

Respiratory syncytial virus (RSV) associated primary care incidence estimates in adults aged 50 years and older in the Netherlands; 2016-2019



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This short report has used data from Nivel Primary Care Database (Nivel-PCD). For the years 2016-2019, pseudonymized registered data from electronic health records were extracted by Nivel from approximately 360-400 GP practices. In addition, data from the national virological surveillance were used. The approximately 40 GP practices that take part in the sentinel surveillance are requested to collect at least two with a maximum of five combined naso- and oropharyngeal swabs per week. These samples are then tested at the national reference laboratory of the RIVM with laboratory developed real-time RT-PCR tests on a number of respiratory viruses, including RSV. Data from multiple years were combined to form respiratory seasons. Each season started on ISO-week 40 of one year and ended on ISO-week 20 of the following year.

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Summary

The aim of this study was to estimate the seasonal incidence rate of adults aged 50 years and older, who consulted their general practitioner (GP) with an RSV infection in the Netherlands. Medically attended RSV incidence rates were calculated by counting the weekly number of acute respiratory infection (ARI) disease episodes recorded by the GP in the electronic health records (EHR) and multiplying this number with the weekly proportion of specimens, with a laboratory-confirmed positive test result for RSV, collected via the national virological sentinel surveillance in primary care. To estimate the total number of adults that consulted the GP with RSV infection in the Netherlands, seasonal RSV infection incidence rate estimates were extrapolated to the Dutch population aged 50 years and older.

The incidence rate of adults aged 50 years and older who contacted their GP with an RSV infection was estimated to be 13.3 (95% confidence interval, CI: 9.8-17.6), 8.3 (95% CI: 6.0-11.2) and 9.3 (95% CI: 6.6-12.7) per 1,000 registered persons in general practice for the respiratory seasons 2016/2017, 2017/2018 and 2018/2019, respectively. RSV incidence rates were estimated to be higher in adults aged 75 years and older, compared to adults aged 50-74 years. Sub-group analyses were conducted to estimate RSV-associated incidence rates for patients groups that are considered to be at increased risk for medically attended RSV infection (e.g., chronic pulmonary disease). The medically attended RSV incidence rates for persons with chronic pulmonary disease were estimated to be higher compared to the total population of adults aged 50 years and older, or patients with e.g. diabetes mellitus or cardiac disease. The estimated total number of adults aged 50 years and older who contacted their GP with a RSV infection were estimated to be 89,100 (95% CI 66,100-118,100), 56,600 (95% CI 41,100-76,200), and 64,000 (95% CI 45,800-87,500) for the respiratory seasons 2016/2017, 2017/2018 and 2018/2019, respectively. These estimates on RSV infection among adults in primary care will help policymakers in making decisions on the implementation of new preventive measures.

1 Introduction

Previous studies showed that the burden of disease of RSV infection among older adults (aged 65 years and older) might be substantial (1-4). However, little is known about the incidence of RSV infection in this older age group, as no standard testing is performed for RSV infection among general practitioners (GPs). Epidemiological information of RSV infection among adults (aged 18 years and older) is mostly derived from hospital data (3, 5-7). For a better understanding of the burden of disease of RSV infection, this study aimed to estimate the incidence of medically attended RSV infection among older adults (aged 50 years and older) in primary care in the Netherlands. The outcomes of this study will inform policy makers and support decision-making about possible preventive measures in the future.

Seasonal incidence of medically attended RSV infection was estimated for persons aged 50 years and older in the Netherlands, from respiratory season 2016/2017 to 2018/2019. A respiratory season was defined as lasting from ISO-week 40 (beginning of October) of a year until ISO-week 20 (mid-May) of the following year. To estimate the incidence of medically attended RSV in each respiratory season, we combined the weekly incidence of ARI diagnosis (i.e., a combination of respiratory conditions including influenza) in Nivel Primary Care Database (Nivel-PCD), with RSV test results among adults aged 50 years and older, obtained from the national virological sentinel surveillance using a subset of GPs from Nivel-PCD who collect naso- and oropharyngeal swabs from a selection of persons that had contacted the GP because of an ARI.

In this short report with preliminary results we present the incidence of ARI and RSV infection in primary care in each season, by age group and by comorbidity. These estimates were then extrapolated to the Dutch population aged 50 years and older, to estimate the seasonal number of medically attended incident RSV infections in primary care.

2 Methods

2.1 Nivel Primary Care Database

Nivel-PCD contains a representative sample of general practices all over the Netherlands, providing electronic health record data of approximately 10% of the Dutch population. Nivel collects routinely recorded information from the electronic health record (EHR) systems of participating general practices. For each contact with the GP, (clinical) diagnosis is recorded using ICPC codes (International Classification of Primary Care, version 1) (8).

The use of electronic health records 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.

2.2 Study population

All persons registered at a general practice that takes part in Nivel-PCD and who were aged 50 years and older at the start (ISO-week 40, beginning of October) of each respiratory season (2016/2017, 2017/2018, and 2018/2019) were included in the analyses for this study. This group consisted of persons with and without a contact at the GP during the selected time period.

Several chronic comorbidities which are considered to increase the risk for medically attended RSV in primary care were selected; chronic pulmonary disease (ICPC-codes R91, R95, R96), diabetes mellitus (T90), cardiac disease (K74-K79, K83, K87), liver disease (D96, D97), kidney disease (U85, U88, U99), and/ with a compromised immune system which is based on the definition used for the target group for season influenza vaccination (9, 10) were included. For this short report with preliminary results, analyses were restricted to chronic pulmonary disease, diabetes mellitus, and cardiac disease. We also present results for a combined group that is considered to be at increased risk for medically attended RSV, based on the prevalence of one or more of the selected comorbidities. These results are preliminary, because more analyses will be conducted for a more elaborative report on this topic that is expected to be published early 2025.

Incident acute respiratory infection (ARI) was defined as having a recorded diagnosis of one of the following: acute upper respiratory infection (ICPC code R74), sinusitis (R75), acute tonsillitis (R76), acute laryngitis (R77), acute bronchitis/bronchiolitis (R78), influenza (R80), or pneumonia (R81). Disease episodes were constructed for each of these diagnoses using the method published by Nielen et al. (11). In short: a disease episode lasted from the first ARI registration until a person did not contact the GP for the same diagnosis for a period of 4, 8, or 16 weeks, depending on the diagnosis. The disease episode was then 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 'ARI episodes' in a respiratory season was divided by the total follow-up time among persons registered at the GP practice. Incidence rates 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). The degree of urbanisation was defined as low (<500), moderate (500-1,000), or high ($\geq 1,000$ addresses per km²). Incidence rates are presented per 1,000 persons.

2.3 Sentinel surveillance

Approximately 40 GP practices of Nivel-PCD, also known as Nivel Sentinel Practices (in Dutch: *Nivel Peilstations*) are asked to collect combined naso- and oropharyngeal swabs from at least two persons of all ages (and a maximum of five) per week, complying to the case definition of influenza-like illness (ILI) or another ARI (12). These samples were tested for multiple respiratory viruses, including RSV, at the laboratory of the National institute of Public Health and the Environment (RIVM). For this study, testing results of all persons with an age of 50 years and older at the date of sampling in the respiratory seasons 2016/2017, 2017/2018, and 2018/2019 were included.

2.4 Estimation of the seasonal incidence of medically attended RSV infection

We calculated the weekly proportion of specimens of persons aged 50 years and older with ARI that tested positive for RSV. To correct for the fluctuating number of weekly persons tested, we used a 5-week moving average in our estimates. The data points and the moving average are presented in Figure 1.

To estimate the seasonal incidence of medically attended RSV infection, we multiplied the weekly number of incident ARI diagnoses in Nivel-PCD with the (moving average of the) proportion of samples that tested positive for RSV in the corresponding week, as obtained from the sentinel surveillance. For each week, we calculated a 95% exact binomial confidence interval (CI) around the incidence rate. The 95% CI is only reported for the estimated (relative and absolute) number of incident RSV cases per respiratory season.

The seasonal number of incidents medically attended RSV infections was obtained by multiplying the estimated incidence rate of medically attended RSV infection with the corresponding number of people per age category in the Netherlands on January 1st of each respiratory season (obtained from Statistics Netherlands). For each respiratory season, the total number of incident RSV infection and 95% CI is presented. To emphasize that these estimated numbers cannot be exact, the extrapolated numbers were rounded to the closest multiple of 100.

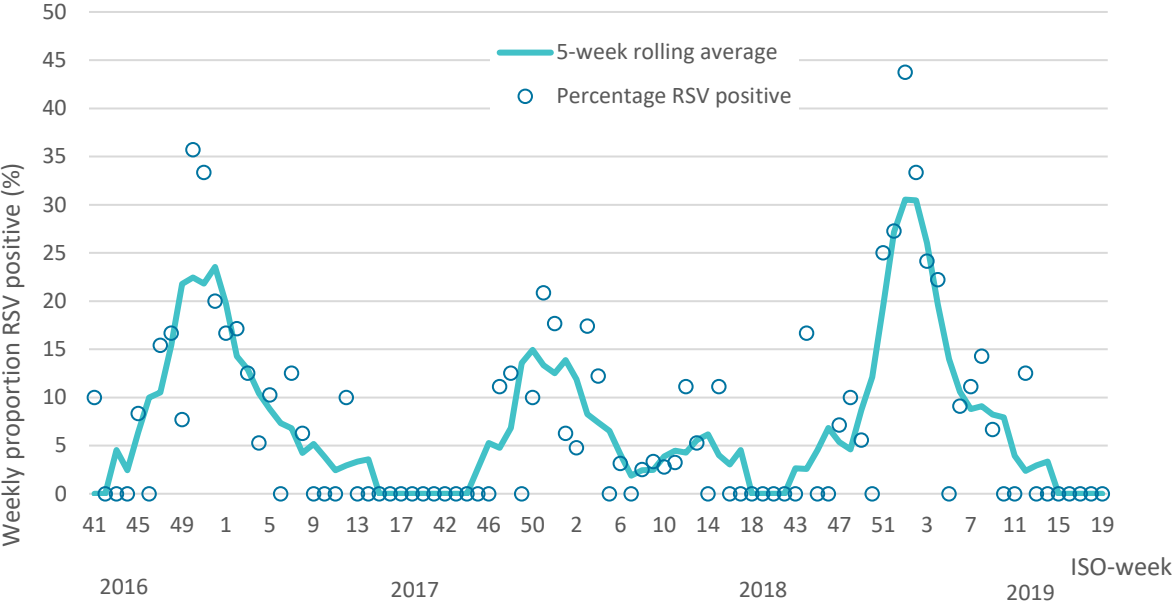
3 Weekly proportion of RSV positive samples in the sentinel surveillance

During the respiratory seasons 2016/2017 to 2018/2019 (ISO weeks 40 to 20), 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 50 years and older that presented with ARI. The total number of specimens collected was 432 in season 2016/2017 (n=50 or 11.6% of which tested positive for RSV), 524 in season 2017/2018 (n=31 or 5.9% of which tested positive for RSV), and 355 in season 2018/2019 (n=44 or 12.4% of which tested positive for RSV). The median number of specimens collected among adults aged 50 years and older for all respiratory seasons was 10 per week (IQR: 7-19).

The proportion and 5-week moving average of positive RSV specimens among persons aged 50 years and older in the virological surveillance data are shown in Figure 1. In seasons 2016/2017 and 2018/2019 one peak (end of December, beginning of January) can be observed, while in season 2017/2018 various smaller peaks can be observed. Each respiratory season had the highest proportion of positive RSV specimens between week 50 (mid-December) and week 2 (beginning of January). The highest proportion of RSV positive specimens was 36% in week 50 of season 2016/2017, 21% in week 51 of season 2017/2018, and 44% in week 1 of season 2018/2019. No samples tested positive after week 16 in these seasons.

The amount of samples and the weekly proportion of samples that tested positive for RSV were fluctuating among the different respiratory seasons. Several factors play a role in the circulation of RSV. For example, the circulation of other respiratory viruses, such as influenza, had an impact on the transmission of RSV. When for instance influenza A circulates earlier in the respiratory season, the pattern of RSV will change as a result in that particular season (13). RSV usually circulates in the beginning of the respiratory season (October-January). If this pattern changes, this will lead to a different amount of positive samples. This may have had an impact on the amount of samples that tested positive for RSV in the sentinel surveillance in primary care.

Figure 1 Weekly proportion* of RSV-positive specimens and 5-week moving average derived from adults aged 50 years and older with ARI (including ILI)# related symptoms through virological sentinel surveillance, 2016-2019, the Netherlands



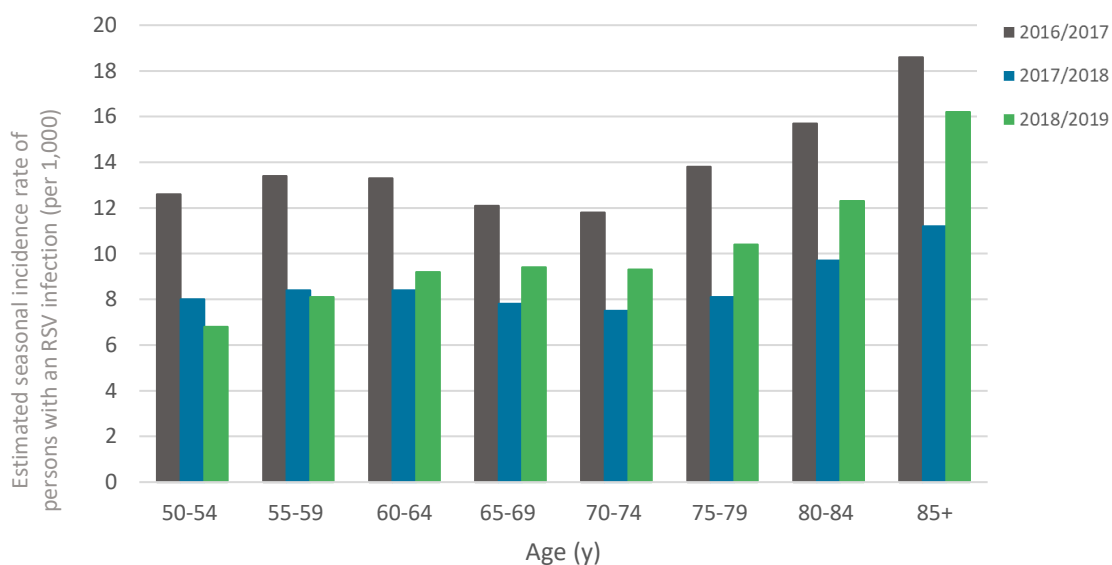
* ISO-weeks 21-39 (mid-May till the end of September) were omitted from this figure

ARI: acute respiratory infection, ILI: Influenza-like illness

4 Estimated incidence rates of RSV infections in primary care

The seasonal incidence rate of adults aged 50 years and older, consulting the GP with an RSV infection was estimated to be 13.3 (95% CI: 9.8-17.6) per 1,000 persons in season 2016/2017, 8.3 (95% CI: 6.0-11.2) per 1,000 persons in season 2017/2018, and 9.3 (95% CI: 6.6-12.7) per 1,000 persons in season 2018/2019. Figure 2 shows the estimated seasonal incidence rates by 5-year age category. An increasing trend in the estimated RSV incidence rates was observed from the age of 75. The lowest estimated incidence rate of RSV infection was observed among those aged 50-54 years in season 2018/2019, with 6.8 per 1,000 persons. The highest estimated RSV incidence rate was found in those aged 85 years or older in season 2016/2017, with 18.6 per 1,000 persons. Despite a higher estimated RSV incidence rate among the older age groups (75 years and older), the estimated total number of RSV cases among these older age groups were lower (Figure 2). This is due to the lower population number of persons of 75 years and older in the Netherlands.

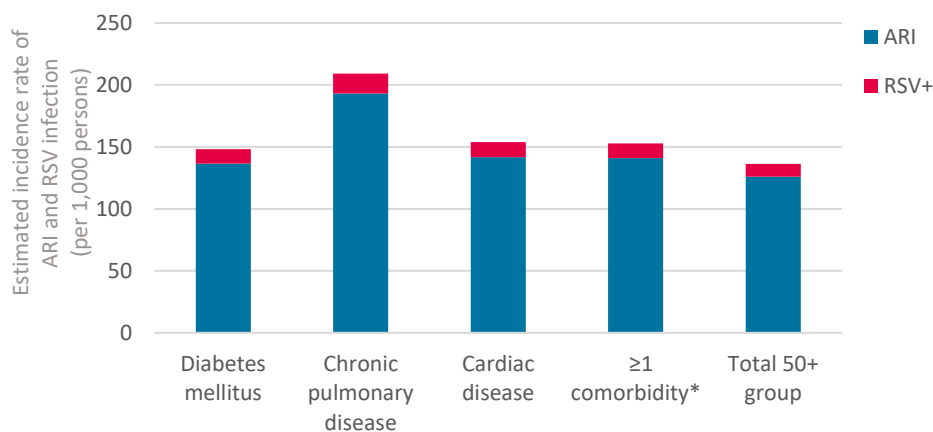
Figure 2 Estimated seasonal incidence rate of adults with an RSV infection in primary care, by age-category, the Netherlands, 2016-2019



5 Estimated incidence rates of ARI and RSV infections, by comorbidity

The estimated incidence rates of ARI and RSV infection in primary care are shown by comorbidity in Figure 3. We estimated a higher incidence rate of RSV infection among persons with chronic pulmonary disease (defined as having asthma and/or COPD), when compared to persons living with e.g. diabetes mellitus or cardiac disease. Persons with chronic pulmonary disease had an estimated incidence rate of RSV infection with 16.0 per 1,000 persons registered at the GP. For diabetes mellitus and cardiac disease these estimated incidence rates for RSV infection were 11.6 per 1,000 persons and 12.1 per 1,000 persons registered at the GP, respectively. 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 (please refer to ‘Methods’ for the selection of comorbidities) also had a lower estimated incidence rate of RSV infection (11.9 per 1,000 persons) compared to persons with chronic pulmonary disease. Finally, the total reference group, aged 50 years and older, had an RSV incidence rate of 10.3 per 1,000 persons registered at the GP.

Figure 3 Estimated incidence rate of ARI and RSV infection among adults aged 50 years and older in primary care, by comorbidity, 2016-2019, 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.

6 Estimated number of persons visiting the GP for RSV infection in the Netherlands

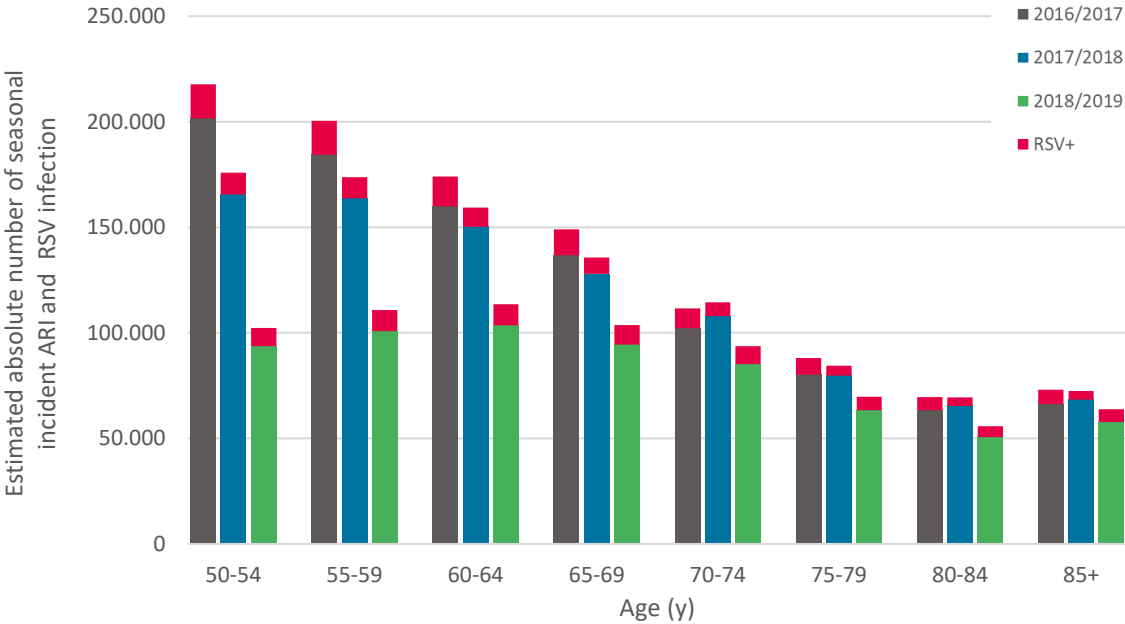
The total number of ARI diagnoses in persons aged 50 years and older in the Netherlands were estimated to be 1,083,700 in 2016/2017, 985,400 in 2017/2018 and 713,300 in 2018/2019. In each respiratory season, the number of persons (aged 50 years and older) that visited their GP with RSV infection was estimated to be 89,100 (95% CI 66,000-118,100) in 2016/2017, 56,600 (95% CI 41,100-76,200) in season 2017/2018, and 64,100 (95% CI 45,800-87,500) in season 2018/2019. These numbers, together with the proportion of ARI diagnoses that was associated with RSV infection are presented per season in Table 1.

Table 1 Estimated number of incident RSV infections among adults aged 50 years and older in primary care, 2016-2019, in the Netherlands

Season	Estimated number of incident RSV infections per respiratory season (95% CI)	Proportion of ARI diagnoses associated with RSV infection (%)
2016/2017	89,100 (66,000-118,100)	8.2
2017/2018	56,600 (41,100-76,200)	5.7
2018/2019	64,100 (45,800-87,500)	9.0

Figure 4 shows the estimated total number ARI diagnoses and RSV infections by 5-year age category in the Netherlands. The total estimated number of ARI diagnoses and RSV infections varied between seasons. For example, in age group 60-64 years the total estimated number of RSV infections per respiratory season varied between 9,100 (in 2017/2018) and 14,200 (in 2016/2017).

Figure 4 Estimated seasonal number of ARI related diagnoses, and (in red) the proportion of ARI diagnoses estimated to be associated with RSV infection among adults aged 50 years and older, by age, 2016-2019, the Netherlands



7 Limitations

It is important to consider some limitations of our study to carefully interpret the results.

The assumption was made that the persons tested in the sentinel surveillance were a representative sample from all persons that presented with ARI symptoms at the GPs participating in Nivel-PCD. However, it has to be mentioned that GPs in the sentinel surveillance are requested specifically to sample the first two to (max.) five patients with ILI symptoms each week. If no patients presented with ILI on Monday or Tuesday, GPs were asked to then sample patients with (other) ARI symptoms. This will have led to an overrepresentation of patients with ILI symptoms in our sample that was tested for RSV infection. Patients with ILI could be either more likely, or less likely to test positive for RSV than patients with ARI, depending on the duration and timing of the influenza epidemic of each specific season. Consequently, our current RSV incidence rates may be over- or underestimated. This, as well as the representativeness of our sample, will be studied more in-depth using data from a larger sample, covering seasons 2011/2012 to 2018/2019.

In Nivel-PCD, detailed data is available on the ARI incidence rates per high-risk subgroup population for RSV. However, there is insufficient data available for the weekly proportion of laboratory-confirmed RSV positive cases in these high-risk patient population. Previous studies suggest that in high-risk patient groups RSV is more frequently the cause of symptomatic ARI-related symptoms compared to the overall older adult population (1). In this study we have used the weekly proportion of RSV-positive samples in persons aged 50 years and older as a proxy for the weekly RSV positivity rate in each subgroup. Consequently, our RSV incidence estimates for high-risk groups may underestimate the actual incidence in these populations.

In this study RSV-associated primary care incidence rates were estimated per 1,000 registered persons aged 50 years and older in primary care. Due to the set-up of the health care system in the Netherlands, frail elderly patients in long-term facilities were mostly not treated, nor registered at a GP practice (they were managed by an elderly care specialist). Consequently, the estimates of medically attended RSV infections of persons aged 50 years and older could have been underestimated in this study. Future research could investigate RSV incidence in long-term care facilities to get a more complete picture of the RSV incidence in the population aged 50 years and older.

8 Conclusions

The estimated seasonal incidence rate of RSV infection among adults aged 50 years and older in primary care was 13.3 (95%CI: 9.8-17.6), 8.3 (95%CI: 6.0-11.2) and 9.3 (95%CI: 6.6-12.7) per 1,000 registered persons in a GP practice for the seasons 2016/2017, 2017/2018, and 2018/2019, respectively.

These estimated seasonal incidence rates were extrapolated to the Dutch population aged 50 years and older to obtain an estimate of the total number of medically attended RSV infection in the Netherlands. These absolute numbers were estimated to be 89,100 (95% CI 66,000-118,100) in 2016/2017, 56,600 (95% CI 41,100-76,200) in season 2017/2018, and 64,100 (95% CI 45,800-87,500) in season 2018/2019.

The estimated seasonal incidence rates of RSV infection in persons aged 75 years and older seemed to be higher than in the persons aged 50-74 years. It was estimated that persons aged 50 years and older with chronic pulmonary disease have a higher seasonal incidence rate of RSV infection compared to the total population aged 50 years and older, or compared to persons with for example diabetes mellitus or cardiac disease.

This study estimated that RSV-associated ARI infections are only a relatively small proportion (6-9%) of the total number of ARI diagnoses seen in primary care. This study could be used by policy makers for decision making on introduction of preventive measures. Certain subgroups in this study were estimated to have a higher incidence rate of RSV infection, i.e., persons aged 75 years and older and persons aged 50 years and older with chronic pulmonary disease. A more elaborative report, including data from respiratory seasons 2011/2012 until 2018/2019 and more analyses, is expected to follow in early 2025.

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