to lack of capacity, the testing policy was mainly restricted to hospitalized SARI (Severe Acute Respiratory Infection) patients, healthcare workers inside hospitals with respiratory symptoms, patients ≥70 years of age or chronically ill patients outside hospitals with symptoms. From June 1 2020 onwards, universal testing, even with mild symptoms, was actively promoted and free of charge for all people. Since December 1 2020, additionally testing without symptoms was advised for persons identified in the source and contact tracing and for people who received a notification from the 'Corona notification app'. After contact with a SARS-CoV-2 positive case, persons need to quarantine for 10 days. However, with a negative test result after day 5, quarantine can be lifted.
From January 2021 onwards, children below 12 years of age were specifically advised to test if they had symptoms. Simultaneously, source and contact tracing at schools was scaled up, resulting in more notifications among children. In April 2021 commercial self-test kits became available in pharmacies and supermarkets. Self-tests can help detect infections in people without symptoms more quickly, but do not replace testing at PHS. Self-tests are not recommended for people identified in PHS source and contact tracing. In case of a positive self-test, people are advised to contact the PHS for retesting and source investigation. Self-tests are not registered in our surveillance data.

Non-pharmaceutical interventions

From week 21 2020, the stringent prevention measures were gradually eased. Schools, cafes, sport clubs partly reopened and the number of allowed visitors at home and indoors was increased. Physical distancing, hand hygiene, isolation and testing when having symptoms compatible with COVID-19, and a ban on large gatherings remained. In September, the beginning of the second period, NPI were reintroduced and became stricter from mid-October (week 43, 2020), until a complete lockdown at the end of December (week 51 2020). Measures during this lockdown included amongst others a curfew, a maximum of 1 visitor at home per day; a maximum group size of 2 persons outside home; closure of schools, non-essential shops and public buildings; and mandatory use of mouth masks in essential public buildings. From February 2021 the prevention measures were gradually eased based on the risk levels per

security region and a 5-step opening plan was used to further downscale the measures. Until week 20 2021, only step 1 of the opening plan was taken by the government. The most important changes were that the curfew was lifted, outdoor seating at restaurants and cafes were partially reopened and home visit advice expanded to
2 people. The basic measures, physical distancing, hand hygiene, isolation and testing when having symptoms, remained in all opening steps.

Vaccination
In January 2021, vaccination against SARS-CoV-2 started. First, nursing home residents and health care workers were invited. Subsequently, everyone aged 18 and over was invited starting with the oldest ages. By week 20 2021, all persons born before 1969 had been invited for vaccination. For more information about the COVID-19 vaccination campaign, we refer to the annual surveillance report of the National Immunization Program (report in preparation).

Variants of Concern
Among the identified variants of the SARS-CoV-2 virus, some variants are labelled as Variant of Concern (VOC) if they are more infectious than other known variants, or if they cause more severe illness. Since January 2021, several countries have reported an increase in the number of SARS-CoV-2 cases of variants of concern (VOC) (ECDC 2021).

2.3 Epidemiological situation 2020-2021 (week 21 2020 up to week 20 in 2021)

During the summer period, following the first period of the COVID-19 epidemic, the incidence of SARS-CoV-2 notifications was low. The second period started in September 2020 and showed two peaks (at the end of October and at the end of December). The third period started in February 2021.

Second period
The second period started mainly with an increase in incidence in younger age groups (10-29 years of age), followed by an increase in the age groups of 40-50 years of age (their parents) and subsequently in the oldest age groups (70+).
At the first peak of the second period in week 43-44 2020, 1,850 tests per 100,000 inhabitants were performed, of which 18.4% was positive (week 43). Furthermore, 66,518 notifications were reported (week 43), 1,983 persons were admitted to the hospital (week 44) and 607 persons deceased (week 43).
At the second peak of the second period (week 51-53 2020) 2,748 tests per 100,000 inhabitants were performed (week 51), of which 13.7% were positive (week 51 and week 53). Furthermore, 78,021 (week 51) notifications were reported, 1,984 persons were admitted to the hospital (week 53) and 720 persons deceased (week 51) (see Chapter 3.3 for detailed information on all-cause mortality).
The lowest number of notifications between the second and third period was 23,894 in week 6 2021.

Third period

From the beginning of February 2021, mainly due to the emerge of Variant Of Concern (VOC) Alpha, the notifications increased again (ECDC 2021). Also other VOCs emerged, but the Alpha variant remained the most dominant variant from the first half of February up to the end of this reporting period (week 20 2021).

In this third period the epidemic stayed at a high level of concern for a longer period of time (week 12-18) compared to the second period. The incidence peaks at week 12 (3,161 tests per 100,000 inhabitants) and the percentage positive at week 18 (12.3%). Highest number of notifications and hospitals admissions were reported in week 16 (56,295 and 1,853 respectively). The number of deceased persons with SARS-CoV-2 per week gradually decreased from 380 in week 5 to 44 deceased in week 20.

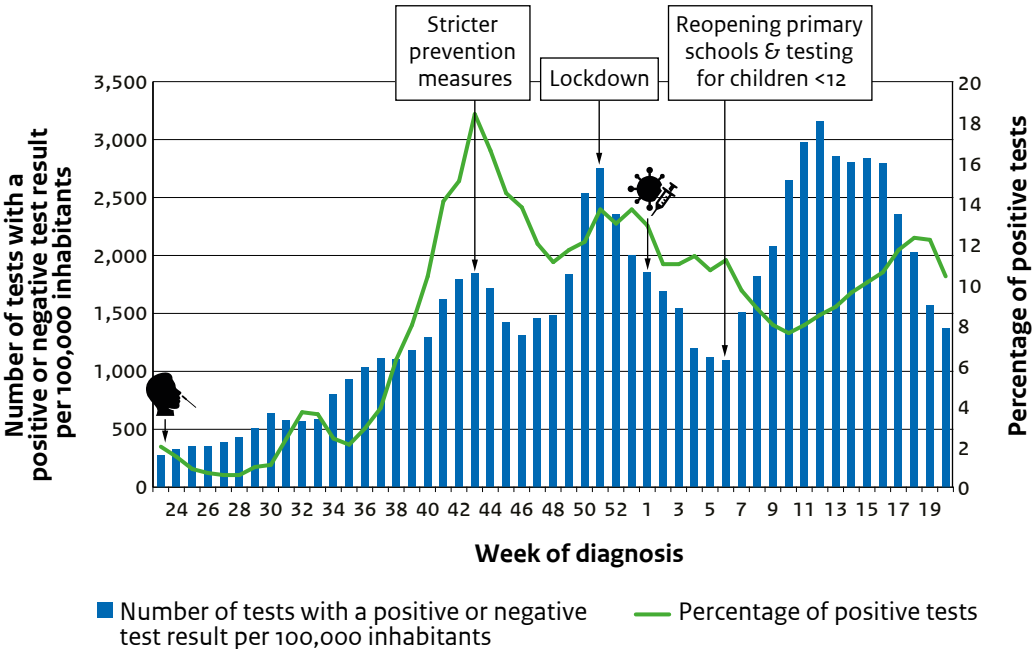
2.4 Discussion

Whereas during the first and second period of the epidemic, mainly elderly people were affected, in the third period the number of notifications, hospitalizations and deaths among the elderly decreased. First, among the elderly in the nursing homes, followed by the elderly living at home. This is associated with the start of the vaccination campaign in these target groups (de Gier B, Kooijman MN et al. 2021), for more information see the annual surveillance report of the National Immunization Program (report in preparation). At the same time, the incidence as well as the number of hospitalised patients increased in the younger age groups. The high number of hospital admissions overwhelmed hospital wards and ICUs again like during the first period (March – April 2020). This led to downscaling regular care and hospital admission stops and weekly scaling up of ICUs.

In the Netherlands, as well as in other countries, a range of new surveillance tools have been rapidly developed in response to the COVID-19 pandemic. The present report only provides selected basic data from the routine respiratory surveillance tools: number of tests performed at PHS test locations; the national infectious diseases register 'Osiris'; national hospitalization system (NICE). The unprecedented spike of excess mortality due to COVID-19 is shown in Chapter 2.3. A weekly comprehensive situation report is published on the RIVM website. National data is weekly uploaded to ECDC.

2.5 Figures

Figure 2.1 Number of tests with a positive or negative test result performed at PHS test locations per 100,000 inhabitants, and percentage of positive tests from week 23 2020 through week 20 2021 (source: CoronIT).



Footnote: Universal testing became available from the first of June 2020 (week 23)

Figure 2.2 Number of SARS-CoV-2 notifications per age group per week from week 21 2020 through week 20 2021 (source: Osiris).

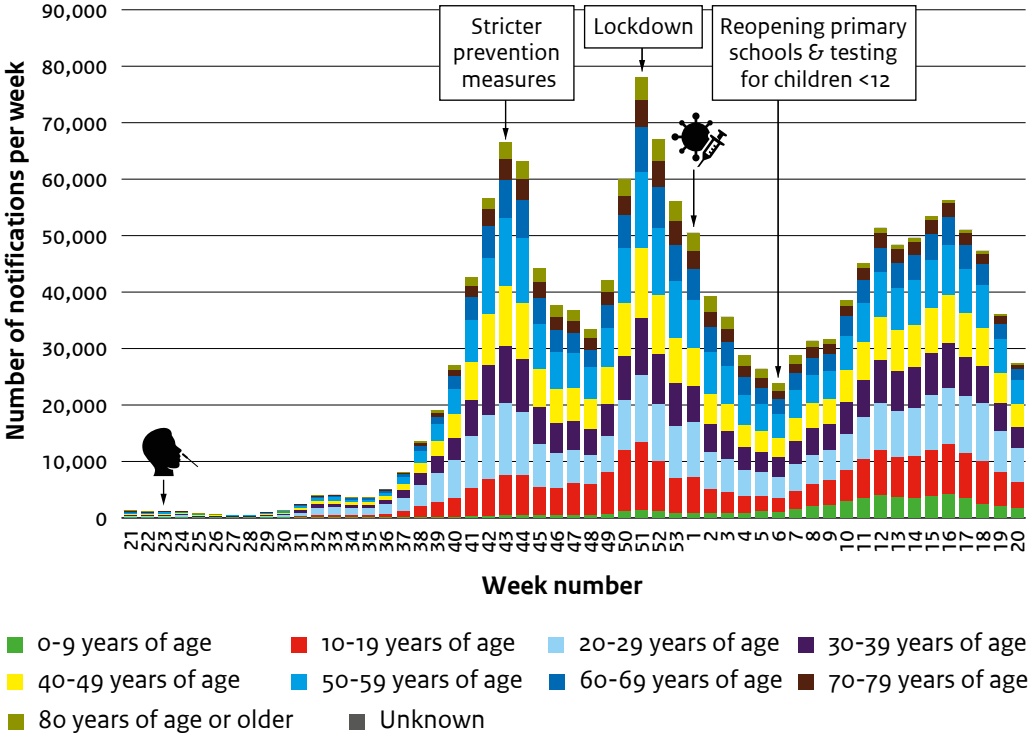


Figure 2.3 Notifications among nursing home residents from week 21 2020 through week 20 2021 (source: Osiris).

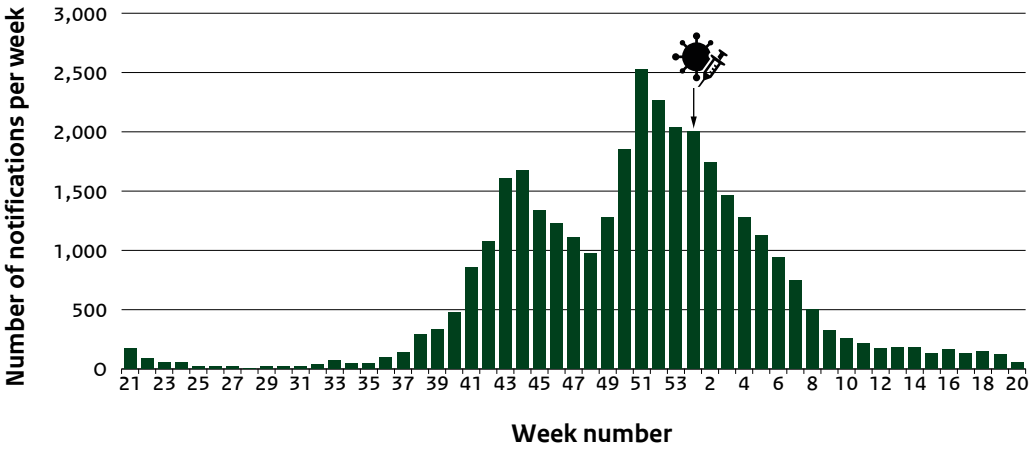


Figure 2.4 Cumulative incidence of notifications per municipality from week 21 2020 through week 20 2021 (source: OSIRIS).

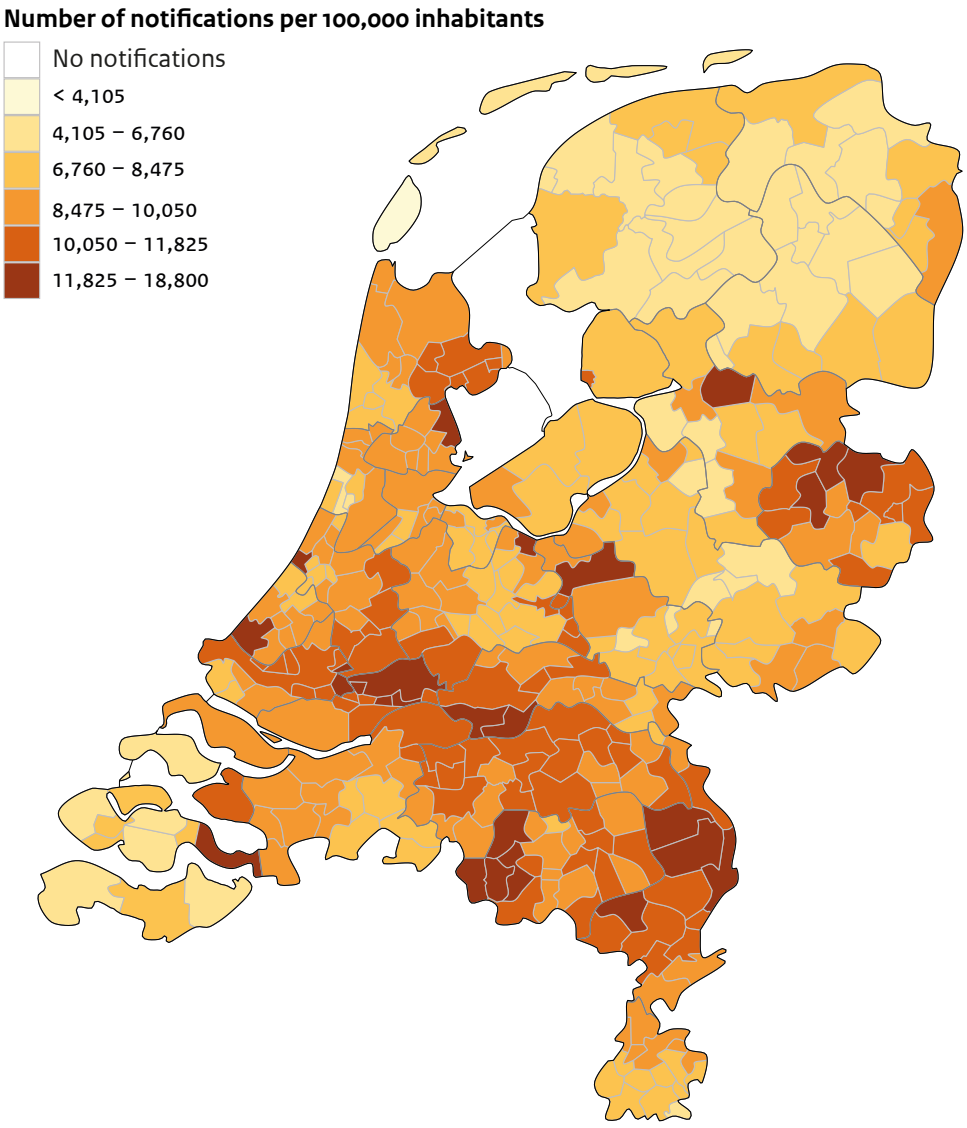
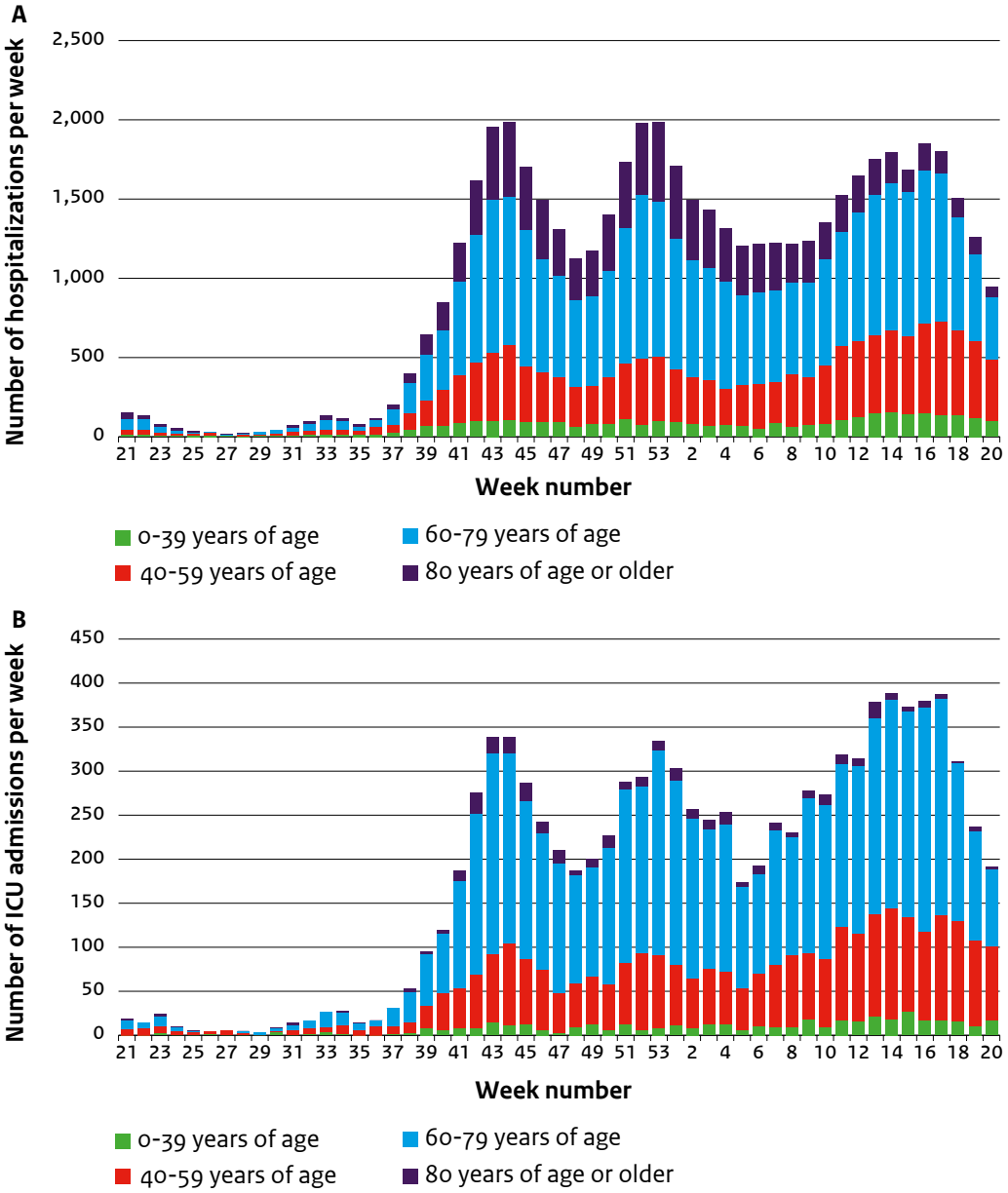


Figure 2.5 Age distribution of A. hospitalizations of COVID-19 patients from week 21 2020 through week 20 2021 (including admissions directly to the ICU), B. admissions to ICU (directly or from hospital wards) (source: NICE).



Footnote: ICU = intensive care unit

Figure 2.6 Cumulative incidence of hospital admissions per municipality from week 21 2020 through week 20 2021 (source: NICE).

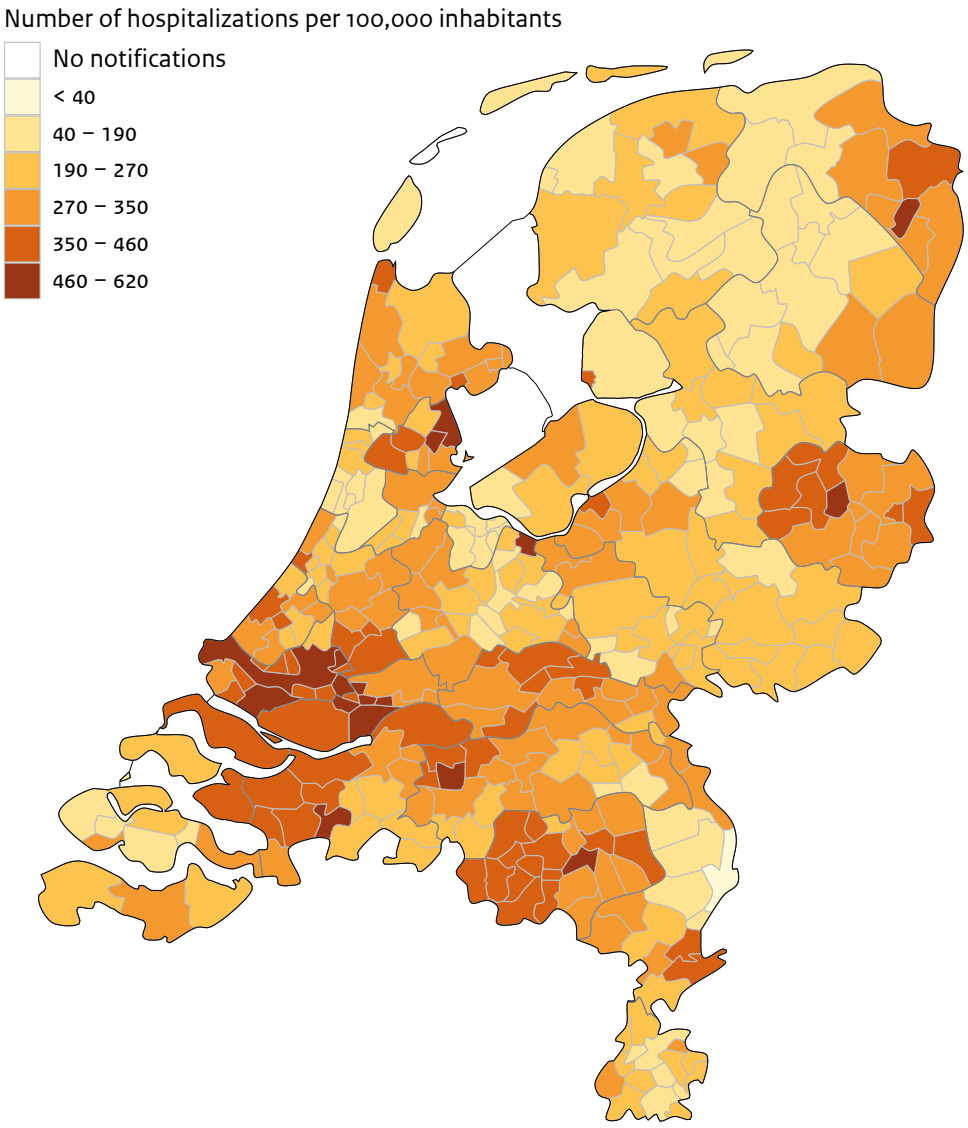


Figure 2.7 Notifications of deceased COVID-19 patients per week from week 21 2020 through week 20 2021 (source: Osiris).

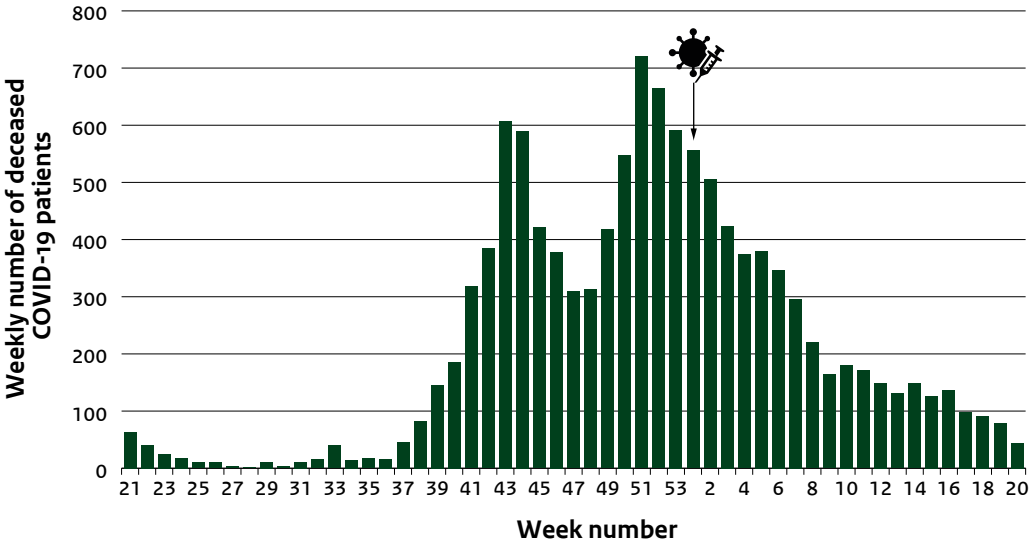
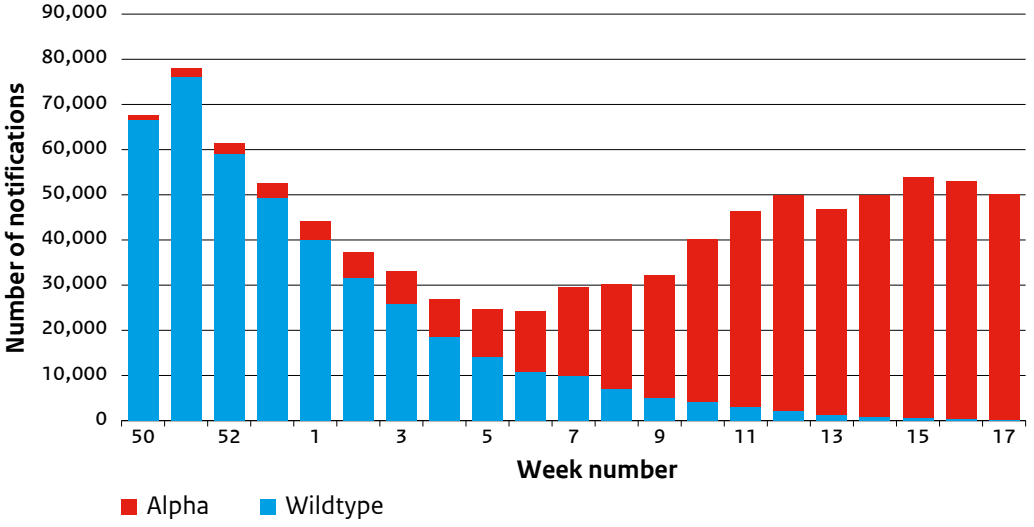


Figure 2.8 The estimate of the number of notifications per variant (wildtype, Alpha) per week (source: Osiris and Genomic surveillance of SARS-CoV-2).



Chapter 3
Syndromic surveillance

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

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Contributors: Daphne Reukers, Anne Teirlinck, Anja Haenen, Janneke Hendriksen

3.1.1 Key points

- In the 2020/2021 winter season, the ILI incidence did not exceed the epidemic threshold, and no influenza virus was detected in the sentinel GP surveillance. Therefore, there was no influenza epidemic in 2020/2021.
- There was very low influenza virus circulation in the 2020/2021 season, likely due to the impact of the various non-pharmaceutical interventions implemented to reduce the spread of SARS-CoV-2.
- The COVID-19 pandemic affected ILI and ARI GP consultations; all persons with respiratory symptoms were requested to get tested at dedicated testing centres.
- Next to the ILI incidence, the number of ARI consultations was also very low in the 2020/2021 season.
- The seasonal number of ARI consultations and ILI incidence reported by GPs was highest in young children (0-4 years), followed by the elderly (65 years or older), which is in line with the four previous seasons.
- The weekly number of ARI consultations was also highest among the children of 0-4 years, and peaked late in the season (week 11-13 2021).
- The ILI incidence among nursing home residents was comparable to the four preceding seasons. In contrast to previous seasons, the ILI incidence was already high at the beginning of the respiratory season and no clear peak in incidence was seen. The ILI incidence declined after week 2 2021. In contrast to people who are living at home who were advised to attend the Municipal Health Service instead of their GP with respiratory complaints, nursing home residents were still attending their nursing home doctors. The notified COVID-19 cases among nursing home residents also declined after week 2 2021 (see Chapter 2). Therefore, the elevation in ILI incidence among the nursing home residents is probably caused by SARS-CoV-2 infections.

3.1.2 Background

Acute respiratory infections (ARI) and the subgroup of influenza-like illness (ILI) are clinical diagnoses caused by a range of viruses and bacteria. However, the case definition for ILI is more specific for influenza virus infection, which is defined according to the 'Pel criteria' (Pel 1965): sudden onset of symptoms, fever ≥ 38°C and at least one of the symptoms cough, rhinorrhoea, sore throat, frontal headache, retrosternal pain, or myalgia. ILI surveillance performed by sentinel general practitioners (GPs) of the Nivel Primary Care Database forms the basis of the influenza surveillance in the Netherlands. Since 1992, it combines the clinical syndrome ILI with virological testing of a combined nose/throat swab of a subset of the ILI patients, to give insights in the main causes of ILI and the influenza virus circulation. Based on these data and using the MEM method, an influenza epidemic for the 2020/2021 season was defined as an ILI incidence above 5.8/10,000 inhabitants during at least two consecutive weeks in combination with at least 10% influenza virus detections in at least 20 specimens of patients with ILI (Hooiveld, Hendriksen et al. 2020). The epidemic threshold is reconsidered every season. The sentinel GP surveillance was altered during the COVID-19 pandemic. In the Netherlands, all people with respiratory complaints were requested to go to testing lanes of the Municipal Health Services. As a result, the patients from whom samples were taken by sentinel GPs were not representative of all patients with acute respiratory infections.

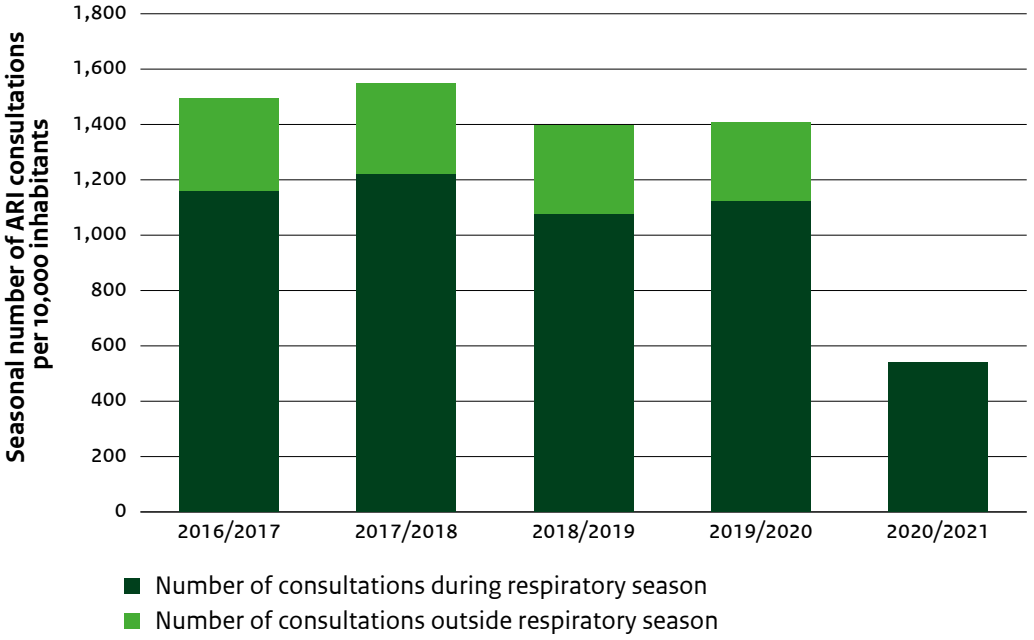
ARI surveillance is a complementary syndromic surveillance system, using data from electronic medical records of GPs participating in the Nivel Primary Care Database. However, it covers a broader respiratory case definition: acute upper respiratory infection, acute/chronic sinusitis, acute laryngitis/tracheitis, acute bronchitis/bronchiolitis or influenza (and therefore includes the ILI case definition). Besides, a larger number of GPs participate in the ARI surveillance and no specimens are taken.

The national sentinel surveillance network for infectious diseases in nursing homes (SNIV) is a third system for respiratory surveillance of ILI. Nursing home residents are vulnerable for influenza virus-related complications, but are not captured in the GP surveillance because they receive primary care from elderly care physicians.

3.1.3 Figures

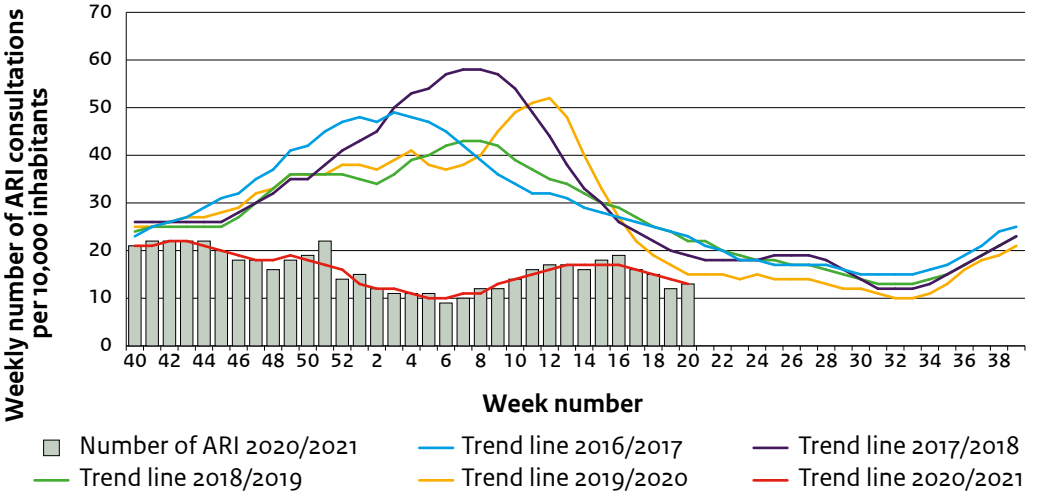
GP consultations for ARI

Figure 3.1 Seasonal cumulative number of ARI consultations in primary care within the respiratory season (week 40 through week 20) and outside the respiratory season (week 21 through week 39) of 2016/2017 - 2020/2021 (source: Nivel Primary Care Database).



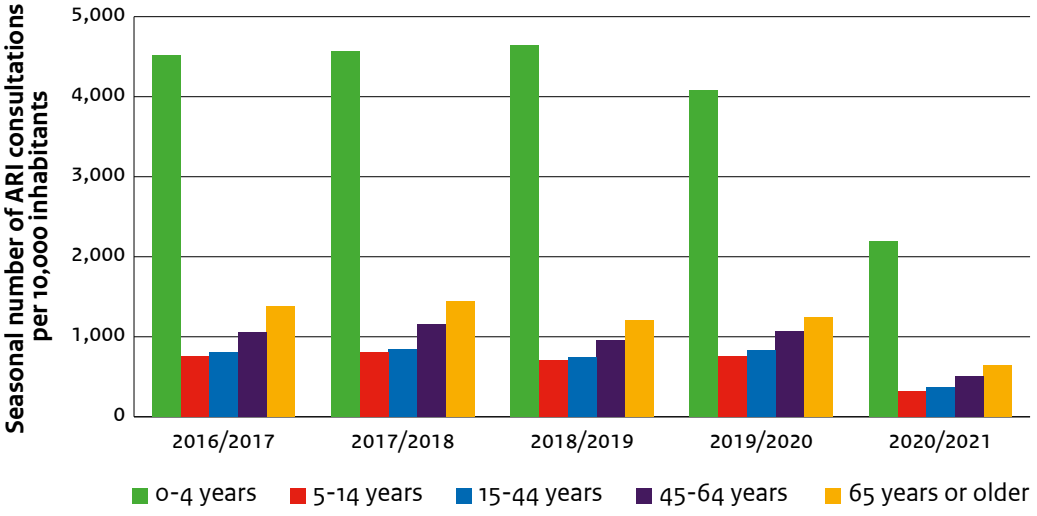
Footnote: ARI = acute respiratory infections (including influenza-like illness); GP = general practitioner.
For the 2020/2021 season, numbers for outside the respiratory season (week 20 through 39 2020) are not yet available.

Figure 3.2 Weekly number of ARI consultations in primary care per 10,000 inhabitants in the respiratory season (week 40 through week 20) of 2020/2021 and trend lines for seasons 2016/2017 - 2020/2021 (source: Nivel Primary Care Database).



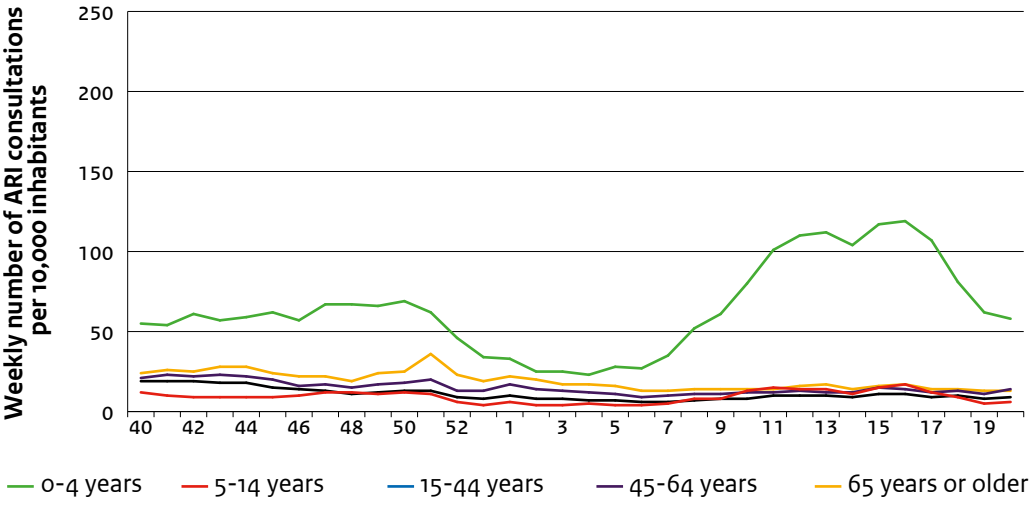
Footnote: Trend lines indicate a 5-weeks moving average. ARI = acute respiratory infection, including influenza-like illness; GP = general practitioner.

Figure 3.3 Seasonal cumulative number of ARI consultations in primary care in the respiratory seasons (weeks 40 through 20) of 2016/2017 through 2020/2021 per 10,000 inhabitants by age group (source: Nivel Primary Care Database).



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

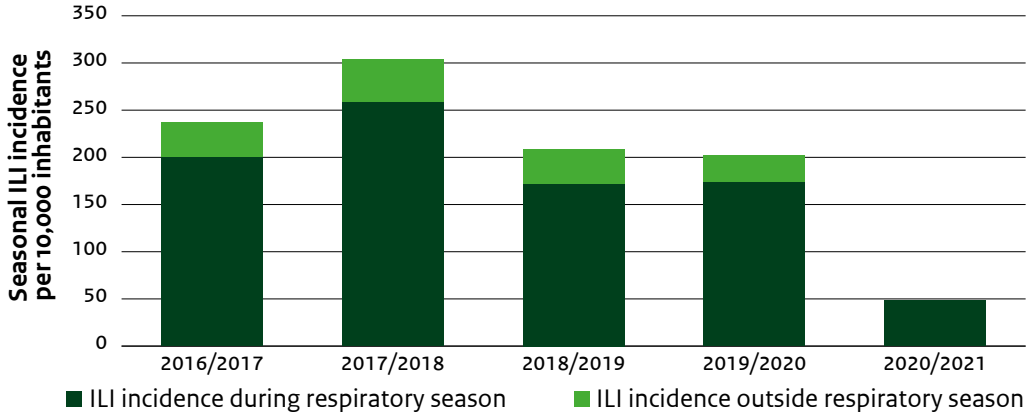
Figure 3.4 Weekly number of ARI consultations in primary care per 10,000 inhabitants in 2020/2021 (weeks 40 through week 20 of 2021) by age group (source: Nivel Primary Care Database).



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

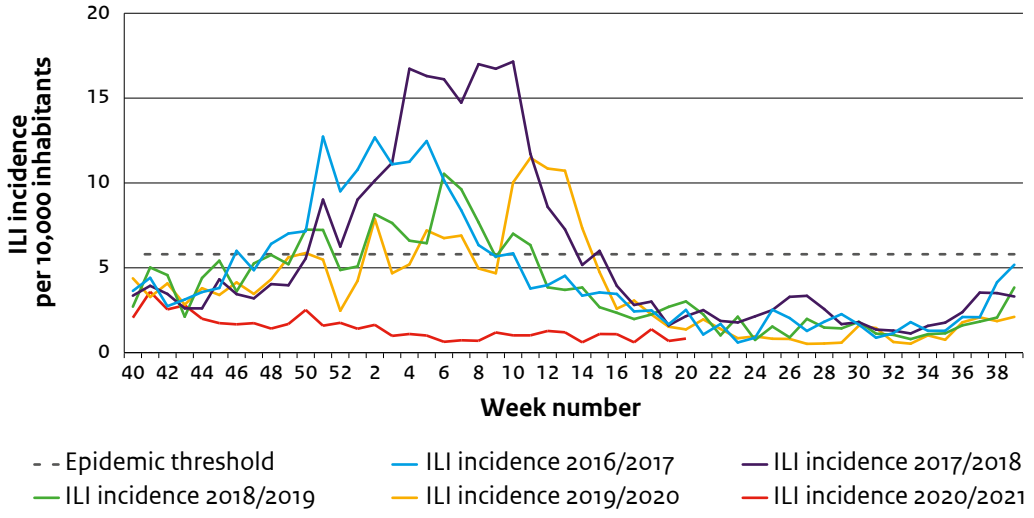
ILI incidence: sentinel GP practices

Figure 3.5 Seasonal ILI incidence in primary care within the respiratory season (week 40 through week 20) and outside the respiratory season (week 21 through week 39) of 2016/2017 - 2020/2021 (source: Nivel Primary Care Database).



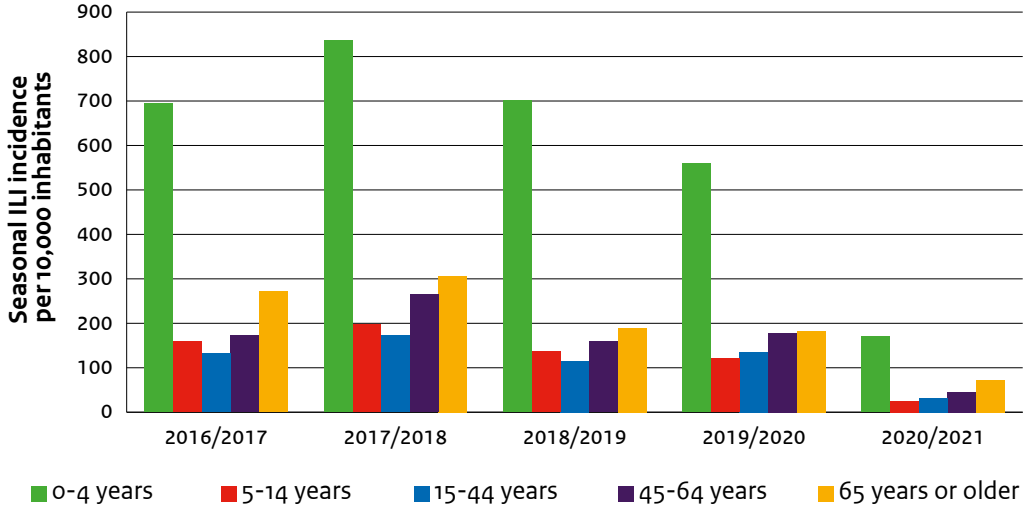
Footnote: ILI = influenza-like illness.
For the 2020/2021 season, numbers for outside the respiratory season (week 20 through 39 2021) are not yet available.

Figure 3.6 Weekly ILI incidence in primary care per 10,000 inhabitants in the respiratory season (week 40 through week 20) of 2020/2021 and trend lines for seasons 2016/2017 - 2020/2021 (source: Nivel Primary Care Database).



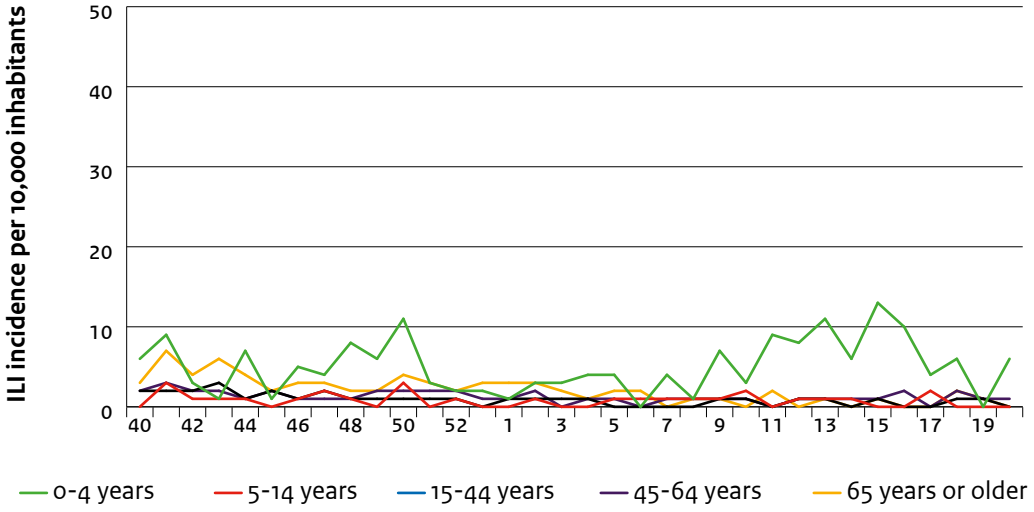
Footnote: Trend lines indicate a 5-weeks moving average. ILI = influenza-like illness.
Epidemic threshold was set at 5.1 per 10,000 inhabitants for the seasons 2016/2017 through 2018/2019, and at 5.8 per 10,000 inhabitants for the 2019/2020 and 2020/2021 seasons.

Figure 3.7 Seasonal ILI incidence in primary care in the respiratory seasons 2016/2017 - 2020/2021 per 10,000 inhabitants by age group (source: Nivel Primary Care Database).



Footnote: ILI = influenza-like illness.

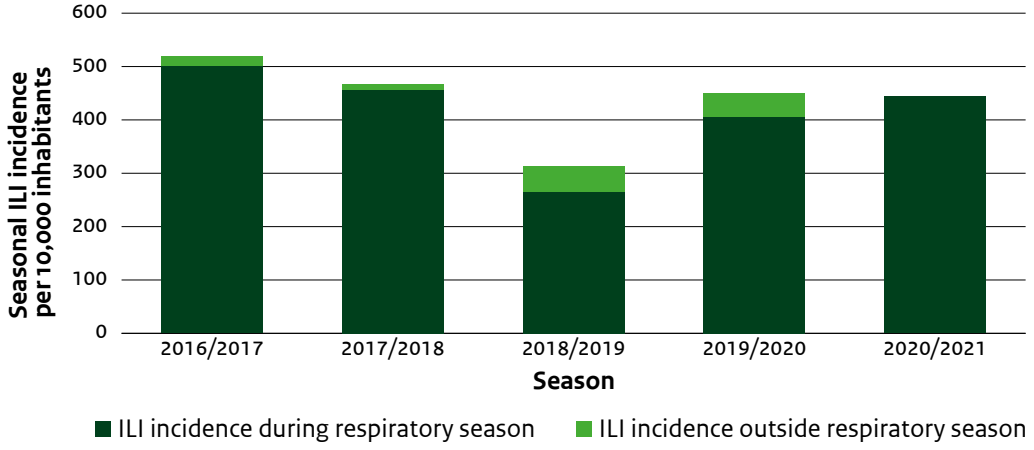
Figure 3.8 Weekly ILI incidence in primary care per 10,000 inhabitants in respiratory season 2020/2021 by age group (source: Nivel Primary Care Database).



Footnote: ILI = influenza-like illness.

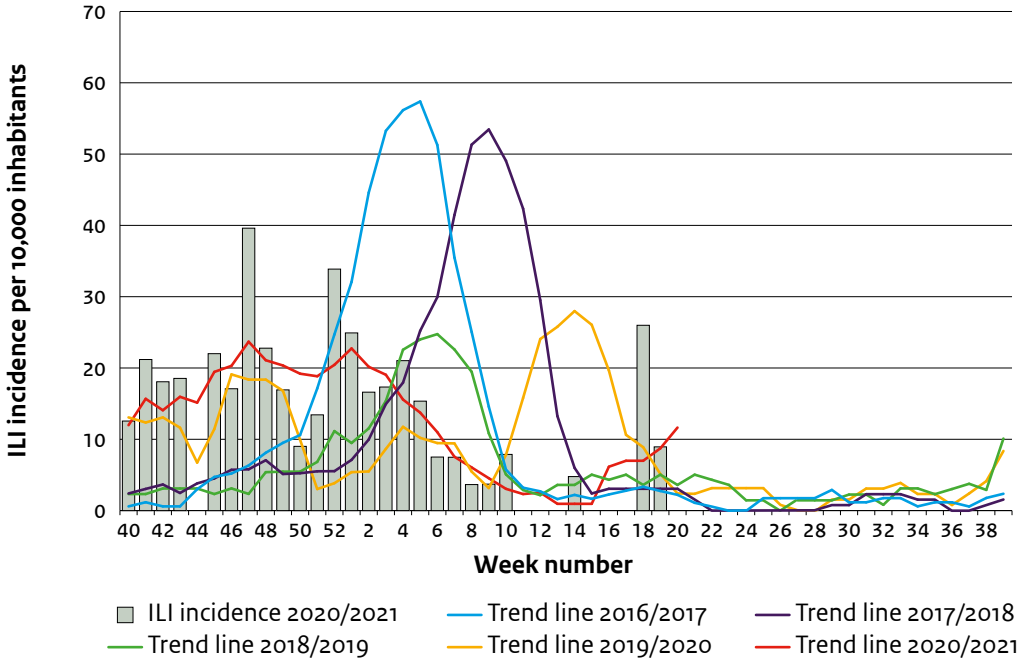
ILI incidence: in nursing homes

Figure 3.9 Seasonal ILI incidence in SNIV nursing homes per 10,000 residents within the respiratory season (week 40 through week 20) and outside the respiratory season (week 21 through week 39) of 2016/2017 - 2020/2021 (source: SNIV, RIVM).



Footnote: ILI = influenza-like illness.
For the 2020/2021 season, numbers for outside the respiratory season (week 20 through 39 2021) are not yet available.

Figure 3.10 Weekly ILI incidence in SNIV nursing homes per 10,000 residents in the 2020/2021 respiratory season (week 40 of 2020 through week 20 of 2021) and trend lines for the seasons 2016/2017 - 2020/2021 (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.

3.2 Community-acquired pneumonia (CAP) in primary care

Authors: Daphne Reukers, Mariëtte Hooiveld
Contributors: Marit de Lange, Anja Haenen, Annabel Niessen

3.2.1 Key points

- The seasonal number of GP consultations for pneumonia (week 40 2020 through week 20 2021) was 73 per 10,000 inhabitants, which was lower than the previous four seasons.
- The weekly pneumonia GP consultations were steadily low throughout the 2020/2021 respiratory season, there was no clear peak. The highest number of GP consultations for pneumonia (2.9 consultations per 10,000 inhabitants) was observed in week 51 of 2020.
- The seasonal number of GP consultations for pneumonia in 2020/2021 (week 40 2020 through week 20 2020) was lower than the previous four seasons for all age groups (0-4, 5-14, 15-44, 45-64 years and 65 years or older, 30, 10, 17, 51 and 178 per 10,000 inhabitants, respectively).
- The seasonal incidence (week 40 2020 through week 20 2021) of pneumonia in nursing homes was 876 per 10,000 residents. Which was lower than the previous four seasons.
- The peak in the weekly incidence for pneumonia (56 patients per 10,000 residents) reported by nursing homes was observed in week 43 of 2020. There were two peaks in the trend line (week 43 2020 and 3 2021) of which the first peak coincided with a peak in the weekly notifications of SARS-CoV-2 (Chapter 2).
- There was no influenza epidemic during the respiratory season of 2020/2021 (Chapter 4), which likely resulted in relatively low numbers of patients consulting their GP with pneumonia and a low incidence of pneumonia in nursing homes. In contrast to people who are living at home who were advised to attend the Municipal Health Service instead of their GP with respiratory complaints, nursing home residents were still attending their elderly care physician. The notified COVID-19 cases among nursing home residents showed a similar peak in number of detections in week 43 as the pneumonia incidence in nursing homes, however the COVID-19 cases declined after week 51, while pneumonia incidence showed a second peak in week 3 (see Chapter 2). The pneumonia incidence among nursing home residents can therefor only partially be explained by SARS-CoV-2 infections.

3.2.2 Background

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

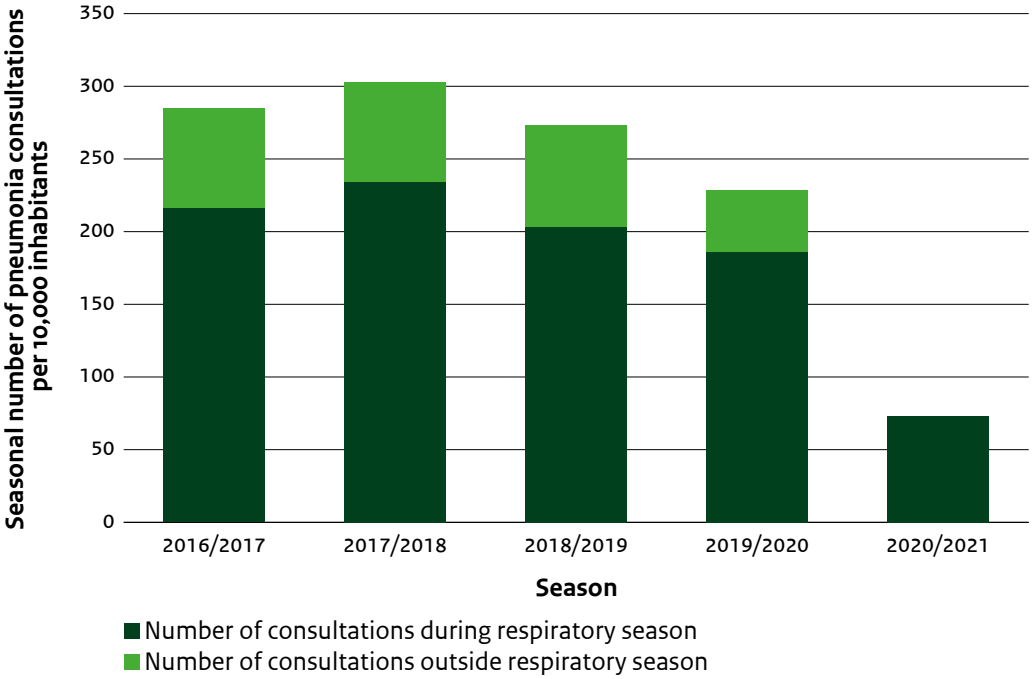
Many studies in the Netherlands and other countries show that *Streptococcus pneumoniae* is the predominant aetiological agent of community-acquired pneumonia (CAP), but CAP can be caused by many other microorganisms, mainly bacteria and viruses (van Gageldonk-Lafeber, Wever et al. 2013). In daily clinical care, a general practitioner (GP) diagnosis of CAP is based on clinical criteria, often without confirming the presence of a new infiltrate on a chest x-ray and without laboratory-confirmed diagnose (Verheij, Hopstaken et al. 2011). Also in hospital settings, there is a lack of guidelines on diagnostic testing in CAP patients. Therefore, the causative pathogens remain unknown in the majority of CAP patients, since microbiological

tests are not systematically used and are usually limited to blood and sputum cultures for bacterial causes. Developing hospital or national guidelines could lead to a more systematic diagnostic testing policy in CAP patients and minimize the amount of testing bias.
The pneumonia surveillance in this report includes both the registration of pneumonia by GPs (Nivel Primary Care Database) and the registration of incidence of pneumonia in nursing homes (SNIV).

3.2.3 Figures

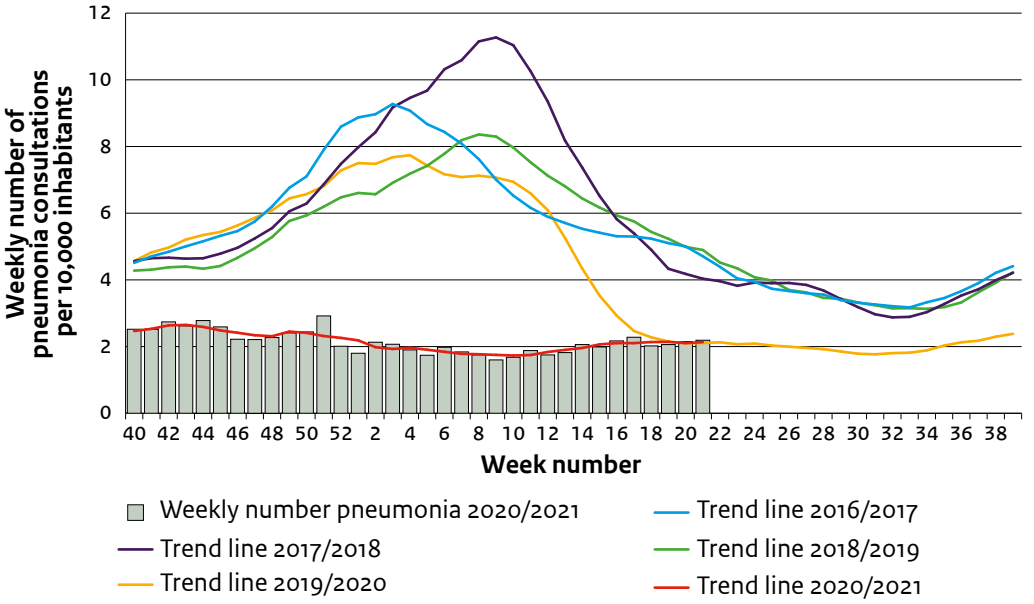
GP consultations for pneumonia

Figure 3.11 Seasonal cumulative numbers of patients consulting their GP for pneumonia per 10,000 inhabitants within the respiratory season (week 40 through week 20) and outside the respiratory season (week 21 through week 39) of 2016/2017 - 2020/2021 (source: Nivel Primary Care Database).



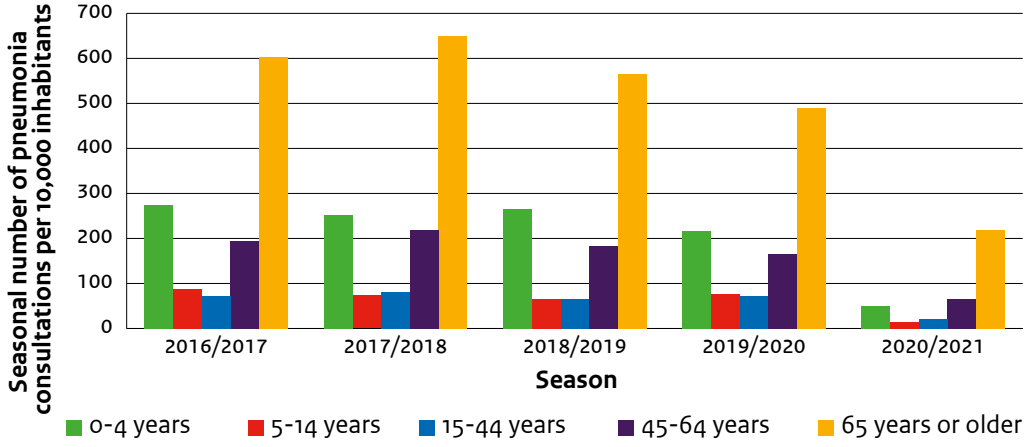
Footnote: GP = general practitioner.

Figure 3.12 Weekly numbers of patients consulting their GP for pneumonia per 10,000 inhabitants in 2020/2021 (week 40 2020 through week 20 2021) and the trend lines for 2016/2017 - 2020/2021 (2020/2021: through week 20) (source: Nivel Primary Care Database).



Footnote: GP = general practitioner. Trend lines are based on a 5-week moving average.

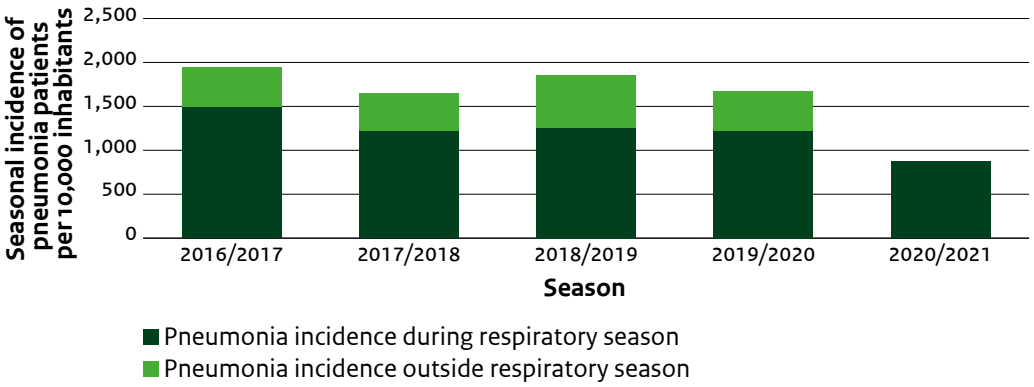
Figure 3.13 Seasonal cumulative number of GP consultations for pneumonia per 10,000 inhabitants by age group in the respiratory seasons 2016/2017 - 2020/2021 (week 40 through week 20) (source: Nivel Primary Care Database).



Footnote: GP = general practitioner.

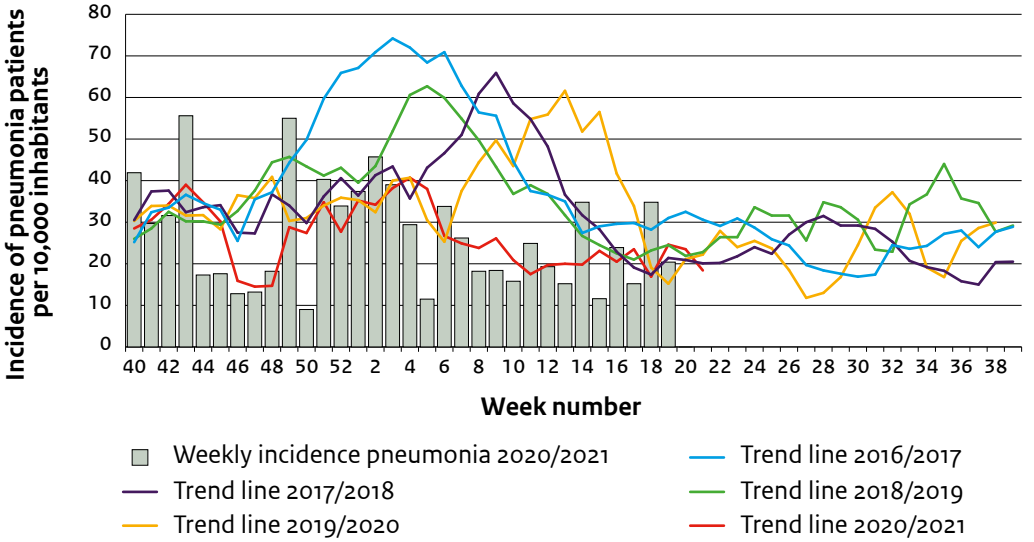
Incidence of pneumonia (nursing homes)

Figure 3.14 Seasonal incidence of pneumonia in SNIV nursing homes per 10,000 residents within the respiratory season (week 40 trough week 20) and outside the respiratory season (week 21 through week 39) of 2016/2017 - 2020/2021 (source: SNIV, RIVM).



Footnote: SNIV = national sentinel surveillance network for infectious diseases in nursing homes.

Figure 3.15 Weekly incidence of pneumonia patients in SNIV nursing homes per 10,000 residents in 2020/2021 and trend lines for the seasons 2016/2017 - 2020/2021 (through week 20) (source: SNIV, RIVM).



Footnote: SNIV = national sentinel surveillance network for infectious diseases in nursing homes. Trend lines are based on a 5-week moving average.

3.3 Weekly mortality monitoring

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

3.3.1 Key Points

- An average of 2,963 deaths occurred weekly in the Netherlands over the past 5 years, 2016-2020.
- There was no documented influenza epidemic in the winter of 2020/2021. Cumulated excess mortality during the past 5 influenza epidemics (2015/2016-2019/2020) was on average 4,848 excess deaths per influenza epidemic.
- During the respiratory season of week 40 2020 to week 20 2021 (mostly overlapping with 2nd and 3rd period of the COVID-19 epidemic) excess deaths were observed from week 41 2020 until week 8 2021 and in week 14, 15, 17 and 19. Cumulated excess deaths in week 40 through week 20 was 14,739. Which is higher than the 9,554 excess deaths during the first COVID-19 period of March-May 2020.
- Mortality peaked at 4098 deaths in week 1 (31 December 2020 - 6 January 2021); 1,087 deaths above expected baseline level.
- In the respiratory season (week 40 2020 - week 20 2021), excess mortality was mostly observed in persons 65 years and older. It lasted longest in 75-79 year-olds followed by 65-74 year-olds. Excess mortality lasted a few weeks shorter in 80-84, 85-89, 90-94 and 95+ age groups (ordered by decreasing duration; ending in week 10 for 80-84 year olds and in week 9 in the oldest 3 age groups).

3.3.2 Background

The Dutch weekly mortality monitoring system was initiated in August 2009, during the influenza A(H1N1)pdm09 pandemic. It is a collaboration between the RIVM Centre for Infectious Disease Control (RIVM CIb) and Statistics Netherlands (CBS). The system monitors the number of deaths reported nationwide (population size of 17.4 million in 2020) from all causes, as information on cause of death is not available in real-time.

Each week, the death notification data is checked for the presence of any excess mortality (i.e. mortality levels above a pre-defined threshold) in deaths reported within 1, 2, and 3 weeks (coverage 45%, 97% and 99% respectively). Excess mortality gives an indication of the impact of any expected and unexpected events that potentially affect population health. Examples of such events are heat waves, cold snaps, or seasonal influenza epidemics for which the morbidity and mortality burden varies due to variations in the circulation of influenza (sub) types.

3.3.3 Discussion

The 2020/2021 season was characterised by high excess mortality during the 2nd and 3rd period of the COVID-19 epidemic in the Netherlands. While a higher mortality peak was reached in the first period in 2019/2020, the cumulated excess mortality was higher in 2020/2021 (9,554 vs 14,399 excess deaths). Notably, there was no documented influenza epidemic in the winter of 2020/2021, potentially due to non-pharmaceutical interventions that were in place for COVID-19.

3.3.4 Figures

Figure 3.16 Weekly number of deaths from 2012 to 2021 (through week 20 of 2021) by date of death (notified within three weeks from date of death) (source: Statistics Netherlands).

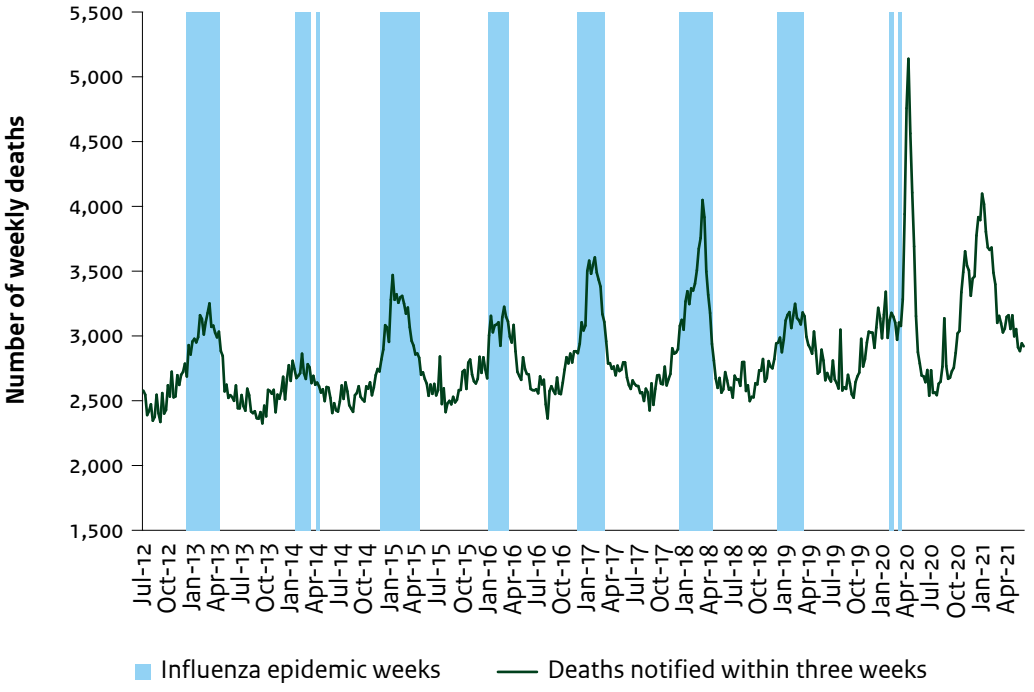
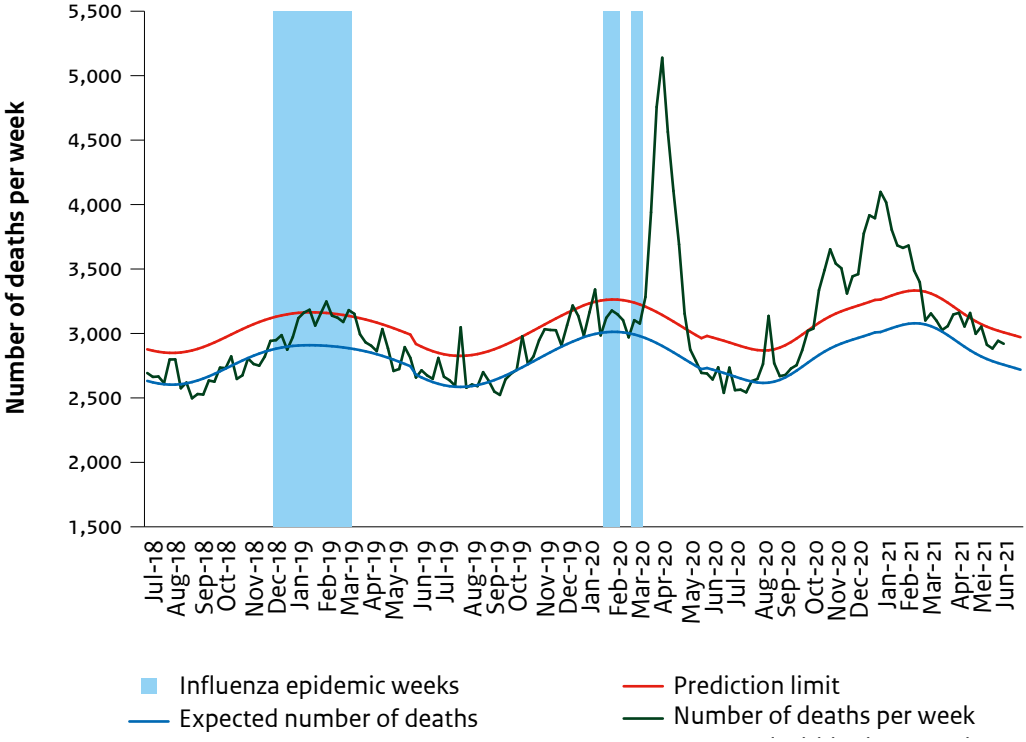


Figure 3.17 Observed and expected ('baseline') weekly number of deaths, July 2018 to June 2021 (source: Statistics Netherlands).



Chapter 4
Influenza

Authors: Marit de Lange, Adam Meijer
Contributors: Anne Teirlinck, Daphne Reukers, Mariëtte Hooiveld, Ron Fouchier

4.1 Key points

- There was no substantial influenza virus circulation in the 2020/2021 season, likely due to the impact of the various non-pharmaceutical interventions implemented to reduce global spread of SARS-CoV-2.
- In the 2020/2021 winter season, no influenza virus was detected in the 118 influenza-like illness (ILI) samples or in the 296 samples from patients that visited the general practitioner (GP) with another acute respiratory infection (ARI).
- The sentinel GP surveillance was altered during the COVID-19 pandemic. As a result, the patients from whom samples were taken may not be fully representative of all patients with acute respiratory infections.
- In the 2020/2021 winter season, no influenza virus positive samples were received by Erasmus MC for characterization.
- Only two influenza virus detections were reported in the virological laboratory surveillance in the 2020/2021 winter season.
- Also in other European countries influenza activity was below baseline level throughout the entire 2020/2021 winter season.

4.2 Background

Influenza is an acute respiratory infection caused by influenza viruses. Most patients recover quickly, although an influenza virus infection can cause severe illness especially in elderly and in patients with an underlying medical condition.
Human influenza viruses cause yearly epidemics, mostly in winter. Most influenza virus infections in humans are caused by influenza virus types A and B. Influenza type A viruses are divided into subtypes, based on proteins on the surface of the virus: hemagglutinin (HA) and

neuraminidase (NA). Different combinations of HA and NA proteins result in various subtypes, for example H1N1 and H3N2, the subtypes currently causing seasonal epidemics. Influenza type B viruses are divided into two genetic lineages based on their gene coding for the HA; lineages B/Yamagata/16/88 and B/Victoria/2/87. Both type A and B influenza viruses are constantly mutating which can result in virus escape from existing immunity induced by prior infections or vaccinations, a process known as antigenic drift.

4.3 Epidemiological situation, season 2020/2021

In the 2020/2021 season, there was no influenza epidemic. The influenza-like illness incidence remained below baseline level for the entire season. In the samples from the low number of patients that visited the GP with ILI or other ARI, no influenza virus was detected. Also, no influenza virus positive samples were received by Erasmus MC for characterization, despite widespread and regular testing for influenza viruses in hospitals. Furthermore, only two influenza virus detections were reported in the virological laboratory surveillance. Concluding, there was no substantial influenza virus circulation in the Netherlands in the 2020/2021 winter season.
The care provided by the GP has been altered due to the COVID-19 pandemic. During the 2020/2021 season, a low number of ILI and other ARI patients were sampled by their GP, compared to two earlier seasons (2020/2021: 118 ILI, 296 other ARI samples; 2019/2020: 777 ILI, 710 other ARI samples; 2018/2019: 470 ILI, 394 other ARI samples; Chapter 3.1). The ILI and other ARI patients sampled by the GP in the 2020/2021 season had more often an underlying lung disease compared to two earlier seasons (2020/2021 43% of ILI and 48% of other ARI patients; 2019/2020: 40% of ILI and 38% of other ARI patients; 2018/2019: 38% of ILI and 41% of other ARI patients). However, this might be partially explained by more elderly being sampled by the sentinel GPS in the 2020/2021 season, compared to two earlier seasons. (Reukers, van Asten et al. 2019; Reukers, van Asten et al. 2021)
For two hospitalized influenza cases, the viruses were analysed for reduced susceptibility markers for antivirals. A case of swine flu A(H1N1)v developed during treatment with oseltamivir resistance against oseltamivir. The case of A(H3N2) introduced from India showed no signs for reduced antiviral susceptibility.

4.4 Discussion

There was no substantial influenza virus circulation in the Netherlands in the 2020/2021 winter season, likely due to the impact of the various public health and social measures implemented to reduce global spread and transmission of SARS-CoV-2. The same was seen in other European countries (see: https://flunewseurope.org/). Because of the low number of influenza virus detections in Europe, no influenza vaccine effectiveness estimate could be calculated by the I-MOVE study group.

The sentinel GP surveillance was altered during the COVID-19 pandemic. In the Netherlands, all people with respiratory complaints were requested to go to testing lanes of the Municipal Health Services. As a result, the patients from whom samples were taken by sentinel GPs were not representative of all patients with acute respiratory infections. SARS-CoV-2 PCR testing was added in 2020 to the GP sentinel surveillance and additional testing for parainfluenza viruses types 1-3, human metapneumovirus and human seasonal coronaviruses was performed on specimens collected since January 2021. These viruses were added due to signals of increased circulation in and outside The Netherlands despite the COVID-19 measures (see Chapter 7). When the intensified COVID-19 surveillance will end, the routine sentinel GP surveillance may be an important tool for the COVID-19 surveillance.

For the 2021/2022 vaccine, the same influenza virus type B components were selected by the WHO (B/Washington/02/2019 (B/Victoria lineage)-like virus and B/Phuket/3073/2013 (B/Yamagata lineage)-like virus). The subtype A(H1N1)pdm09 and A(H3N2) components were updated with more recently circulating viruses (A/Victoria/2570/2019 (H1N1)pdm09-like virus and A/Cambodia/e0826360/2020 (H3N2)-like virus). (WHO 2021)

Since January 2021, Baloxavir marboxil is authorised as an antiviral medicine for treating and preventing influenza virus infections. At the RIVM, antiviral resistance testing is already implemented and known genetic resistance markers are monitored by sequence analyses of the PA gene.

4.5 Tables and figures

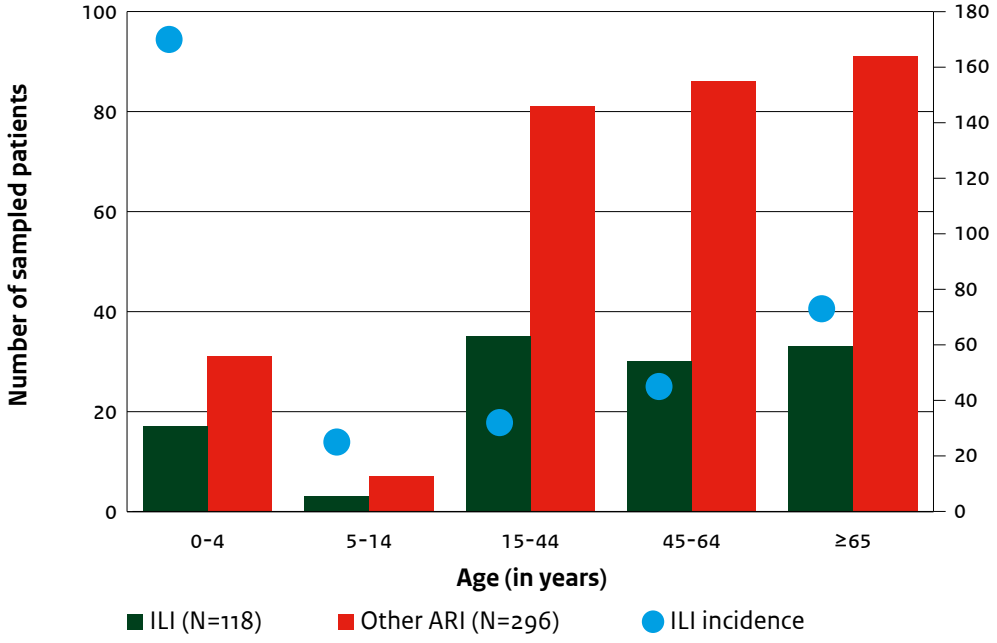
Virus surveillance

Table 4.1 Characteristics of influenza-like illness (ILI) and other acute respiratory infection (ARI) patients, who were sampled in the Nivel GP sentinel surveillance in the 2020/2021 season (through week 20 of 2021) (source: NIC location RIVM).

Characteristics	ILI patients n/N (%)	Other ARI patients n/N (%)
Male gender	45/118 (38)	114/296 (39)
Vaccinated against influenza	35/118 (30)	91/295 (30)
If yes, brand was Influvac If yes, brand was Vaxigrip	22/26 (85) 4/26 (15)	58/66 (88) 8/66 (12
Belongs to target group for vaccination	63/118 (53)	154/296 (52)
Lung disease (e.g. asthma, COPD)	27/63 (43)	74/154 (48)
Immune deficiency due to treatment (e.g. chemotherapy and radiotherapy)	2/63 (3)	7/154 (5)
Immune deficiency due to disease (e.g. HIV)	3/63 (5)	7/154 (5)
Cardiac disease (myocardial infarction, angina pectoris, arrhythmias, valvular heart disease, heart failure)	10/63 (16)	44/154 (29)
Diabetes mellitus	6/63 (9)	27/154 (18)
Obese (BMI > 30)	17/112 (15)	43/286 (15)
Smoking: Yes or stopped less than one year ago No, stopped more than one year ago Never	 20/107 (19) 18/107 (17) 69/107 (64)	 58/281 (21) 64/281 (23) 159/281 (56)
Women: Pregnant	 1/73 (1)	 1/182 (1)
Delay in sampling, in days[a]	4 (2-9)	4 (3-9)

[a] Number of days between the symptom onset and the day of sampling (median, 1st, and 3rd quartile)
Footnote: ILI =influenza-like illness; ARI = acute respiratory tract infection; GP = general practitioner; n = the number in the corresponding group; N = total number of patients, for whom the information was available. Please note that the 'other ARI' patients do not include the ILI patients.

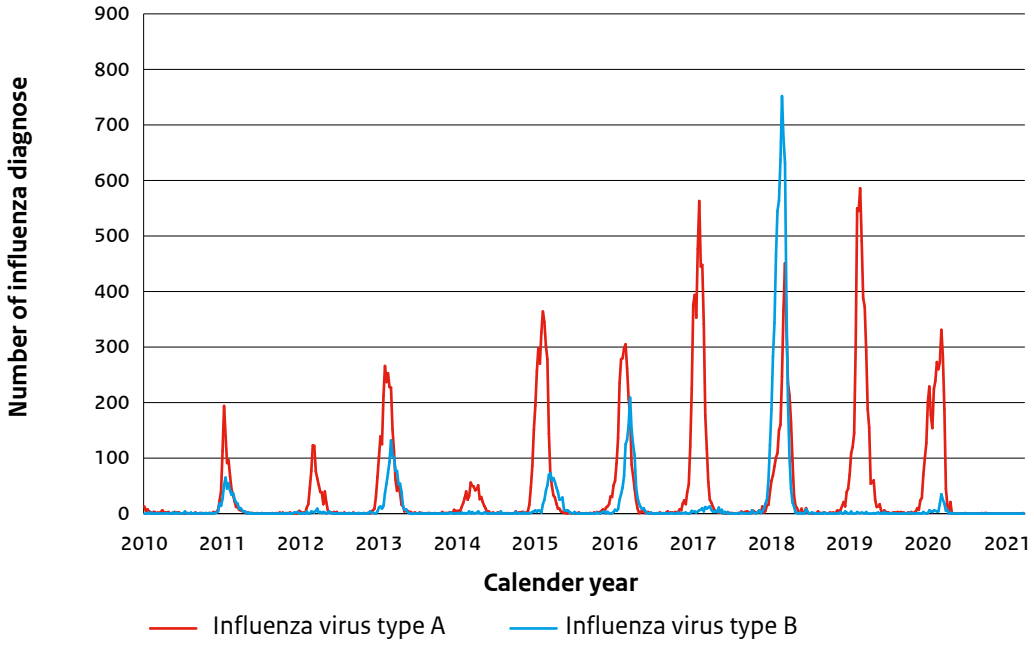
Figure 4.1 Age distribution of ILI and other ARI patients, sampled by Nivel sentinel GPs, and the ILI cumulative seasonal incidence per age category in the 2020/2021 respiratory season (week 40 of 2020 through week 20 of 2021) (source: Nivel Primary Care Database, NIC location RIVM).



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

Influenza diagnostics in virological laboratories

Figure 4.2 Weekly number of influenza virus type A and B diagnoses, reported by the virological laboratory surveillance in the period week 1 of 2011 through week 20 of 2021 (source: virological laboratory surveillance, NWKV).



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

Chapter 5
RS-Virus

Authors: Anne Teirlinck, Adam Meijer
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5.1 Keypoints

- During respiratory season 2020/2021, the number of Respiratory Syncytial Virus (RSV) detections in the virological laboratory surveillance was extremely low, and never exceeded the epidemic threshold.
- The total number of diagnoses from week 40 of 2020 through week 20 of 2021 was 42, fluctuating between zero and 8 with still 7 detections in week 20/2021.
- During this 2020/2021 respiratory season, in none of the 414 patients with an acute respiratory infection (ARI) including Influenza-Like Illness (ILI), RSV was detected in nose swabs and throat swabs, collected by sentinel GPs.
- Shortly after the end of the reporting period of this report, an out-of-season RSV epidemic started in the Netherlands.

5.2 Background

Respiratory Syncytial Virus (RSV) causes respiratory infection and is commonly contracted by children, in temperate countries 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 new-borns and preterm infants, infection can lead to severe illness, hospitalization and even death. Studies suggest that RSV is also a common cause for respiratory infections in the elderly causing outbreaks in elderly care facilities (Meijer, Overduin et al. 2013). RSV is subdivided in RSV-A and RSV-B, based on the different antigenic properties of their attachment glycoprotein G. These two types may circulate simultaneously in the population. The only prophylaxis available for preterm born infants is a monoclonal antibody that needs to be given monthly during the first year of life. Currently, no vaccine for RSV is

available, but many vaccine candidates are in the pipeline. Most vaccine and monoclonal antibody candidates that are currently in phase 2 and phase 3 clinical trials are based on the fusion protein (F-protein). The RSV surveillance in this report includes both the virological laboratory surveillance and GP sentinel surveillance.

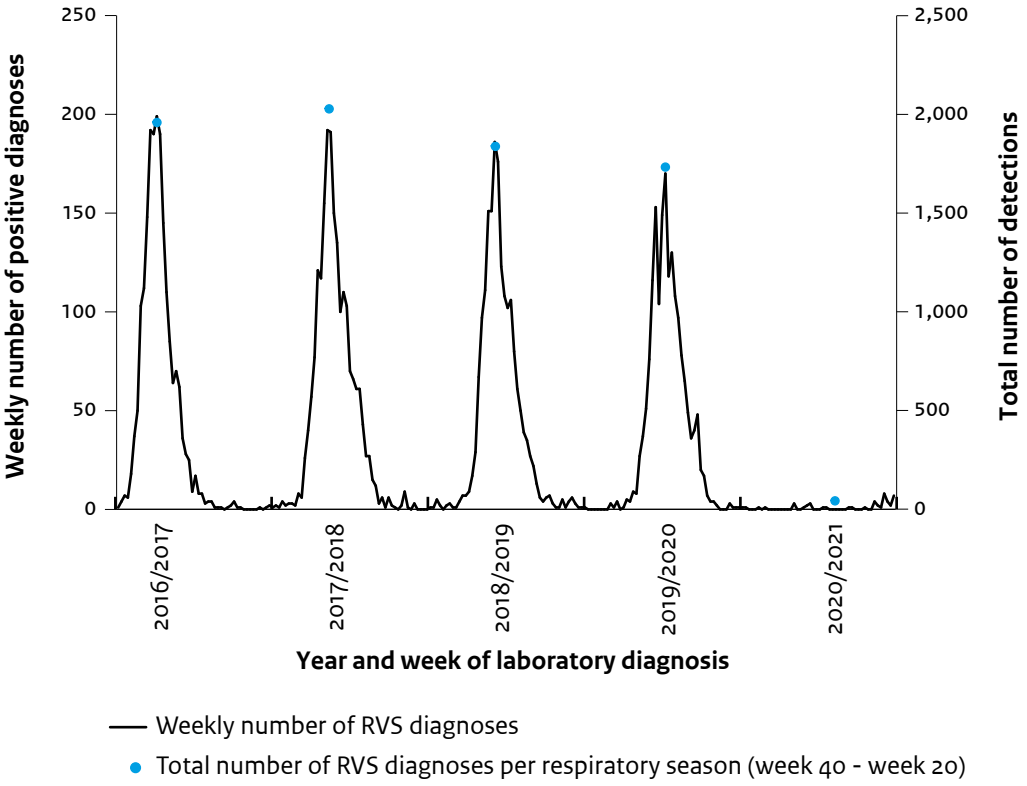
5.3 Discussion

Both in the virological laboratory surveillance, mainly representing RSV laboratory analysis from hospitalized paediatric patients, and in the GP sentinel surveillance, hardly any RSV was detected. This indicates an extremely low circulation of RSV, most likely due to the COVID-19 pandemic and accompanying non-pharmaceutical interventions. Due to this pandemic, healthcare provided by GPs has been altered, which can cause an underrepresentation of the data. The patients from whom samples were taken in the sentinel GP surveillance may not be fully representative of all patients with acute respiratory infections. However, these very low numbers clearly indicate a much lower circulation of RSV. Indeed, no pediatric hospital admissions because of RSV had occurred in the winter season. What the consequences of the very low circulation of RSV in the population and consequently lack of exposure to RSV will be monitored carefully. Shortly after the end of the reporting period of this report, an out-of-season RSV epidemic started in the Netherlands. In week 23 2021, the number of detections in the virological laboratory surveillance was above the epidemic threshold and the numbers continued to increase until the moment of writing (last update 21 July 2021; 164 detections in week 28). In the sentinel GP surveillance, RSV was first detected in week 26. At the moment of writing (21 July 2021) many children were hospitalized and hospital and ICU-admissions for RSV were at the level of a winter epidemic.

A reliable RSV surveillance, both at national and European scale, is important for monitoring RSV trends and, given the current developments in vaccine and monoclonal antibodies, for establishing a platform for future estimation of immunization impact. Therefore, RIVM works closely together with the European Centre for Disease Prevention and Control (ECDC) and other public health institutes, specifically Statens Serum Institut (SSI, Denmark) in order to strengthen international collaboration on RSV surveillance. Furthermore, RIVM is partner in the RESCEU project, which aims to explore the burden (clinical, economic and social) from RSV. The aim is to create a sound epidemiological and virological baseline, before the introduction of a vaccine, to identify appropriate target groups for vaccination. RESCEU has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement 116019. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and the European Federation of Pharmaceutical Industries and Associations.

5.4 Tables and figures

Figure 5.1 Number of weekly reported RSV diagnoses (black line) and total number of RSV diagnoses in the respiratory season (blue dot) in the virological laboratory surveillance for the period 2016/2017-2020/2021 (until week 20) (source: virological laboratory surveillance, NWKV).



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

Table 5.1 Number of reported respiratory syncytial virus (RSV) diagnoses in the virological laboratory surveillance for the period 2011/2012-2020/2021 (through week 20).

RSV diagnoses	weeks 40-20 (N)[a]	weeks 21-39 (N)[b]	weeks 40-39 (N)[c]
2011/2012	1838	51	1889
2012/2013	2199	12	2211
2013/2014	1629	16	1645
2014/2015	1670	32	1702
2015/2016	1348	42	1390
2016/2017	1938	21	1959
2017/2018	1996	32	2028
2018/2019	1807	31	1838
2019/2020	1731	8	1739
2020/2021	42[d]	-[e]	-[e]

[a] Previous year to next year respiratory season
[b] Summer period
[c] Previous year to next year respiratory season and subsequent summer period
[d] Data for weeks 40 of 2020 through week 20 of 2021 are preliminary.
[e] Data for weeks 21-39 of 2021 are not yet available.

Chapter 6
Notifiable Respiratory Diseases

6.1 Legionnaires' disease

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Contributor: Sjoerd Euser

6.1.1 Key points

- In 2020, a total of 461 cases with Legionnaires' disease (LD) were notified, a decrease of 19% compared to 2019. The incidence in 2020 was 2.6 per 100.000 inhabitants.
- The decline was fully explained by the 72 % decrease in LD cases with travel abroad. This is most likely the result of reduced international travel due to the Covid-19 pandemic.
- Italy, Germany, France, and the United Arabic Emirates were the most frequently reported countries of travel. Eight Travel associated LD (TALD) cases (17%) were linked to a cluster in a travel accommodation abroad.
- 411 LD cases acquired disease in the Netherlands (domestic cases) in 2020, which is similar to the annual number of domestic cases in 2017-2019.
- The majority of domestic cases (387 cases, 94%) is community acquired LD (CALD).
- Most notified patients (98%) were admitted to hospital, and 112 patients (26%) required admission at the Intensive Care Unit (ICU). The highest ICU admission was seen in the age groups from 50-79 (30%).
- With 31 deaths, the case fatality was 7.5% in domestic cases. This was higher than in 2019 (4%), but similar to 2017 and 2018 (6.9%). No deaths were reported in cases that had travelled abroad.
- In June and July, a high number of LD cases were notified. The cases were geographically dispersed throughout the country and no large clusters or common sources were seen. The warm and wet weather in June may have been a driver of the increase in cases.
- Although more Dutch residents than usual stayed in the Netherlands for the holidays, there were no clusters in Dutch accommodations and no increase of cases with domestic travel

was observed. However, one rental holiday home was confirmed as source of infection for one case (see source finding and matching).
- Three cases were reported with a co-infection or subsequent infection of SARS-CoV-2 and *Legionella*.
- In 15% of culture positive cases, the pathogen was a *Legionella pneumophila* nonserogroup 1 (5%) or *Legionella* non*pneumophila* (10%). These infections can usually not be detected with the urinary antigen test for *Legionella*.

Source finding and matching:
- A genotypical match was found for 5 patients, which is 1% of patients. The proportion genotypical matches for patients with a match possibility was 22% (5 of 23 patients). In total 101 environmental investigations with sampling of potential sources were done.
- A cluster of six patients, with two cases in 2020, was linked to a wellness centre. Sampling results of the wellness centre in 2020 were negative, but in previous years three different *Legionella pneumophila* serogroup 1 strains were found in this wellness centre. The clinical strain of one patient in 2020 was identical to the *L. pneumophila* serogroup 1 strain found in a cold-water shower hose, a footbath and a warm jacuzzi of the wellness sauna found in sampling in previous years (genotypical match).
- A small geographic cluster of four cases was detected after which various environmental sources were sampled. *Legionella pneumophila* serogroup 3 and 7-14 was found in five wet cooling towers of two different companies and in the wastewater treatment plant of the town, and *Legionella pneumophila* serogroup 1 was found in industrial wastewater. A source of infection could not be confirmed, because no clinical isolates for comparison were available.
- For two LD patients the residential water installation was identified as source of infection by genotypical matching. One patient was matched with a *L. pneumophila* serogroup 3 strain found in a warm and cold-water tap. The other patient stayed with relatives, and a swab of the shower hose confirmed the shower as source of infection (*L. pneumophila* serogroup 1 ST1 strain).
- For one LD case an outdoor shower with whirlpool of a rental holiday home was identified as source of infection (genotypical match).
- Five LD cases had a *L. pneumophila* sg1 ST1646 as clinical isolate. One of these cases had worked on a short distance from a wastewater treatment plant (WWTP). Environmental sampling found ST1646 in the WWTP and a wet cooling tower, confirming the WWTP or cooling tower as most likely source of infection (genotypical match). The other cases with ST1646 lived in different regions of the country and their source of infection remained unidentified. This specific genotype, ST1646, has previously been linked to two LD outbreaks caused by industrial wastewater treatment plants in the Netherlands.
- 17 cases reported exposure to a spa pool in a private setting and 4 cases reported the use of a CPAP (respirator used by patients with apnoea). These sources are known to have an increased risk for a legionella infection, especially in case of insufficient maintenance.

6.1.2 Background

Legionellosis is an infection caused by inhalation of *Legionella* bacteria. Symptoms may range from mild to severe disease, but most diagnosed patients have a pneumonia (Legionnaires' disease (LD)). The incubation period of LD is usually 2-10 days and rarely exceeds 14 days. LD affects mostly the middle aged and elderly population, and men are more at risk than women. Furthermore, smoking, impaired health status and travel are risk factors for LD. Legionellosis without pneumonia is called pontiac fever (PF), but this syndrome is rarely diagnosed outside a cluster setting. PF is excluded from the European case definition for LD used in this report.
Legionella bacteria are common in the natural environment, usually in low numbers. At present, 61 different species of *Legionella* have been described and 28 species have been associated with human disease. Most LD outbreaks are associated with manmade water systems, such as wet cooling towers, whirlpools, water distribution systems and wastewater treatment plants. For the majority of non-outbreak cases (sporadic cases) however, the source of infection remains unknown. The common seasonal pattern of LD shows an increase in summer, especially after warm weather with heavy rainfall. These wet weather conditions are favorable for the survival of aerosolized *Legionella* bacteria, and this may lead to increased transmission. However, it remains unclear which environmental sources are driving the weather-related increase of Legionnaires' disease.
Most LD patients are diagnosed with a urine antigen test for *Legionella pneumophila* serogroup 1, which is the causative agent in most LD patients. Other serogroups or *Legionella* species can be diagnosed using culture or PCR on sputum or bronchial lavage. *Legionella pneumophila* or *Legionella* species PCR using specimens from the upper respiratory tract have very low sensitivity and are of limited diagnostic value. The culture method is important for obtaining a clinical isolate for typing. This is especially relevant for identification of sources through comparison of clinical strains to *Legionella* strains found in environmental sources. However, a clinical isolate is available for only one out of five Dutch patients, which is a limitation for source finding.

In this report all authorized LD notifications reported in Osiris with a date of onset in 2020 were analyzed. If date of onset date was unknown, the date of diagnosis minus the median diagnostic delay was used instead. LD cases in non-residents, and cases that do not meet the EU case definition of Legionnaires 'disease are excluded from further analysis.

6.1.3 Tables and figures

Figure 6.1 Annual numbers of notified Legionnaires' disease, 2011 through 2020, by infection acquired abroad or domestic (acquired within the Netherlands) (source: Osiris).

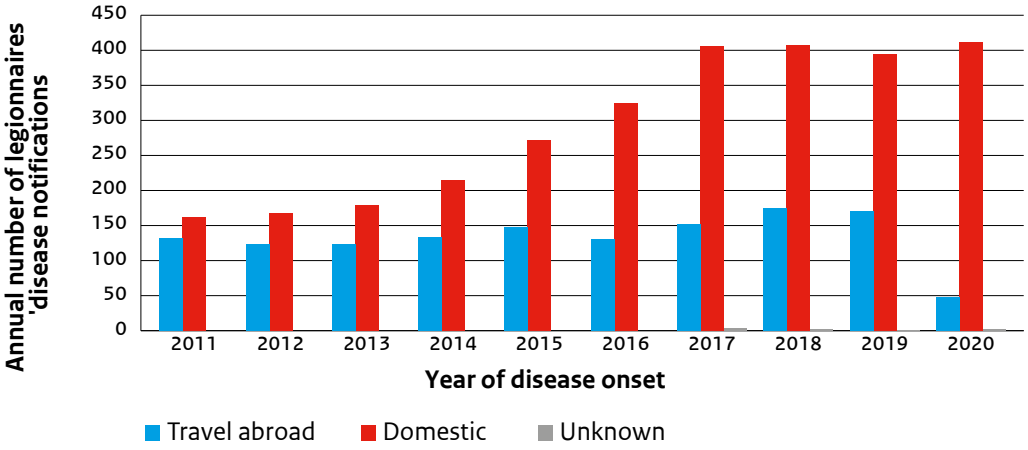

Figure 6.2 Notifications of Legionnaires' disease acquired abroad or acquired in The Netherlands (domestic), by month of disease onset in 2020 and the monthly average, minimum, maximum of domestic cases in the period 2015-2019 (source: Osiris).

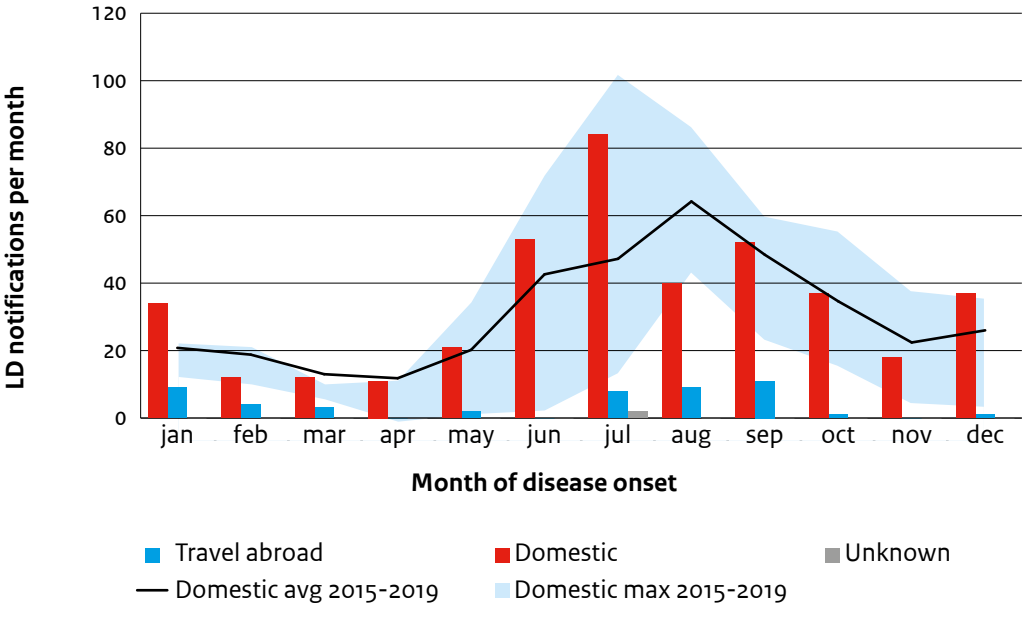

Table 6.1 Number of legionellosis notifications in 2016-2020, incidence, clinical and epidemiological background, mortality and diagnostics (source: Osiris).

Year of onset disease[a]	2016	2017	2018	2019	2020
Number of Legionellosis notifications[b]	468	575	594	587	475
Non-residents	6	7	10	8	2
Not fulfilling EU case definition:[b]	8	7	-	13	12
Pontiac fever or extrapulmonal	2	2	-	4	1
LD	6	5	-	1	1
Single high titre[c]	-	-	-	8	10
PCR nose or throat swab sample	14	14	10	21	14
Total excluded from analysis					
Total included	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**
Legionnaires'disease (LD) (=100%)[b]	**454 (100)**	**561 (100)**	**584 (100)**	**566 (100)**	**461 (100)**
% Difference to year before	+8%	+24%	+4%	-3%	-19%
Confirmed Legionnaires' disease[b]	422 (93)	519 (93)	536 (92)	524 (93)	425 (92)
Probable Legionnaires' disease[b]	32 (7)	42 (7)	48 (8)	42 (7)	36 (8)
LD Incidence (per 100,000 residents)	2.7	3.3	3.4	3.3	2.6
Male gender	327 (72)	401 (71)	420 (72)	407 (72)	342 (74)
Median age (Q1-Q3)	63 (55-72)	64 (54-73)	64 (57-74)	65 (55-73)	64 (56-73)
Hospital admission[d]	449 (99)	543 (97)	571 (98)	551 (97)	450 (98)
ICU admission[d]	unk	unk	unk	99/353 (28)	112 (26)
X-thorax confirmed pneumonia[d]	436 (96)	540 (99)	546 (98)	549 (99)	443 (98)
Deaths[d]	20 (4)	31 (6)	29 (5)	22 (4)	31 (7)
Acquired abroad of domestic					
Imported[e]	130 (29)	152 (27)	177 (30)	170 (30)	48 (10)
% Difference to year before	-10%	+17%	+17%	-4%	-72%
Not imported	324 (71)	406 (72)	405 (69)	395 (70)	411 (89)
% Difference to year before	+19%	+25%	-0.5%	-3%	+4%
Country unknown	-	3 (<1)	2(1)	1 (<1)	2 (<1)
Setting of infection					
Travel abroad[f]	130 (29)	152 (27)	177 (30)	169 (30)	48 (10)
Domestic travel[e,f]	17 (4)	45 (8)	35 (6)	38 (7)	19 (4)
Nosocomial (hospital acquired)	-	1 (<1)	-	2 (<1)	2 (<1)

Year of onset disease[a]	2016	2017	2018	2019	2020
Other healthcare facilities	7 (2)	5 (<1)	5 (<1)	4 (<1)	3 (<1)
Community acquired	300 (66)	355 (63)	361(62)	352 (62)	387 (84)
Setting unknown	-	3 (<1)	6 (1)	1 (<1)	2 (<1)
Diagnostics					
Legionella cultured performed (=yes)	209 (46)	229 (41)	263 (45)	271 (48)	205 (46)
Positive culture	84 (19)	92 (16)	111 (19)	113 (20)	107 (23)
Proportion *L.pneumophila* sg1 in culture (or PCR) positives[g]	85%	82%	85%	85%	84%
Positive urine antigen test	404 (89)	501 (89)	515 (88)	503 (89)	400 (87)
Positive PCR	88 (19)	103 (18)	102(17)	115 (20)	100 (22)
of which PCR only[h]	26 (6)	39 (7)	46 (8)	39 (7)	22 (5)
Significant titer rise	6 (1)	6 (1)	2(<1)	4 (<1)	2 (<1)
Diagnostic delay in days: median(Q1-Q3)	6 (4-8)	5 (4-7)	5 (4-7)	5 (4-7)	5 (4-7)

Analysis based on data as available on March 2020, including all authorized notifications.

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

[b] 2012 EU/EEA case definition for confirmed cases or probable cases of Legionnaires' disease. The numbers do not add up to the total excluded as categories for exclusion may overlap. PCR on upper respiratory samples such as swabs are reported in osiris from 2019 onward. Depending on the type of PCR used, these may be clinical valid diagnosis, but it does not fulfill the EU case definition for surveillance. Pontiac Fever cases are clinical cases without pneumonia with an epidemiological link. Extra pulmonal LD can for example be endocarditis or wound infection.

[c] Diagnosis based on a single high titer not specific for *L. pneumophila* serogroup1 or single high titer without information on type of serology.

[d] Percentage based on the number of patients for which this specific information was available. Admission at Intensive Care Unit (ICU) was registered from July 2019 onwards.

[e] An imported case is a case with travel abroad in the 2-10 days before onset or a community acquired case with probable or confirmed source abroad but without overnight stay, or a nosocomial case in a hospital abroad.

[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 (2015) or 2-10 days before disease onset (from 2016 onward), unless source finding suggests a non-travel associated source. A case with travel in the 11-14 days before onset will also be classified as travel associated if the case is part of a travel associated cluster or when environmental sampling confirms the travel site as source.

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

[h] No other diagnostic method reported in Osiris.

Figure 6.3 Age and gender distribution of cases with Legionnaires' disease with onset of disease in 2020 and age and gender specific incidence (LD notifications per 100,000 inhabitants (source: Osiris and CBS statline).

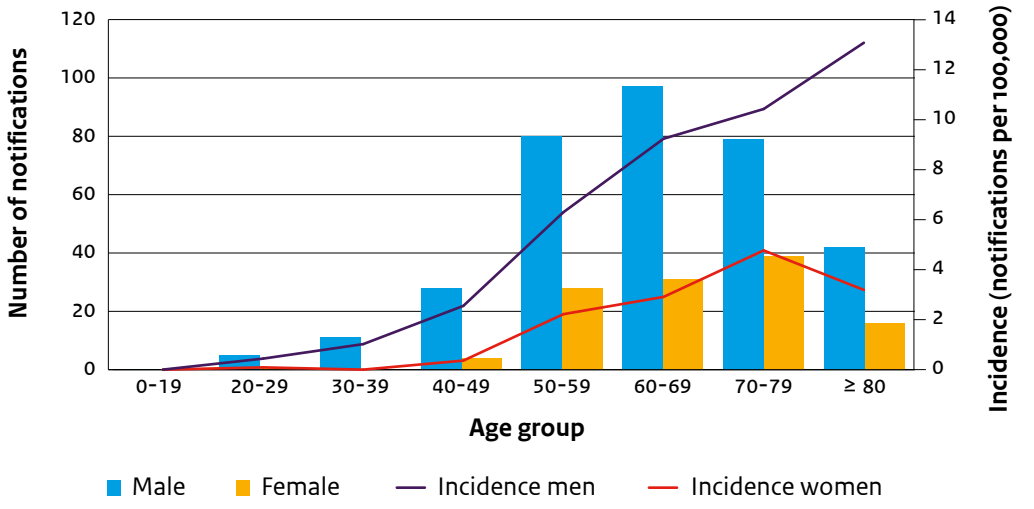

Figure 6.4 Distribution of the risk factors smoking and relevant underlying illness per age group reported in cases with Legionnaires' disease with onset disease in 2020 (source: Osiris).

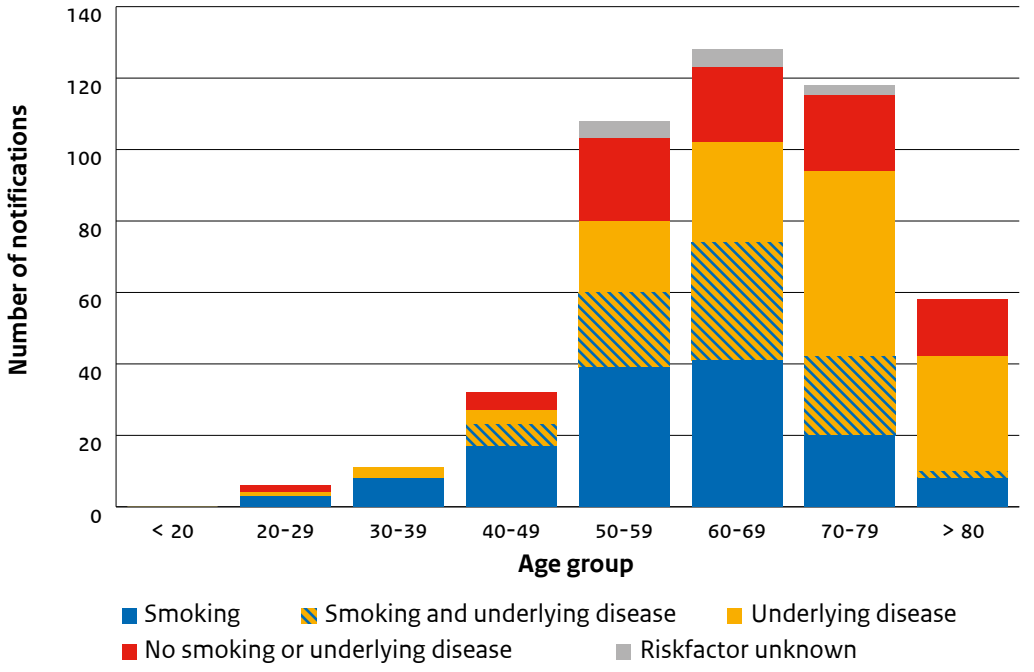

Table 6.2 Number of deaths and case fatality (CF) reported in cases of Legionnaires' disease with onset of disease in 2018-2020 by setting of infection and by age group and gender (source Osiris).

Setting of infection	2018			2019			2020		
	Deaths n	Total n	CF %	Deaths n	Total n	CF %	Deaths n	Total n	CF %
Travel abroad	1	177	**0.5**	6	169	**3.6**	0	48	**0**
Domestic	28	405	**6.9**	16	396	**4.0**	31	411	**7.5**
Country unknown	0	3	**0**	0	1	**0**	0	2	**0**
Domestic categories									
Domestic travel	2	35	**5.7**	3	38	**7.9**	2	19	**5.3**
Community acquired	24	361	**6.6**	13	352	**3.7**	27	387	**7.0**
Nosocomial	-	-	**-**	0	2	**0**	1	2	**50.0**
Healthcare associated	0	5	**0**	0	4	**0**	1	3	**33.3**
Setting unknown	2	6	**33**	0	1	**0**	0	2	**0**
Age group									
0-39	0	12	**0**	0	30	**0**	0	17	**0**
40-49	1	50	**2.0**	0	49	**0**	2	32	**6.3**
50-59	3	139	**2.2**	2	127	**1.6**	5	108	**4.6**
60-69	7	165	**4.2**	5	158	**3.2**	7	128	**5.5**
70-79	11	136	**8.1**	7	142	**4.9**	8	118	**6.8**
>= 80	7	82	**8.5**	8	60	**13.3**	9	58	**15.5**
Gender									
Male	15	420	**3.6**	15	407	**3.7**	23	342	**6.7**
Female	14	164	**8.5**	7	159	**4.4**	8	119	**6.7**
Total	**29**	**584**	**5.0**	**22**	**566**	**3.9**	**31**	**461**	**6.7**

Figure 6.5 Total number and proportion of patients admitted at Intensive Care in 2020 per age group (source Osiris).

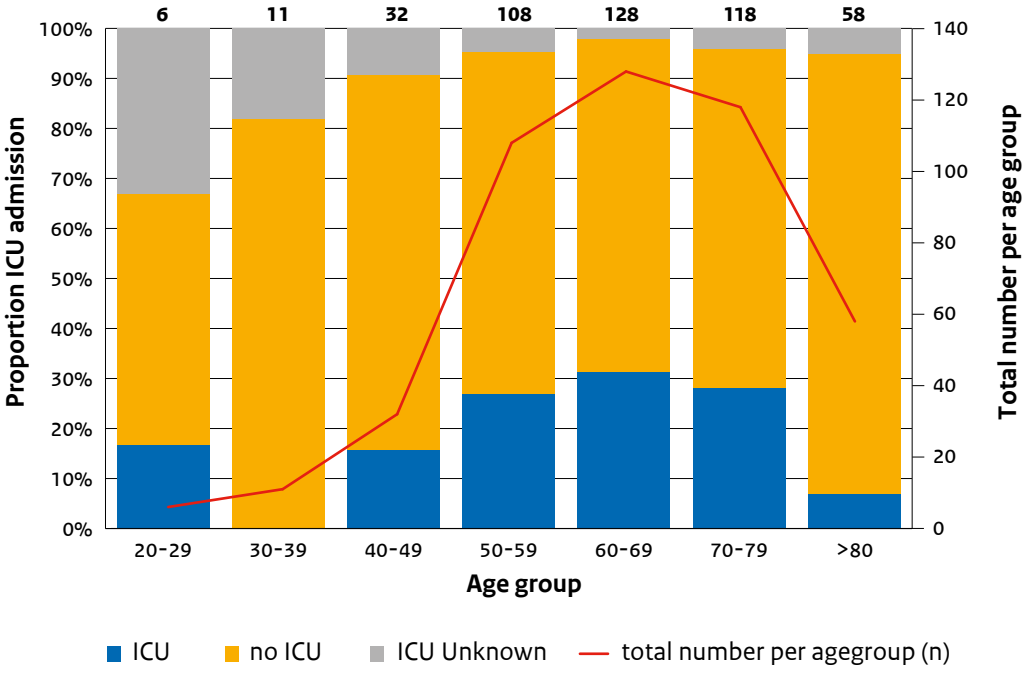

Figure 6.6 Regional incidence of domestic Legionnaires' disease per 100,000 inhabitants in 2020 by two-digit postcode area.

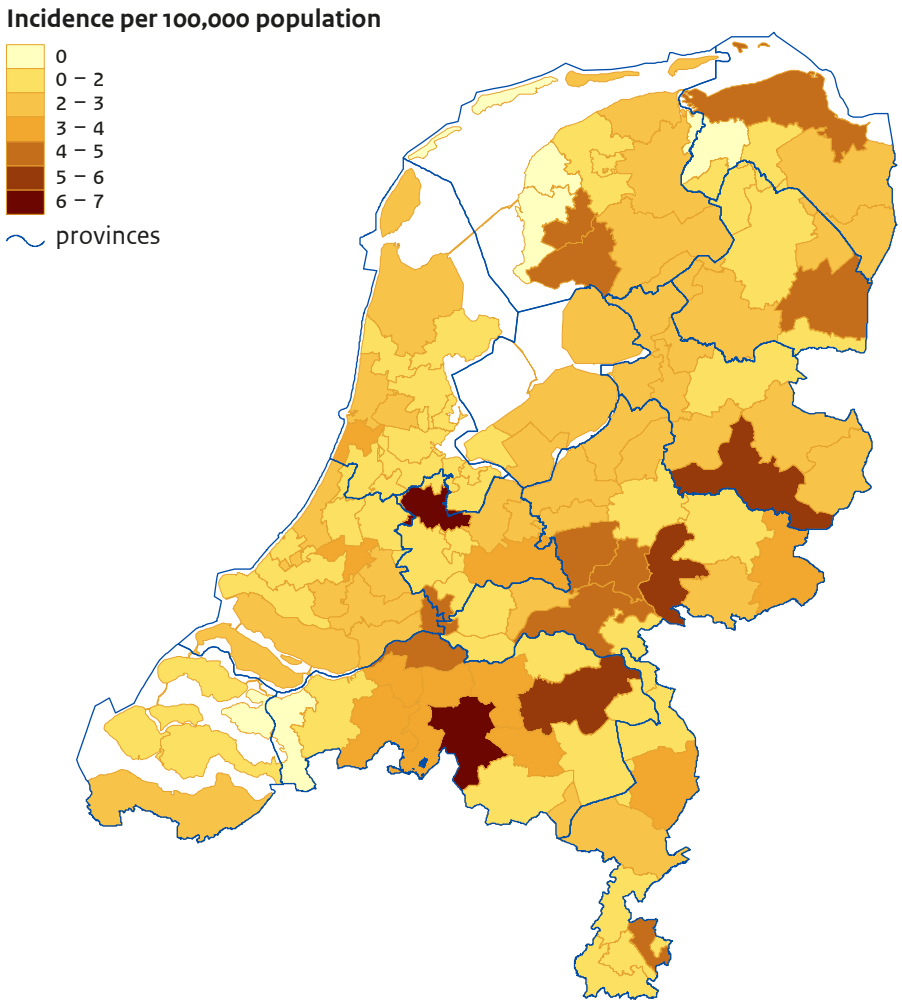

Table 6.3 Number and percentage of *Legionella* species, serogroup and Sequence Based typing (ST-type) of patients with Legionnaires'disease with onset in 2020, compared to 2010-2014 and 2015-2019. (Source: BEL, Osiris). The table includes both LD patients with disease acquired in the Netherlands (domestic cases) and patients with disease acquired abroad (imported cases).

Type *Legionella* isolates available for typing at reference lab[a]	**2010- 2014 n=318[a]**	**2015-2019 n=446[a]**	**2020 n=104[a]**
L. pneumophila (total)[a]	312 (98%)	420 (93%)	94 (90%)
L. pneumophila serogroup 1	286 (90%)	382 (86%)	89 (86%)
L. pneumophila serogroup 2	3 (1%)	6 (1%)	1 (1%)
L. pneumophila serogroup 3	8 (2%)	9 (2%)	2 (2%)
L. pneumophila serogroup 4	-	3 (<1%)	-
L. pneumophila serogroup 5	1 (<1%)	3 (<1%)	-
L. pneumophila serogroup 6	4 (1%)	9 (2%)	-
L. pneumophila serogroup 7-14	5 (2%)	7 (1%)	1 (1%)
L. pneumophila serogroup unknown	5 (1%)	1 (<1%)	1 (1%)
Legionella nonpneumophila (total)[a]	6 (2%)	26 (6%)	10 (10%)
L. longbeachae	3 (1%)	20 (4%)	5 (5%)
L. bozemanii	-	2 (<1%)	2 (2%)
L. anisa	-	2 (<1%)	1 (1%)
L. micdadei	1 (<1%)	-	2 (2%)
L. other species	1 (<1%)	2 (<1%)	-
Isolates reported, but not available at reference lab[b]	n=20	n=34	n=3
L. pneumophila	19	29	1
L. longbeachae	-	5	1
L. species unknown	1	-	1
Most frequent ST-types[a]	n=255	n=401	n=90
ST47	51 (20%)	115 (29%)	22 (24%)
ST62	18 (7%)	21 (5%)	6 (7%)
ST48	6 (2%)	8 (2%)	5 (6%)
ST82	3 (1%)	22 (5%)	5 (6%)
ST1646	4 (2%)	13 (3%)	5 (6%)
ST45	7 (3%)	2 (<1%)	4 (4%)
ST46	16 (6%)	13 (3%)	4 (4%)
ST289	-	3 (<1%))	4 (4%)
ST1	9 (4%)	13 (3%)	3 (3%)
ST23	11 (4%)	11 (3%)	3 (3%)
ST42	17 (7%)	13 (3%)	2 (2%)
ST37	12 (5%)	11 (3%)	2 (2%)
Total number different ST-types	80	98	33

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

[b] Patients with positive culture, *Legionella* species based on information reported in Osiris without confirmation reference lab.

6.2 Psittacosis and other zoonotic *Chlamydia* infections

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Contributors: Ingrid Keur en Edou Heddema

6.2.1 Key points

- In 2020, 94 patients with psittacosis were notified. This is slightly higher than 2019 (N=91), but a vast increase compared to previous years (on average 63 in previous four years).
- The higher numbers of notifications in 2019 and2020 are mainly due to the increased number of notifications in the autumn and winter of 2019/2020, which started in the east of the country, and expanded to the middle and south of the country. For detailed description see Chapter 3 'Uitgelicht' of the report 'Staat van Zoonosen 2019' (Vlaanderen, Cuperus et al. 2020)
- The median age of the patients was 67 years, similar to 2018 and 2019.
- Most of the notified patients were admitted to the hospital (94%), which was similar to previous years.
- Four deaths were reported in 2020, which was striking, as 2016 was the last year any psittacosis-related deaths were reported (1).
- Almost all patients were diagnosed by PCR (96%).
- Seventy-six (84%) samples from notified patients were sent for genotyping.
- Similar to previous years, genotype A (mainly, but not exclusively associated with parrots) and genotype B (associated with pigeons) were most prevalent (respectively 43% and 30%).
- In three patients a quite recently described *C. psittaci* genotype was detected with characteristics of genotype B and E. In two patients a previously unknown *C. psittaci* genotype was found (one SNP difference with type A).
- With the typing method used, also other closely related Chlamydia species can be detected. This resulted in the detection of *C. caviae* in one patient and *C. abortus* in one patient.
- In consultation between the PHS and the Netherlands Food and Consumer Product Safety Authority (NVWA), it is decided whether sampling of a possible source location is useful for tracing the source of a human case. Data from the Source Tracing Tool showed that for 33 patients at least one possible source location was sampled by the NVWA. Out of these in total 37 possible source locations, 14 possible source locations tested positive (38%). On 13 locations genotyping of *C. psittaci* positive material was performed. Nine positive locations had a genotypical match with material of the related patient(s). On two locations this concerned genotype A and on seven locations genotype B. There was no location with a genotypical mismatch with the material of the related patient. Furthermore, on four location no genotypical comparison was possible, because assessment of the patient sample was not possible by ZuyerlandMC.
- In addition to the human notifications that the NVWA received for human source tracing, they also receive notifications of clinical ill birds or positive laboratory test results of birds. In 2020, 36 of such veterinary notifications were received, 28 times a location was visited and birds were sampled (cloaca and/or faecal swabs). At 14 locations the birds had not been treated yet with any antibiotic, the NVWA sampled these birds and at 9 locations *C. psittaci* DNA was detected by the NVWA. The other 5 locations tested negative. The other 14 times a

location was visited by the NVWA after the birds were given an antibiotic treatment, in 2 cases *C. psittaci* DNA was still detected and in the other 12 cases the bacteria were eliminated after the antibiotic treatment. In the 11 positive samples, genotype A was found in 7 of these cases and for 4 samples the genotype could not be determined.
- In addition, the NVWA was able to back trace in 1 of these cases to the previous location of the animals. Several animals were sampled at this location. The animals tested negative.

6.2.2 Tables and figures

Figure 6.7 Number of notifications of human psittacosis by year and laboratory confirmation method, 2011 through 2020 (source: Osiris).

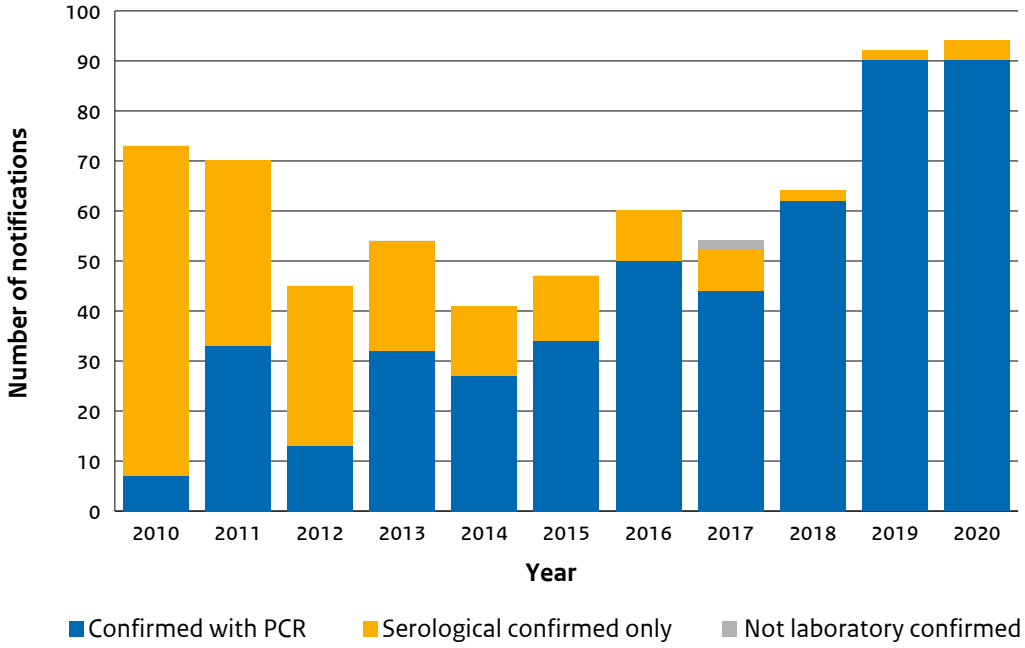


Table 6.4 Demographic, clinical and diagnostic characteristics of notified patients with psittacosis and positive diagnoses in the virological laboratory surveillance, in 2016-2020 (source: Osiris and virological laboratory surveillance, NWKV). Numbers between brackets are percentages, unless otherwise specified.

N (%), unless otherwise specified	2016	2017	2018	2019	2020
Notifications					
Number of notifications[a]	60 (100)	52 (100)	64 (100)	91 (100)	94 (100)
Incidence per 100,000 inhabitants	0.35	0.30	0.37	0.53	0.54
Median age in years (Q1-Q3)	58 (45 – 71)	55 (39 – 69)	65 (56 – 72)	65 (50 – 74)	67 (57 – 75)
Male gender[b]	48 (80)	27 (52)	50 (78)	71 (78)	70 (74)
Hospitalised[b]	49 (82)	44 (85)	58 (91)	86 (94)	89 (95)
Deaths[b]	1 (2)	0	0	0	4 (4)
Infected abroad[b]	4 (7)	0	1 (2)	3 (3)	1 (1)
Diagnostics used for notifications					
Median diagnostic delay in days (Q1-Q3)[d]	9 (6 – 14)	11 (7 – 27)	9 (6 – 12)	9 (7 – 14)	8 (6 – 12)
Mode of confirmation of laboratory diagnosis					
PCR[e]	50 (83)	44 (85)	62 (97)	90 (98)	90 (96)
Serological only	10 (17)	6 (12)	2 (3)	2 (2)	4 (4)
None	0	2 (4)	0	0	0
Number of patients eligible for genotyping[f]	50	44	62	89	90
Notified patients for whom diagnostic material for genotyping was received by Zuyderland MC[g]	37 (74)	36 (82)	55 (89)	75 (84)	76 (84)
Typing outcomes					
C. psittaci genotype A	12 (32)	11 (31)	19 (35)	36 (48)	33 (43)
C. psittaci genotype B	13 (35)	13 (36)	13 (24)	19 (25)	23 (30)
C. psittaci genotype C	1 (3)	0	1 (2)	2 (3)	0
C. psittaci genotype E/B	0	0	0	0	0
C. psittaci genotype most similar to A (1 SNP difference)	0	0	0	2 (3)	2 (3)
C. psittaci genotype most similar to C (93% homology)	0	2 (6)	0	0	0
C. psittaci genotype with characteristics of B and E	2 (5)	0	3 (5)	5 (7)	3 (4)

N (%), unless otherwise specified	2016	2017	2018	2019	2020
Negative for any *C. psittaci* genotype	7 (19)	8 (22)	3 (5)	2 (3)	4 (5)
Of which further diagnostics revealed					
C. caviae	0	2 (6)	2 (4)	2 (3)	1 (1)
C. felis	0	1 (3)	0	0	0
C. abortus	0	0	0	0	1 (1)
No assessement possible	2 (5)	2 (6)	16 (29)	9 (12)	11 (12)
Virological laboratory surveillance					
Number of positive diagnoses	32	15	26	30	31

[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 yet definite) are included.

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

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

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

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

[f] Genotyping of notified patients was started on 27 Augustus 2012. *C. psittaci* strains of notified psittacosis patients are genotyped at the Zuyderland MC in Sittard-Geleen/Heerlen using ompA genotyping. This method distinguishes at least nine avian genotypes of *C. psittaci* (A – F, E/B, M56, and WC). Each genotype is more or less bird type specific. This method can furthermore identify *C. abortus*. Genotyping is only possible if diagnosis is based on PCR.

[g] Percentage based on the number of patients eligible for genotyping.

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

6.3 Q-fever

Author: Daphne Reukers, Frederika Dijkstra
Contributor: Ingrid Keur

6.3.1 Key points

- In 2020, 7 patients with acute Q fever were notified. This is the lowest number of notifications since the Q fever epidemic. After 2013, the annual numbers varied from 14 to 26.
- Similar to previous years, the number of notifications (7) was lower than in the virological laboratory surveillance (53 positive diagnoses).
- As in previous years, most patients were male (86%). The median age was 48 years, which is younger than the median age in the previous 4 years.
- The median diagnostic delay in 2020 was 17 days. Which is within the range of the median diagnostic delay in the years 2008 – 2019 (between 16 and 43 days).
- Possible animal sources of infection can be sampled in the following situations:
  - *Bulk milk monitoring:* In 2020, the NVWA received no notifications of a positive sample in the bulk milk monitoring from the GD Animal Health (GD).
  - *Investigation of veterinary abortion waves:* In 2020, the NVWA received no notifications of abortion among small ruminants.
  - *Source finding following human cases:* In 2020, PHS reported three human cases to the NVWA for source finding. For these three human cases no likely/possible source could be identified.

6.3.2 Tables and figures

Figure 6.8 Number of notifications of acute Q fever by case classification and year, 2016-2020 (source: Osiris).

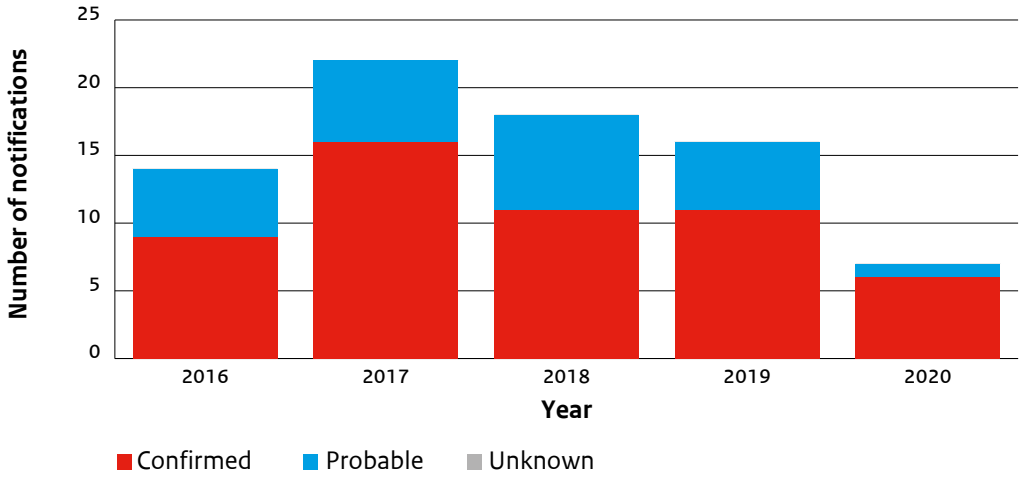


Table 6.5 Demographic, clinical and diagnostic characteristics of notified acute Q fever patients and positive diagnoses in the laboratory surveillance, 2016-2020 (source: Osiris and virological laboratory surveillance, NWKV).

N (%), unless otherwise specified	2016	2017	2018	2019	2020
Notifications					
Number of notifications[a]	14 (100)	22 (100)	18 (100)	16 (100)	7 (100)
Confirmed[b]	9 (64)	16 (73)	11 (61)	11 (69)	6 (86)
Probable[c]	5 (36)	6 (27)	7 (39)	5 (31)	1 (14)
Unknown	0	0	0	0	0
Incidence per 100,000 inhabitants	0.08	0.13	0.10	0.10	0.04
Median age in years (Q1-Q3)	49 (30 – 66)	53 (28 – 64)	50 (40 – 71)	62 (49 - 68)	48 (37 – 56)
Male gender[d]	11 (79)	16 (73)	15 (83)	14 (88)	6 (86)
Hospitalised[d]	7 (50)	13 (59)	15 (83)	11 (69)	5 (71)
Deaths notified in Osiris[d]	0	0	0	0	0
Infected abroad[d]	3 (21)	8 (36)	3 (17)	4 (27)	2 (29)
Median notification delay in days (Q1-Q3)[e]	1 (0 – 3)	0 (0 – 5)	0 (0 – 2)	1 (0 – 7)	0 (0 – 1)
Median diagnostic delay in days (Q1-Q3)[f]	14 (11 – 31)	29 (15 – 43)	16 (7 – 32)	43 (17 – 57)	17 (14 – 21)
Virological laboratory surveillance					
Number of positive diagnoses	89	65	44	69	53

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

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

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

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

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

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

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

6.4 Tuberculosis

Authors: Erika Slump
Contributors: Henrieke Schimmel, Karlijn van Beurden, Gerard de Vries, Jossy van den Boogaard

6.4.1 Key points

- In 2020, 623 tuberculosis (TB) patients were notified, a decrease of 17% compared to 2019 (754 notifications) and the largest decline in notifications in 50 years.
- The incidence rate of TB in 2020 was 3.6 per 100,000 population.
- The number of TB notifications was considerably lower during the COVID-19 lockdown months (particularly in April and November) in the Netherlands than in the same months in previous years.
- Less TB patients were found by active case-finding in 2020: n=69 (11%) compared to n=138 (18%) in 2019 and n=161 (20%) in 2018.
  - Less patients were detected by screening of risk groups such as immigrants and asylum seekers: n=45 (7%) in 2020 compared to n=89 (12%) in 2019 and n=115 (14%) in 2018, which was related to a lower number of migrants arriving in the Netherlands in 2020 during the COVID-19 pandemic.
  - Less patients were detected by contact investigation: n=24 (4%) in 2020 compared to n=49 (7%) in 2019 and n=46 (6%) in 2018, probably related to reduced TB transmission because of COVID-19 non-pharmaceutical interventions, such as social distancing.
- The absolute number of patients found through passive case-finding was also lower in 2020 (n=530) than in 2019 (n=593) and 2018 (n=609). This could possibly be caused by delays in diagnoses due to scaling down of healthcare services during the COVID-19 pandemic. However, due to the even lower number of patients found by active case finding the proportion of patients found by passive case finding was higher than usual, 85% in 2020, compared to 79% in 2019 and 77% in 2018.
- Most patients were foreign born (72%), mainly from Eritrea (n=74), followed by Morocco (n=61), India (n=42), Indonesia (n=29) and Somalia (n=20), and 62 other countries (n=233).
- 221 (49%) of the foreign-born patients resided less than 5 years in the country.
- 342 patients (55%) had pulmonary TB, 159 with smear-positive sputum, the most infectious form of TB. 279 patients (45%) had extrapulmonary TB. In 2 notifications the site of disease is still missing.
- Twelve patients had rifampicin-resistant TB, including nine patients with multidrug-resistant (MDR) TB. Ten patients with rifampicin-resistant TB were foreign born.
- 444 TB patients (71%) were tested for HIV in 2020, of whom 14 were HIV positive (2.2% of all TB patients and 3.2% of TB patients tested for HIV).
- In 2019, 87% of TB patients with rifampicin-sensitive TB completed treatment successfully (89% over the years 2014-2018[1]).
- 28 of 37 patients (76%) with rifampicin-resistant TB diagnosed in 2016-2018 completed treatment successfully.

[1] Treatment takes at least 6 months for drug-sensitive TB and often 20 months for rifampicin-resistant TB. Treatment outcome of drug-sensitive TB patients of 2020 and rifampicin-resistant TB patients of 2019 is not yet known.

6.4.2 Tables and figures

Figure 6.9 Tuberculosis incidence (per 100,000 population) in 2019 and in 2020 by two-digit postal code area.

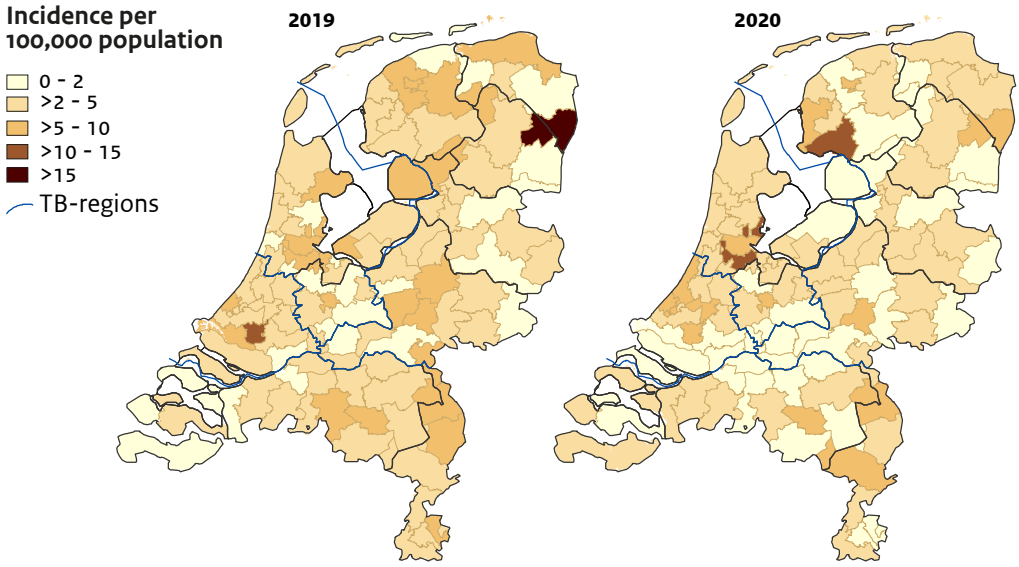


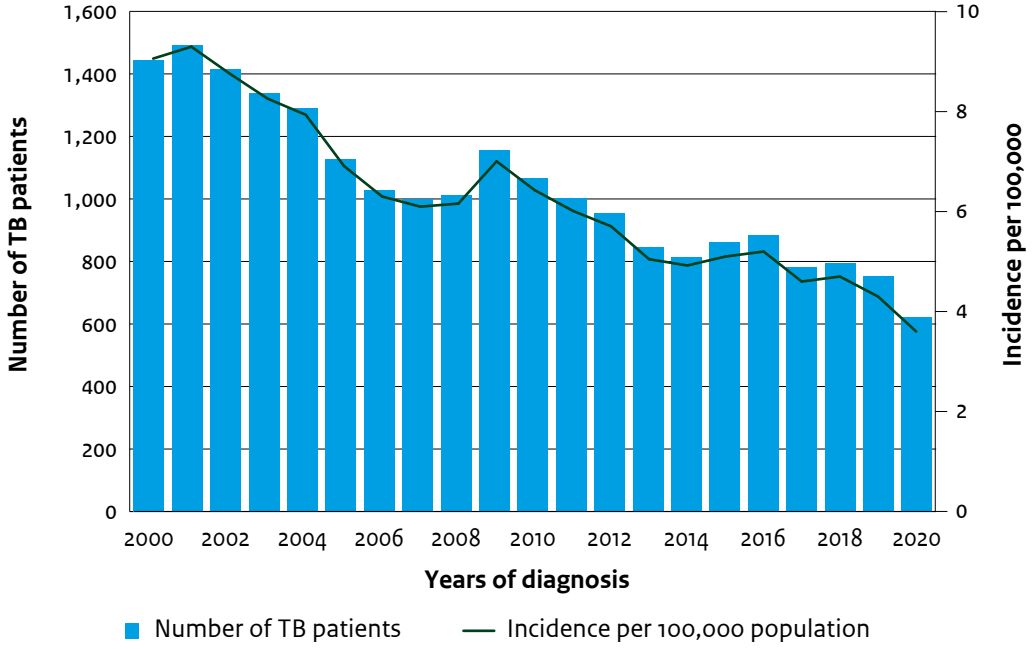
Table 6.6 Summary tuberculosis data the Netherlands, 2018, 2019 and 2020.

	2018	2019	2020
	N(%)	N(%)	N(%)
Number of notifications	795	754	623
Incidence per 100,000 population	4.6	4.3	3.6
Age (median in years)	35	37	36
Age <15 years	21 (2.6)	48 (6.4)	19 (3.0)
Age ≥65 years	113 (14)	112 (15)	90 (14)
Male to female ratio	1.7	1.4	1.3
Foreign born	616 (77)	570 (76)	451 (72)
<5 years in the Netherlands	318 (52)	277 (49)	221 (49)
Residence in 1 of 4 largest cities[a]	216 (27)	204 (27)	179 (29)
Pulmonary tuberculosis (PTB & EPTB)	460 (58)	444 (59)	342 (55)
Sputum-smear positive PTB	210 (26)	196 (26)	159 (26)
Culture-confirmed TB	556 (70)	503 (67)	423 (68)
Previous episode of TB (treatment)	40 (5.0)	30 (4.0)	30 (4,8)
HIV status known	624 (78)	597 (79)	444 (71)
HIV positive [c]	21 (3.4)	21 (3.5)	14 (3.2)
TNF-alpha inhibitors	12 (1.5)	10 (1.3)	7 (1.1)
Rifampicin resistant TB (incl. MDR TB/XDR TB)[b]	6 (1.1)	9 (1.8)	12 (2.8)
Isoniazid resistance[b]	35 (6.3)	18 (3.6)	26 (6.1)
Found by active case finding	161 (20)	138 (18)	69 (11)
TB patients in migrants			
Immigrants <2.5 years in the Netherlands	75 (9)	63 (8)	62 (10)
Asylum seekers <2.5 years in the Netherlands	129 (16)	108 (14)	61 (10)
Latent tuberculosis Infection	1,523	1,256	896

TB=tuberculosis, PTB= pulmonary TB, EPTB= combination of pulmonary and extrapulmonary TB
HIV= Human Immunodeficiency Virus, TNF = Tumor Necrosis Factor, MDR = Multidrug-resistant, XDR = extensively drug-resistant.

[a] Amsterdam, Rotterdam, The Hague and Utrecht
[b] percentage of culture-confirmed TB
[c] percentage of cases with known HIV status

Figure 6.10 Number of tuberculosis (TB) patients and incidence per 100,000 population, 2000-2020.



More detailed information about the TB surveillance in the Netherlands is available through the tuberculosis webpage of the RIVM (only available in Dutch). The *'TB Keypoints in the Netherlands 2020'* infographic is available through the (English) tuberculosis webpage. The next surveillance report 'Tuberculose in Nederland, 2020' will be published in December 2021.

The web-based application TBC-online provides information about TB in the Netherlands. TBC-online offers the opportunity to make tables and graphs of selected variables in the National Tuberculosis Register.

6.5 Animal influenza viruses

Authors: Marit de Lange, Adam Meijer

6.5.1 Key points

- In 2020, avian influenza virus outbreaks among poultry with HPAI H5N8 and H5N1 in the Netherlands occurred. Two exposed humans were tested for avian influenza viruses in the Netherlands, all were negative for influenza virus.
- One hospitalised patient in the South of the Netherlands, was retrospectively tested positive for Eurasian swine influenza virus A (H1N1)v clade 1C.2.1.

6.5.2 Background

Many different animals, including ducks, chickens and pigs, can be infected by influenza A viruses. Humans can be infected with avian, swine and other zoonotic influenza viruses, such as avian influenza virus subtypes A(H5), A(H7), and A(H9) and swine influenza virus subtypes A(H1)v, and A(H3)v, sometimes with high morbidity and mortality. In the Netherlands, the influenza virus surveillance on poultry farms consists of three parts. First, on poultry farms regular serological monitoring takes place to detect possible avian influenza infections. Second, poultry farmers also have the obligation to report clinical influenza symptoms in the poultry. Last, in cases where autopsy of the poultry cannot (fully) explain the cause of the condition, the veterinarian can send in samples for avian influenza virus testing. For pig farms there is no surveillance system for influenza virus infections in the Netherlands. The WHO provides a monthly overview of animal influenza virus infections in humans worldwide (WHO 2021). In the Netherlands, human infection with an animal influenza virus is a notifiable disease group B1, meaning that the attending physician and the laboratory are obliged to report a suspected patient to the PHS within 24 hours. This allows timely implementation of legal measures if necessary, such as mandatory hospitalization or isolation, mandatory investigation and prohibition of profession as possible options for containment. In case of suspicion of human infection, because of exposure to an infected farm or wildlife, or because of possible infected bird exposure during foreign travel, diagnostics are performed by the RIVM (CIb/IDS).

6.5.3 Epidemiological situation

In 2020, there were 10 commercial and one hobby poultry holdings infected with avian influenza virus, except for one with subtype A(H5N1) all were subtype A(H5N8) (WBVR 2021, Rijksoverheid 2021). Two people were tested with influenza-like illness that was associated with an infected poultry farm in the Netherlands. All were negative for influenza virus. In the same period, no returning travellers with possible animal influenza virus exposure were tested.

One human infection with a swine influenza virus A(H1N1)v was notified in 2020 from the South of the Netherlands. The case dates from the beginning of September 2020. The patient was in hospital for stem cell transplantation when he developed the influenza related symptoms (fever, headache). The patient's airway material tested positive by PCR for influenza A virus several times. However, during the validation of a new PCR test for SARS-CoV-2 and

influenza virus in the laboratory these specimens tested negative for influenza virus type A. Multiple initially influenza A virus positive specimens were sent to the National Influenza Centre location RIVM-IDS for further characterization. Characterization with Whole Genome Sequencing revealed a Eurasian swine influenza virus A(H1N1)v clade 1C.2.1. This virus has been detected in the swine population in recent years in different European countries, and does not have any human influenza virus A(H1N1)pdm09 gene segments as origin. The patient was treated with a course of Tamiflu. Under that therapy, the virus developed a resistance mutation. After the treatment, the patient tested positive for influenza A virus for another 14 days. This is relatively long but not unusual in immune supressed individuals. The patient recovered from influenza and was discharged healthy late November 2020. The patient's source research shows that the patient has not had direct contact with pigs or other animals. It is now being further investigated whether there has been exposure to pigs among the patient's contacts in and outside the hospital using serology.

6.6 MERS-CoV

Authors: Daphne Reukers, Adam Meijer

5.6.1 Background

In 2012, a new type of coronavirus was discovered in the Kingdom of Saudi Arabia (KSA): the Middle East respiratory syndrome corona-virus (MERS-CoV). This virus can cause Acute Respiratory Distress Syndrome (ARDS). Most common symptoms are fever, cough and shortness of breath. There is no evidence of sustained human-to-human transmission, although a large outbreak of nosocomial transmission starting with one imported case occurred in South-Korea. Dromedary camels are a major reservoir host for MERS-CoV and a source of MERS-infections in humans, although the route of transmission from animals to humans is not fully understood. 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 PHS. This enables the PHS to take immediate appropriate action aimed at preventing further transmission by tracing and follow-up of potential contacts. In case of suspected MERS-CoV infection in the Netherlands, diagnostics are performed at ErasmusMC. In May 2014, Middle East respiratory syndrome coronavirus (MERS-CoV) infection, with closely related viral genomes, was diagnosed in two Dutch residents, returning from a pilgrimage to Medina and Mecca, Kingdom of Saudi Arabia (Fanoy, van der Sande et al. 2014, Kraaij-Dirkzwager, Timen et al. 2014).

5.6.2 Epidemiological situation

In 2020, a total of 6 patients with (severe) acute respiratory illness, returning from countries where exposure to MERS-CoV is possible, were tested for MERS-CoV and none in 2021 (until May 2021). None of them had an infection with MERS-CoV.

Chapter 7
Other respiratory infections reported in the weekly virological surveillance

Authors: Daphne Reukers
Contributors: Adam Meijer, Anne Teirlinck, Frederika Dijkstra

7.1 Key points

- SARS-CoV-2 detections are not included in the weekly virological surveillance (see Chapter 2 COVID-19).
- In the first weeks of 2020, influenzavirus A, RSV and rhinovirus were most often detected. Rhinovirus and adenovirus were the primary detections in spring, summer and towards the end of the year 2020.
- The total number of positive rhinovirus (N=3,381 in 2020) steadily increased since 2016, when 2,589 positive test results were reported. The total number of reports as well as the peak in reports (N=153) was highest in 2020 compared to the previous four years.
- The total number of positive hMPV (N=591) test results in 2020 has decreased compared to 2019 (N=806). However, the total number was still higher than in 2016 (N=542) and the peak in number of positive hMPV test results was also higher than previous seasons (N=85 and N=43-60 in previous four seasons). There was no increase in number of hMPV test results during the respiratory season at the end of 2020 as in previous seasons.
- The total number of detections of all parainfluenza virus types 1 through 4 significantly decreased in 2020. They were the lowest reported in 5 years, except for type 1 (N=85) for which reports were lower in 2016 (N=55). The total number of positive parainfluenza virus test results was also highest for type 1. All parainfluenza types did not show a regular increase during the respiratory season (type 1, 2 and 4) or during spring (type 3) corresponding to previous seasons.

- The total number of positive adenovirus (N=1,040) test results was steadily low in 2020 and also the lowest reported since five years (range 2016-2019: 1,379-1,664).
- The total number of positive bocavirus (N=154) test results in 2020 was lower than 2019 (N=207) and 2017 (N=177), but comparable with the numbers in 2016 (N=159) and 2018 (N=150). The trend line also showed a regular pattern corresponding with previous seasons.
- The number of positive diagnoses for *Mycoplasma pneumoniae*, coronavirus (excluding SARS-CoV-2) and *Chlamydia pneumoniae* were the lowest reported since five years.

7.2 Discussion

The virological laboratory surveillance includes weekly data on the number of positive test results for respiratory pathogens originating from both primary care and hospitals. Patient's background and information on clinical presentation is lacking in the virological laboratory surveillance, and no distinction can be made between data from primary care and hospitals (Lagerweij, Schimmer et al. 2021). It is likely that patient population and disease severity differs between primary care and hospitals. In the last three years, generally higher numbers of positive test results were found than the years before. Changes in the number of positive test results in the virological laboratory surveillance data are not necessarily caused by actual changes in the incidence of infection, but can also be caused by changes in the policy of testing and testing procedures by the physicians and/or microbiological laboratories. One such change in testing might be the increased application of respiratory panels, which can be used for detection of the causative agent of disease in patients displaying a respiratory disease syndrome. In these panels, molecular detection of the most common viruses is performed in one test. However, which viruses are included in the respiratory panels and the extent to which the panels are used, differs between laboratories and between years. Furthermore, the impact of the COVID-19 epidemic on testing policy and procedure should not be overlooked. The numbers and figures in 2020 might be affected by a major focus on SARS-CoV-2 diagnostics in many laboratories, which makes interpretation and comparison of these numbers more difficult. After inquiring with the laboratories that participate in the weekly virological surveillance, most indicated that they have generally performed routine testing for the most common respiratory viruses in addition to SARS-CoV-2 during the winter season in patients with respiratory symptoms. Some laboratories only performed routine testing in the case of a negative SARS-CoV-2 test. Furthermore, non-pharmaceutical interventions targeted at reducing SARS-CoV-2 transmission, including social distancing and hygiene measures, impacted on the transmission of other respiratory viruses. This can partly explain why almost all respiratory viruses reported in this chapter show a significant decrease or a different pattern in the trend line in 2020 for most pathogens.

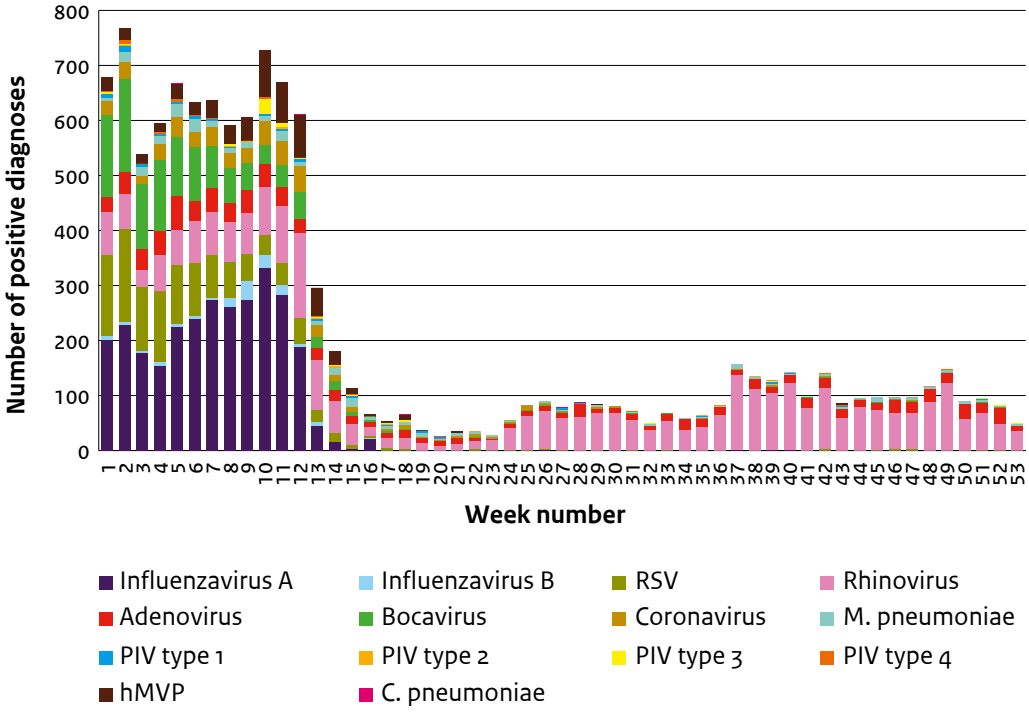
7.3 Tables and figures

Table 7.1 Number of reported positive tests of rhinovirus, *Mycoplasma pneumoniae*, human metapneumovirus, coronavirus (excluding SARS-CoV-2), parainfluenza virus type 1-4, *Chlamydia pneumoniae*, adenovirus and bocavirus in the virological laboratory surveillance for the period 2016-2020 (source: Virological laboratory surveillance, NWKV).

Number of positive diagnoses											
Year	Rhinovirus	*M. pneumoniae*	hMPV	Coronavirus (excl. SARS-CoV-2)	PIV type 1	PIV type 2	PIV type 3	PIV type 4	*C. pneumoniae*	Adenovirus	Bocavirus
2016	2589	608	542	712	55	108	411	65	19	1612	159
2017	2706	400	629	708	208	70	585	145	17	1379	177
2018	2755	328	846	682	94	150	476	112	17	1623	150
2019	3313	360	806	600	291	102	610	190	21	1664	207
2020	3381	328	591	486	85	22	74	43	12	1040	154

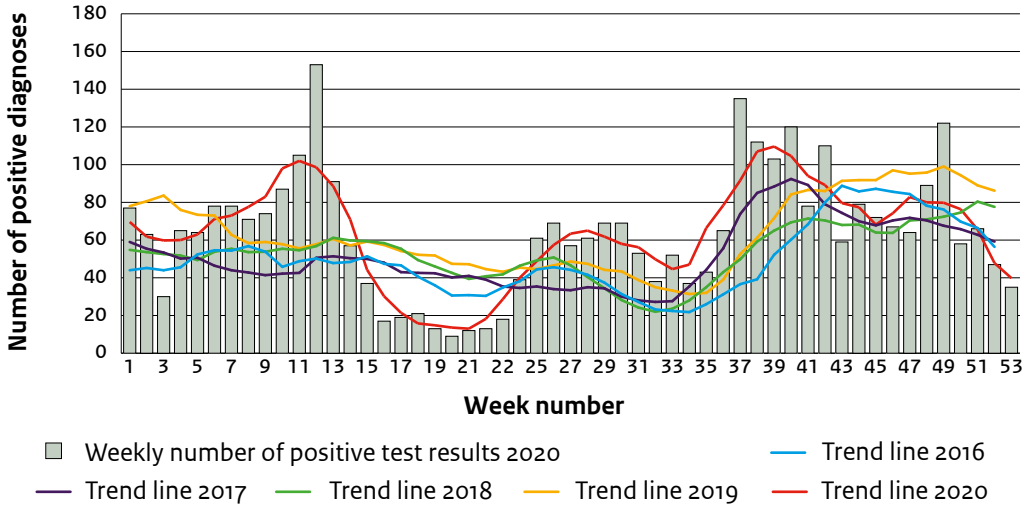
M. pneumoniae = *Mycoplasma pneumoniae*
hMPV= human metapneumovirus
PIV= parainfluenza virus
C. pneumoniae = *Chlamydia pneumonia*
NWKV = Dutch Working Group for Clinical Virology of the Dutch Society for Medical Microbiology (NVMM).

Figure 7.1 Number of reported positive tests of influenzavirus type A and B, respiratory syncytial virus , rhinovirus, *Mycoplasma pneumoniae*, human metapneumovirus, coronavirus (excluding SARS-CoV-2), parainfluenza virus type 1-4, *Chlamydia pneumoniae*, adenovirus and bocavirus in the virological laboratory surveillance for the year 2020 (source: Virological laboratory surveillance, NWKV).



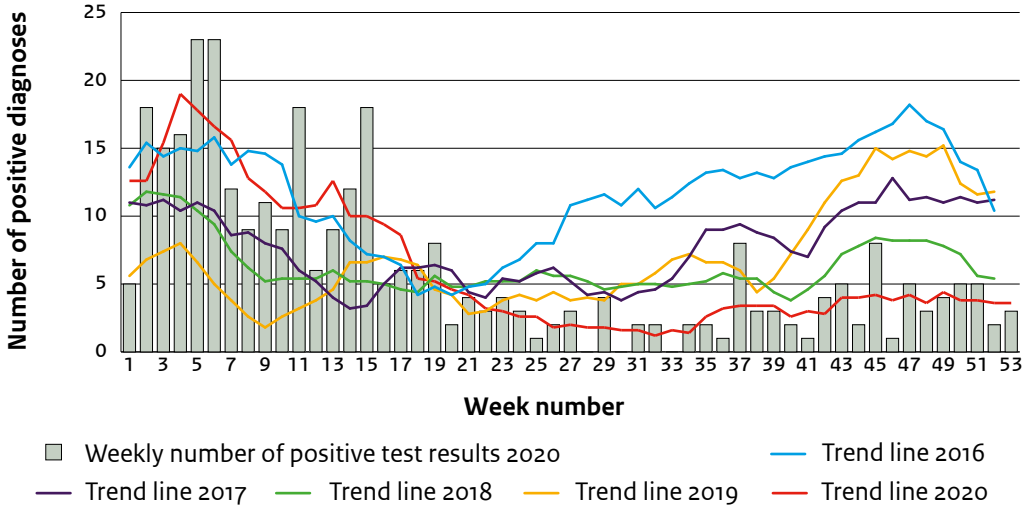
Footnote: *M. pneumoniae* = *Mycoplasma pneumoniae;* hMPV= human metapneumovirus; PIV= parainfluenza virus; *C. pneumoniae* = *Chlamydia pneumonia*; RSV= Respiratory Syncytial Virus; NWKV = Dutch Working Group for Clinical Virology of the Dutch Society for Medical Microbiology (NVMM).

Figure 7.2 Number of weekly reported positive test results of rhinovirus in the virological laboratory surveillance for the calendar year 2020 and the trend lines* for the calendar years 2016 – 2020.



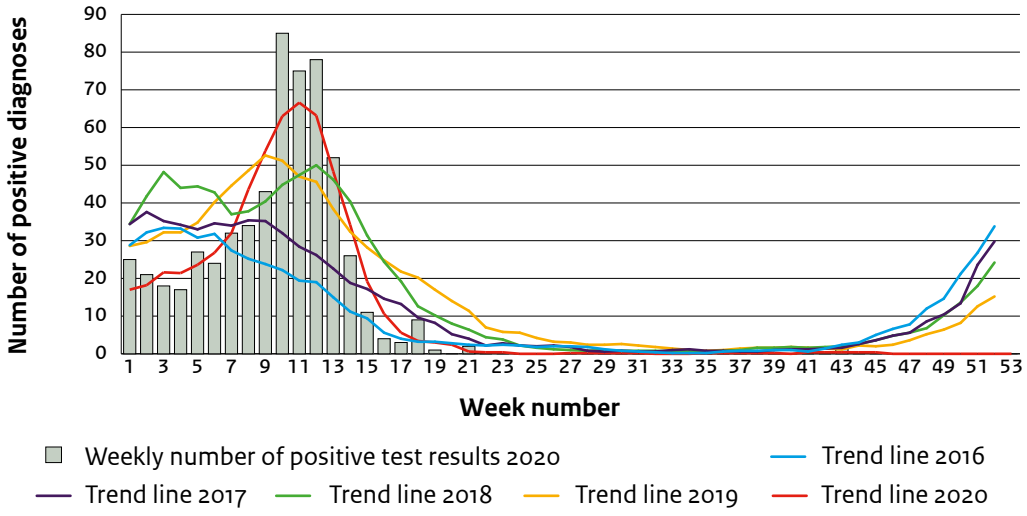
* 5-week moving average.

Figure 7.3 Number of weekly reported positive test results of *Mycoplasma pneumoniae* in the virological laboratory surveillance for the calendar year 2020 and the trend lines* for the calendar years 2016 – 2020.



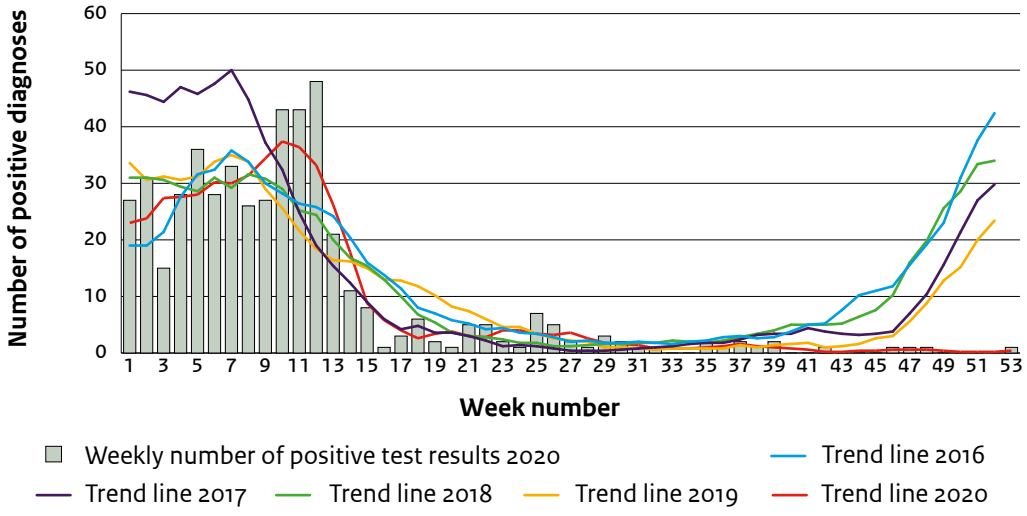
* 5-week moving average.

Figure 7.4 Number of weekly reported positive test results of human metapneumovirus in the virological laboratory surveillance for the calendar year 2020 and the trend lines* for the calendar years 2016 – 2020.



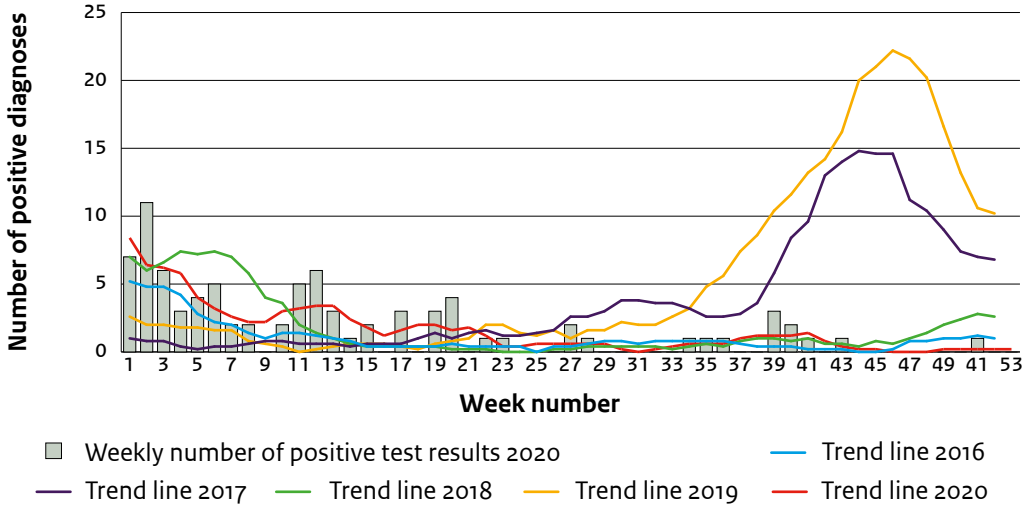
* 5-week moving average.

Figure 7.5 Number of weekly reported positive test results of coronavirus (excluding SARS-CoV-2) in the virological laboratory surveillance for the calendar year 2020 and the trend lines* for the calendar years 2016 – 2020.



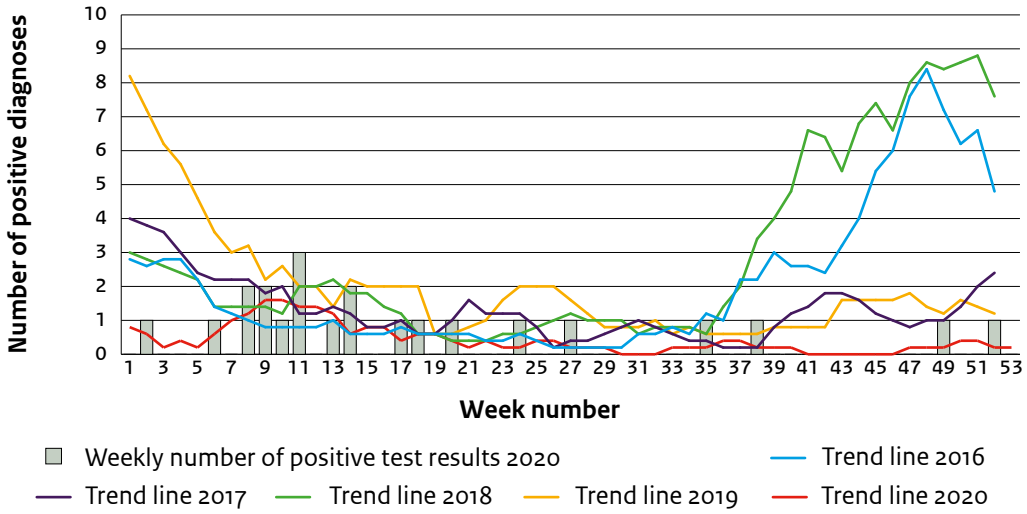
* 5-week moving average.

Figure 7.6 Number of weekly reported positive test results of parainfluenza virus type 1 in the virological laboratory surveillance for the calendar year 2020 and the trend lines* for the calendar years 2016 – 2020.



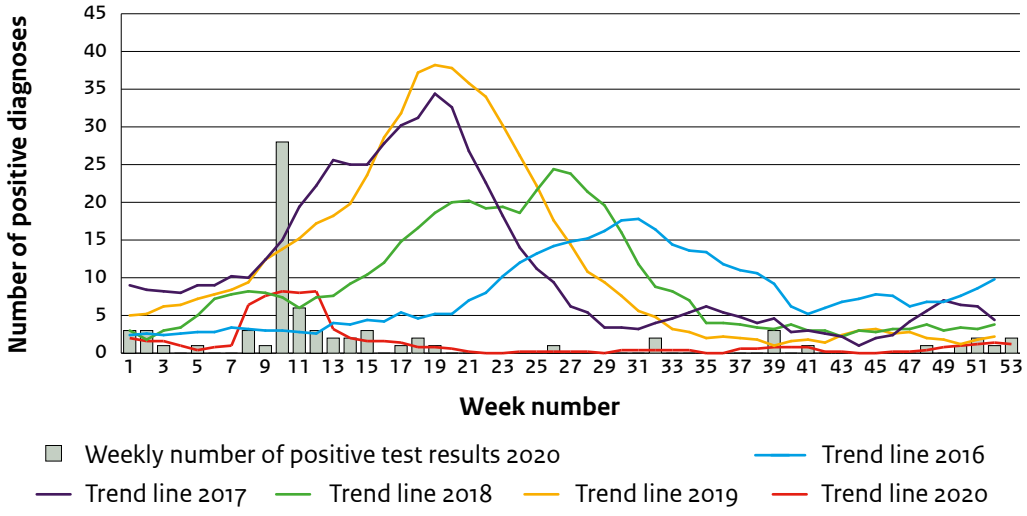
* 5-week moving average.

Figure 7.7 Number of weekly reported positive test results of parainfluenza virus type 2 in the virological laboratory surveillance for the calendar year 2020 and the trend lines* for the calendar years 2016 – 2020.



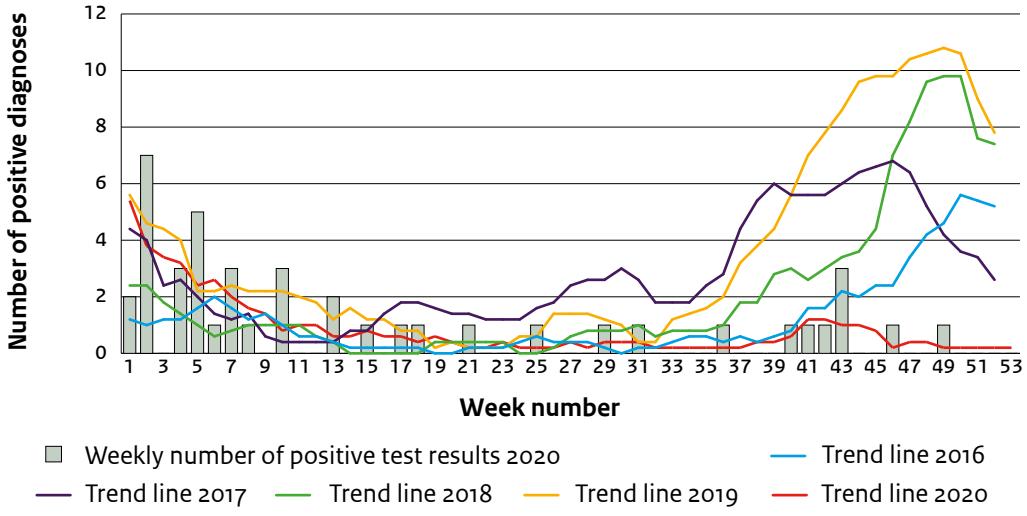
* 5-week moving average.

Figure 7.8 Number of weekly reported positive test results of parainfluenza virus type 3 in the virological laboratory surveillance for the calendar year 2020 and the trend lines* for the calendar years 2016 – 2020.



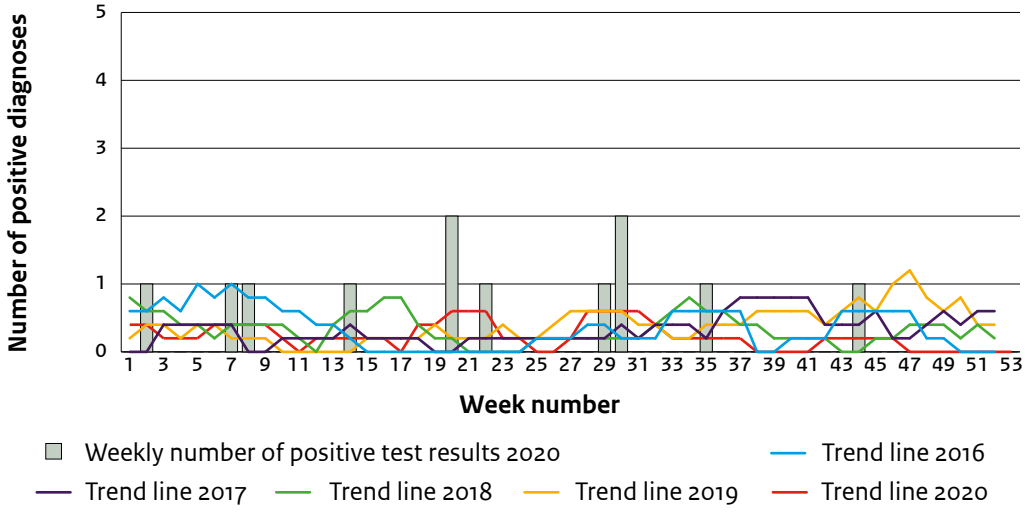
* 5-week moving average.

Figure 7.9 Number of weekly reported positive test results of parainfluenza virus type 4 in the virological laboratory surveillance for the calendar year 2020 and the trend lines* for the calendar years 2016 – 2020.



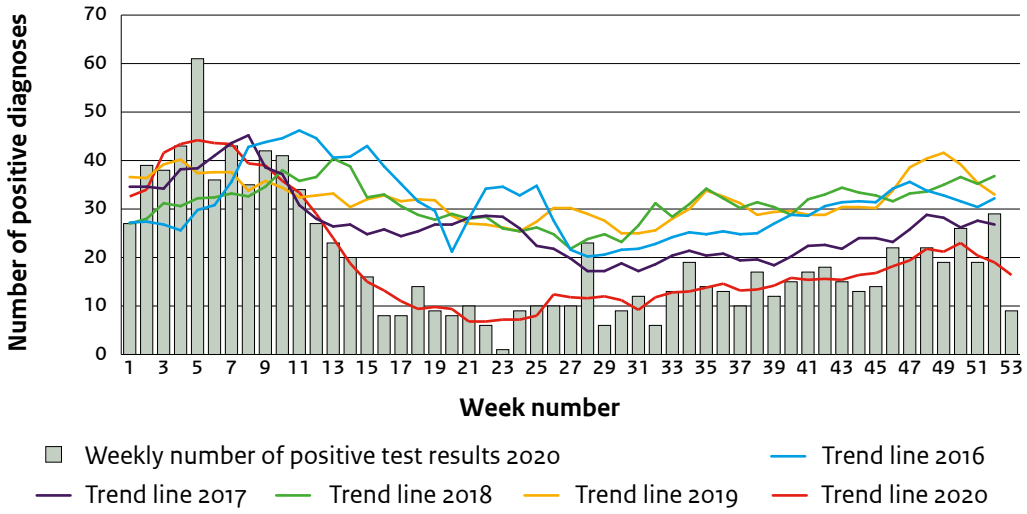
* 5-week moving average.

Figure 7.10 Number of weekly reported positive test results of *Chlamydia pneumoniae* in the virological laboratory surveillance for the calendar year 2020 and the trend lines* for the calendar years 2016 – 2020.



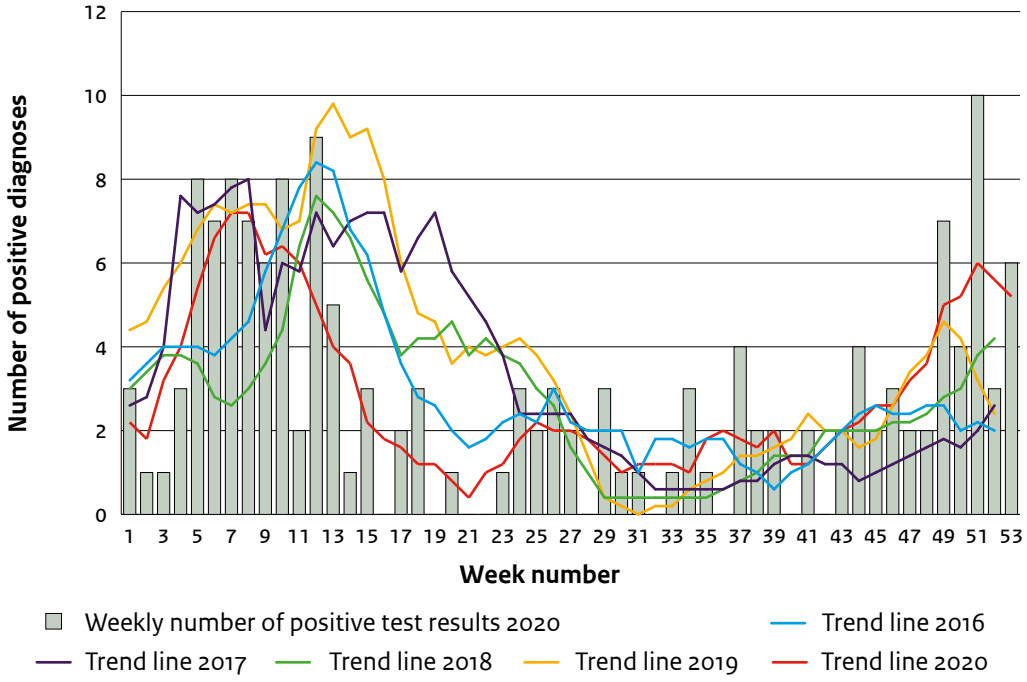
* 5-week moving average.

Figure 7.11 Number of weekly reported positive test results of adenovirus in the virological laboratory surveillance for the calendar year 2020 and the trend lines* for the calendar years 2016 – 2020.



* 5-week moving average.

Figure 7.12 Number of weekly reported positive test results of bocavirus in the virological laboratory surveillance for the calendar year 2020 and the trend lines* for the calendar years 2016 – 2020.



* 5-week moving average.

Chapter 8
Burden of respiratory infectious diseases in the Netherlands

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Contributors: Daphne Reukers, Erika Slump, Petra Brandsema, Marit de Lange, Anne Teirlinck

8.1 Key points

- The respiratory infectious disease with the highest disease burden in 2020 was COVID-19 with an estimated 169,000 DALY (166,000-173,000), followed by legionellosis with an estimated 6300 DALY (5600-7100). Disease burden in 2020 was estimated at 1800 DALYs (1700-1800) for tuberculosis; 610 DALYs (470-770) for psittacosis, and 23 DALY (19-27) for Q fever.
- The influenza burden of season 2020/2021 was negligible, likely due to the non-pharmaceutical interventions (NPI) taken to curb the spread of SARS-CoV-2 in the Netherlands. Since there were no cases reported by the NIVEL sentinel GP practices, the influenza burden was expected to be extremely low. Therefore, the burden of influenza is not included in the results below.
- For psittacosis, the burden estimate for 2020 has increased and is the highest reported since 2015. There was a cluster of psittacosis cases in the winter of 2019/2020, which resulted in the highest number of reported cases in 2020 since 2010 and therefore also a high disease burden in 2020.
- The burden of legionellosis has steadily increased during the past four years, but has decreased in 2020 compared to 2019. The burden of tuberculosis and Q-fever has also decreased in 2020 compared to the previous four years. This is likely due to the low number of reported cases in 2020 in these three infectious diseases, likely as a result of the COVID-19 pandemic and the corresponding NPI.

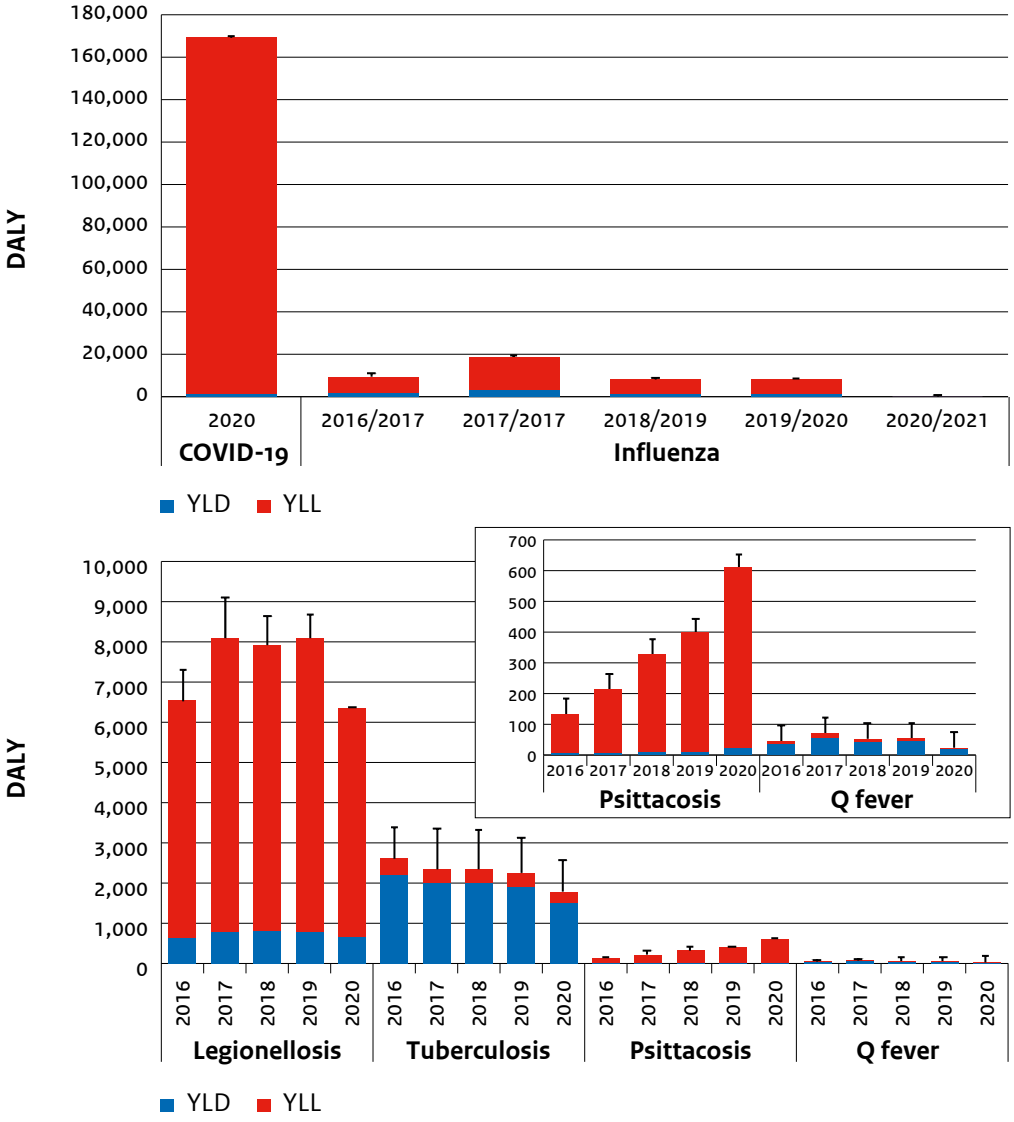
- The burden of COVID-19 is reported for the first time in this report. The burden of COVID-19 is estimated to be 169,000 DALY for 2020 where 99% of the burden is due to excess mortality caused by COVID-19 (see Chapter 2 and 3.3). The presented burden estimate of COVID-19 is an underestimation of the actual burden since long-term consequences of the disease are not taken into account. Furthermore, there is insufficient data about the epidemiology and long-term impact of COVID-19 at this time to properly estimate the disease burden in DALY/100 cases.

8.2 Background

Estimates of the burden of infectious diseases are used to compare health impact between different infectious diseases in the Dutch population and to follow trends in time. The burden of a disease is a combination of incidence and severity. Disease burden is expressed here in disability-adjusted life years (DALYs), which indicates the number of healthy life years lost due to a disease. DALY is the sum of years of life lost due to mortality (YLL) and years lived with disability due to morbidity (YLD) (Mangen, Plass et al. 2013). The burden of infectious diseases (except for COVID-19 burden estimate) in the Netherlands was estimated using the Burden of Communicable Diseases in Europe (BCoDE) methodology, which adopts the 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 number of respiratory infections that occurred in the years 2016 to 2020, or the disease burden that theoretically could have been avoided by preventing infections in those years.

8.3 Tables and figures

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 2016-2020 (seasons 2016/2017 through 2019/2021 for influenza and only 2020 for COVID-19).



Footnote: Error bars indicate 95% confidence intervals. The insert zooms in for psittacosis and Q fever.

Table 8.1 Estimated annual disease burden in YLD per year, YLL per year, DALY per year, DALY per 100 cases (with 95% confidence intervals) and estimated annual number of acute infections in the years 2015 to 2019 (season 2015/2016 to 2020/2021 for influenza) in the Netherlands in order of highest to lowest average DALY/year in 2020.

Disease	YLD/ year	YLL/ year	DALY/ year	DALY/ 100 cases[a,b,d]	Annual acute infections[c]
Covid					
2020[d]	1200 (1200-1300)	168000 (164000-171000)	169000 (166000-173000)	-	-
Influenza					
2016/ 2017	1500 (1300-1600)	7900 (7300-8600	9400 (8600-10200)		471000
2017/ 2018	2900 (2700-3100)	15700 (14800-16600)	18600 (17500-19600)		933000
2018/ 2019	1300 (1200-1400)	6800 (6300-7300)	8000 (7400-8700)		402000
2019/ 2020	1300 (1200-1400)	6800 (6300-7300)	8100 (7600-8700)		405000
2020/ 2021[e]	-	-	-	-	-
Legionellosis					
2016	640 (1200-1400)	5900 (5200-6600)	6500 (5800-7300)		5900
2017	790 (720-870)	7300 (6500-8100)	8000 (7200-9000)		7300
2018	820 (750-900)	7100 (6300-8000)	7900 (7100-8900)		7600
2019	790 (730-870)	7300 (6500-8100)	8100 (7300-9000)		7400
2020	650 (590-710	5700 (5000-6400)	6300 (5600-7100)	110 (97-110)	6000

Disease	YLD/ year	YLL/ year	DALY/ year	DALY/ 100 cases[a,b,d]	Annual acute infections[c]
Tuberculosis					
2016	2200 (2200-2200)	400 (360-440)	2600 (2500-2600)		990
2017	2000 (1900-2000)	350 (320-390)	2300 (2300-2400)		880
2018	2000 (2000-2010)	340 (310-380)	2300 (2300-2400)		890
2019	1900 (1800-1900)	350 (320-390)	2200 (2200-2200)		850
2020	1500 (1500-1500)	280 (250-310)	1800 (1700-1800)	250 (250-260)	700
Psittacosis					
2016	4 (3-4)	120 (90-170)	130 (100-170)		950
2017	5 (5-6)	210 (160-270)	220 (170-280)		1500
2018	7 (5-8)	320 (240-420)	330 (250-430)		1800
2019	9 (8-11)	390 (290-500)	400 (300-510)		2500
2020	20 (15-26)	590 (450-750)	610 (470-770)	12 (9-14)	5200
Q fever					
2016	34 (27-43)	11 (9-14)	46 (36-56)		190
2017	54 (45-64)	18 (15-22)	72 (60-86)		300
2018	40 (33-46)	12 (10-15)	52 (43-61)		250
2019	44 (37-53)	11 (9-14)	56 (46-66)		250
2020	17 (14-21)	6 (5-7)	23 (19-27)	60 (59-61)	96

[a] for Q fever, asymptomatic acute infections can lead to disease burden from sequelae, the estimated annual DALY were therefore divided by the sum of both symptomatic and asymptomatic acute infections per year.

[b] DALY/ 100 cases is only shown for 2020 since this measure is a characteristic of the disease and is independent of time.

[c] this number includes asymptomatic acute infections for Q fever.

[d] At this time, there is insufficient data about the epidemiology and long-term impact of COVID-19 to properly estimate the disease burden in DALY/100 cases.

[e] Since there were no influenza cases reported by the NIVEL sentinel GP practices during the 2020/2021 respiratory season, the influenza burden could not be calculated.

Chapter 9
General discussion and conclusion

Authors: Rianne van Gageldonk-Lafeber, Anne Teirlinck, Daphne Reukers

COVID-19

The COVID-19 pandemic has caused an unprecedented rise in hospitalizations and deaths in 2020 and 2021. While insight in the circulation of SARS-CoV-2 in the community during the first period was blurred by the restricted testing policy, during the second and third period, this could be monitored more closely. The number of SARS-CoV-2 notifications in relation to the number of hospitalizations of SARS-CoV-2 positive patients and confirmed COVID-19 deaths were relatively lower during the first period and relatively higher during the second and third period due to these testing policies. As could be expected, the burden of COVID-19 (as expressed in DALYs) was far higher (more than 25 times higher) than any other respiratory diseases in 2020 and 9 times higher than the burden of influenza during the high endemic season 2017/2018) despite all strict transmission prevention measures.

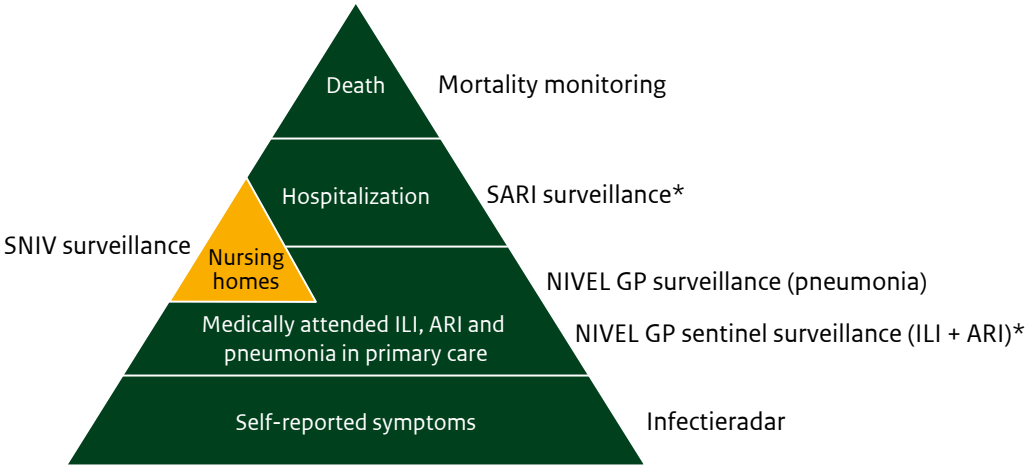
Besides the direct impact on health and society, the COVID-19 pandemic also greatly impacted the circulation of other respiratory pathogens, and the surveillance of respiratory infections. Due to non-pharmaceutical interventions, such as social distancing and travel restrictions, circulation of other viruses was highly diminished, resulting in hardly any cases of influenza, RSV, and other seasonal respiratory viruses that normally circulate in wintertime. The timing of circulation of most respiratory viruses was different and the number of virus detections as well as the height of the peak was much lower than previous seasons. Although this report only shows the trend lines for the year 2020, recent surveillance reports showed that other respiratory viruses started to circulate in the spring of 2021. Some started circulating more or less in their usual pattern (e.g. parainfluenza type 3, circulating in March and April 2021), or totally outside their usual pattern (e.g. RSV, seasonal human coronaviruses and hMPV). At the moment of writing (July 2021), RSV detections are vastly increasing and above the epidemic threshold. Also in many other northern hemisphere countries, including many European countries, a delayed RSV epidemic with increased RSV activity and a rise in hospital admissions

for (RSV) bronchiolitis was observed in spring 2021. The same phenomenon had already been reported in the southern hemisphere (van Summeren, Meijer et al. 2021). How this will influence the circulation of these viruses in the future cannot be easily predicted and depends on many factors, including the possible circulation of SARS-CoV-2 and accompanying measures in autumn and winter 2021.
In addition to the altered circulation of viruses, healthcare seeking behavior was also different during the respiratory season, and patients with (mild) respiratory complaints were advised to test for SARS-CoV-2 at the PHS test locations. This resulted in very low ILI and ARI notifications by the GPs. In nursing homes, on the contrary, the reported ILI incidence was similar to previous seasons, since nursing home residents still consulted the elderly care physician and were therefore still notified in the nursing home surveillance (SNIV) in 2020/2021. The number of consultations for pneumonia was also lower than usual throughout the entire year, both at the GP's and in nursing homes. This might indicate that while (pneumococcal)pneumonia is a common complication of influenza, this only happens to a lesser extend with COVID-19 (Rouze, Martin-Loeches et al. 2021). Many other sequelae of COVID-19 such as chronic fatigue and lung fibrosis (all together referred to as long COVID) have been described and are an important topic of research in many settings, including at RIVM.

Influenza surveillance

During the 2020/2021 winter season, there was no substantial influenza virus circulation and therefore no influenza epidemic. The ILI incidence did not exceed the epidemic threshold, no influenza virus was detected in the Nivel sentinel GP surveillance and only two influenza virus detections were reported in the virological laboratory surveillance. This was likely due to the impact of the various non-pharmaceutical interventions (NPI) implemented to reduce the spread of SARS-CoV-2. The request to all persons with respiratory symptoms to get tested for SARS-CoV-2 at dedicated testing centres of the PHS likely affected the respiratory surveillance (Karlsson, Mook et al. 2021). This will have influenced the incidence of ILI consultations and may have influenced the representativeness of virus detections in the sentinel GP surveillance compared to previous seasons. The number of notifications, hospitalizations and ICU admissions of persons positive SARS-CoV-2 have been decreasing steadily since the start of the vaccination campaign. If these trends persist, the current extensive COVID-19 surveillance that has been set up needs to be incorporated into existing systems (figure 9.1). Therefore, for the upcoming winter season, it is important to strengthen the sentinel GP surveillance, as this has always been the basis of the national respiratory surveillance.

Figure 9.1 The respiratory infections surveillance pyramid in the Netherlands.



Footnote: Systems with * also include virological surveillance.

In addition, the COVID-19 pandemic has once again emphasized the importance of surveillance of severe acute respiratory infections (SARI), which is still the missing link in the Dutch respiratory surveillance system (figure 9.1). As described in previous editions of this annual report, we are planning to set up a SARI surveillance system making use of the Dutch financial 'DBC' codes. A pilot study showed that these financial codes are currently the only routinely collected data suitable for an automated SARI-surveillance generating near real-time (weekly) data on the number of hospitalised patients with an acute respiratory infection. These data will be combined with patient demographics and microbiological test results (Groeneveld, Dalhuijsen et al. 2017, Marbus, van der Hoek et al. 2020). The SARI surveillance system is not in place yet, because of shifting priorities due to the COVID-19 epidemic, but would be a valuable source of information for monitoring the situation of the COVID-19 pandemic, but also all other respiratory diseases. Since circulation of other respiratory pathogens is greatly affected by the COVID-19 pandemic, the occurrence and circulation of these pathogens will be more unpredictable in the coming period and hence careful monitoring, also at the hospital level, is essential.

Accelerated by the COVID-19 outbreak, a new platform Infectieradar has started by RIVM and has been operational since November 2020. This platform provides information on the base of the surveillance pyramid: the self-reported ILI incidence in the general population (figure 9.1). It is again based on Influenzanet, an existing European partnership between different universities and governments. The aim of this collaboration is to monitor and map symptoms of viral infections, such as influenza, in humans in the Netherlands. Participants complete an online application form, which contains various medical, geographical and behavioural questions. Subsequently, participants are reminded weekly to report any symptoms they have experienced in the past week. The incidence of ILI is determined on the basis of a uniform case definition, so it can also be compared between countries participating in Influenzanet.

Influenzanet has also been adapted to collect additional information on trends and symptoms related to COVID-19 in order to provide useful insights to limit the spread of this virus.
A weekly overview of the results of Infectieradar are published on the RIVM website (https://www.rivm.nl/infectie-radar/resultaten). These results provide a good sense of the number of persons with respiratory symptoms, which is an important base in the respiratory surveillance pyramid in addition to the respiratory Nivel GP sentinel surveillance and the extensive COVID-19 surveillance system currently in place. These results will be added to the next annual report in 2022, reporting over season 2021/2022.

Notifiable respiratory diseases

The effect of the COVID-19 epidemic and NPI on other notifiable respiratory diseases and zoonotic diseases, such as Q-fever and psittacosis, is not likely to be a direct effect, as social distancing between humans does not influence zoonotic transmission. However, measures such as closing of schools, restaurants and gyms and working more from home, can have an indirect effect.
In the case of Legionella, the reduced amount of international travel has lessened the number of infections acquired abroad and therefore the total number of Legionella infections has also decreased in 2020 compared to the previous four years.
The number of TB notifications was also considerably lower during the 2020 COVID-19 lockdown months (particularly in April and November) in the Netherlands than in the same months in previous years. This is likely a result of several factors, such as the effect of COVID-19 NPI on TB transmission clusters and decline in healthcare seeking behavior possibly causing a diagnostic delay, but also an accelerated decline in the number of immigrants and asylum seekers due to border closings because of COVID-19.
Furthermore, as people still wanted to exercise and go outside, parks, forests and other nature reserves became overcrowded, and hiking, cycling and gardening became popular activities. This could have affected the amount of contact between humans and animals, but did not result in an increased number of Q-fever notifications. In the virological laboratory surveillance 53 diagnoses of *C. burnetii* were reported and 7 acute Q fever cases were notified in Osiris. This is the lowest number of notifications since the Q fever epidemic. After 2013, the annual numbers varied between 14 to 26. Similar to previous years, the number of notified cases are fewer than the number of cases in the virological surveillance, as a positive laboratory result can also indicate a past infection and these do not fulfil the national notification criteria for acute Q fever.
There was a high number of psittacosis notifications in 2020, which was mainly caused by a cluster in the winter of 2019/2020 (Vlaanderen, Cuperus et al. 2020). The outbreak investigation showed that beside petting birds, also wild (garden) birds played a role in this increase. Until July 2020, (possible) zoonotic *Chlamydia* species other than *C. psittaci* were not notifiable in both humans and animals in the Netherlands. Source tracing and infection control is important for infections with all *Chlamydia spp.* of zoonotic origin in addition to *C. psittaci*, therefore the notification criteria have been expanded to include these different species, such as *C. abortus*, *C. caviae* and *C. felis*. Several related *Chlamydia spp.* have been notified so far, such as the one *C. caviae* and one *C. abortus* case in 2020. Furthermore, four psittacosis-related deaths were reported in 2020. This was striking, as 2016 was the last year any psittacosis-related deaths were reported (1).

This annual report provides an update on the burden of respiratory infectious diseases expressed in disability-adjusted life years (DALY). Since there were no influenza cases reported by the NIVEL sentinel GP practices, the influenza burden was so low that it could not be calculated and was not reported for the 2020/2021 respiratory season. In 2020, COVID-19 was the respiratory infectious disease with the highest burden by far (Lagerweij, Schimmer et al. 2021). This high burden is primarily due to the high COVID-19 mortality in 2020. The burden of psittacosis in 2020 has also increased and was the highest estimated since 2015. This is likely due to the increased number of psittacosis notifications in 2020 as a result of the cluster in the winter of 2019/2020.

An overall objective of RIVM is to make surveillance information available to the public as quickly as possible. A weekly comprehensive situation report on COVID-19 is published on the RIVM website (https://www.rivm.nl/coronavirus-covid-19/actueel). Furthermore, the RIVM website provides weekly updated information on influenza and RSV trends and all-cause mortality. Information on tuberculosis is updated every quarter, data on psittacosis and Q fever monthly, or more frequently if indicated, such as during outbreaks. Up-to-date information on the incidence of legionellosis, psittacosis and Q fever is also available at https://www.atlasinfectieziekten.nl/.

Chapter 10
Methods for respiratory surveillance

10.1 Respiratory season, respiratory year and calendar year

The aim of this annual report is to describe the surveillance of influenza and other respiratory infections in the Netherlands. Since respiratory illnesses mainly occur in winter, the data is usually presented for the respiratory season or the respiratory year. A respiratory season is defined as the period from week 40 through week 20 of the next year and the respiratory year is defined as the period from week 40 through week 39 of the next year. In this report, data on the respiratory year 2020/2021 is limited to the respiratory season to allow a timely reporting. Respiratory infections may occur outside the respiratory season to a limited extend. Because the notifiable diseases legionellosis, tuberculosis, Q fever and psittacosis as well as the majority of pathogens monitored in the virological laboratory surveillance occur without typical winter seasonality, the results of these diseases refer to the 2020 calendar year (weeks 1-53).

10.2 Data sources

Nivel Primary Care Database

Nivel (Netherlands institute for health services research) holds the integral monitoring and information services for primary care, called 'Nivel Primary Care Database' (Verheij and Koppes 2019). The Nivel Primary Care Database holds longitudinal data recorded in electronic medical files by general practitioners (GPs) and other primary health care providers. For the surveillance of respiratory infectious diseases, the following data of Nivel is used:

- Near real-time (weekly) surveillance data concerning pneumonia and acute respiratory infections, based on consultation data in electronic medical records from about 380 participating general practices spread over the country.
- In the 2020/2021 respiratory season, the coverage was about 1.6 million persons (9% of the Dutch population, representative for age). The participating GPs do not actively report

patients and do not take laboratory specimens for surveillance purposes but make their electronic patient information systems available for automatic, anonymised, data extraction (de Gier, Nijsten et al. 2017).
- A proportion of the GPs participating in Nivel Primary Care Database take part in sentinel influenza surveillance. These GPs actively report on the number of patients who consult them for ILI. From a subset of patients with ILI or other ARI, they collect a throat swab and nose swab and send it to RIVM for virological laboratory diagnostics (influenza virus, RSV, rhinovirus, enterovirus, since February 2020, SARS-CoV-2 and since January 2021 parainfluenza viruses types 1-3, human metapneumovirus and human seasonal coronaviruses). The population of these 40 sentinel practices covers approximately 0.9% of the Dutch population and is representative for age, sex, regional distribution and population density (Donker 2018).

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

The nursing homes participating in this network serve as sentinels for the national surveillance of infectious diseases in nursing homes. In the 2020/2021 respiratory year, 27 locations from 11 different institutions participated. The participating nursing homes weekly report the number of residents with ILI and lower respiratory tract infections (LRTI) 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 once a 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.

Death notification data, Statistics Netherlands (CBS)

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

Virological laboratory surveillance

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

trends of respiratory infections over a prolonged period, because of their relative robust reporting history.
In order to monitor the total number of people tested and the number of people tested positive for SARS-CoV-2 virus in the Netherlands, all laboratories in the Netherlands that perform diagnostics for SARS-CoV-2 were asked to report these data from March 9th onwards. These data does not always contain background information concerning patient status, clinical data or origin of specimen (primary or hospital care). The laboratories report daily numbers of the previous week every Monday before noon. The number of people with a positive result differs from the number of COVID-19 patients reported by the PHS, because people may be tested more than once and positive laboratory results are reported more rapidly than disease notifications.

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. In January 2020, COVID-19 was added to the list of notifiable diseases. Medical doctors and medical-microbiological laboratories notify cases to the PHS, 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 PHS and registered in Osiris-NTR. Osiris is a dynamic system and due to corrections and additions of the PHS, small differences may exist between the data reported in this report and earlier or elsewhere reported data. Osiris notifications consist of anonymous patient data, date of disease onset, diagnostic information (dates, diagnostic methods and outcome) and information on source finding and contact tracing. For tuberculosis, Osiris also registers information regarding treatment and treatment outcome.

New respiratory virus infections

In case of a suspected human infection with animal influenza virus, such as influenza A(H_5N_1) virus or influenza A(H_7N_9) virus, diagnostics are performed by the RIVM (CIb/IDS). For suspected infection with the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), diagnostics are performed by the ErasmusMC. Both human infection with animal influenza and MERS-CoV are notifiable in the Netherlands.

10.3 Data analysis

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

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

ILI incidence is calculated as the number of patients with a new episode of ILI, divided by the total number of enlisted patients of the participating sentinel GP Practices (Donker 2018).
For chapter 2.1 and 3, the preliminary weekly numbers as reported during the season are used. The influenza epidemic threshold during the 2020/2021 season is set at an ILI incidence of 5.8 per 10,000 persons per week, based on historical data (Hooiveld, Hendriksen et al. 2020). An influenza epidemic is defined as a period of at least two consecutive weeks with ILI incidence above the influenza epidemic threshold, during which influenza virus is detected in nose swabs and throat swabs of ILI patients.

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

And at least one of the following four systemic symptoms:
  - Fever or feverishness
  - Malaise
  - Headache
  - Myalgia

And at least one of the following three respiratory symptoms:
  - Cough
  - Sore throat
  - Shortness of breath

Acute respiratory infections (ARI)
Weekly numbers on patients consulting for an acute respiratory infection (ICPC code R74), including acute/chronic sinusitis (ICPC code R75), acute laryngitis/tracheitis (ICPC code R77), acute bronchitis/bronchiolitis (ICPC code R78) or influenza (ICPC code R80) are obtained from

Nivel Primary Care Database. Please note that the ILI syndrome is a subset of, and included in the ARI syndrome. Although ARI is less specific for an influenza virus infection than ILI, seasonal estimates are highly correlated. Weekly ARI consultation rates are calculated as the number of patients consulting their GP in a given week, divided by the total number of enlisted patients. Cumulation of this weekly surveillance data over the season (separated for week 40 through 20 and week 21 through 39) is reported as the seasonal number of consultations.

Pneumonia

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

Determining excess mortality

Every Thursday the number of reported deaths, as provided by Statistics Netherlands (CBS), is evaluated for the presence of significant excess deaths above the expected levels of death (the baseline), at 2 different time-lags: deaths reported within 1 week (45% of all deaths) and deaths reported within 2 weeks after date of death (97% of all deaths). The baselines and prediction limits are calculated using a Serfling type algorithm on historical mortality data from the 5 previous years. In the historical data, any weeks with extreme underreporting were removed (the 7.5% most underreported values, often coinciding with public holidays). Also periods with high excess mortality in winter and summer were removed so as not to influence the calculated baseline with time-periods with previous excess mortality. When the observed number of deaths exceeds the upper limit of the prediction interval mortality is considered to be significantly increased (excess deaths calculated as the number of deaths above the baseline).

Influenza virus, RS-virus and other respiratory viruses

Surveillance of circulating viruses

At the National Influenza Centre (NIC) location RIVM the respiratory specimens are analysed that are taken for the influenza virus surveillance at the GP sentinel practices. Additionally, a selection of Dutch virology laboratories submit a representative set of influenza virus positive specimens (5-6 specimens per week is the request) to the Erasmus MC. For laboratories that continued to send all influenza virus positive specimen this selection of 5-6 specimens per week for further characterisation is done by Erasmus MC. Therefore, the trend in the specimens received by Erasmus MC is not a reflection of the course of the epidemic since 2018 when this procedure was installed.

The GP sentinel practices from Nivel Primary Care Database were requested to take specimens (combined throat swabs and nose swabs) of ILI or other ARI patients. The criteria for specimen collection have changed over de years to comply with standards in international influenza vaccine effectiveness studies (see previous reports for more details, (Reukers, van Asten et al. 2019)). Since the 2018/2019 season, after the I-MOVE+ study stopped but I-MOVE continued, the GPs were instructed to swab

- at least two ILI patients on Monday through Wednesday;
- when on those days no ILI patients attended the GP or no ILI patients were willing to participate, on Thursday through Sunday, GPs were instructed to swab at least the first two ILI patients or patients with an acute respiratory infection other than ILI (ARI);
- at least one child below the age of 10 with ILI or other ARI throughout the week.

The GP specimens are analysed by NIC location RIVM for influenza viruses, RSV, rhinoviruses, enteroviruses, since February 2020, SARS-CoV-2, and since January 2021 parainfluenza viruses types 1-3, human metapneumovirus and human seasonal coronaviruses. 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. Parainfluenza viruses types 1-3, human metapneumovirus and human seasonal coronaviruses are added due to signals of increased circulation in and outside The Netherlands despite the COVID-19 measures. 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.

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

Influenza virus antigenic and genetic characterization
Whereas subtyping and lineage determination at RIVM are performed using RT-PCR assays, Erasmus MC changed since the 2018/2019 season to MinION next generation sequencing of the HA and NA and PA genes for simultaneous subtyping/lineage determination and genetic characterisation of influenza viruses.

Antigenic characterization is performed by NIC location Erasmus MC in Rotterdam for a subset of influenza viruses and influenza virus positive clinical specimens submitted by peripheral laboratories and the sentinel GP surveillance after successful virus isolation at RIVM. This provides an indication of the degree of antigenic match between the circulating influenza viruses and the vaccine virus. Because new ferret sera have to be generated at Erasmus MC, the results of this thorough antigenic characterisation takes some time and is completed after this report has been published.

A subset of influenza viruses are characterized genetically by sequence analysis of the haemagglutinin genome segment at RIVM. This is done on a systematic sample of most prevalent influenza virus types, lineage and subtypes if the number of detections is high and on all if the number of detections is moderate and variation is low, and on all sporadically detected types, lineages and subtypes from the GP sentinel surveillance. At Erasmus MC this is done using MinION sequencing of all received specimens with high virus load, as described above. Sequences from both locations are combined for detailed phylogenetic and amino acid substitution analysis giving information about the evolution of influenza viruses and changes that might lead to the emergence of potential antigenic variants. In addition, this type of information complements the antigenic analysis, especially when antigenic characterization is cumbersome, as has been the case for increasing numbers of A(H3N2) viruses since 2013.

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 from the Nivel sentinel influenza surveillance, the phenotypic antiviral susceptibility for neuraminidase inhibitors (oseltamivir and zanamivir) is determined by NIC location RIVM. For a subset of virus isolates derived from specimens sent to NIC location Erasmus MC, the phenotypic antiviral susceptibility for neuraminidase inhibitors is determined at that location. Of viruses that appear reduced susceptible, the neuraminidase genome segment is sequenced to determine the amino acid substitution that explains the reduced susceptible phenotype. In addition, the virus in the clinical specimen is sequenced to exclude that the resistance substitution emerged during the virus isolation procedure. For all influenza virus type A positive specimens, the most important molecular markers for reduced sensitivity for neuraminidase-inhibitors are determined by a rapid molecular test at NIC location RIVM. Of all viruses tested at Erasmus MC and a subset of viruses tested at RIVM as described above, the neuraminidase gene is sequenced and analysed for any markers previously associated with reduced neuraminidase inhibitor susceptibility. From a systematic sample of influenza virus positive clinical specimens the whole genome is sequenced at the NIC location RIVM in order to screen for other and new molecular markers for reduced susceptibility for antivirals and markers for virulence. In case of mutations with previously unknown impact on antiviral susceptibility, the phenotypical neuraminidase inhibition test is the final proof for the degree of inhibition. This is done at both locations of the NIC for their own set of viruses. Molecular markers for resistance to adamantanes (M2 ion channel blockers: amantadine and rimantadine) are assessed in a subset of influenza virus type A positive clinical specimens by sequencing at NIC location RIVM. Molecular markers indidicative for resistance to the polymerase inhibitor baloxavir are assessed in a subset of influenza virus positive clinical specimens by sequencing at NIC location Erasmus MC and RIVM. 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.

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 2019 calendar year. Number of diagnoses of psittacosis, Q fever, influenza and RSV as reported in virological laboratory surveillance, as well as the number of persons tested positive for SARS-CoV-2 in the daily virological laboratory surveillance are given in their respective chapters.

Moving Epidemic Method (MEM) for RSV seasonality

Previously, we defined the RSV season as the period with at least 20 RSV-diagnoses per week reported by the virological laboratory surveillance. We now used the Moving Epidemic Method (MEM), that was originally developed to assess influenza seasonality (Vega, Lozano et al. 2013), to establish the epidemic thresholds for RSV, using the virological laboratory surveillance data of the previous 12 seasons (Vos, Teirlinck et al. 2019). MEM was applied with the Moving Epidemic Method Web Application (Lozano 2018) and absolute detection numbers per week for all 12 seasons in the fixed criterium model and a manually optimised slope parameter of 1.4 that had been established previously (Vos, Teirlinck et al. 2019). We calculated the mean length, timing and coverage of the epidemic period by calculating pre-and post-epidemic thresholds using the arithmetic mean and its one-sided 95% point confidence interval (CI). The start of the RSV season is defined as the first week when the number of RSV-diagnoses is above the pre-epidemic threshold, lasting for at least two consecutive weeks. The end of the RSV season is defined as the first week when the number of diagnosis is below the post-epidemic threshold, lasting for at least two consecutive weeks. We also calculated epidemic intensity levels using the geometric mean and its one sided 40% (medium), 90% (high) and 97.5% (very high) point CI. For the MEM calculations, a season was defined from week 30 through week 29 of the next year to be able to include enough data points to calculate a precise pre-epidemic threshold as RSV circulation might start as early as week 40. The epidemic thresholds for seasons up to and including 2016/2017 were calculated based on data of seasons 2005/2006 up to and including 2016/2017 (Vos, Teirlinck et al. 2019). The thresholds of the seasons from 2017/2018 onward were calculated separately per season, based on data of the previous ten seasons. For displaying results in this annual report, the respiratory season as defined for influenza (week 40- week 39) is used.

Burden of disease

To estimate disease burden in DALY, an incidence- and pathogen-based approach was applied to quantify the burden due to illness, disability and premature mortality associated with all short and long-term consequences of infection. The underlying outcome trees, disease progression probabilities, and other parameters have been previously described (Reukers, van Asten et al. 2018). DALY estimates incorporate both years of life lost (YLL) due to premature mortality and years lived with disability (YLD) (Murray and Lopez 2013). YLD were calculated by multiplying the number of acute cases, duration of a health state and the disability weight of the health state. The disability weight is a value between 0 (perfect health) and 1 (death). We used the European disability weights collected by Haagsma et al. (Haagsma, Maertens de

Noordhout et al. 2015). To estimate YLL, remaining life expectancy tables were taken from the GBD 2010 study (WHO 2013).

We estimated the disease burden associated with tuberculosis, legionellosis, psittacosis and Q fever incident in 2016, 2017, 2018, 2019 and 2020 separately. We estimated the burden of influenza for respiratory seasons (week 40 to week 20) for the seasons 2016/2017 through 2019/2020. Since there were no influenza cases reported by the NIVEL sentinel GP practices during the 2020/2021 respiratory season, the influenza burden could not be calculated. No time discounting was applied.

Because we had direct data on the incidence of Severe and Critical health outcomes and COVID-19 related mortality, we did not need to estimate the progression (or transitional) probabilities between health outcomes, as is the case for most of the other infectious diseases for which disease burden is routinely computed and reported in the Netherlands. The notified and reported cases of COVID-19 are directly used as input to estimate the burden of COVID-19. In short, the cumulative incidence of mild/moderate (symptomatic infection) cases is estimated from seroprevalence survey data (Pienter Corona study (PICO3), RIVM), which provides an estimate of the cumulative incidence of infection until mid-September 2020, adjusted by the estimated proportion symptomatic (derived using PICO1 and PICO2 (McDonald, Miura et al. 2021, Vos, Den Hartog et al. 2021, Vos, van Boven et al. 2021) data, and the estimated cumulative incidence of infection from mid-September until 31 December 2020, derived using OSIRIS notification data adjusted for case ascertainment and the proportion symptomatic. The number of severe and critical cases, that is, the number of non-ICU and ICU hospital admissions, is based on NICE data (National Intensive Care Evaluation). The number of fatal cases is derived from notified fatal cases in OSIRIS and corrected for underreporting based on age-specific COVID-19 cumulative mortality rates published by Statistics Netherlands. However, there is insufficient information about the epidemiology and long-term impact of COVID-19 to properly estimate the disease burden in DALY/100 cases and compare this with the disease burden of other respiratory infections. First, the probabilities of progression from mild to severe disease and death are not yet well established. In addition, it is still unclear what the long-term effects are of people with mild COVID-19 as well as for people with a more severe disease course. Since there is insufficient data to accurately calculate the long-term sequelae for COVID-19, the burden estimate of COVID-19 is based on the acute phase of the disease. For details on the parameter values to estimate the YLD, see the State of Infectious Disease 2019 (Lagerweij, Schimmer et al. 2021). To estimate YLL, age-dependent life expectancy tables for the Netherlands in 2019 were taken from Statistics Netherlands.

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Abbreviations

ARDS	Acute Respiratory Distress Syndrome
ARI	acute respiratory infection
BCoDE	burden of communicable diseases in Europe
BEL	Legionella Source Identification Unit (NL: Bronopsporingseenheid legionellapneumonie)
BWTP	biological wastewater treatment plant
CAP	community-acquired pneumonia
CBS	Statistics Netherlands (NL: Centraal Bureau voor de Statistiek)
CFR	case fatality rate
CIb	Centre for Infectious Disease Control (Centre of RIVM) (NL: Centrum Infectieziektebestrijding)
CIb/EPI	Centre for Infectious Diseases, Epidemiology and Surveillance of CIb (NL: Centrum Epidemiologie en Surveillance van Infectieziekten)
CIb/IDS	Centre for Infectious Disease Research, Diagnostics and Screening of CIb (NL: Centrum Infectieziekteonderzoek, Diagnostiek en Screening)
CIb/LCI	National Coordination Centre for Communicable Disease Control of CIb (NL: Landelijke Coördinatie Infectieziektebestrijding)
COVID-19	coronavirus disease 2019
DALY	disability-adjusted life years
ECDC	European Centre for Disease Prevention and Control
EISN	European Influenza Surveillance Network
ELDSNet	European Legionnaires Disease Surveillance Network
EPTB	combination of pulmonary and extrapulmonary TB
ETB	extrapulmonary tuberculosis
EuroMOMO	European monitoring of excess mortality
GGD	PHS (NL: Gemeentelijke Gezondheidsdienst)
GP	general practitioner
HIV	Human Immunodeficiency Virus
hMPV	human metapneumovirus
ICARES	Integrated Crisis Alert and Response System
ICU	intensive care unit
ILI	influenza-like illness
I-MOVE	influenza monitoring vaccine effectiveness
LD	Legionnaires' Disease
LTBI	latent tuberculosis infection
MDR-TB	Multi Drug Resistant tuberculosis
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
NVWA	the Netherlands Food and Consumer Product Safety Authority (NL: Nederlandse Voedsel- en Waren Autoriteit)
NIC	National Influenza Centre

Nivel	Netherlands institute for health services research (NL: Nederlands instituut voor onderzoek van de gezondheidszorg)
NPI	non-pharmaceutical interventions
NTR	Dutch Tuberculosis Registry (NL: Nederlands Tuberculose Register)
NVMM	Dutch Society for Medical Microbiology (NL: Nederlandse Vereniging voor Medische Microbiologie)
NZa	Dutch Healthcare Authority (NL: Nederlandse Zorgautoriteit)
PCR	Polymerase Chain Reaction
PHS	PHS (NL: Gemeentelijke Gezondheidsdienst)
PIV	parainfluenza virus
POCT	point-of-care test
PTB	pulmonary tuberculosis
QIV	quadrivalent influenza vaccine
RIVM	National Institute for Public Health and the Environment
RSV	respiratory syncytial virus
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SNIV	national sentinel surveillance network for infectious diseases in nursing homes
TALD	Travel Associated Legionnaires' disease
VE	vaccine effectiveness
WHO	World Health Organization
YLD	years lived with disability due to morbidity
YLL	years of life lost due to mortality

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