Respiratory syncytial virus (RSV) incidence estimates in primary care among adults aged 50 years and older in the Netherlands; 2011-2019

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Background

The aim of this study was to estimate the incidence of respiratory syncytial virus (RSV) infections seeking medical attendance in primary care in adults aged 50 years and older in the Netherlands.

Methods

Seasonal incidence for medically attended RSV in adults aged 50 years and older in primary care were estimated for the respiratory seasons 2011/2012 to 2018/2019, ISO-weeks 40 to 20. These incidence estimates were calculated by combining data from two data sources: (1) the weekly number of new acute respiratory infection (ARI) episodes recorded by general practitioners (GPs) in Nivel Primary Care Database, and (2) the weekly proportion of RSV positive specimens obtained from naso-/oropharyngeal specimen collected by GPs from patients with ARI as part of the national sentinel respiratory surveillance. The weekly proportion of RSV positive specimen was multiplied with the weekly number of ARI episodes to obtain the weekly RSV incidence estimates. To estimate the total number of adults seeking medical attendance for an RSV infection in primary care, we have extrapolated the incidence estimate of patients with a medically attended RSV infection to the Dutch population aged 50 years and older. Additionally, the number of GP consultations for patients with an ARI diagnosis was estimated using the weekly proportion of RSV positive specimen and the weekly number of GP consultations for ARI. By doing this we could estimate the total number of contacts with the GP practice related to a presumed RSV infection in the Netherlands. Analyses were conducted for all persons aged 50 years and older, for 5-years age categories, and for patients considered to be at increased risk for medically attended RSV infection due to having ≥1 prevalent chronic conditions (e.g., diabetes mellitus, COPD/asthma).

Results

The ARI incidence rate and incidence estimates for medically attended RSV varied per season. Estimates of the seasonal incidence of medically attended RSV ranged from 3 (95% CI 2-4) to 13 (95% CI 12-15) per 1,000 persons (for seasons 2011/2012 and 2016/2017, respectively) and increased with age, especially over the age of 75 years. RSV incidence in persons with chronic pulmonary disease were estimated to be higher compared to other chronic comorbidities. The estimated overall number of persons who sought medical attendance for their RSV infection ranged from 17,000 (95% CI 11,200-24,800) to 89,100 (95% CI 79,100-100,500) for seasons 2011/2012 and 2016/2017, respectively. The number of contacts with the GP practice for patients who had a registered ARI was estimated to be 169 per 1,000 persons of which approximately 13 per 1,000 persons was estimated to be the number of contacts attributed to an RSV infection (average for the seasons 2011/2012-2018/2019). These contacts included both single and repeated contacts.

Conclusion

This study provided incidence estimates of RSV infections based on ARI incidence rates in persons aged 50 years and older in primary care in the Netherlands, with seasonal estimates ranging from 3 to 13 per 1,000 persons. Persons aged over 75 years and persons of 50 years and older with an underlying chronic pulmonary disease were at highest risk for infection with RSV. Knowledge about the incidence of RSV among adults in primary care will help policymakers in making decisions on the need and evaluation of new RSV prevention strategies, e.g. vaccination for older adults.

1 Introduction

The global burden of respiratory syncytial virus (RSV) infections has traditionally been emphasized in paediatric populations. The global incidence for children younger than 5 years of age has been estimated to be 17.0 (95% confidence interval; CI: 10.6-26.2) per 1,000 persons (1, 2). In addition, a considerable number of children below the age of 5 in high-income countries have to attend primary care and emergency departments because of RSV infection (3). Globally, it was estimated that a total of 3.6 million hospital admissions took place, and 26,300 children died as a result of their RSV infection in 2019 (4).

RSV is also recognized as a substantial health concern in older adults (5, 6). In adults of older age, mostly defined as 60 years and older, RSV infection may lead to (severe) lower respiratory tract infection, hospital admission, and increased mortality (1, 7). Complications may occur in persons who survive a severe initial RSV infection. These complications include deterioration of cardiac or lung function and a decline in general functioning (8, 9).

A systematic review and meta-analysis study on the global burden of RSV infection in adults in the period 1970-2017, found that RSV was accountable for 1 to 10% of all cases with ILI (influenza like illness) and ARI (acute respiratory infections) in adults aged 50 years and older (10). A systematic review study conducted by Shi et al. (2020) found an annual incidence of RSV-associated ARI infections of 6.7/1,000 persons in adults in industrialized countries in 2015 (11). The authors of this study made use of various published studies and a few unpublished studies. Although it was intended to give a global incidence estimate, most studies were conducted in high-income countries (11). As a consequence of the limitations of the previous mentioned study, Savic et al. (2022) conducted a systematic review and meta-analysis on the RSV infection rate among adults aged 60 years and older in high income countries in 2019. They found a RSV-ARI infection rate of 16.2/1,000 persons (12).

For medically attended RSV among adults the best known risk factors are advanced age (60 years or older) and the presence of comorbidities (5, 12-14). A systematic review and meta-analysis found an incidence rate of RSV-ARI of 37.6/1,000 persons for patients with any comorbidity (15), which was higher than the community-based incidence rates mentioned earlier. Further, also adults aged ≥45 are expected to have a higher risk for seeking medical attention for RSV if they have comorbidities (14, 16). These comorbidities include chronic heart failure, COPD, diabetes mellitus, immunosuppression, and chronic kidney disease (5). Another important risk factor for seeking medical attention due to RSV, is residency in a long term care facility (17, 18).

Until now, most epidemiological information on RSV for adults aged 18 years and older is based on hospital data with only a few studies conducted in a community setting. Even less information is available on the incidence of RSV infection in primary care (11, 12, 19). A study in primary care conducted in the United Kingdom during season 2009-2010 found that 17.9% and 26.5% of the specimen were positive for RSV in age categories 45-64 and 65+, respectively (20). Bruyndonckx et al. (2020) found in a study conducted in multiple European countries that the prevalence of RSV was associated with higher age. In addition, they reported an RSV prevalence of 8.5% among adults of 75 years and older with acute cough (21).

Collecting epidemiological information on RSV in primary care is challenging, because clinical testing for RSV and other viruses is usually not part of routine care in primary care. In the Netherlands, sentinel surveillance of respiratory viruses in primary care is performed through a collaborative effort between Nivel (the Netherlands institute for health services research) and the National Institute of Public Health and the Environment (in Dutch: RIVM). They conduct virological surveillance on respiratory pathogens, including RSV, through sentinel surveillance in primary care with a sample of GP practices distributed evenly throughout the Netherlands that represent approximately 1% of the Dutch population (22). Due to the relatively low number of GP practices (approximately 40) that supply data for virological surveillance during the years 2011-2019, it is challenging to estimate national RSV incidence rates by (only) analysing the specimen data (23). To increase our ability to estimate the national incidence of RSV infection, sentinel surveillance data were combined with electronic health records (EHR) data from GP practices that participate in Nivel Primary Care Database (Nivel-PCD).

Nivel-PCD consists of approximately 400 participating GP practices that record health problems using ICPC (International Classification of Primary Care) codes (24, 25). By combining primary care virological surveillance data with GP EHR data, the incidence of medically attended RSV infections in primary care can be estimated. It also allowed us to stratify by comorbidity. Almost every Dutch citizen is registered at a GP practice located in the broader vicinity of their residence. The EHR registration system ensures that information on both consulting and non-consulting patients is available. GPs record information about consultations, diagnosis, prescribed medication and referrals in the EHR. Because all GP contacts are recorded, it is possible to also calculate the number of contacts with the GP practice associated with ARI and estimate the number of contacts associated with ARI caused by RSV infection.

This study aimed to estimate the incidence and total number of persons seeking medical attendance for RSV infection in adults aged 50 years and older in primary care in the Netherlands. In addition, we estimated the number of GP contacts that could be attributed to RSV infection among adults aged 50 years and older with a registered ARI diagnosis.

2 Methods

2.1 Data sources

For this study, data from Nivel-PCD were used from respiratory seasons 2011/2012 through 2018/2019. Each respiratory season was defined as ISO-week 40 (i.e., beginning of October) through ISO-week 20 (i.e., mid-May) of the following year.

2.1.1 Nivel Primary Care Database (Nivel-PCD)

Nivel-PCD contains a representative sample of general practices from all over the Netherlands, providing EHR data of approximately 10% of the Dutch population (25). Nivel collects routinely recorded information of the EHR systems from participating general practices. Every GP consultation provides information on the patients' health problem(s) by recording (an) ICPC-code(s) (International Classification of Primary Care, version 1) (24).

The use of EHR for research purposes is allowed under certain conditions. When these conditions are fulfilled, neither obtaining informed consent from patients nor approval by a medical ethics committee is obligatory for this type of observational studies containing no directly identifiable data (art. 24 GDPR Implementation Act jo art. 9.2 sub j GDPR). This study has been approved according to the governance code of Nivel Primary Care Database, under number NZR-00324.001.

2.1.2 Nivel Sentinel Practices

Before the COVID-19 pandemic, on average, 40 GP practices known as Nivel Sentinel Practices, were asked to collect combined naso- and oropharyngeal swabs from at least two and a maximum of five persons of all ages per week. For the sentinel surveillance, they are required to comply to the case definition of influenza-like illness (ILI) or other ARI (23). During 2011 to 2019, specimens were tested with a commercial multiplex RT-qPCR test on several respiratory viruses at the laboratory of the National institute of Public Health and the Environment (RIVM,), including among others: influenza A/B, human rhinovirus, human coronaviruses, human parainfluenza, human metapneumoviruses A/B, human bocavirus, human adenovirus, enterovirus, human parechovirus, and Mycoplasma pneumoniae (26). Specimens were handled anonymously and there was no linkage between a persons' EHR at the GP and test results of their provided specimen.

2.2 Study population

All persons aged 50 years and older at the start of each respiratory season, registered at one of the (on average) 395 general practices that participated in Nivel-PCD in the years 2011-2019 were included, regardless of whether they had contact with the GP during the selected time period.

2.3 Outcomes

ARI incidence

Incident ARI was defined as having a new registration (i.e. diagnosis) recorded of one of the following ICPC-codes: acute upper respiratory infection (R74), sinusitis (R75), acute tonsillitis (R76), acute laryngitis (R77), acute bronchitis/bronchiolitis (R78), influenza (R80), or pneumonia (R81) and was derived from the Nivel-PCD data. So-called ‘disease episodes’ were constructed for each of these diagnoses using the method developed by Nivel (27). In short, a disease episode started at the first registration of the ICPC-code by the GP and ended when a person did not contact the GP for a period of 4, 8, or 16 weeks, depending on the diagnosis. A period of 4 weeks was used for upper respiratory infection (R74), acute tonsillitis (R76), acute laryngitis (R77), and influenza (R80). For sinusitis (R75) and acute bronchitis/bronchiolitis (R78) a period of 8 weeks was used and for pneumonia (R81) the contact-free interval used was 16 weeks. The disease episode was then retrospectively set to have ended at respectively 2, 4, or 8 weeks after the last contact with the GP. To calculate the seasonal ARI incidence rate in primary care, the number of new ARI episodes in a respiratory season was divided by the total follow-up time among persons registered at the GP practice. Incidence rates and estimates were standardized for age, sex, and urbanisation level of the Dutch population on January 1st of each year in the respiratory season according to Statistics Netherlands (CBS). Urbanisation level of the persons living environment was inferred by the urbanisation level of the GP practice they were registered at. The degree of urbanisation was defined as low (less than 500), moderate (500-1,000), or high (1,000 or more addresses per km^2). Incidence rates and estimates are presented per 1,000 persons.

Proportion of positive RSV specimens

To calculate the proportion of positive RSV specimen data of the Nivel sentinel practices was used. The weekly proportion of specimens, collected in persons aged 50 years and older with ILI or ARI symptoms, that tested positive for RSV was calculated by dividing the weekly number of positive RSV specimens by the number of specimens that were collected and tested in corresponding week, by the laboratory at RIVM. To correct for the fluctuation in the number of specimens collected each week, we used a 5-week moving average in our estimates. As mentioned earlier, only data of ISO-weeks 40-20 were used.

Estimated incidence of medically attended RSV infection

To estimate the incidence of medically attended RSV infections per season, we multiplied the weekly number of incident ARI cases in Nivel-PCD with the (moving average of the) proportion of specimen that tested positive for RSV in the sentinel surveillance of the corresponding week. For each week, we calculated a 95% exact binomial confidence interval (CI) around the incidence estimate.

In advance, we tested the generalisability of the GP practices of the sentinel surveillance that collected specimen and the GP practices that participated in the Nivel-PCD. We compared the age and sex distribution as well as the urbanisation level of the GP practices and we did not find large differences in these distributions. Further, the incidence rates of both ARI and ILI (ICPC-code R80) were comparable for all Nivel-PCD practices and the sentinel GP practices.

Number of adults aged 50 years and older seeking medical attendance for RSV infection

The estimated number of adults seeking medical attendance in primary care for RSV infection was obtained by multiplying the estimated incidence of medically attended RSV infections with the corresponding number of people per 5-year age category in the Netherlands on January 1st of each respiratory season (obtained from Statistics Netherlands). To emphasize that these estimated numbers cannot be exact, the extrapolated numbers were rounded to the closest multiple of 100.

Number of GP contacts for ARI and RSV infection

For each week the total number of GP contacts for ARI disease episodes were counted. The number of contacts were based on claim codes 12000 (consultation shorter than 20 minutes), 12001 (consultation longer than 20 minutes), 12002 (home visit shorter than 20 minutes), 12003 (home visit longer than 20 minutes), 12004 (consultation by telephone), 12006 (consultation for vaccination), 12007 (consultation by e-mail), 12010 (consultation shorter than 5 minutes), and 12011 (consultation between 5 and 20 minutes). Claim codes 12010 and 12011 were only used during 2019, these were combined to align with code 12000, in order to compare the different seasons (28, 29).

To estimate the seasonal number of GP contacts attributed to an RSV infection, we multiplied the weekly number of contacts of ARI patients with the GP practice recorded in Nivel-PCD with the (5-week moving average of the) proportion of specimen from the sentinel surveillance that tested positive for RSV in the corresponding week. The sum of these weekly numbers were then used to calculate a seasonal number of contacts for ARI associated with RSV infection.

2.4 Sub-group analyses

Incidence estimates of medically attended RSV infections were analysed for several sub-groups. We defined 5-year age categories, starting from 50-54 up and till 85+ years of age. In addition, we selected chronic comorbidities which are considered to increase the risk for medically attended RSV in primary care; chronic pulmonary disease (used ICPC-codes: R91, R95, R96), diabetes mellitus (T90), cardiac disease (K74-K79, K83, K87), liver disease (D96, D97), kidney disease (U85, U88, U99), and a compromised immune system - which was based on the definition that is used for the target group for seasonal influenza vaccination in the Netherlands (30, 31). When selecting for asthma, we also required the use of maintenance medication for prevalent cases (32). Based on the prevalence of one or more of the abovementioned comorbidities, we constructed a combined group which was considered to be at increased risk for medically attended RSV infection. Incident ARI cases and estimated RSV incidence were calculated for each age category and each comorbidity. Moreover, the estimated number of persons seeking medical attendance for RSV infection was calculated for each age category.

3 Results

3.1 Population

Table A1 in the appendix shows the number of persons in our database, and rates for incident ARI and comorbidities by age for the different seasons. Rates for incident ARI and prevalence of different comorbidities were relatively stable throughout the studied period 2011-2019.

Table 1 gives an overview of the estimated number of persons with ≥1 comorbidity. As mentioned in the methods section, the following comorbidities were considered to increase risk for medically attended RSV: cardiac disease, diabetes mellitus, chronic pulmonary disease, liver disease, kidney disease, and a compromised immune system. On average, and by our definition, approximately 2,783,000 persons (i.e., 43% of those aged 50 years or older) were at increased risk for medically attended RSV in the Netherlands during seasons 2011/2012-2018/2019.

In Table 2 an overview is given of the collected number of respiratory specimen per age category in the sentinel surveillance in each respiratory season. The total number of specimens collected and tested for RSV in the studied period was 3,724.

Table 1 Estimated number of persons with ≥1 comorbidity (chronic pulmonary disease, diabetes mellitus, cardiac disease, liver disease, kidney disease, or a compromised immune system) associated with increased risk of medically attended RSV, by age and respiratory season; the Netherlands, 2011-2019.

Age group	2011/2012	2012/2013	2013/2014	2014/2015	2015/2016	2016/2017	2017/2018	2018/2019
50-54	247,200	249,300	265,100	267,000	264,100	319,900	326,500	267,900
55-59	307,300	310,100	325,900	329,600	332,500	396,600	410,000	351,800
60-64	380,500	377,300	386,400	386,400	388,800	449,500	461,900	410,600
65-69	387,800	417,400	447,400	460,700	475,800	505,900	511,800	462,200
70-74	342,300	356,700	375,300	390,800	399,700	479,600	510,900	503,000
75-79	308,400	314,500	328,900	338,600	347,500	376,600	392,100	387,900
80-84	244,100	253,800	264,500	270,300	274,200	291,900	299,900	300,500
85 years and older	216,800	225,900	238,000	249,400	258,000	276,100	283,100	284,500
Number of adults aged 50+ with ≥1 comorbidity (% of the total Dutch population aged 50+)	2,434,400 (40)	2,505,000 (40)	2,631,500 (41)	2,692,800 (42)	2,740,600 (42)	3,096,100 (46)	3,196,300 (47)	2,968,500 (43)

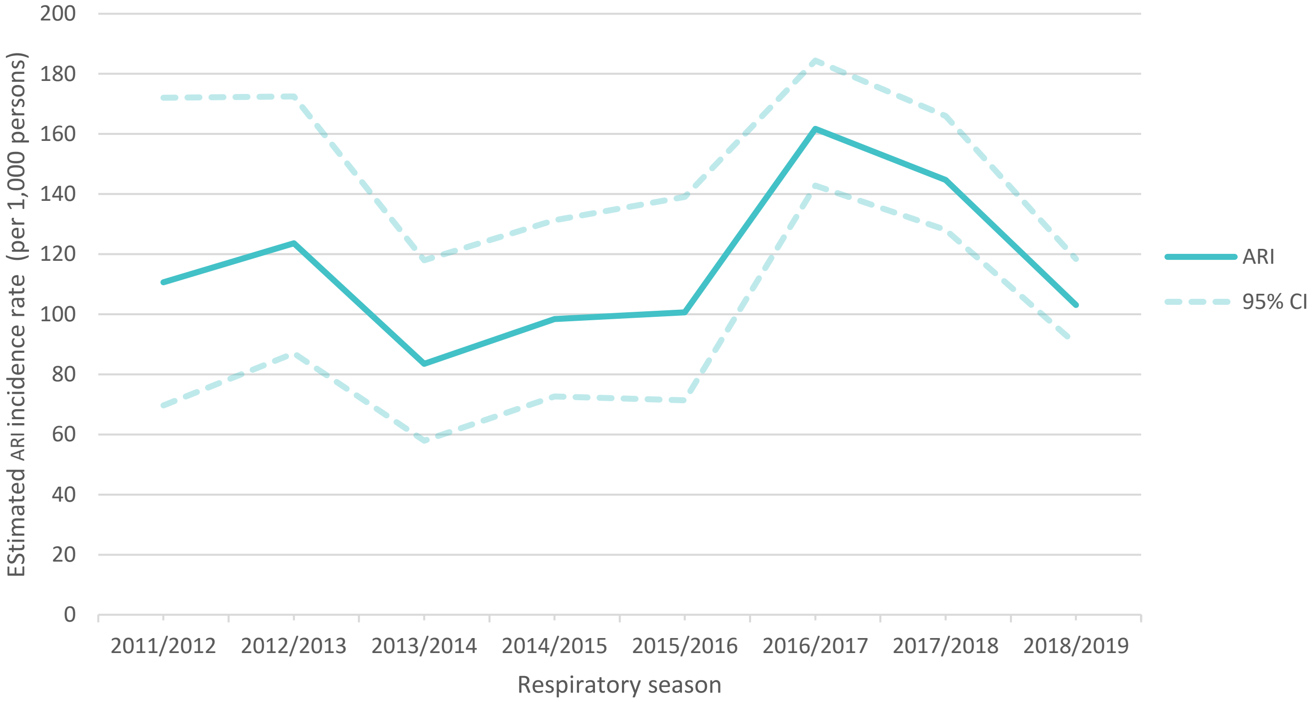
Table 2 Number of naso-/oropharyngeal specimens collected and tested for RSV in sentinel surveillance, by age and respiratory season; the Netherlands, 2011-2019

Age category	Season							
	2011/2012	2012/2013	2013/2014	2014/2015	2015/2016	2016/2017	2017/2018	2018/2019
50-54	75	94	60	90	107	78	130	77
55-59	77	109	69	135	107	85	98	83
60-64	73	84	69	92	77	83	84	74
65-69	58	67	75	104	68	68	92	53
70-74	36	50	50	77	52	76	70	62
75-79	27	39	24	42	42	51	41	20
80-84	12	16	17	26	19	26	40	26
85+	7	9	3	19	17	11	15	7
Total	365	468	367	585	489	478	570	402

3.2 Incidence of acute respiratory infection

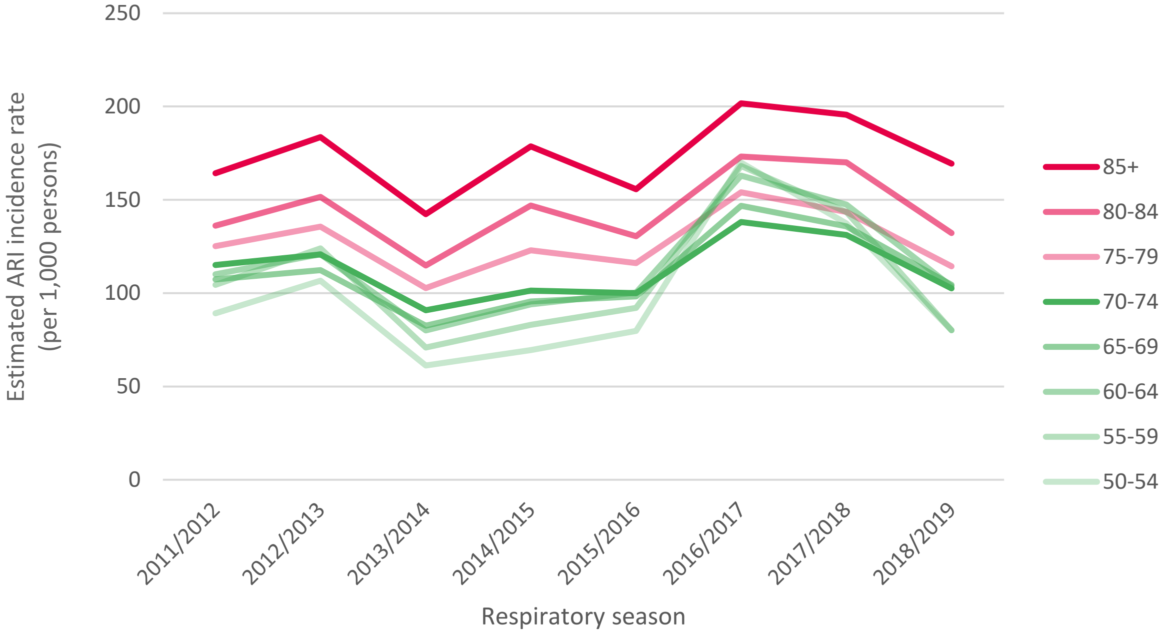
The ARI incidence rate among persons aged 50 years and older varied among respiratory seasons and ranged from 84 (95% CI 58-118) for season 2013/2014 to 162 (95% CI 143-184) per 1,000 persons for season 2016/2017. An overview of the ARI incidence rate by season is shown in Figure 1 and Table A2 in the Appendix.

Figure 1 Estimated seasonal acute respiratory infection (ARI) incidence rate for adults aged 50 years and older in primary care, by respiratory season; the Netherlands, 2011-2019



Persons in the age categories of 80 years and older had a higher estimated ARI incidence rate in all respiratory seasons compared to those aged 50-79 (Figure 2). The range of the estimated ARI incidence rates ranged for age group 50-54 from 61 to 170 per 1,000 persons. The age category of 85 years and older had a range of 142 to 202 per 1,000 persons. Age categories 50-54 and 55-59 had higher estimated ARI incidence rates in seasons 2016/2017 and 2017/2018 compared to age categories 65-69, 70-74, and 75-79. For the other seasons, age category 50-54 had the lowest estimated ARI incidence rates. Overall, the estimated seasonal incidence rates were highest for all age categories in season 2016-2017. The same pattern for the total population 50 years and older can be observed for all age categories separately.

Figure 2   Estimated seasonal acute respiratory infection (ARI) incidence rate for adults aged 50 years and older in primary care, by age, and respiratory season; the Netherlands, 2011-2019

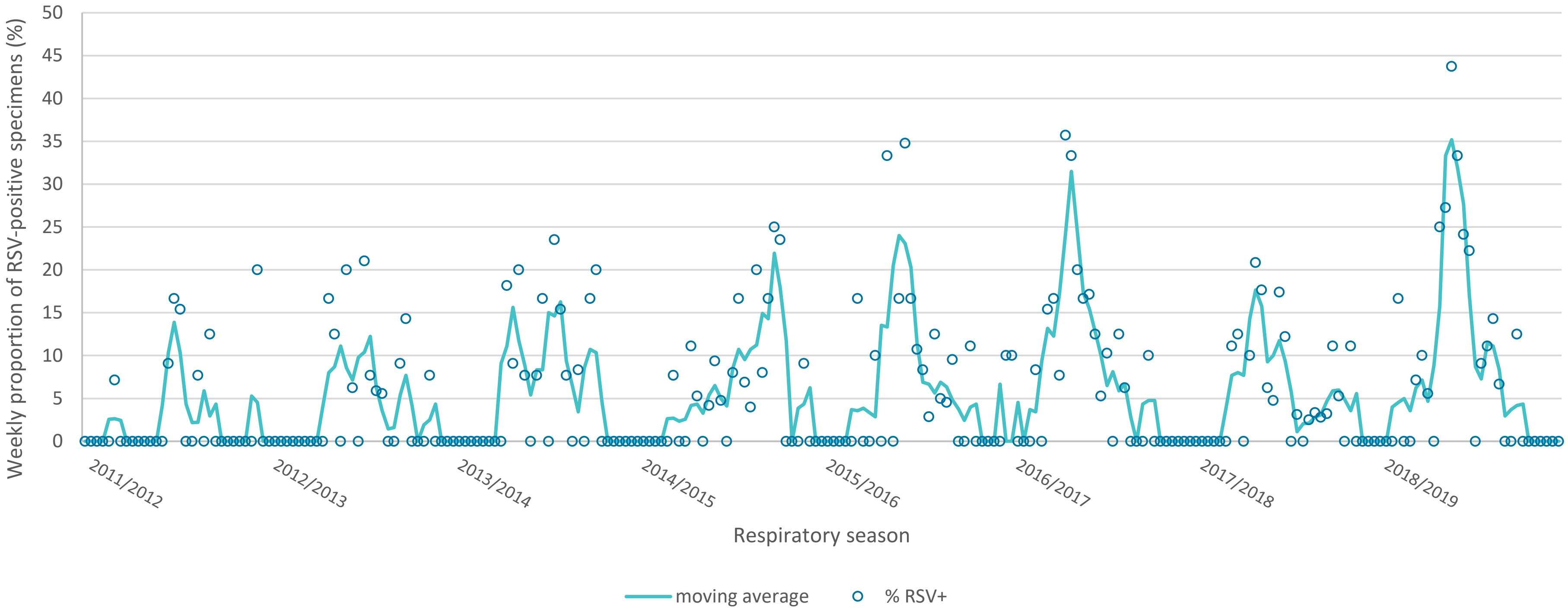


3.3 Weekly proportion of RSV positivity

The weekly proportion and 5-week moving average of RSV positive specimens among persons aged 50 years and older in the virological surveillance data are shown in Figure 3. In four seasons, one distinct peak can be observed in the proportion of positive specimen, while in the other seasons, several elevations can be seen (see Figure 3). For most respiratory seasons, specimens tested positive for RSV between weeks 46 (mid-November) and 16 (mid-April).

The total number of specimens collected per season ranged from 365 to 585 for seasons 2011/2012 and 2014/2015, respectively (Table A3 in Appendix). The median number of specimens collected was 8 per week (IQR: 3-13). Of the total number of specimen collected, the number of RSV positive specimen ranged from 9 in season 2011/2012 to 51 in season 2016/2017. During respiratory seasons 2011/2012 to 2018/2019, the weekly proportion of RSV positive specimens ranged between 3% and 44% of the total number of specimens collected in the sentinel surveillance among adults aged 50 years and older that presented with ARI at the GP. The seasonal proportion of RSV positive specimen ranged from 2.5% to 10.9% for respectively season 2011/2012 and 2018/2019.

*Figure 3 Weekly proportion of RSV-positive specimens and 5-week moving average from adults aged 50 years and older with acute respiratory infection (ARI) related symptoms through virological sentinel surveillance; the Netherlands, 2011-2019**



*ISO-weeks 21-39 (mid-May till the end of September) were omitted from this figure

3.4 Incidence of patients seeking medical attention for RSV infection

3.4.1 Estimated RSV incidence

The seasonal incidence estimates of medically attended RSV infection varied between 3 (95% CI 2-4) and 13 (95% CI 12-15) per 1,000 persons for seasons 2011/2012 and 2016/2017, respectively. In Figure 4, the RSV incidence estimates are shown for each respiratory season.

Figure 4 Incidence estimates of medically attended RSV infection in adults aged 50 years and older in primary care, by respiratory season; the Netherlands, 2011-2019

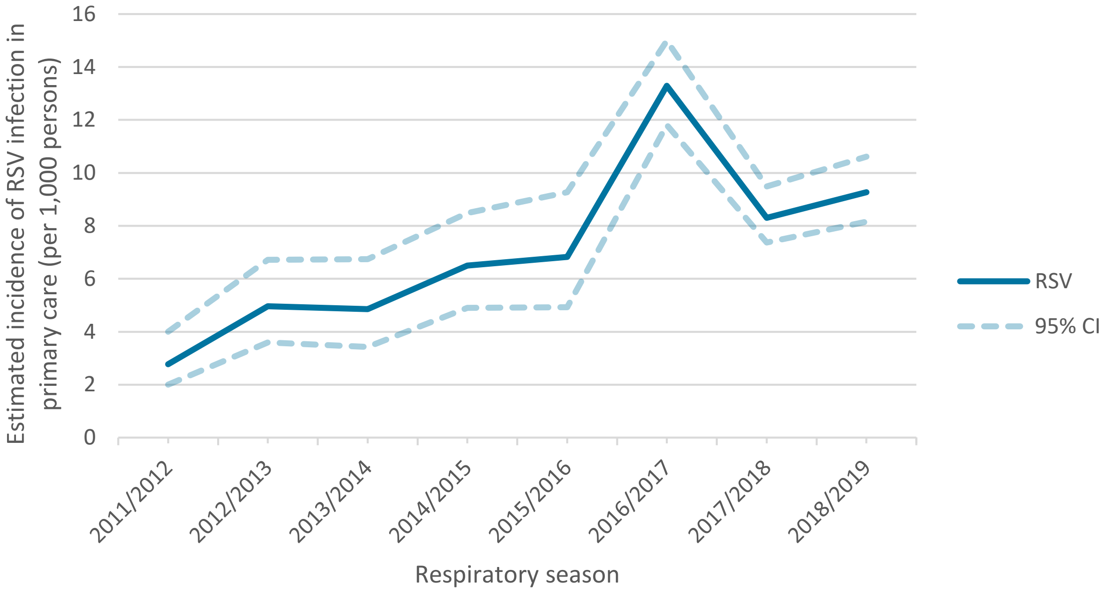
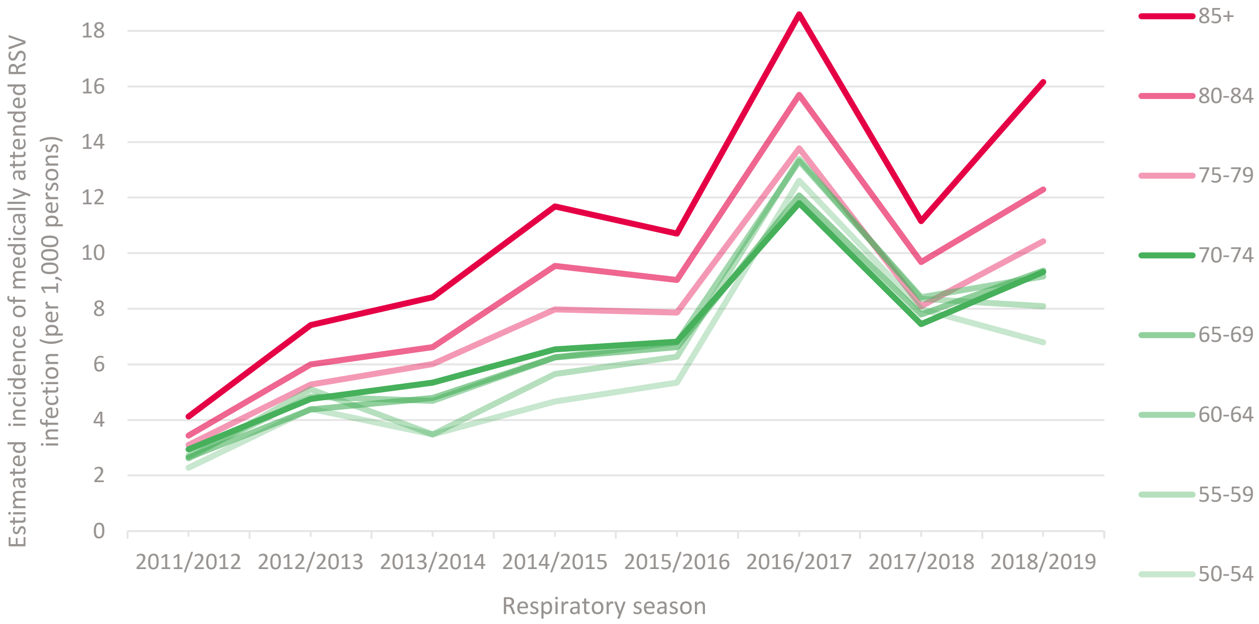


Figure 5 shows the seasonal incidence estimates of RSV infection by age during respiratory seasons 2011/2012 to 2018/2019. The seasonal RSV incidence estimates varied between the different respiratory seasons with the lowest estimates in season 2011/2012 and the highest estimates in season 2016/2017. Furthermore, incidence estimates were observed to be higher among those aged 75 years and older. The incidence estimates ranged from 2.3 to 12.6 per 1,000 persons for age category 50-54 in seasons 2011/2012 and 2016/2017, respectively. For age category 85 years and older the estimated seasonal RSV incidence range varied from 4.1 (2011/2012) to 18.6 (2016/2017) per 1,000 persons. Despite a higher estimated RSV incidence among those aged 75 years and older, the estimated overall number of incident RSV cases seeking medical attendance among these older categories were lower. This is due to the lower population number of persons aged 75 years and older in the Netherlands.

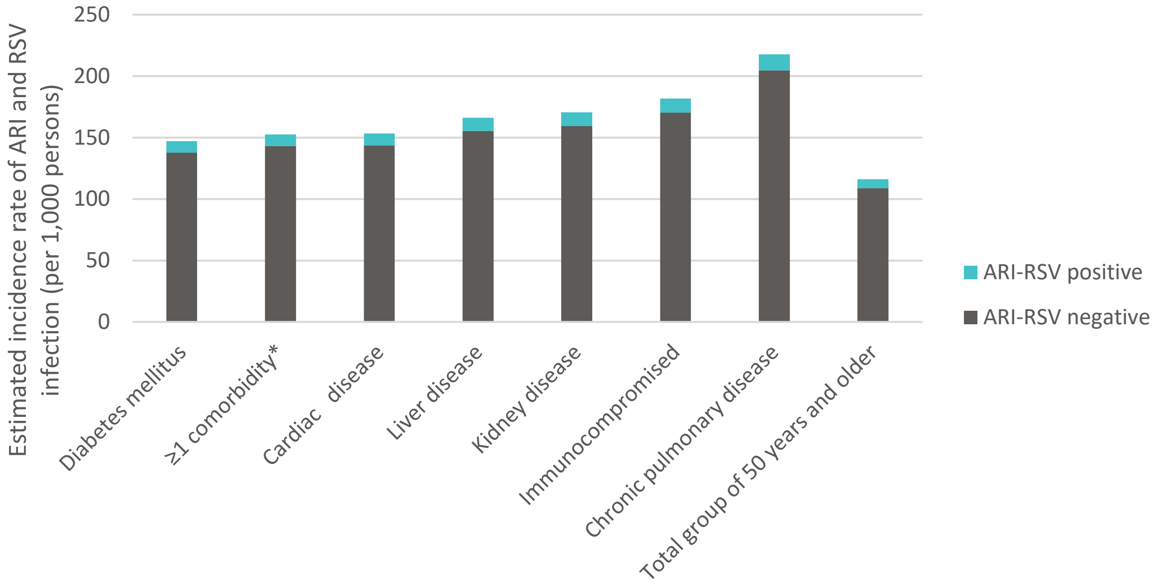
Figure 5 Seasonal incidence estimates rate of medically attended RSV infection in adults aged 50 years and older in primary care, by age and respiratory season; the Netherlands, 2011-2019



The average RSV incidence estimates by comorbidity in respiratory seasons 2011/2012 to 2018/2019 are shown in Figure 6. The incidence estimates for ARI and medically attended RSV infection are shown in Table A4 in the Appendix. The proportion of incident ARI cases estimated to be associated with RSV infection was approximately 6% for all comorbidities. The number of persons with a specific comorbidity per respiratory season can be found in Table A1 in the Appendix.

We estimated a higher ARI incidence rate among persons with chronic pulmonary disease, when compared to other comorbidities, such as diabetes mellitus or cardiac disease. This resulted in higher RSV incidence estimates among persons with chronic pulmonary disease with an incidence estimate of 13 per 1,000 persons. Persons with a compromised immune system, kidney or liver disease had an RSV incidence estimate of 11 per 1,000 persons. The combined patient group that is expected to have an increased risk for incident medically attended RSV based on the prevalence of ≥1 chronic comorbidities had an RSV incidence estimate of 10 per 1,000 persons. The total study population of persons aged 50 years and older had an RSV incidence estimate of 7 per 1,000 persons.

Figure 6 Estimated incidence rates of ARI and estimates of medically attended RSV infection among adults aged 50 years and older in primary care, by comorbidity, average of respiratory seasons 2011/2012-2018/2019; the Netherlands



*The group ≥1 comorbidity consisted of persons aged 50 years and older with chronic pulmonary disease, diabetes mellitus, cardiac disease, liver disease, kidney disease and/or a compromised immune system

3.4.2 Estimation of the seasonal number of persons with RSV infection

The number of persons aged 50 years and older with RSV infection varied per respiratory season (Figure 7). The lowest estimated number of persons with RSV infection was in season 2011/2012 with 17,000 (95% CI 11,200-24,800), while season 2016/2017 had the highest estimated number of persons with RSV infection with 89,100 (95% CI 79,100-100,500).

The average number of persons with incident RSV infection between 2011-2019 is shown by age in Figure 8. The highest estimated number was in age category 55-59 with 7,900 (95% CI 6,600-9,400), while the lowest was in age category 80-84 with 3,600 (95% CI 2,700-4,800). The number of estimated seasonal incident RSV infections was again higher in younger age groups due to the higher population number in these age categories.

Figure 7 Estimated number of adults aged 50 years and older seeking medical attendance in primary care for RSV infection, by respiratory season; the Netherlands, 2011-2019

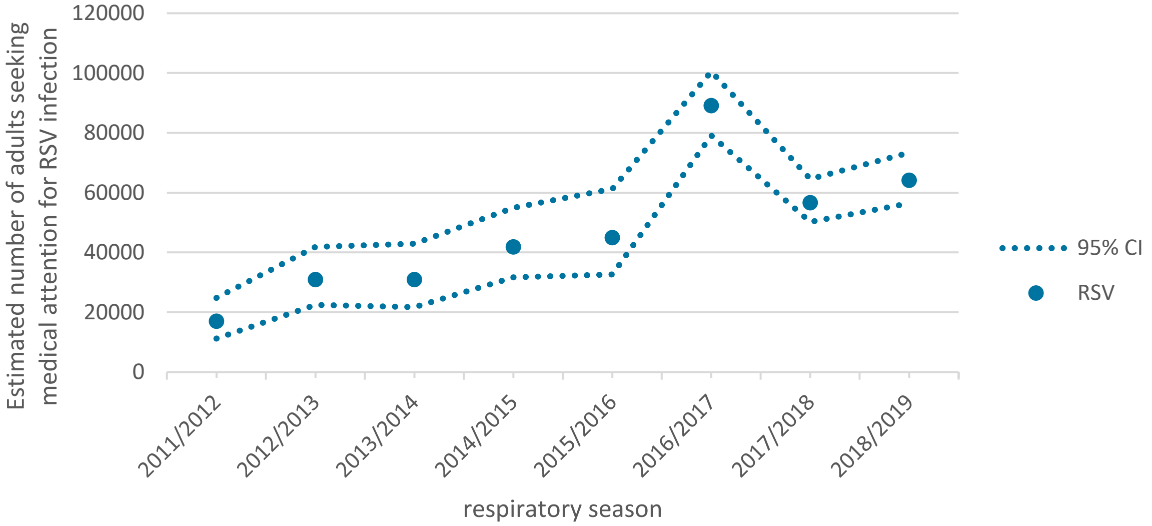
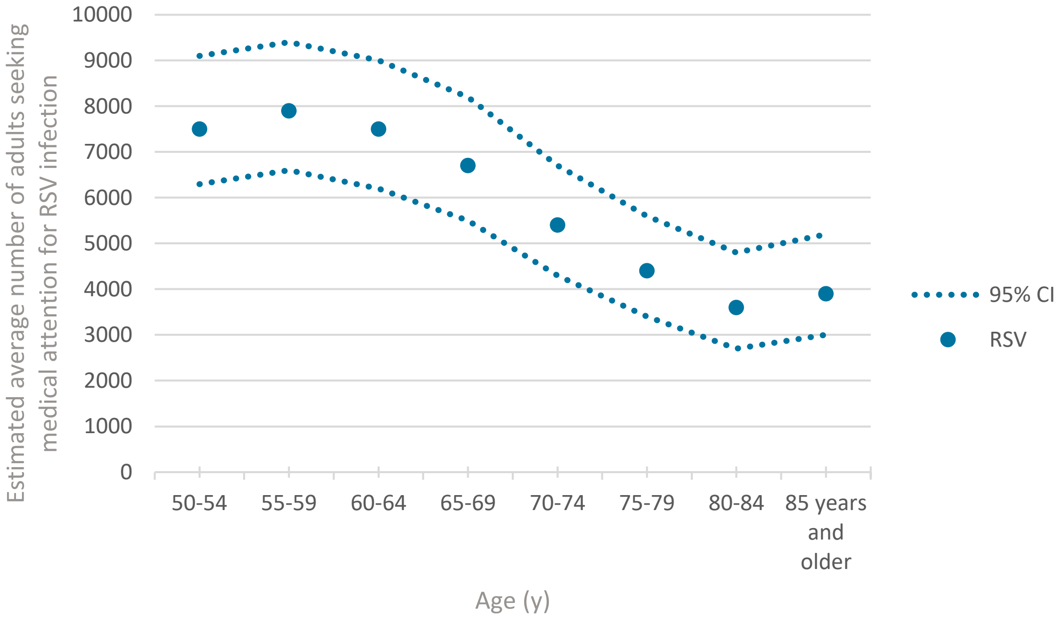


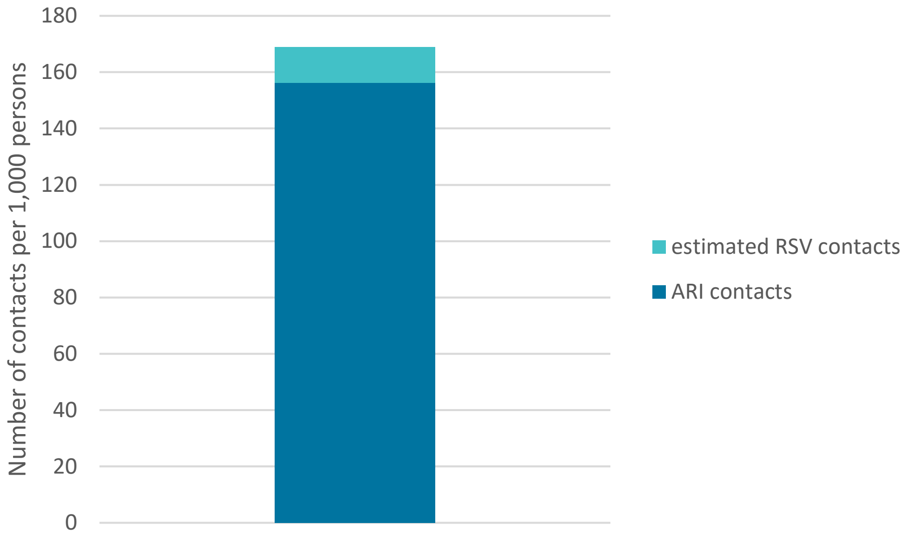
Figure 8 Estimated number of adults aged 50 years and older seeking medical attendance in primary care for RSV infection, by age, average of respiratory seasons 2011/2012-2018/2019; the Netherlands



3.5 GP contacts for ARI and RSV infection

For the respiratory seasons 2011/2012-2018/2019, the average number of contacts with the GP for persons with a registered ARI was estimated to be 169 per 1,000 persons. When multiplied with the RSV positivity proportion from the sentinel surveillance, we estimated that the average number of GP contacts attributed to an RSV infection was approximately 13 per 1,000 persons per season (Figure 9).

Figure 9 Estimated number of contacts with the GP practice for ARI and estimated RSV infection, in the Netherlands, average of respiratory seasons 2011/2012-2018/2019



4 Discussion

In this study we estimated the seasonal incidence of medically attended RSV infection between 2011/2012 and 2018/2019 among adults aged 50 years and older in primary care in the Netherlands. These estimates ranged from 3 (95% CI 2-4) per 1,000 persons in 2011/2012 to 13 (95% CI 12-15) per 1,000 persons in 2016/2017. These estimates for primary care in the Netherlands were comparable or lower than previously reported RSV incidence rates among older adults (6.7/1,000 and 16.2/1,000) for community settings in mostly high-income countries (11, 12).

In our study, the incidence of RSV infection increased throughout the studied period of 2011/2012 to 2018/2019. A recently published paper conducted in Canada showed a similar trend for the same time period for hospitalization rates among older adults due to RSV infection (14). However, a study conducted in the US did not confirm the recent increasing trend for RSV-associated hospitalization rates for the period 2016 up and till 2023 (33). In both studies, hospitalization rates associated with RSV also increased with age (14, 33). Thereby, a study conducted in western Australia found an increase in RSV detection rates in adults during 2017-2023 (34). Our study confirms the increase in estimated incident RSV infections in primary care with increasing age. Other studies performed in primary care did find an increase in RSV positivity in collected specimen from adults of increasing age, especially in collected specimen of adults aged 75 years and older (20, 21). Older age was also associated with more severe RSV in multiple study settings (5). When comparing our seasonal RSV positivity rates for adults aged 50 years and older with rates in other studies, our rates are comparable, except for the positivity rate of 26.5% for season 2009-2010 found in Tanner et al. for adults aged 65 years and older. We did not study season 2009-2010, but the last mentioned rate is considerably higher than our positivity rates for seasons 2011/2012-2018/2019 (20, 21). When persons of older age have more (severe) symptoms of their RSV infection, they are more likely to contact the GP more often.

In our study, the incidence estimates for medically attended RSV in primary care were higher in patients with chronic pulmonary disease compared to the other comorbidities under study. This is in agreement with previous literature showing persons with chronic pulmonary diseases are more likely to experience more severe respiratory symptoms, and consequently will contact the GP practice more often when infected with a virus or bacteria (5, 12, 13). Our study showed that during respiratory seasons 2011/2012-2018/2019, the number of persons who were at increased risk for medically attended RSV in the Netherlands was on average 2,783,000 persons per season (i.e., 43% of the 50+ population in the Netherlands). The prevalence rates of the different studied comorbidities were relatively stable throughout the seasons 2011/2012-2018/2019.

During respiratory seasons 2011/2012-2018/2019, the proportion of RSV positive specimen varied between 0% to 44%.The finding of 44% specimen that tested positive for RSV among sampled patients with ARI in 1 week, is most likely, caused by the small number of samples collected weekly by the GP sentinel practices. This is also why we used the moving average for our estimates. Since 2022, the number of GP practices that collect specimen for the respiratory surveillance has increased to 100-140 GP practices.

The proportion of positive RSV specimen could have varied by age, or for certain comorbidities. However, due to relatively small numbers of specimen collected in older age groups, and the insufficient information and registration of comorbidity in the sentinel surveillance, we only used the overall RSV positivity rate to obtain estimates of RSV incidence by age or comorbidity. This may have led to an underestimation of the RSV incidence estimate among certain high risk groups as patients with older age, and in persons with certain comorbidities. Therefore, it may have led to over- or underestimation of the RSV incidence estimates, depending on the comorbidity. The RSV incidence estimates presented should thus be interpreted with care. However, because the ARI incidence and prevalence of comorbidity were established based on the EHR data from a representative 10% sample of the Dutch population (i.e., Nivel-PCD), we consider the current estimates to be of high quality. Further research on RSV susceptibility in specific high-risk populations is needed.

Previous studies have indicated that patients residing in long-term care or other chronic care facilities are at a higher risk of experiencing severe clinical outcomes from RSV infections compared to those living at home (17, 18). In the Netherlands, individuals living in long-term care facilities often are not registered in a GP practise, resulting in their underrepresentation in our study population. Consequently, the incidence of RSV infections requiring medical consultation in primary care may be underestimated, particularly for the oldest patients, and those with comorbidities.

Some assumptions were made in this study. Firstly, persons tested in the sentinel surveillance were assumed to be representative for all persons that visited their GP with ARI symptoms and who were registered in Nivel-PCD. GPs participating in the sentinel surveillance were instructed to collect between two and five naso- and oropharyngeal specimens on a weekly basis, prioritizing patients with ILI. This restricted sampling approach may have limited the collection of samples from patients with other ARI symptoms potentially resulting in an overrepresentation of ILI specimens among the total samples and a possible underestimation of the percentage of RSV-positive cases. Secondly, naso- and oropharyngeal specimens were tested using a multiplex RT-qPCR assay to detect multiple respiratory viruses, including RSV. While combining naso- and oropharyngeal specimens improves the sensitivity of RSV detection compared to using nasopharyngeal specimens alone, more comprehensive diagnostic strategies—such as combining PCR with antigen testing or serological assays—could further enhance sensitivity (35). The reliance on PCR testing alone may have led to an underestimation of the proportion of RSV-positive specimens, however for surveillance purposes, this is the most efficient diagnostic practice currently available.

Several diagnosis codes (based on ICPC) were included to construct ARI disease episodes in this study, including pneumonia. By including pneumonia in our definition of ARI, we may have overestimated the incidence estimate of RSV infection. We know that multiple viruses, bacteria and fungi are able to cause pneumonia. In a study conducted to determine the incidence of community acquired pneumonia in hospitalized adults multiple pathogens were found. Viral pathogens were found in 23% of the patients, 11% had a bacterial pathogen, and in 3% both viral and bacterial pathogens were found. In the remaining patients no pathogen was found (36). Further, also secondary bacterial infection may play a role in the development of pneumonia after an initial viral infection (37). In our study it was not possible to detect pneumonia patients in the sentinel surveillance to conduct a sensitivity analysis in which we excluded pneumonia, because the specific diagnosis pneumonia was not registered consistently.

In this study, incidence rates of ARI and estimates of medically attended RSV infection varied among different respiratory seasons. Several factors are important when considering the circulation of RSV. For example, the co-circulation of other respiratory viruses, e.g. influenza virus, has an impact on the transmission of RSV. When for example influenza virus A circulates earlier in the respiratory season, the pattern of RSV circulation will change in that particular season (38). In the northern hemisphere, RSV circulation usually starts mid-October. If this pattern changes, this will lead to different incidence estimates for medically attended RSV infection.

As mentioned earlier, the incidence estimates for medically attended RSV infection were based on ARI incidence recorded in the EHR by the GP and the proportion of collected RSV positive specimens in the sentinel surveillance. Multiple viruses and bacteria may have induced an increase in ARI diagnoses which we used to estimate the RSV incidence estimates. We cannot confirm with this study that RSV is solely responsible for the observed increase.

In this study the estimated number of contacts for an RSV infection was derived from the number of contacts with the GP for ARI and the proportion of positive specimen for RSV found in the sentinel surveillance. These contacts included single contacts as well as repeated contacts due to the same health problem. We cannot make these estimations more specific, because we do not have any information on disease severity. Disease severity influences both the occurrence of a contact with the GP as well as the number of repeated contacts for the same diagnosis. Diagnostic testing for respiratory viruses (e.g. RSV) in GP practices after ARI diagnosis as usual care, would help inform us on both disease severity as well as the proportion of ARI patients that actually have an RSV infection.

In the Netherlands, the Health Council is the organisation that advises the Dutch Ministry of Health on the implementation of vaccination. Multiple RSV-vaccines for older adults have recently been approved by the European Medicines Agency (EMA). The burden of RSV in both primary care and hospitals, as well as the expected efficiency and costs of the RSV vaccines are important to project the impact of vaccines on incidence and severity of disease due to RSV infection. The possible effects of vaccines should also consider the economic burden of RSV infection in older adults, including direct healthcare costs, indirect costs (e.g., lost productivity), and the impact on healthcare system capacity, especially during peak seasons. High-quality incidence estimates of the RSV disease burden and follow-up studies in vaccine eligible populations are needed to assess the need and the impact for public health of new vaccine prevention strategies in older adults.

Conclusion

During respiratory seasons 2011/2012 up and till 2018/2019, the estimated incidence of medically attended RSV infection in adults aged 50 years and older in primary care in the Netherlands, varied between 3 (95% CI 2-4) per 1,000 persons in 2011/2012 and 13 (95% CI 12-15) per 1,000 persons in 2016/2017. The incidence estimate of RSV infection increased over time, and estimates were higher among persons with older age and in patients with one or more chronic comorbidities (especially chronic pulmonary disease). The estimated absolute number of adults aged 50 years and older seeking medical attendance for RSV infection in the Netherlands ranged from 17,000 (95% CI 11,200-24,800) in season 2011/2012 to 89,100 (95% CI 79,100-100,500) in season 2016/2017.
During the respiratory seasons 2011/2012-2018/2019, each season there were on average 2,783,000 persons aged 50 years and older considered to be at increased risk for medically attended RSV infection due to having ≥1 comorbidity the Netherlands. This corresponded to approximately 43% of the total population of persons aged 50 years and older in the Netherlands.
The average seasonal number of contacts with a GP practice was 169 per 1,000 persons aged 50 years and older with a registered ARI. Based on this contact rate and the RSV positivity proportion we obtained, it was estimated that the seasonal number of contacts attributed to an RSV infection was approximately 13 per 1,000 persons.

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Appendix A Supplementary material

Table A1 Rates (n/1,000) for ARI incidence and comorbidity prevalence, by age and respiratory season; the Netherlands, 2011-2019.

Age	Incident ARI[1]	Diabetes mellitus[2]	Cardiac disease[3]	Compromised immunesystem[4]	Liver disease[5]	Kidney disease[6]	Chronic pulmonary disease[7]
Season 2011/2012							
50-54	6.9	6.6	8.4	2.6	0.8	0.8	5.4
55-59	8.0	9.9	12.9	3.1	0.9	1.0	7.3
60-64	8.3	13.7	18.5	3.6	1.0	1.5	8.8
65-69	8.3	18.2	25.0	4.5	1.1	2.2	10.5
70-74	8.7	20.8	32.8	5.8	1.0	3.4	12.9
75-79	9.5	23.4	41.3	7.0	0.8	5.2	14.6
80-84	10.6	24.0	48.7	8.1	0.8	7.1	15.9
85+	12.3	21.2	54.6	7.9	0.5	8.4	14.1
Season 2012/2013							
50-54	8.4	6.6	8.3	2.7	0.8	0.8	5.4
55-59	9.5	9.7	12.7	3.3	1.0	1.1	7.4
60-64	9.3	13.6	18.4	3.9	1.2	1.6	9.0
65-69	8.7	17.9	25.0	4.8	1.2	2.4	10.6
70-74	9.4	21.2	33.2	6.2	1.1	3.7	13.0
75-79	10.5	23.5	41.8	7.6	1.0	5.8	15.1
80-84	11.5	24.5	49.1	8.8	0.8	7.7	16.1
85+	14.2	21.8	55.5	8.8	0.6	9.6	14.4
Season 2013/2014							
50-54	6.0	6.7	8.5	3.3	1.0	0.9	5.6
55-59	6.7	9.8	13.0	4.2	1.2	1.3	7.7

60-64	7.2	13.6	18.8	5.1	1.3	1.9	9.4
65-69	7.4	17.8	25.6	6.3	1.4	2.8	10.8
70-74	7.9	21.4	33.5	8.0	1.3	4.3	13.0
75-79	8.7	23.5	42.2	10.1	1.1	6.6	15.0
80-84	9.5	25.0	50.5	11.7	0.9	8.8	16.0
85+	11.6	22.1	56.7	11.4	0.7	10.7	14.5
Season 2014/2015							
50-54	7.5	6.7	9.1	2.7	1.0	1.0	5.2
55-59	8.4	9.7	13.6	3.4	1.3	1.3	7.4
60-64	9.0	13.3	19.5	4.2	1.4	1.9	9.2
65-69	8.9	17.6	26.4	5.2	1.5	2.9	10.5
70-74	9.1	21.5	34.6	6.5	1.4	4.3	12.6
75-79	10.3	23.7	43.2	8.1	1.2	6.3	14.4
80-84	11.9	25.3	51.7	9.2	0.9	8.7	15.5
85+	14.3	22.6	58.7	9.0	0.7	10.4	14.3
Season 2015/2016							
50-54	6.4	6.5	9.0	2.6	1.1	1.0	4.9
55-59	7.2	9.6	13.5	3.3	1.5	1.3	7.1
60-64	7.9	13.2	19.6	4.1	1.5	1.9	9.1
65-69	7.7	17.4	26.6	5.2	1.7	3.0	10.6
70-74	7.8	21.5	34.9	6.3	1.5	4.3	12.5
75-79	8.9	23.4	42.9	8.0	1.4	6.5	14.2
80-84	9.7	25.3	52.1	9.2	1.1	8.6	15.2
85+	11.3	22.9	59.1	8.9	0.7	11.1	14.2
Season 2016/2017							
50-54	8.1	7.8	11.0	3.2	1.5	1.2	5.9
55-59	8.9	11.2	15.9	3.9	1.9	1.6	8.3
60-64	9.7	14.8	22.6	4.8	2.0	2.3	10.4
65-69	9.2	18.6	29.4	5.9	2.0	3.2	11.7
70-74	9.4	23.0	38.3	7.3	1.9	4.8	13.4

75-79	10.7	24.7	45.9	9.1	1.7	6.9	15.0
80-84	12.2	26.4	54.8	10.4	1.3	9.1	15.5
85+	14.4	23.9	62.4	10.0	0.9	11.5	14.5
Season 2017/2018							
50-54	8.4	8.1	11.4	3.2	1.7	1.2	5.8
55-59	9.3	11.4	16.5	4.0	2.1	1.6	8.0
60-64	9.9	15.0	23.3	5.0	2.1	2.3	10.5
65-69	9.6	19.0	30.4	6.3	2.3	3.4	11.9
70-74	9.5	22.5	38.1	7.5	2.1	4.7	13.0
75-79	10.5	25.1	46.6	9.2	1.8	6.8	14.7
80-84	12.1	26.7	55.5	10.4	1.5	9.1	15.6
85+	14.2	24.2	62.8	10.4	1.0	11.7	14.3
Season 2018/2019							
50-54	5.5	6.2	8.7	4.0	1.3	1.0	4.7
55-59	6.3	9.0	13.2	5.1	1.7	1.3	6.6
60-64	7.1	12.4	19.4	6.4	1.9	1.9	9.0
65-69	7.3	16.3	26.7	8.7	2.0	3.3	10.6
70-74	7.3	21.5	34.5	11.1	1.9	4.9	11.9
75-79	8.0	23.2	43.4	14.1	1.7	7.3	13.3
80-84	9.3	25.0	52.4	16.8	1.4	10.2	14.5
85+	11.6	23.6	60.5	18.5	1.0	13.0	13.5

[1]ICPC-codes R74, R75, R76, R77, R78, R80, or R81
[2]ICPC-code T90
[3]ICPC-codes K74-K79, K83, K87
[4]Based on the definition used for seasonal influenza vaccination in the Netherlands (30, 31)
[5]ICPC-codes D96, D97
[6]ICPC-codes U85, U88, U99
[7]ICPC-codes R91, R95, R96

Table A2 Estimated seasonal ARI incidence rate (n/1,000 persons) for adults aged 50 years and older in primary care, by respiratory season; the Netherlands, 2011-2019

Age	Season							
	2011/2012	2012/2013	2013/2014	2014/2015	2015/2016	2016/2017	2017/2018	2018/2019
50-54	89.2	106.6	61.2	69.4	79.8	169.9	137.4	80.2
55-59	104.4	123.9	70.9	83.1	92.1	168.1	143.4	80.2
60-64	110.1	120.9	80.0	94.0	100.3	162.9	147.5	103.5
65-69	107.3	112.3	82.6	95.5	98.3	146.8	135.7	104.4
70-74	115.1	120.7	90.8	101.3	100.0	138.1	131.2	102.5
75-79	125.1	135.6	102.7	122.9	116.0	154.0	143.5	114.5
80-84	136.1	151.5	114.8	147.0	130.5	173.2	170.1	132.2
85+	164.3	183.7	142.3	178.7	155.6	201.7	195.7	169.4
Total (95% CI)	110.7 (69.7-172.1)	123.6 (87.0-172.5)	83.5 (57.9-118.0)	98.4 (72.6-131.3)	100.6 (71.3-139.0)	161.7 (142.8-184.0)	144.7 (128.0-166.0)	103.1 (90.1-118.4)

Table A3 Incidence estimates of medically attended RSV infection (n/1,000 persons) in adults aged 50 years and older in primary care, by respiratory season; the Netherlands, 2011-2019

Age	Season							
	2011/2012	2012/2013	2013/2014	2014/2015	2015/2016	2016/2017	2017/2018	2018/2019
50-54	2.3	4.4	3.5	4.7	5.3	12.6	8.0	6.8
55-59	2.6	5.1	3.5	5.6	6.3	13.4	8.4	8.1
60-64	2.7	4.8	4.7	6.3	6.8	13.3	8.4	9.2
65-69	2.6	4.4	4.8	6.3	6.6	12.1	7.8	9.4
70-74	2.9	4.8	5.3	6.5	6.8	11.8	7.5	9.3
75-79	3.1	5.3	6.0	8.0	7.9	13.8	8.1	10.4
80-84	3.4	6.0	6.6	9.5	9.0	15.7	9.7	12.3
85+	4.1	7.4	8.4	11.7	10.7	18.6	11.2	16.2
Total (95% CI)	2.8 (2.0-4.0)	5.0 (3.6-6.7)	4.9 (3.4-6.7)	6.5 (4.9-8.5)	6.8 (4.9-9.3)	13.3 (11.8-15.0)	8.3 (7.4-9.5)	9.3 (8.2-10.6)

Table A4 Incidence rates of ARI and estimates of medically attended RSV infection (n/1,000) among adults aged 50 years and older in primary care, by comorbidity, average of respiratory seasons 2011/2012-2018/2019; the Netherlands

Comorbidity	ARI	RSV
diabetes mellitus	147	9
≥1 comorbidity	153	10
cardiac disease	153	10
liver disease	166	11
kidney disease	171	11
immunocompromised	182	11
chronic pulmonary disease	218	13
Total group 50+	116	7

Table A5 Estimated number of adults aged 50 years and older seeking medical attendance in primary care for RSV infection, by respiratory season; the Netherlands, 2011-2019

Season	RSV	95% lower bound	95% upper bound
2011/2012	17,000	11,200	24,800
2012/2013	30,900	22,500	41,900
2013/2014	30,900	21,700	42,900
2014/2015	41,900	31,700	54,900
2015/2016	45,000	32,600	61,200
2016/2017	89,100	79,100	100,500
2017/2018	56,600	50,200	64,600
2018/2019	64,100	56,400	73,400

Table A6 Estimated seasonal number of adults aged 50 years and older seeking medical attendance in primary care for RSV infection, by age, average of respiratory seasons 2011/2012-2018/2019; the Netherlands

Age	RSV	95% lower bound	95% upper bound
50-54	7,500	6,300	9,100
55-59	7,900	6,600	9,400
60-64	7,500	6,200	9,000
65-69	6,700	5,500	8,200
70-74	5,400	4,300	6,700
75-79	4,400	3,400	5,600
80-84	3,600	2,700	4,800
85+	3,900	3,000	5,200