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

RSV vaccination in the elderly

Background information for the Health Council

RIVM letter report 2024-0206
M.J. Knol et al.

RSV vaccination in the elderly

Background information for the Health Council

RIVM letter report 2024-0206

Colophon

DOI 10.21945/RIVM-2024-0206

M.J. Knol (author), RIVM
A.C. Teirlinck (author), RIVM
M. van Boven (author), RIVM
A.B. van Gageldonk-Lafeber (author), RIVM
H.E. de Melker (author), RIVM

Contact:
Mirjam Knol
Center for Epidemiology and surveillance of infectious diseases
Mirjam.knol@rivm.nl

This investigation was performed by order, and for the account, of the Ministry of Health, Welfare and Sports and the Health Council of the Netherlands.

Dit is een uitgave van:
Rijksinstituut voor Volksgezondheid en Milieu
Postbus 1 | 3720 BA Bilthoven
Nederland
www.rivm.nl

Synopsis

RSV vaccination in the elderly

Background information for the Health Council

Respiratory syncytial virus (RSV) is a virus that causes respiratory infections. An RSV infection usually results in mild symptoms, but it can also be more severe, requiring hospitalisation. RSV is common among young children, particularly in autumn and winter, and can cause them to become seriously ill. It can also affect older adults, sometimes leading to hospitalisation and even death.

The European Medicines Agency (EMA) has approved three vaccines for adults aged 60 and over to prevent illness caused by RSV. The Ministry of Health, Welfare and Sport (VWS) has asked the Health Council for advice on RSV vaccination for the elderly. To support this advice, the National Institute for Public Health and the Environment (RIVM) has gathered information for the Health Council.

This information mainly concerns the estimated number of elderly people with RSV in the Netherlands and how severe their resulting symptoms are (disease burden). For various reasons, this is difficult to estimate. Firstly, the cause of a respiratory infection is not always investigated. This laboratory confirmation is usually not necessary because most infections resolve without treatment. Secondly, the laboratory test to detect RSV does not always give accurate results. Especially in older people, it is therefore not possible to detect all infections. Thirdly, hospitals do not always record a confirmed RSV infection in their data (coding).

Using this limited available information, RIVM has estimated how many people are hospitalised each year due to an RSV infection by conducting an attribution analysis. It was estimated that, in the Netherlands, approximately 3,000 people aged 65 or older are hospitalised for RSV each year. This is about 1 in 1,000 people aged 65 and over. The likelihood of being hospitalised due to RSV increases with age. These results are in line with other (inter)national data.

Keywords: RSV, respiratory infection, vaccination, burden of disease, elderly, hospitalisation, attribution analysis

Publiekssamenvatting

RSV-vaccinatie in ouderen

Achtergrondinformatie voor de Gezondheidsraad

Het respiratoir syncytieel virus (RSV) is een virus dat infecties aan de luchtwegen veroorzaakt. RSV komt in de herfst en winter veel voor bij jonge kinderen. Een RSV-infectie geeft meestal milde klachten, maar kan ook ernstiger verlopen waardoor kinderen in het ziekenhuis moeten worden opgenomen. Maar ook ouderen kunnen ziek worden van RSV. Zij kunnen hierdoor in het ziekenhuis terechtkomen en er ook aan overlijden.

Het Europees Medicijnagentschap (EMA) heeft drie vaccins goedgekeurd voor volwassenen vanaf 60 jaar om ziekte door RSV te voorkomen. Het ministerie van VWS heeft de Gezondheidsraad gevraagd om een advies te geven over RSV-vaccinatie bij ouderen.

Als ondersteuning voor dit advies heeft het RIVM informatie verzameld voor de Gezondheidsraad. Deze informatie gaat vooral over het geschatte aantal ouderen met RSV in Nederland en hoe ernstig ziek ze daarvan worden (ziektelast). Om verschillende redenen blijkt dat moeilijk te schatten.

Ten eerste wordt bij een luchtweginfectie meestal niet onderzocht wat de oorzaak van de infectie is. Dat is ook niet nodig omdat de meeste infecties vanzelf, dus zonder behandeling, overgaan. Ten tweede geeft de laboratoriumtest om RSV aan te tonen niet altijd de goede uitslag. Daardoor worden vooral bij oudere mensen niet alle infecties aangetoond. Ten derde verwerken ziekenhuizen een aangetoonde RSV-infectie niet altijd in hun gegevens (coderingen).

Het RIVM heeft met deze beperkt beschikbare informatie geschat hoeveel mensen per jaar vanwege een RSV-infectie worden opgenomen in het ziekenhuis. Een voorzichtige schatting is dat in Nederland elk jaar ongeveer 3000 mensen van 65 jaar of ouder voor RSV worden opgenomen. Dit is ongeveer 1 op de 1000 65-plussers. De kans om door RSV in het ziekenhuis te worden opgenomen is groter naarmate mensen ouder zijn. In de (inter)nationale wetenschappelijke literatuur zijn dezelfde vergelijkbare resultaten te zien.

Kernwoorden: RSV, luchtweginfectie, vaccinatie, ziektelast, ouderen, ziekenhuisopname, attributie-analyse

Contents

Summary

Respiratory syncytial virus (RSV) causes respiratory infection, which can present as mild disease or severe disease requiring hospitalization. RSV is well-known to cause disease in infants, but RSV can also cause disease in older adults and adults with comorbidity. RSV circulation follows a seasonal pattern with a peak in December-January and little circulation in the rest of the year.
The burden of disease of RSV, in terms of infections, hospitalizations and deaths, is difficult to estimate because of several reasons. First, testing of persons with respiratory infection is often not done in a primary care or hospital setting, because treatment or clinical course is not dependent on the specific viral cause. Second, the validity of diagnostic tests for RSV is not optimal, and worse in older adults than in children. Third, even if RSV is laboratory-confirmed, hospital admissions are not always coded as RSV infections; instead more general codes for respiratory infection would be used.
The percentage of RSV positive samples of patients that consulted their GP for an acute respiratory infection is around 10% during the respiratory season for patients 60 years and older. This is lower than for young children (~30%). The incidence rates for RSV-related GP visits was estimated in a range of 8.3 - 13.3 per 1,000 registered persons of 50 years and older in general practice for the respiratory seasons 2016/2017, 2017/2018 and 2018/2019.
In the Netherlands, the yearly number of hospital admissions that have an RSV code in persons 65 years or older is ~200 when only including main diagnoses and ~700 when including all diagnoses (main and secondary diagnoses). This is an underestimation of the true RSV burden. A so-called attribution analysis was performed in which data on the circulation of RSV is used to estimate which part of the hospitalizations for respiratory tract infections could be attributed to RSV. It was estimated that among persons 65 years or older ~2900 hospital admissions per year could be attributed to RSV based on the main diagnosis and ~6000 hospital admission based on all diagnoses. The latter is probably an overestimation as RSV could be an incident finding rather than the cause of the hospitalization. Around 2900 hospitalizations per year in persons 65 years or older corresponds with an hospitalization rate of ~1 per 1000. The rate increases with increasing age from ~0.4/1000 in 65-74 year olds to ~2.7/1000 in persons 85 years or older. The estimated hospitalization rate attributable to RSV is lower than the hospitalization rate attributable to influenza (using a similar method), which was estimated to be ~1.5/1000 among persons 65 years or older. A recent study where patients hospitalized for respiratory infections in two general hospitals in the Netherlands were routinely tested for RSV, estimated a population risk of RSV-hospitalization in a range of 0.4-2.4 per 1000 for those aged ≥60 years for the seasons 2022/2023 and 2023/2024.
Systematic reviews including studies from high income/industrialized countries found an RSV infection rate of 6-16/1000 persons per year and an RSV hospitalization rate of 1-1.5/1000 persons per year.

There is little data on RSV mortality among elderly. Based on international data, the burden of RSV disease among adults with certain comorbidities is higher than among adults without comorbidity.

1 Introduction

Respiratory syncytial virus (RSV) is a seasonal respiratory virus which can cause morbidity and mortality, mainly in children but also in elderly. Currently, two RSV subunit vaccines are registered by the European Medicines Agency (EMA) for use in elderly and an mRNA vaccine is in a late development phase (1). The Dutch Ministry of Health, Welfare and Sports has asked the Health Council on advice about RSV vaccination for elderly. This document provides information about disease burden of RSV in elderly based on data from the Netherlands and international data to inform the advice of the Health Council.
In 2023, the RIVM published a report with background information for the Health Council on prevention of RSV disease in infants (2).

Estimating the burden of disease of RSV in elderly is complex for several reasons. First, there is no routine testing on RSV of elderly that seek health care with respiratory symptoms. This is definitely the case in primary care; therefore, burden of disease estimation in primary care relies on active data collection in sentinel surveillance systems. In a hospital setting, more testing is done but also here routine testing is not performed in every patient, as knowledge on the virus causing the symptoms is generally not relevant for clinical practice. However, with the availability of point-of-care tests that test for influenza, SARS-CoV-2 and RSV simultaneously, RSV testing may have increased in recent years and may increase further in coming years.
Second, the sensitivity of diagnostic tests for RSV is not optimal (3, 4) and is lower in elderly than e.g. children because of a lower viral load. Also, RSV resides in the lower respiratory tract, decreasing sensitivity when using either nasal, or nasopharyngeal or oropharyngeal swabs.
Third, RSV-coded registry data underestimates the actual burden of RSV disease because of coding practices. Even if there is laboratory confirmation of RSV, a hospital admission may not be coded as such, for example because it is uncertain whether RSV is the actual cause of the admission or because a more general code is used. On the other hand, even if a hospital admission includes one or more of the four ICD10 codes specific for RSV, it may be that the main reason for the admission was not the coded RSV infection.

These complexities should be taken into account when describing burden of disease of RSV. Therefore, different sources and approaches are combined to get an overall picture of the burden of disease.

2 Data from the Netherlands

2.1 Seasonality and virus circulation

Based on data of RSV detections reported by laboratories of the virological laboratory surveillance, virus circulation is monitored. These detections (most likely (5)) come from primary care or hospital care, but this surveillance source does not contain data on the setting or any demographic information like age.
RSV shows a clear seasonality with a peak in winter which occurs before the influenza peak (Figure 1). During the COVID-19 pandemic, RSV circulation showed a different pattern with a summer peak in 2020/2021 and limited year-round circulation during 2021/2022. Since 2022/2023 the usual pattern has been seen again with a winter peak, although the peak was higher in 2022/2023 and 2023/2024 than before the pandemic, at least partly explained by more testing.
In the Caribbean Netherlands (Bonaire, St. Eustatius and Saba) only scarce data on RSV circulation is available. It should be noted that the seasonal pattern of RSV in tropical regions is much more variable than in temperate regions with longer seasons and more variability in start and peaks of the season (6).

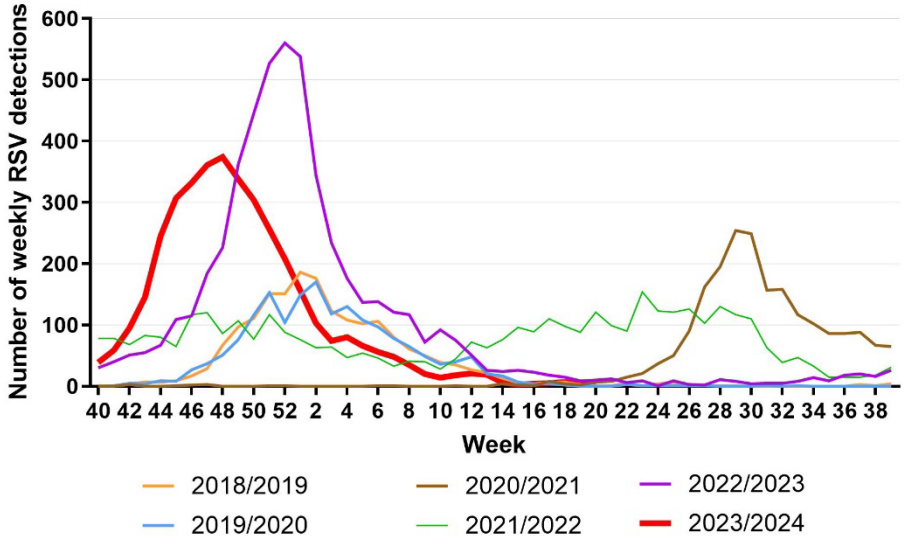

Figure 1 Weekly number of RSV detections in the virological laboratory surveillance by season from 2019/2020 to 2023/2024 (until week 20). Source: RIVM annual report surveillance of respiratory infections 2023/2024 – RSV (7).

2.2 Mild RSV infection - community or primary care setting

2.2.1 Nivel sentinel surveillance

Within the Nivel sentinel surveillance, a selection of patients who consult their GP with influenza-like-illness (ILI) or other acute respiratory infection (ARI) symptoms are sampled for RSV and other respiratory pathogens. The resulting 'percentage positive for RSV' can be compared between seasons and between age groups. The percentage positive for

RSV in patients of 60 years or older who visited their GP with ARI symptoms was 5-12% during the winter season of 2017/18 to 2022/23 (Figure 2). There are no clear differences between 60-69 year olds, 70-79 year olds and 80+ year olds; percentages vary by year due to small numbers. In young children, the percentage positive for RSV is clearly higher than in other age groups: 25-55% for <2 year olds during 2017/18 to 2022/23.
A recent study by Nivel and RIVM estimated the incidence rate of adults aged 50 years and older that contacted their GP for an RSV-infection. They combined the weekly number of visits for ARI with the percentage of RSV-positive patients that were sampled for ARI in the GP sentinel surveillance. The incidence rates for RSV-related GP visits 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 of 50 years and older in general practice for the respiratory seasons 2016/2017, 2017/2018 and 2018/2019, respectively (8) Estimating the incidence of GP-attended RSV disease requires careful interpretation, because of the sampling strategy in the sentinel surveillance that has a focus on influenza-like illness (ILI). Also, for this study, that is not published in a peer-reviewed journal yet, the representativeness of the sampled ARI patients for all patients presenting at the GP with ARI will be studied more in depth.

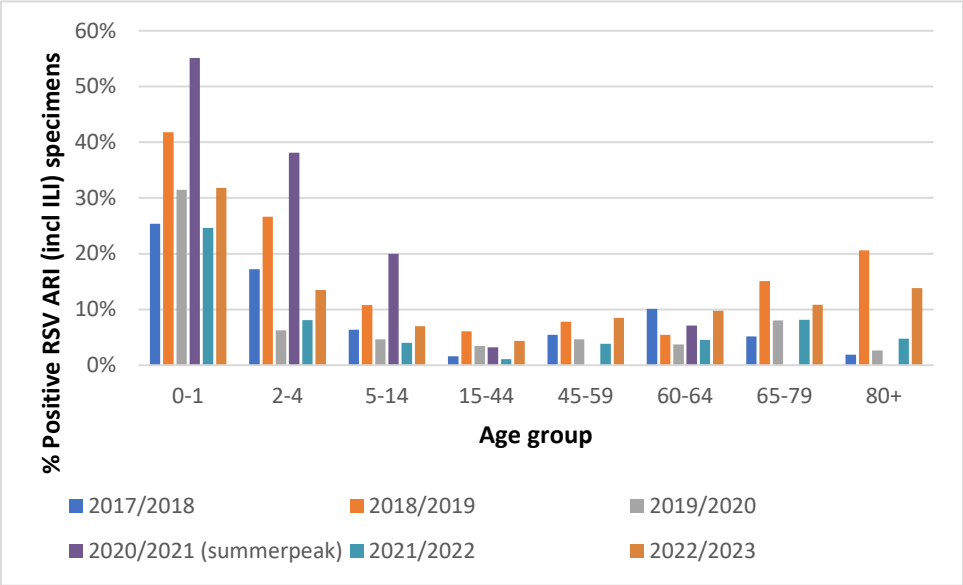

Figure 2 Percentage of RSV positive samples of patients that consulted the GP for an acute respiratory infection (ARI) during the respiratory season (week 40- week 20), from season 2017/2018 until season 2022/2023, per age group. In the season 2020/2021, data is shown from the summer peak (week 26-39 of 2021).

2.2.2 *Prospective cohort studies*

In 2017/18 and 2018/19, a prospective cohort study was performed in three European countries (NL, UK, Belgium) to estimate the community burden of RSV in adults aged 60 years or over (9); about one-third of the cohort were Dutch adults. They found an RSV incidence of 4.2% (22/527) and 7.2% (37/513 participants) in the two respective seasons, based on PCR and serology. Notably, 20 of the RSV cases were detected by PCR only, 23 by serum only and 16 by PCR and serum, showing the

value of multiple methods to identify RSV infection. No patients were hospitalized or died from RSV disease.
In a study of the RIVM among adults aged 60 years or older across three seasons (2011/12, 2012/13, 2014/15), 5-7% of the ILI samples were positive for RSV (10, 11). In contrast, 20-40% of the ILI samples were positive for influenza. Note that the focus was on ILI, which is more specific for influenza than for RSV and that 67-82% of the ILI patients was vaccinated for influenza in these seasons.

2.2.3 Long-term care facilities

It is known that RSV outbreaks occur in long-term care facilities (12, 13). But there is no surveillance system in place, therefore the burden of RSV disease in long-term care facilities is not known in the Netherlands.

2.3 Severe RSV infection – hospital setting

2.3.1 Hospital registration data

Reported RSV (i.e. RSV-coded) infections are likely a substantial underestimation of the true number of hospital admissions caused by RSV, especially in older adults, for reasons described at the beginning of this chapter. Therefore, we here present data of yearly coded RSV admissions in Dutch hospitals over the years 2013-2019, and supplement these analyses with an attribution analysis of RTI hospital admissions using similar methods as an earlier analysis (14). As in the earlier analyses, coded RSV is based on the ICD10 codes J12.1, J20.5, J21.0, B97.4. We present two sets of results. In the first set, RSV or RTI codes are present in either main, primary, or secondary diagnoses. In the second set, we restrict the data to RSV or RTI codes that are present in the main diagnosis. By combining the analyses for coded RSV with those of attributed RSV we aim to get reasonable approximate lower and upper bounds of the yearly number of hospital admissions caused by RSV.

2.3.1.1 RSV-coded hospital and ICU admissions

We use Dutch hospital admission data spanning the period 2013-2019 (7 years) and Dutch ICU admission data spanning the period 2016-2019 (4 years) to determine the yearly numbers and yearly incidences per 100,000 of RSV coded hospital and ICU admissions. For hospital admissions – that also include the ICU admissions - we report data for all diagnosis types (main, primary, and secondary) (Figure 3) and for main diagnosis only (Figure 4).

Figure 3 shows the characteristic winter epidemics of RSV, which invariably peaks around New year. Since the 2016/2017 season the number of hospital admissions has increased in all age groups. This has been observed earlier and may be related with mutations in the RSV-A strain (15). However, also changing testing policy can play a role; during the seasons 2011/2012 to 2015/2016 a lower number of positive diagnoses was seen in the virological laboratory surveillance, while before 2011/2012 higher numbers were observed than in 2016/2017 (16). On average, the number of admissions was highest in the 75-84 year age group (282 per year), and slightly lower in the 65-74 year and 85+ year age groups (257 and 157 per year). The hospitalisation

incidence increased monotonically with increasing age, from 14 per 100,000 per in the 65-74 year age group, to 29 and 45 in the 75-84 year and 85+ year age groups.

Restricting the analysis to RSV coded hospital admissions in the main diagnosis (Figure 4), the number of hospital admissions are approximately three- to fourfold lower than in comparison with Figure 3. The pattern of a strongly and consistently increased incidence since the 2016/2017 season is still observed. Of note, this pattern is not consistently observed for influenza A (which had large 2016/2017 and 2017/2018 epidemics but small 2018/2019 epidemic), making it unlikely that the increase has been caused solely by increased reporting rates.

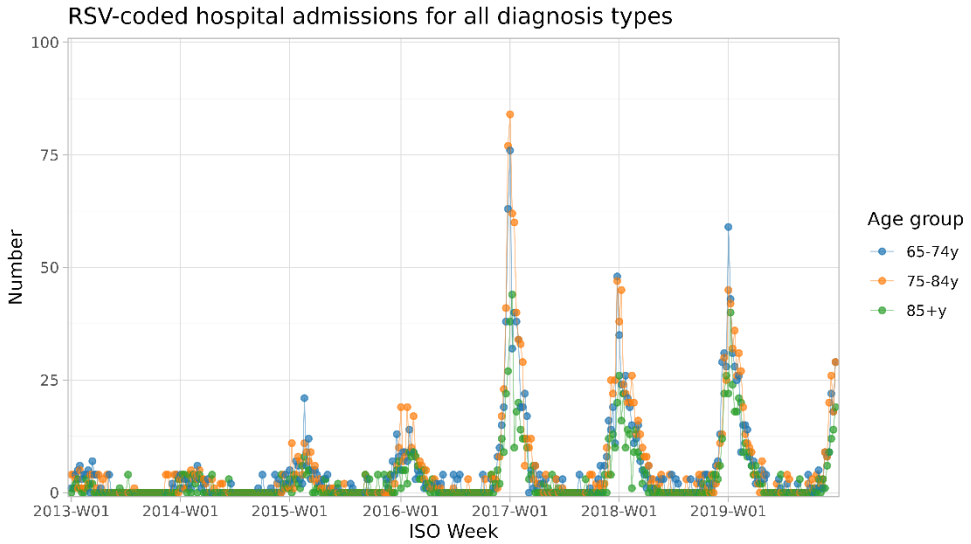

Figure 3 RSV-coded hospital admissions for all diagnosis types (main, primary, and secondary). Mean number of admissions per year in each of the age groups over the prepandemic years (2013-2019, n=7 years) was 257 in persons 65-74 years, 282 in persons 75-84 years, and 157 in persons 85 years and older. This corresponds to yearly incidences per 100,000 of 14, 29, and 45. Notice that numbers were higher in the 2016-2017, 2017-2018, and 2018-2019 winter seasons than in earlier seasons. Also notice that, for privacy reasons, small numbers (between 1 and 4) were imputed.

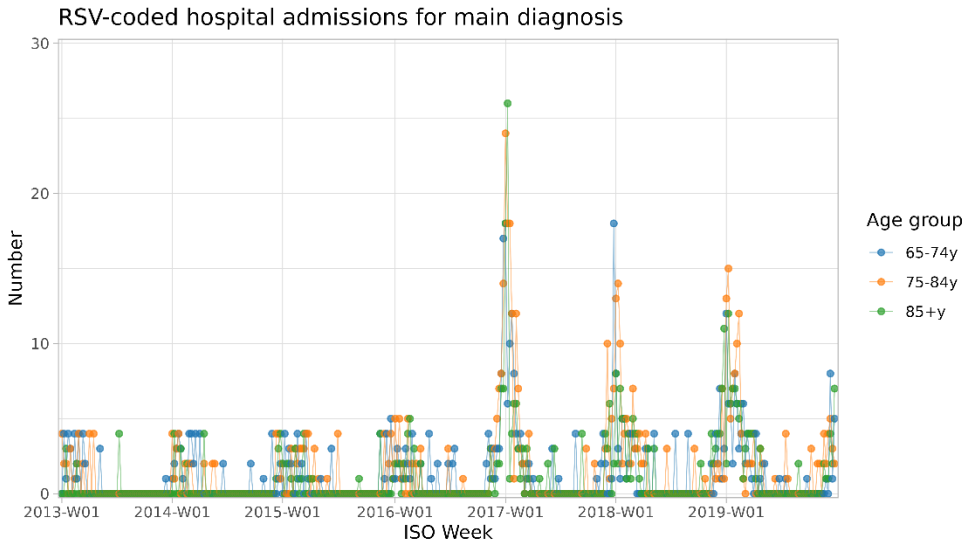

Figure 4 RSV-coded hospital admissions for main diagnosis. Mean number of admissions per year in each of the age groups over the prepandemic years (2013-2019, n=7 years) was 65 in persons 65-74 years, 77 in persons 75-84 years, and 54 in persons 85 years and older. This corresponds to yearly incidences per 100,000 of 3.7, 8.0, and 15. Notice that numbers were higher in the 2016-2017, 2017-2018, and 2018-2019 winter seasons than in earlier seasons. Also notice that, for privacy reasons, small numbers (between 1 and 4) were imputed.

For ICU admissions, numbers are much lower than for hospital admissions. Here, only data from the period 2016-2019 are available. Figure 5 shows the data for all diagnosis types. Notice that numbers are much smaller than for the RSV coded hospitalisations. For RSV coded ICU admissions by main diagnosis only, numbers are even lower, and not reported here, in view of the uncertainties with cells with small values.

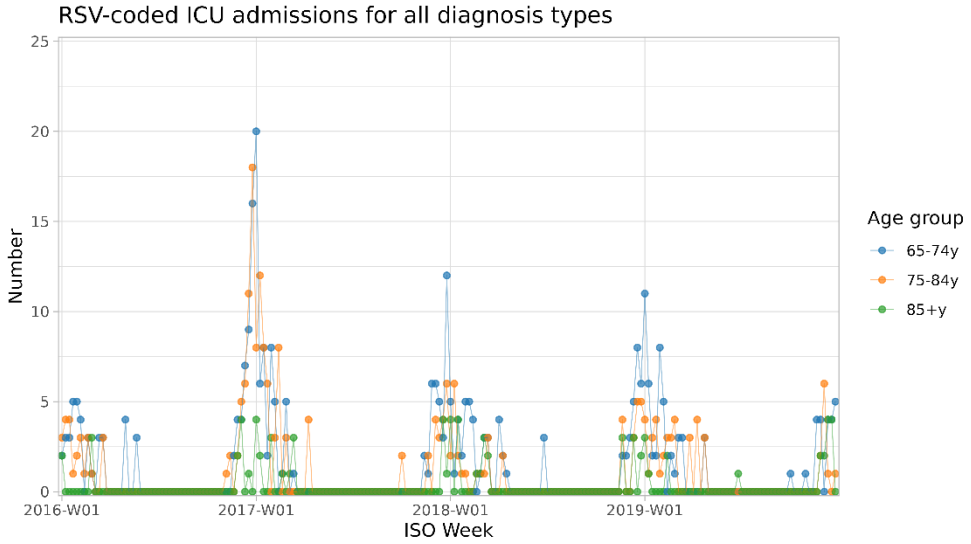

Figure 5 RSV-coded ICU admissions for all diagnosis types (main, primary, and secondary). Mean number of admissions per year in each of the age groups over the prepandemic years (2016-2019, n=4 years) was 44 in persons 65-74 years, 32 in persons 75-84 years, and 10 in persons 85 years and older. This corresponds to yearly incidences per 100,000 of less than 4 in all age groups. Notice that small numbers (between 1 and 4) were imputed.

2.3.1.2 Attribution analysis - methods

Given the potentially considerable underreporting of RSV, we performed an attribution analysis of RTI hospital admissions to better assess the true burden of RSV in Dutch hospitals. The analyses of the attribution analyses have not yet been published and are part of an ongoing study to uncover the burden of RSV in European hospitals. We here briefly summarise the gist of the methodology.

Attribution of respiratory tract infections (RTIs) in the hospital to RSV was performed using regression analyses. In these analyses, the number of RTIs in each age group is explained by the background rate at which RTIs are generated, and by main respiratory pathogens influenza A and B, and RSV. Specifically, the background rate was modelled using penalized splines, and covariates included the numbers of positives for the respiratory pathogens in virological surveillance data. In addition, we allowed lags or leaps of the time series of the respiratory pathogen positives relative to the RTI case data from –3 to +3 weeks to account for the fact that epidemics in different age groups may be shifted relative to each other and relative to the virological data (14). Throughout, we employed second-order spline penalization, and the number of knots was set to 50. Fitting of the regression models was performed using restricted maximum likelihood (REML), and for each age group selection of the optimal shifts was based on the Akaike Information Criterion (AIC). For each age group attribution of RTI cases to RSV was based on the best fitting model. Specifically, attribution was based on the difference between the expected number of RTI cases in the best fitting model and the best fitting model with the number of virological positives set to zero.

2.3.1.3 Attribution analysis - all diagnoses

The results of the analyses using RTI coded admissions in all admission types (main diagnosis, primary diagnoses, secondary diagnoses) are presented in Figure 6 and Table 1. Figure 6 shows the age-stratified RTI admissions (dots, all diagnoses), model fit (grey lines), and attributions to RSV (orange lines) or influenza (A and B; green lines). In the older age strata (65+ years) both influenza and RSV are estimated to be important contributors to RTI admissions, although the attributed incidence of influenza is (slightly) higher than that of RSV (65+ years; 6,645 versus 5,946 attributed hospital admissions).

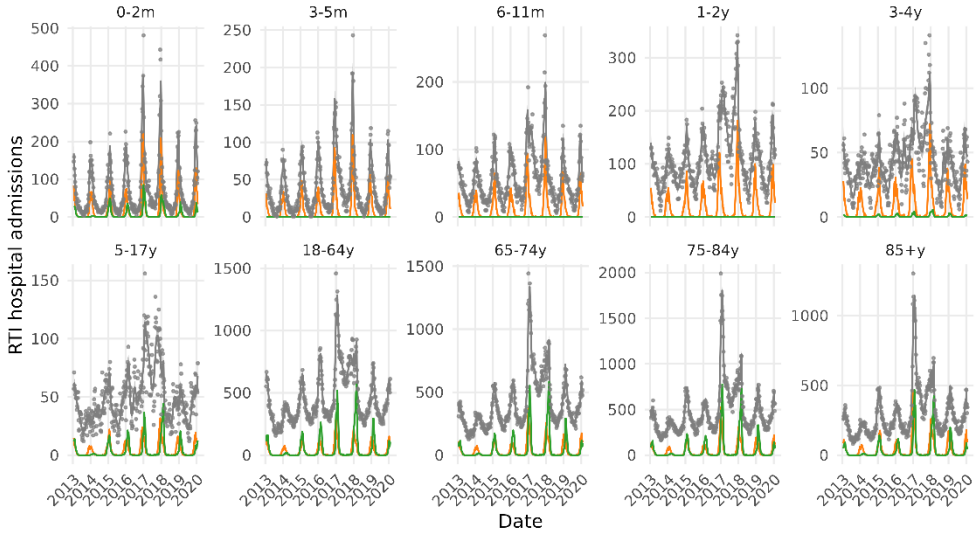

Figure 6 RTI hospital admissions for all diagnoses (main, primary, and secondary) in the prepandemic period (2013-2019) (grey dots), model fits (grey lines), and attributions to RSV (orange lines) and influenza (green lines). See Table 1 for estimates of yearly numbers and incidences in each of the age groups.

Table 1 Comparison of yearly RSV coded hospital admissions (all diagnoses) with yearly attributed number of RSV hospital admissions using RTI hospital admission data (all diagnoses) in the prepandemic period (2013-2019). For comparison, for influenza (A and B combined) the attributed yearly numbers and the corresponding yearly incidences (per 100,000) are added to the table.

Age group	Coded RSV (number per year)	Attributed RSV (number per year)	Coded RSV incidence (per 100,000 per year)	Attributed RSV incidence (per 100,000 per year)	Attributed influenza (number per year)	Attributed influenza incidence (per 100,000 per year)
0-2m	1,057	984	2,463	2,293	355	828
3-5m	419	481	976	1,122	0	0
6-11m	322	604	375	703	0	0
1-2y	262	943	75	268	0	0
3-4y	52	412	0	4	26	0
5-17y	31	208	9	57	184	51
18-64y	291	1,639	11	65	2,351	93
65-74y	261	1,776	15	100	2,214	125
75-84y	281	2,277	29	238	2,775	290
85+y	156	1,893	44	537	1,656	470
65+y	**698**	**5,946**	**23**	**193**	**6645**	**216**

2.3.1.4 Attribution analysis - main diagnosis

It is likely that a fraction of RTI hospital admissions that are attributed to RSV in the previous section do not actually have RSV as the main cause of hospital admission. Therefore, we here provide a complementary analysis that focuses on RTI coded admissions in the main diagnosis only. We subset these data by RTI admissions that have specific RSV and influenza codes in the main diagnosis ('coded RSV' and 'coded influenza'), and those that have another RTI code in the main diagnosis ('other RTI'). As those other RTIs may still be caused by RSV or influenza we perform an attribution analysis as in the previous section on those data. Table 2 reports the results for RSV and influenza (A and B combined). Here the total estimated number of RSV and influenza hospital admissions is given by the sums of the coded and attributed admissions. In infants and children the total estimated number of RSV admissions is much higher than the total estimated number of influenza infections. In older adults (65 years and older) the reverse is true. Here, the total yearly number of influenza admissions is estimated at 4,544, while the number of RSV admissions is estimated at 2,877. Interestingly, in older adults only a small fraction of RSV admissions is coded as RSV in the main diagnosis. Figure 7 shows the data of other RTI admissions in the main diagnosis, together with the numbers attributed to RSV and influenza. Interestingly, in older adults, a substantial proportion of these RTI admissions are neither attributed to RSV nor to influenza.

Table 2 Comparison of yearly RSV coded and Influenza coded hospital admissions (main diagnosis) with yearly attributed number of RSV and Influenza hospital admissions using RTI hospital admission data (main diagnoses) in the prepandemic period (2013-2019).

Age group	Coded RSV (number per year)	Attributed RSV (number per year)	Total RSV (number per year)	Total RSV incidence (per 100,000 per year)	Coded Influenza (number per year)	Attributed Influenza (number per year)	Total Influenza (number per year)	Total influenza incidence (per 100,000 per year)
0-2m	889	593	1,482	3453	62	0	62	144
3-5m	373	314	687	1601	27	0	27	63
6-11m	286	472	758	883	36	0	36	42
1-2y	217	683	900	256	69	0	69	20
3-4y	43	234	277	3	48	0	48	0
5-17y	16	78	94	26	110	88	198	55
18-64y	89	656	745	29	1,323	496	1,819	72
65-74y	81	659	740	42	1,049	408	1,457	82
75-84y	84	1,103	1,184	124	1,263	659	1,922	201
85+y	58	883	941	267	744	421	1,165	331
65+y	**223**	**2,654**	**2,877**	**93**	**3,056**	**1,488**	**4,544**	**148**

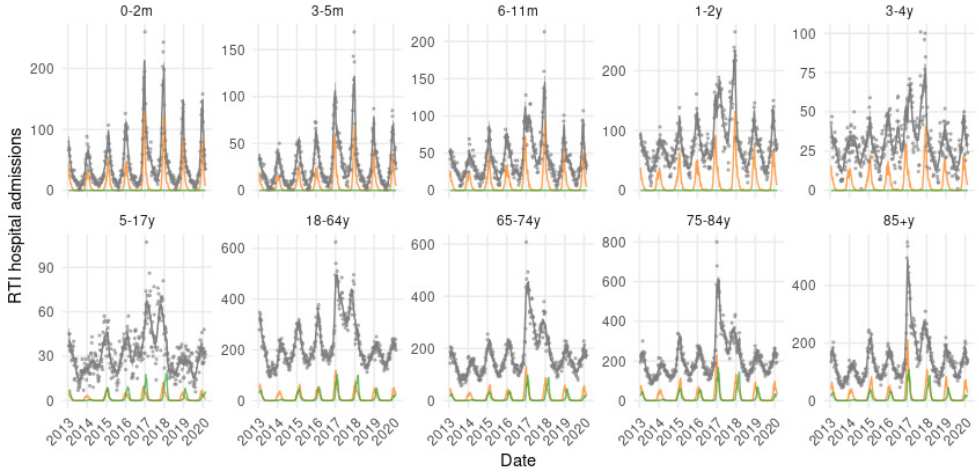

Figure 7 RTI hospital admissions for main diagnoses in the prepandemic period (2013-2019), excluding main diagnoses "coded RSV" and "coded Influenza"(grey dots), model fits (grey lines), and attributions to RSV (orange lines) and influenza (green lines).

2.3.2 *Retrospective cohort study*

A recent study by Korsten et al., that was published at pre-print on MedRxiv (17) retrospectively analysed RSV-related hospitalizations in three hospitals in the Netherlands from January 2022 until April 2024. All patients presenting with respiratory symptoms in these hospitals were tested for RSV, because of the routine testing for SARS-CoV-2 that was implemented since the start of the COVID-19 pandemic, using a combined test for SARS-CoV-2, influenza and RSV. During the RSV

seasons (September – April) of 2022/2023 and 2023/2024 the authors estimated a population risk of RSV-hospitalization of 1.1 and 0.4 per 1000 in the Flevo Hospital and 2.4 and 1.4 per 1000 in the Jeroen Bosch Hospital for those aged ≥60 years in the two respective seasons. Although not directly comparable, the RSV hospitalization rates that were found in the attribution study (see above) of 1.9 per 1000 (all RSV diagnoses) and 0.93 per 1000 (RSV main diagnoses) per year, are in the same order of magnitude.

2.4 Mortality

Using all-cause mortality data and data of the virological laboratory surveillance from 1999-2007, the number of deaths attributable to RSV and other viruses was estimated in elderly using similar methodology as described above for hospitalizations (18). Among persons aged 65 years or over, 1.4% of deaths (n=13902) could be attributed to RSV; 1.5% could be attributed to influenza A and 0.6% to influenza B. The yearly RSV-attributed death rate calculated from the numbers in the paper was 0.69/1000; for influenza this was 1.08/1000. Note that this is an attribution/association study. Therefore, it is uncertain whether these deaths are truly caused by RSV (or influenza), so the level of evidence is relatively low. In the study of Korsten et al. (17), 35 out of 434 patients (8.1%) that were hospitalized with a clinically relevant RSV infection died.

2.5 Comorbidity

The above mentioned study of Korsten et al.(17) indicated that, although numbers were low, patients with chronic obstructive pulmonary disease (COPD) and congestive heart disease (CHD) had higher hospitalization rates than found in the general population. In 46% (201/434) of the patients that were hospitalized with a clinically relevant RSV infection, RSV was a factor in the exacerbation of an underlying disease. A prospective cohort study performed within the RESCEU project assessed the frequency of RSV-related exacerbations of COPD (19). Among 377 patients with COPD, 27 RSV-related exacerbations (8.7% of total exacerbations) were reported.

3 International data

Table 3 summarizes estimates of RSV burden indicators from data of the Netherlands and of international data from systematic reviews. We only describe data from high income/industrialized countries.

3.1 Systematic reviews

A systematic review of Shi *et al.* (funded by IMI project RESCEU) estimated RSV-ARI incidence, hospitalization rate for RSV-ARI, proportion of RSV positives among ARI cases hospitalized and the in-hospital case fatality rate of RSV-ARI, based on studies published between Jan 1996 and April 2018 and 8 unpublished studies (20). The review stratified for industrialized and developing regions and included 20 studies from industrialized countries. Based on five studies with active case finding in industrialized countries, the incidence rate of RSV-ARI was estimated to be 6.7/1000 persons per year. Remarkably, this is 10 times lower than the incidence found in the prospective cohort study including Dutch participants (note that this incidence was per 100 *persons*, not 100 *person years*, so the estimates are not completely comparable). This could be partly explained by the detection method as the prospective study used both PCR and serology while some of the studies included in the review only used PCR which has lower sensitivity. Also, the prospective study was performed in the seasons 2017-2018 and 2018-2019, which were seasons with relatively high RSV circulation in the Netherlands.
Based on six hospital-based studies with passive case ascertainment in industrialized countries, an RSV-ARI hospitalization rate of 1.0 per 1000 persons per year was estimated. This is somewhat lower than the hospitalization rate estimated in the attribution analysis in the Netherlands (1.9/1000) in persons 65 years or older, but higher than the RSV-coded hospitalization rate in the Netherlands (0.23/1000) (Table 1).
Based on three hospital-based studies without a clear population denominator in industrialized countries, a proportion of RSV-positive cases among hospital admission for ARI of 4.4% was estimated.
Based on three studies in industrialized countries, an in-hospital case fatality rate of 1.6% was estimated, while this was 9.1% based on five studies from developing countries.

A systematic review of Nguyen-van-Tam *et al.* (funded by Janssen Pharmaceuticals) included 103 peer-reviewed articles published between 2000 and 2019 to assess incidence of RSV infection, percentage positive among ARI and the infection case fatality rate among older adults (21). They distinguished estimates from annual and seasonal studies. In addition, they separately assessed RSV disease burden in adult patients with comorbidity (high-risk patients).
Based on three studies, a seasonal incidence of RSV infection of 16.1 per 1000 persons per year was estimated. According to 18 annual studies, the proportion of RSV among those with ARI was 4.7%, and according to 23 seasonal studies this proportion was 7.8%.

Among high-risk adults the incidence of RSV infection was clearly higher, although the proportion of RSV positive among ARI was quite similar to older adults. Risk of hospital admission or ICU admission was higher among the high-risk population compared with older adults.

A systematic review of Savic *et al.* (funded by GSK) assessed RSV disease burden in those 60 years or older and included articles published between January 2000 and November 2021 that were conducted in high-income countries in the Northern hemisphere (22). Retrospective studies were excluded from this review due to the potential underreporting bias caused by the lack of systematic RSV testing in older adults. Based on data from 14 studies, a RSV-ARI attack rate of 1.6% was estimated. A pooled RSV-ARI hospitalization attack rate of 0.15% was estimated based on data of eight studies. The in-hospital case fatality rate was estimated to be 7.1% based on eight studies.

Another systematic review of Shi *et al.* (funded by IMI project RESCEU) assessed the burden of RSV disease among adults with comorbidity using articles published between Jan 1996 and March 2020 (23). The review included 18 studies from industrialized countries and only results from these countries are presented here. Based on seven community-based studies, the incidence rate of RSV-ARI in adults with any comorbidity was 30.3 per 1000 persons per year/season. Comorbidities included cystic fibrosis, congestive heart failure, COPD and immunocompromised status due to stem cell transplantation. One study estimated the hospitalization rate in older adults with congestive heart failure or COPD at 13.2 per 1000 persons per year. Based on six studies, an in-hospital case fatality rate of 11.7% was estimated. As also found by Nguyen-van-Tam *et al.* RSV disease burden seems considerably higher in adults with comorbidity compared with those without comorbidity.
Osei-Yeboah *et al.* conducted an attribution study using national hospital registries and virologic surveillance data from Denmark and Scotland to estimate the risk of ARI hospitalizations associated with RSV among adults who had at least 1 of 7 predefined comorbidities (24). They found increased risks of RSV hospitalization for adults with COPD, ischemic heart disease, stroke, diabetes, asthma and chronic kidney disease.

3.2 Other data

The registration trials of the vaccines of Pfizer and GSK found an RSV-ARI incidence rate of 6.3 and 13.9 per 1000 persons per year (25, 26), respectively, which is in the same order of magnitude of what the reviews by Shi *et al.* and Nguyen *et al.* found. Both studies were performed during the autumn-winter season of 2021-2022, which had an atypical RSV season because of the COVID-19 pandemic.

Belgium has a sentinel SARI surveillance in which since 2012 6 hospitals participate and since 2023 10 hospitals (27). Every hospital admission for SARI (until 2023 fever was included in the case definition) in one of these hospitals is followed during hospital stay, collecting data on demographics, symptoms, risk factors and comorbidity, vaccination status, treatment, severity and outcome. In every SARI patient, a swab is taken for testing on respiratory viruses.

From the SARI surveillance, an RSV hospitalization rate of 0.48/1000 persons of 65 years or older was estimated during the 2022-2023 season. This is probably an underestimation because of the strict case definition, including fever.

The UK also has a SARI surveillance system in place (SARI-Watch). In the 2022-2023 season an RSV hospitalization rate of 0.43/1000 persons was estimated in persons aged 65 years or older, while this was 1.80/1000 persons for influenza (28).

Table 3 Summary of estimates for different RSV burden indicators among older adults from Dutch data and from systematic reviews of data from high income/industrialized countries

Indicator	**Dutch data**				**Systematic reviews of high income/industrialized countries**		
	Korsten et al. (9)	**Laarman et al. (8)**	**Korsten et al. (17)**	**Calculation RIVM (unpublished)**	**Shi et al. (20)**	**Nguyen et al. (21)**	**Savic et al. (22)**
Infection rate	64/1000 persons (60+)	8.3 to 13.3 per 1000 persons (50+)			6.7/1000 person years	16.1/1000 person years	1.6/100 persons
Percentage positive among ARI				5-10% (60+) (RIVM/Nivel sentinel surveillance)	-	4.7-7.8%	-
Hospitalization rate			Range 0.4 – 2.4 per 1000 persons (60+)	1.9/1000 person years (Attribution analysis – all diagnoses, 65+) 0.93/1000 person years (Attribution analysis – main diagnosis, 65+)	1.0/1000 person years	-	1.5/1000 persons
Percentage positive among hospitalized ARI					4.4%	-	
Case fatality rate among hospitalized	-		8.1%		1.6%	-	7.1%
Death rate				0.69/1000 person years (Attribution analysis, 65+)	-	-	

References

1. PATH. RSV vaccine and mAb snapshot 2024 [Available from: https://www.path.org/our-impact/resources/rsv-vaccine-and-mab-snapshot/.
2. Teirlinck A, van Kasteren P. Prevention of respiratory syncytial virus (RSV) disease in infants. Background information for the Health Council of the Netherlands. Bilthoven: National Institute for Public Health and the Environment; 2023. Report No.: 2023-0355.
3. Hou N, Wang K, Zhang H, Bai M, Chen H, Song W, et al. Comparison of detection rate of 16 sampling methods for respiratory viruses: a Bayesian network meta-analysis of clinical data and systematic review. BMJ Glob Health. 2020;5(11).
4. Onwuchekwa C, Moreo LM, Menon S, Machado B, Curcio D, Kalina W, et al. Underascertainment of Respiratory Syncytial Virus Infection in Adults Due to Diagnostic Testing Limitations: A Systematic Literature Review and Meta-analysis. J Infect Dis. 2023;228(2):173-84.
5. van den Brandhof WE, Kroes ACM, Bosman A, Peeters MF, Heijnen MLA. Rapportage van virologische diagnostiek in Nederland. Infectieziekten Bulletin. 2002;13(4):137-43.
6. Shan S, Zhang W, Gao H, Huang PY, Du Z, Bai Y, et al. Global Seasonal Activities of Respiratory Syncytial Virus Before the Coronavirus Disease 2019 Pandemic: A Systematic Review. Open Forum Infect Dis. 2024;11(5):ofae238.
7. Rijksinstituut voor Volksgezondheid en Milieu (RIVM). Terugblik surveillance van luchtweginfecties 2023/2024 – RS-virus 2024 [Available from: https://www.rivm.nl/rs-virus/terugblik-2023-2024.
8. Laarman C, vanHommerig J, van Summeren J, Hooiveld M, Meijer A, Teirlinck AC, et al. Respiratory syncytial virus (RSV) associated primary care incidence estimates in adults aged 50 years and older in the Netherlands; 2016-2019. Utrecht: Nivel; 2024.
9. Korsten K, Adriaenssens N, Coenen S, Butler C, Ravanfar B, Rutter H, et al. Burden of respiratory syncytial virus infection in community-dwelling older adults in Europe (RESCEU): an international prospective cohort study. The European respiratory journal. 2021;57(4).
10. Kaaijk P, Swaans N, Nicolaie AM, Bruin JP, van Boxtel RAJ, de Lange MMA, et al. Contribution of Influenza Viruses, Other Respiratory Viruses and Viral Co-Infections to Influenza-like Illness in Older Adults. Viruses. 2022;14(4).
11. van Beek J, Veenhoven RH, Bruin JP, van Boxtel RAJ, de Lange MMA, Meijer A, et al. Influenza-like Illness Incidence Is Not Reduced by Influenza Vaccination in a Cohort of Older Adults, Despite Effectively Reducing Laboratory-Confirmed Influenza Virus Infections. The Journal of infectious diseases. 2017;216(4):415-24.

12. Meijer A, Overduin P, Hommel D, van Rijnsoever-Greven Y, Haenen A, Veldman-Ariesen MJ. Outbreak of respiratory syncytial virus infections in a nursing home and possible sources of introduction: the Netherlands, winter 2012/2013. J Am Geriatr Soc. 2013;61(12):2230-1.
13. Childs A, Zullo AR, Joyce NR, McConeghy KW, van Aalst R, Moyo P, et al. The burden of respiratory infections among older adults in long-term care: a systematic review. BMC Geriatr. 2019;19(1):210.
14. Johannesen CK, van Wijhe M, Tong S, Fernández LV, Heikkinen T, van Boven M, et al. Age-Specific Estimates of Respiratory Syncytial Virus-Associated Hospitalizations in 6 European Countries: A Time Series Analysis. The Journal of infectious diseases. 2022;226(Suppl 1):S29-s37.
15. Vos LM, Oosterheert JJ, Kuil SD, Viveen M, Bont LJ, Hoepelman AIM, et al. High epidemic burden of RSV disease coinciding with genetic alterations causing amino acid substitutions in the RSV G-protein during the 2016/2017 season in The Netherlands. Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology. 2019;112:20-6.
16. Teirlinck AC, van Asten L, Brandsema PS, Dijkstra F, Donker GA, van Gageldonk-Lafeber AB, et al. Annual report Surveillance of influenza and other respiratory infections in the Netherlands: : Winter 2016/2017. Bilthoven: National Institute for Public Health and the Environment; 2017. Report No.: 2017-0096.
17. Korsten K, Welkers MRA, van de Laar T, Wagemakers A, van Hengel P, Wever PC, et al. Unveiling the spectrum of Respiratory Syncytial Virus disease in Adults: from Community to Hospital. medRxiv. 2024:2024.10.17.24315581.
18. van Asten L, van den Wijngaard C, van Pelt W, van de Kassteele J, Meijer A, van der Hoek W, et al. Mortality attributable to 9 common infections: significant effect of influenza A, respiratory syncytial virus, influenza B, norovirus, and parainfluenza in elderly persons. J Infect Dis. 2012;206(5):628-39.
19. Wiseman DJ, Thwaites RS, Ritchie AI, Finney L, Macleod M, Kamal F, et al. RSV-related Community COPD Exacerbations and Novel Diagnostics: A Binational Prospective Cohort Study. American journal of respiratory and critical care medicine. 2024.
20. Shi T, Denouel A, Tietjen AK, Campbell I, Moran E, Li X, et al. Global Disease Burden Estimates of Respiratory Syncytial Virus-Associated Acute Respiratory Infection in Older Adults in 2015: A Systematic Review and Meta-Analysis. The Journal of infectious diseases. 2020;222(Suppl 7):S577-s83.
21. Nguyen-Van-Tam JS, O'Leary M, Martin ET, Heijnen E, Callendret B, Fleischhackl R, et al. Burden of respiratory syncytial virus infection in older and high-risk adults: a systematic review and meta-analysis of the evidence from developed countries. Eur Respir Rev. 2022;31(166).
22. Savic M, Penders Y, Shi T, Branche A, Pircon JY. Respiratory syncytial virus disease burden in adults aged 60 years and older in high-income countries: A systematic literature review and meta-analysis. Influenza Other Respir Viruses. 2023;17(1):e13031.

23. Shi T, Vennard S, Jasiewicz F, Brogden R, Nair H. Disease Burden Estimates of Respiratory Syncytial Virus related Acute Respiratory Infections in Adults With Comorbidity: A Systematic Review and Meta-Analysis. The Journal of infectious diseases. 2022;226(Suppl 1):S17-s21.
24. Osei-Yeboah R, Johannesen CK, Egeskov-Cavling AM, Chen J, Lehtonen T, Fornes AU, et al. Respiratory Syncytial Virus-Associated Hospitalization in Adults With Comorbidities in 2 European Countries: A Modeling Study. The Journal of infectious diseases. 2024;229(Supplement_1):S70-s7.
25. Papi A, Ison MG, Langley JM, Lee DG, Leroux-Roels I, Martinon-Torres F, et al. Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults. The New England journal of medicine. 2023;388(7):595-608.
26. Walsh EE, Pérez Marc G, Zareba AM, Falsey AR, Jiang Q, Patton M, et al. Efficacy and Safety of a Bivalent RSV Prefusion F Vaccine in Older Adults. The New England journal of medicine. 2023;388(16):1465-77.
27. Sciensano. Wekelijks bulletin acute luchtweginfecties. Week 16 (15/04/2024 - 21/04/2024) Sciensano; 2024.
28. JCVI. Respiratory syncytial virus (RSV) immunisation programme for infants and older adults: JCVI full statement, 11 September 2023. Joint Committee on Vaccination and Immunisation; 2023.

Published by:

National Institute for Public Health and the Enviroment, RIVM
P.O. Box 1 | 3720 BA Bilthoven
The Netherlands
www.rivm.nl/en

November 2024

Committed to
health and sustainability