Burden of respiratory syncytial virus infection in community-dwelling older adults in Europe (RESCEU)

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Burden of respiratory syncytial virus infection in community-dwelling older adults in Europe (RESCEU): an international prospective cohort study

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Respiratory syncytial virus (RSV) infection in older adults is recognised, but the burden in the community is still uncertain. This European study found that RSV infection is prevalent but rarely caused severe disease in community-dwelling older adults. https://bit.ly/30gsiMD

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ABSTRACT

Background: Respiratory syncytial virus (RSV) infection in older adults is recognised as an important health issue. We aimed to assess the community burden of RSV in Europe in older adults aged ⩾60 years.

Methods: This international, prospective, observational cohort study is part of work by the REspiratory Syncytial virus Consortium in EUrope (RESCEU). Participants were recruited through general practitioners' (GPs) offices before two independent RSV seasons. Participants reported weekly about symptoms of acute respiratory tract infection (ARTI) during one RSV season. ARTI patients were tested for RSV during home visits and completed a daily symptom diary. RSV illness included PCR-confirmed ARTI and those showing seroconversion over the season. RSV ARTI was based on PCR alone (ClinicalTrials.gov, NCT03621930).

Results: We recruited 1040 participants (527 in season 2017–2018 and 513 in season 2018–2019) with a median age of 75 years (range 60–100 years). Of these, 1023 (99%) lived independently at home at baseline. RSV illness incidence was 22 out of 527 (4.2%) and 37 out of 513 (7.2%) in the respective seasons. RSV illness did not affect frailty or cardiopulmonary status during the course of the study. No patients were hospitalised or died from RSV illness. In the 36 patients with PCR confirmed RSV ARTI, symptom duration averaged 19 days, while a doctor's visit took place in 11 out of 36 cases (31%). RSV ARTI could not be differentiated clinically from all other ARTIs based on symptoms.

Conclusion: This European study showed that RSV is prevalent in community-dwelling older adults and rarely causes severe disease. This suggests that watchful waiting, using a continuity of care approach to identify those who do need more intensive care, is often justified when RSV is suspected in family practice.

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Introduction

Respiratory syncytial virus (RSV) is responsible for a significant burden of disease amongst adults [1, 2]. RSV infections in adulthood are often milder than primary childhood infections, but can still cause severe respiratory disease [1, 3]. This is illustrated by the fact that the overwhelming majority of RSV mortality in industrialised countries occurs in those that are above 65 years of age [2, 4]. Studies in hospitalised patients and nursing home residents showed that severe RSV infection occurs in those who are older, have an immunodeficiency or an underlying cardiopulmonary disease [1, 3, 5, 6]. Although RSV awareness in medical settings is increasing, we still know surprisingly little about RSV-related disease in the general population. The only two cohort studies in older adults living in the community, so-called community-dwelling older adults, indicated an overall annual incidence of RSV infection of 3–7% in generally healthy older adults [1, 7]. However, both single-centre studies were conducted 15 years ago and only the study by Falsey *et al.* [1] used both serology and PCR to confirm RSV infection. Therefore, the exact current burden of RSV in older adults in the general population is still uncertain. With a rising number of clinical trials investigating new therapeutics to treat or prevent RSV [8], relevant, precise and up-to-date evidence to inform about their value in community-dwelling older adults is urgently required. To address this gap in the evidence base, the REspiratory Syncytial virus Consortium in EUrope (RESCEU; www.resc-eu.org) project set out to assess the incidence and severity of RSV infection in community-dwelling older adults aged 60 years and above in its older adult cohort study.

Methods

Study design

The RESCEU older adult study is an international, prospective, observational cohort study conducted in Antwerp (Belgium), Oxford (United Kingdom) and Utrecht (The Netherlands) across two consecutive RSV seasons (2017–2018 and 2018–2019). Before the start of each RSV season (October 01–May 01) an independent cohort of participants was recruited from 17 general practitioners' (GPs) offices and followed-up during one RSV season.

Study population

Community-dwelling adults were eligible for inclusion if they were at least 60 years of age. Exclusion criteria were an estimated life expectancy of <1 year, chronic immunosuppressive illnesses or medication and conditions such as severe dementia which would make it impossible to complete the necessary study procedures. The complete list of exclusion criteria can be found on in the trial registry (ClinicalTrials.gov, identifier: NCT03621930) and in the study protocol (supplementary material). Eligible patients received an initial invitation letter from their GP after which they were contacted by the study team for recruitment (supplementary material). This study was approved by the Ethical Review Authority in Belgium (reference: B300201732907), The Netherlands (reference: NL60910.041.17) and the United Kingdom (ethics reference: 17/LO/1210; IRAS reference: 224156). Participants gave informed consent before taking part in the study.

Study procedures

Between August and September a pre-season, baseline home visit was performed during which patient characteristics were obtained and sampling was performed (*e.g.* blood for RSV serology). Participants were contacted weekly by email or telephone during the RSV season to ask for symptoms of acute respiratory tract infection (ARTI). ARTI was defined as the presence of one or more of the following symptoms for at least 1 day: cough, nasal congestion or discharge, wheezing or shortness of breath. Patients with ARTI were visited at home by the study team for viral testing within 72 h of notification. RSV and influenza

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were tested for within 24 h of the home visit (from the nasopharyngeal sample) using a molecular point-of-case test (Xpert Xpress Flu/RSV assay; Cepheid, Sunnyvale, CA, USA) [9]. A second nasopharyngeal swab was collected for validation of RSV by quantitative PCR. RSV antibody titers (pre-F, post-F and neutralizing antibodies) were determined before and after the RSV season (supplementary material). Vital signs (heart rate, respiratory rate, oxygen saturation measured by pulse oximetry (S_{pO_2}) and temperature) were measured during the home visit and patients were instructed to complete a daily symptom log (supplementary material) and note doctors' visits and medication used over 28 days or for as long as symptoms were present. A post-season home visit was performed within 2 months of the RSV season, during which clinical data and samples were collected similar to the baseline visit. Reported pneumonia and hospitalisations were verified by a medical notes review.

Definitions

The primary outcome, RSV illness, was defined as either a PCR-confirmed RSV ARTI or a four-fold or greater increase in any RSV antibody titer post-season compared to baseline (supplementary material). We distinguished within RSV illness for RSV ARTI (clinical ARTI, only based on PCR). Frailty was scored using the validated Groningen frailty indicator (GFI) questionnaire [10]. Higher scores represent increased frailty and the cut-off for "frail" is at a score of four or more. We classified ARTI for severity, whereby severe disease included hospitalisation within 28 days of ARTI onset and moderate disease included any medical attendance (except hospitalisation) or new or increased use of inhaled respiratory medication, antibiotics, antivirals or corticosteroids. All other respiratory episodes were classified as mild disease.

Statistical analysis

Incidence of RSV illness was calculated as the number of confirmed illnesses divided by the study population per season. ARTI incidence was calculated similarly for PCR-confirmed clinical infections. Confidence intervals (CIs) were calculated using the Clopper–Pearson exact method. Sensitivity analysis of RSV incidence was performed to correct for uncertainty associated with the diagnostic tests. Test results were imputed in those with ARTI and a missed visit (no molecular test) or delayed testing (swab collected after 7 days of symptom onset) if serology was not available. Subsequently, patients with a two-fold or more to less than four-fold rise in serum RSV antibodies (probable RSV) were added as cases to obtain the sensitivity estimates (supplementary material).

Patient characteristics, symptoms and vital signs, severity, and changes in frailty and cardiopulmonary status were compared between ARTIs with different viral aetiology. We only compared PCR-confirmed ARTI since these cases could be linked directly to respiratory illness. Multivariable logistic regression analysis was performed to evaluate the prognostic performance (area under the curve (AUC)) of symptoms for predicting RSV ARTI. Clinically relevant symptoms (cough, dyspnoea, wheeze, phlegm and fever) were included in this model. Missing data was not imputed except for the sensitivity analysis. Available data from cases that were lost to follow-up during the study was used if permitted. All analyses were performed in R software, version 4.0.1 (www.r-project.org) and the mice package [11] was used for multiple imputation.

Results

Study population

Of 6398 invitations sent out by the GPs we included 1040 participants (16%) (figure 1), of which 527 participated during the 2017–2018 season and 513 participated during the 2018–2019 season (table 1). Participants in the second season were older, lived alone more frequently, had a higher prevalence of cardiac comorbidity and used more medication. Thirty-eight participants (3.7%) were lost to follow-up during the study, including nine who died during its course (figure 1), although no deaths were associated with respiratory infection. Participants lost to follow-up were older, had more comorbidity and were more often considered frail than those successfully followed-up (data not shown).

Acute respiratory tract infections

In total, 844 ARTIs were reported by 616 out of 1040 participants (59%, range: 1–5 episodes). Study team visits were performed in 805 out of 844 ARTIs (95%). Median time between onset of symptoms and the study visit was 4 days (range: 0–33 days) and 88% of tested ARTIs were visited within 1 week of symptom onset (78% in the first season and 97% in the second season). Thirty-nine out of 844 ARTIs in 39 individual patients were reported but were not tested (missed visits), most often because the study team was not notified until after the ARTI was resolved (n=31).

Incidence of RSV and influenza

RSV illness, based on PCR or a four-fold or greater seroconversion, was diagnosed in 59 out of 1040 participants. We diagnosed 22 out of 527 participants (4.2%, 95% CI 2.6–6.3%) in the first season and 37

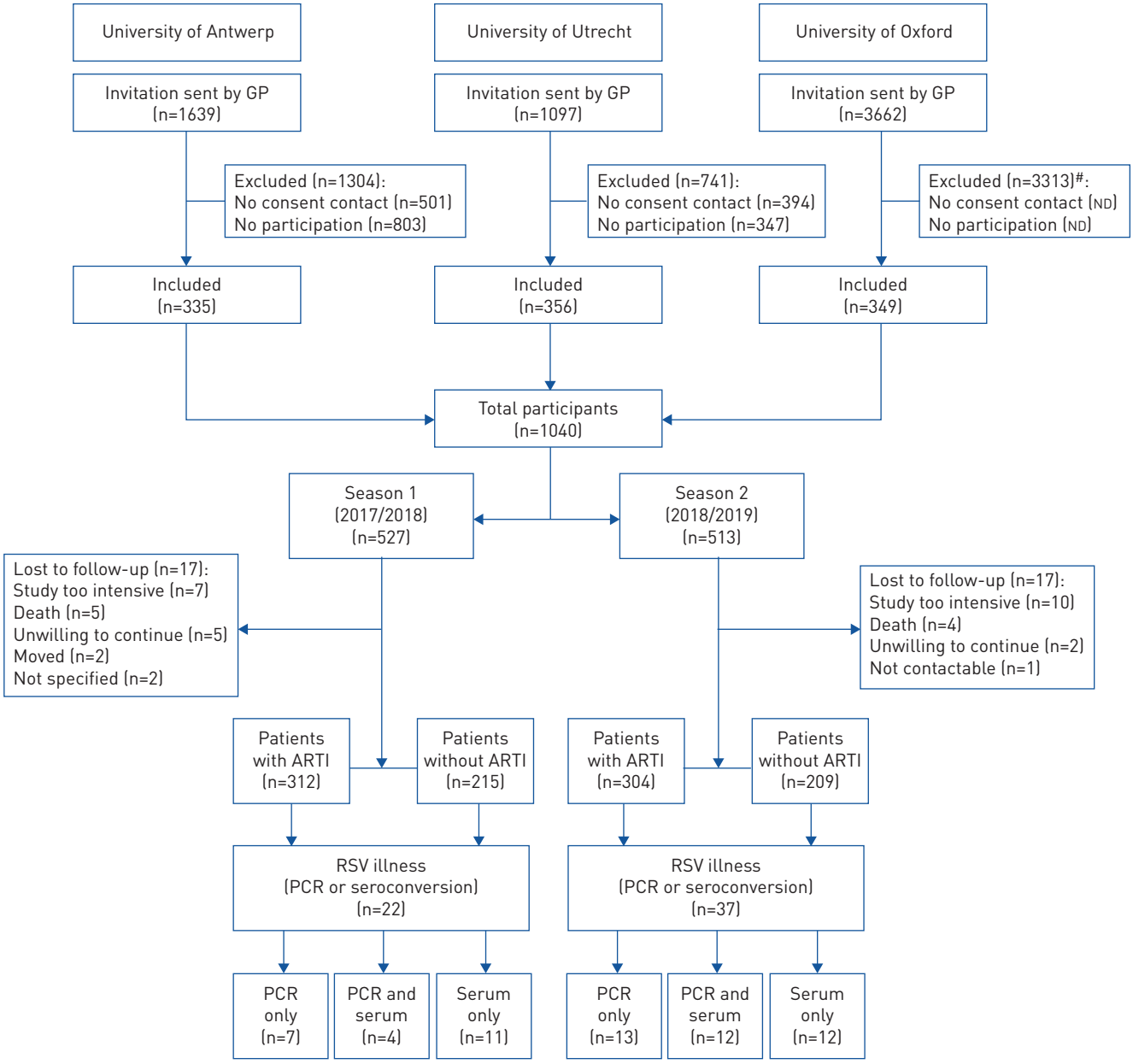


FIGURE 1 Recruitment, workflow and outcomes in the older-adult cohort study. GP: General Practitioner; ND: not determined; ARTI: acute respiratory tract infection; RSV: respiratory syncytial virus. #: although precise numbers could not be determined, the majority (>80%) of non-inclusions did not actively return consent and were therefore never approached for recruitment in the study (an "opt-in" procedure).

out of 513 participants (7.2%, 95% CI 5.5–10.2%) in the second season (table 2). RSV illness was detected by PCR (n=20), serology (n=23) or both PCR and serology (n=16) (table 2). Most RSV illnesses identified only by serology did experience an ARTI during follow-up (16 out of 23, 70%), which was either PCR negative (20 ARTIs in 13 patients) or from a missed visit (3 patients) (supplementary tables S1–S3). RSV ARTI based on PCR only was diagnosed in 11 out of 527 patients (2.1%, 95% CI 1.0–3.7%) in the first season and 25 out of 513 patients (4.9%, 95% CI 3.2–7.1%) in the second season (table 2 and figure 2). Medically-attended RSV (MA-RSV) was seen in four out of 527 patients (0.8%) in the first season and in seven out of 513 patients (1.4%) in the second season. RSV B was most often detected RSV ARTI subtype (26 out of 32 cases) during both seasons (supplementary table S1). No RSV reinfection or coinfections with influenza occurred. Sensitivity analyses showed an incidence of 8.0% (95% CI 5.8–10.6%) in the first season and 9.9% (95% CI 7.5–12.8%) in the second season (supplementary material).

Influenza ARTI based on PCR only was detected in 59 participants (supplementary table S1). Influenza A incidence was 14 out of 527 (2.7%) in the first season and 17 out of 513 (3.3%) in the second season.

TABLE 1 Characteristics of study participants

Characteristic	Total study population (n=1040)	Season 2017–2018 (n=527)	Season 2018–2019 (n=513)
Study site			
Belgium	335 (32)	204 (39)	131 (25)
The Netherlands	356 (34)	148 (28)	208 (41)
United Kingdom	349 (34)	175 (33)	174 (34)
Age			
Average	75 (60–100)	70 (60–95)	78 (60–100)
Age >75 years	562 (54)	174 (33)	388 (76)
Female sex	554 (54)	268 (51)	286 (56)
North Western European[#]	999 (97)	515 (98)	484 (94)
Living situation			
Living alone	338 (33)	146 (28)	192 (37)
Living with partner	666 (64)	363 (69)	303 (59)
Other	36 (3)	18 (3)	18 (4)
High educational level[¶]	394 (38)	217 (41)	177 (35)
Comorbidities (any)	697 (67)	316 (60)	381 (75)
Cardiovascular disease[+]	212 (21)	78 (15)	134 (26)
Congestive heart disease	11 (1)	5 (1)	6 (1)
Lung disease[+]	120 (12)	55 (10)	65 (13)
Asthma	54 (5)	29 (6)	25 (5)
COPD	54 (5)	22 (4)	32 (6)
Cardiovascular or lung disease[+]	307 (30)	121 (23)	186 (37)
Diabetes[+]	80 (8)	35 (7)	45 (9)
Allergies (any)[§]	276 (27)	131 (25)	145 (29)
Hay fever	59 (6)	23 (4)	36 (7)
House dust mites	32 (3)	21 (4)	11 (2)
Polypharmacy (>4 medicines)	372 (36)	165 (31)	207 (40)
Respiratory medication	174 (17)	88 (17)	86 (17)
Previous pneumococcal vaccination[f]	118 (13)	75 (16)	43 (9)
Previous influenza vaccination[##]	752 (76)	359 (73)	386 (80)
Smoking status			
Current smoker	80 (8)	42 (8)	38 (7)
Former smoker	409 (39)	200 (38)	209 (41)
Alcohol status			
Current drinker at ⩾1 unit·week^{-1}	666 (64)	349 (66)	317 (62)
Average consumption units·week^{-1}	1–7	1–7	1–7
Frailty[¶¶]			
GFI score	2 (0–12)	2 (0–12)	2 (0–12)
Frail (GFI score ⩾4 points)	148 (15)	70 (14)	78 (17)

Data are presented as n (%), range, or median (range). COPD: chronic obstructive pulmonary disease; GFI: Groningen frailty indicator. [#]: born in one of the three participating countries or in directly surrounding countries; [¶]: defined as university of applied sciences or higher; [+]: cardiovascular comorbidities included all arrhythmias and structural heart diseases, as well as angina and cardiac events such as infarction, percutaneous coronary intervention and bypass surgery. Hypertension was not included in this definition. Lung disease included asthma, COPD, chronic bronchitis and emphysema. Diabetes was defined as either Type 1, Type 2 or unspecified diabetes. Missing data of less than 1% is not shown; however, if more than 1% of data is missing the percentages are indicated as footnotes, [§]: missing data (n=20, 2%); [f]: vaccination in the past 5 years, missing data (n=95, 9%); [##]: vaccination in the current season, missing data (n=52, 5%); [¶¶]: missing data (n=78, 8%).

Influenza B was only detected in the first season, in 28 out of 527 participants (5.5%) (figure 2). RSV ARTI incidence was lower compared to influenza ARTI in the first season (1.9% *versus* 8.2%, respectively), but not in the second season (4.7% *versus* 3.3%, respectively) (supplementary table S1). Baseline characteristics were similar for patients with ARTI by different viral aetiologies (table 3 and supplementary table S3).

Severity of infection

Severity was compared between 805 PCR-confirmed ARTIs (table 4). Four ARTI episodes required hospitalisation: all were PCR-negative for RSV (one was PCR-positive for influenza) and there was no ARTI-related mortality. RSV ARTI required less medical attendance compared to influenza ARTI (31% *versus* 60%, p=0.006) and fewer antibiotic prescriptions (6% *versus* 31%, p=0.004). Symptom duration for RSV ARTI averaged 19 days and was significantly longer compared to other infections (19 days *versus*

TABLE 2 Respiratory syncytial virus (RSV) infection

	Season 2017–2018 (n=527)		Season 2018–2019 (n=513)	
	Cases	% (95% CI)	Cases	% (95% CI)
RSV illness[#]	22	4.2 (2.6–6.3)	37	7.2 (5.5–10.2)
PCR positive[¶]	11	2.1 (1.0–3.7)	25	4.9 (3.2–7.1)
Seroconversion[+]	15	2.8 (1.6–4.7)	24	4.7 (3.0–6.9)

CI: confidence interval; POCT: Xpert Xpress Flu/RSV assay. [#]: either positive PCR or evidence of seroconversion; [¶]: based on positive PCR or POCT; [+]: based on four-fold or greater increase in any antibody titer.

12 days, p=0.006), but was similar to influenza ARTI (19 days *versus* 18 days, p=0.53). Some 22% of RSV ARTI patients still had symptoms after 28 days. Similar results were observed for both the A and B subtypes of RSV and influenza (supplementary table S4). Another four patients were hospitalised from amongst the 39 missed visits, who therefore had no molecular test. However, no evidence of RSV infection was seen in three of those hospitalised for whom serology was available.

Frailty and comorbidity

GFI scores were significantly higher at baseline in those with older age (p=0.001), with comorbidities (p<0.001), who lived alone (p=0.001) and who had a low educational level (p<0.001) (data not shown). Neither the GFI score at baseline nor age and comorbidity were associated with occurrence or severity of RSV illness or RSV ARTI (supplementary table S5). Neither RSV infection nor ARTI affected frailty or cardiopulmonary status in this generally healthy older adult population (table 3).

Clinical symptoms

Diary information was available for 750 out of 805 ARTIs (93%). Patients with RSV and influenza generally reported more symptoms compared to other ARTIs (table 5). We observed substantial variation in symptomatology with little specificity for RSV or influenza. Multivariable modelling including cough, phlegm, dyspnoea, wheeze and feeling feverish showed limited prognostic accuracy (AUC 0.66, 95% CI 0.59–0.74) (data not shown).

Discussion

In this study we found an annual incidence of RSV illness of 4.2% and 7.2%, respectively, in community-dwelling older adults in Europe. While prevalent, our study shows that most RSV infections were mild and did not require hospitalisation or lead to worsening of frailty or cardiopulmonary status. There were no RSV-associated deaths. To our knowledge, this is the first prospective, multi-country, observational cohort study providing estimates of the incidence and severity of RSV infection in community-dwelling older adults.

RSV incidence

Our RSV incidence is in line with other prospective cohort studies in healthy, community-dwelling older adults, indicating an annual incidence of 1.6% to 7% [1, 7, 12–14]. The most comparable study is that by Falsey *et al.* [1]. Amongst other groups, they studied 608 older adults (without disabling comorbidities) aged ⩾65 years during four RSV seasons from 1999–2003. RSV incidence ranged from 3–7% between the seasons based on viral culture, PCR and serology. Nicholson *et al.* [7] followed a cohort of 533 community-dwelling older adults and found an incidence of 3.2%, although RSV diagnosis was solely based on serology. This is in line with our serology-based incidences (2.8% and 4.7%, respectively). RSV vaccine trials typically showed lower estimates ranging from 1.6–3.4% in published studies [13, 14] and 1.97–4.9% in unpublished studies [12]. However, estimates were often based on single seasons, with different ARTI definitions and participation criteria, and generally did not include serology.

RSV incidence in our study varied substantially by season, although CIs overlapped. Several factors may explain this difference. First, national surveillance indicated a higher RSV peak in Belgium and the United Kingdom in 2018–2019 compared to 2017–2018 [15–19]. Secondly, delayed sampling was more common in our first season, which might have resulted in misclassification by PCR [20]. Thirdly, viral interference between RSV and influenza is suggested [21, 22] and the large 2017–2018 influenza B outbreak may have influenced the RSV epidemic. Finally, RSV incidence was higher in the second season, when the cohort was significantly older and had a higher degree of comorbidity compared to the first season. Although

TABLE 3 Characteristics of patients with PCR-confirmed acute respiratory tract infection (ARTI)

Characteristic	RSV ARTI patients (n=36)	Influenza ARTI patients (n=59)	Other ARTI patients (n=477)	Patients without ARTI (n=417)
Age years	75 (70–79)	71 (67–78)	75 (68–80)	76 (69–81)
Female sex	20 (56)	30 (51)	261 (55)	216 (51)
High educational level[#]	17 (47)	28 (48)	183 (38)	154 (37)
Comorbidities (any)	23 (64)	37 (63)	338 (71)	268 (65)
Cardiovascular disease[¶]	7 (19)	10 (17)	103 (22)	84 (20)
Congestive heart disease	1 (3)	1 (2)	4 (1)	5 (1)
Lung disease[¶]	5 (14)	7 (12)	63 (13)	39 (9)
Asthma	2 (6)	5 (9)	31 (7)	16 (4)
COPD	1 (3)	3 (5)	25 (5)	20 (5)
Diabetes[¶]	2 (6)	5 (9)	51 (11)	19 (5)
Polypharmacy (>4 medicines)	12 (33)	17 (29)	187 (39)	136 (33)
Respiratory medication	6 (17)	13 (22)	92 (19)	48 (12)
Previous influenza vaccination[§]	30 (86)	46 (78)	359 (78)	278 (72)
Previous pneumococcal vaccination[f]	4 (12)	10 (20)	55 (13)	41 (10)
Smoking status				
Current smoker	3 (8)	3 (5)	29 (6)	39 (9)
Former smoker	14 (39)	17 (29)	206 (43)	153 (37)
Frailty[##]				
Frail baseline[+]	2 (6)	6 (11)	71 (16)	60 (16)
GFI score baseline	1.5 (1–3)	2 (1–3)	2 (1–4)	2 (1–4)
GFI change over season	0 (–1 to 1)	0 (–1 to 1)	0 (–1 to 1)	0 (–1 to 1)
Developed frailty	0 (0)	3 (6)	19 (5)	15 (5)
Lost frailty	1 (3)	0 (0)	36 (9)	28 (9)
Worsening of cardiorespiratory status[¶¶]				
New lung disease	0 (0)	0 (0)	9 (2)	3 (1)
New cardiac disease	0 (0)	1 (2)	3 (1)	1 (0.3)
Increased respiratory medication	1 (3)	3 (5)	18 (4)	8 (2)

Data are presented as n (%) or median (IQR). Twenty-three patients with only serologic evidence of RSV infection and 28 patients with a missed visit were excluded. Three patients had separated RSV and influenza ARTI during follow-up and were counted in both groups, while one patient experienced two separate influenza B infections and was counted once. RSV: respiratory syncytial virus; COPD: chronic obstructive pulmonary disease; GFI: Groningen frailty indicator; IQR: interquartile range. [#]: defined as university of applied sciences or higher; [¶]: cardiovascular comorbidities included all arrhythmias and structural heart diseases, as well as angina and cardiac events such as infarction, percutaneous coronary intervention and bypass surgery. Hypertension was not included in this definition. Lung disease included asthma, COPD, chronic bronchitis and emphysema. Diabetes was defined as either Type 1, Type 2 or unspecified diabetes; [+]: GFI score ⩾4 points. Missing data of less than 1% is not shown; however, if more than 1% is missing the percentages are added as footnotes; [§]: vaccination in the current season, missing data (n=52, 5%); [f]: vaccination in the past 5 years, missing data (n=95, 9%); [##]: missing data as follows: baseline (n=78, 8%), end-of-season (n=114, 11%), either baseline or end-of-season (n=180, 17%); [¶¶]: missing data (n=62).

severity is associated with older age and comorbidity [1, 3, 23–25], RSV incidence was not associated with these factors in our study or those of others [23, 26].

RSV severity

While in-hospital RSV infections are associated with high morbidity and mortality [1, 6, 27], our results suggest that RSV infections in community-dwelling older adults are generally mild and require limited intervention. Although contrasting, this finding is not unexpected since the lack of mortality [1], nonexistent to very low hospitalisation rates [1, 2] and lower rate of doctor visits and antibiotic

TABLE 4 Severity of PCR-confirmed acute respiratory tract infection (ARTI) episodes

	RSV ARTI episodes (n=36)	Influenza ARTI episodes (n=60)	Other ARTI episodes[#] (n=690)
Duration of symptoms days	19 (13–27)	18 (14–22)	12 (8–21)[f]
Unresolved illness[¶]	8 (22)	9 (16)	105 (17)
Medication[+]	10 (28)	26 (44)	99 (15)
Respiratory medication	9 (25)	13 (22)	68 (10)[##]
Antibiotics	2 (6)	18 (31)[f]	49 (7)
Antivirals	0 (0)	2 (3)	0 (0)
Corticosteroids	0 (0)	2 (3)	9 (1)
Medical attendance	11 (31)	36 (60)[f]	138 (20)
Hospitalisation	0 (0)	1 (2)	3 (0.4)
Emergency department	0 (0)	0 (0)	1 (0.2)
GP visit	10 (28)	32 (55)[##]	122 (18)
Telephone call to doctor	2 (6)	3 (5)	7 (1)
LRTI[§]	0 (0)	1 (2)	3 (0.4)
Death	0 (0)	0 (0)	0 (0)
Severity classification			
Mild	22 (61)	20 (33)[##]	505 (75)
Moderate	14 (39)	39 (65)[##]	169 (25)
Severe	0 (0)	1 (2)	3 (0.4)

Data are presented as n (%) or median (IQR). Statistical significance is compared to RSV ARTI episodes. RSV: respiratory syncytial virus; GP: General Practitioner; LRTI: lower respiratory tract infection; IQR: interquartile range. [#]: 19 episodes with other infection but positive seroconversion for RSV and 39 missed visits were excluded; [¶]: illness that persisted beyond the 28 diary days; [+]: enhanced use or newly prescribed inhaled respiratory medication, antibiotics, antivirals or corticosteroids; [§]: clinically diagnosed or radiologically confirmed pneumonia; [f]: p<0.01; [##]: p<0.05; [+]: p<0.001 (not indicated if non-significant).

TABLE 5 Clinical symptoms of respiratory episodes

Patient reported symptoms[#]	RSV ARTI episodes (n=36)	Influenza ARTI episodes (n=57)	Other ARTI episodes[¶] (n=657)
Rhinitis	36 (100)	55 (96)	624 (95)
Cough	35 (97)	55 (96)	572 (87)
Wheeze	16 (44)	26 (46)	223 (34)
Phlegm	34 (94)	52 (91)	466 (71)[+]
Dyspneoa	24 (67)	42 (74)	309 (47)[§]
Fever ⩾38 °C	2 (6)	11 (19)	26 (4)
Feeling feverish	12 (33)	37 (65)[+]	191 (29)
Headache	27 (75)	45 (79)	348 (53)[§]
Myalgia	19 (53)	41 (72)	263 (40)
Disturbed sleep	26 (72)	51 (89)[§]	440 (67)
Feeling unwell	33 (91)	56 (98)	499 (76)[§]
Disturbance in daily activity	27 (75)	51 (89)	348 (53)[+]
Vital signs from home visit[##]			
Fever ⩾38 °C	2 (6)	9 (16)	13 (2)
Respiratory rate >20 breaths·min^{-1}	6 (17)	8 (14)	63 (10)
S_{pO_2} <95%	5 (14)	10 (18)	39 (6)

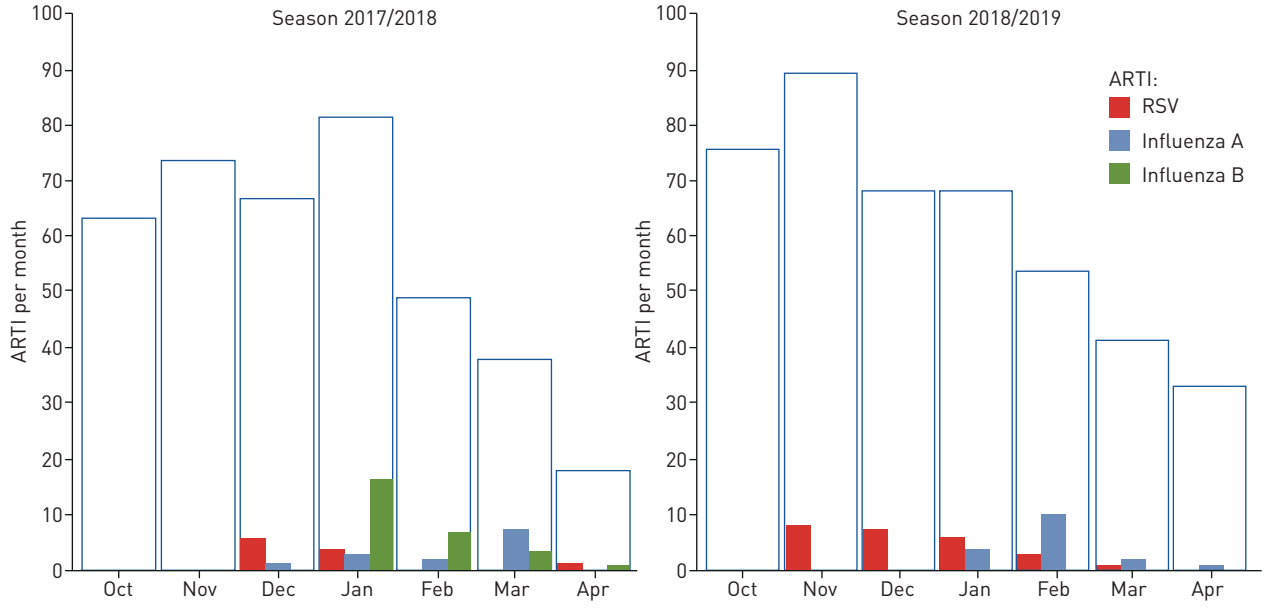
Data are presented as n (%). Numbers represent respiratory episodes unless stated otherwise and statistical significance is compared to RSV ARTI episodes. RSV: respiratory syncytial virus; ARTI: acute respiratory tract infection; S_{pO_2}: oxygen saturation measured by pulse oximetry. [#]: at least once during the respiratory infection based on the symptom diary; [¶]: RSV and influenza negative infections based on PCR; [+]: p<0.01; [§]: p<0.05; [f]: p<0.001 (not indicated if non-significant); [##]: measured by the study team.

prescriptions compared to influenza has been observed before in this population [1]. Symptoms and duration of illness were comparable with influenza ARTI, except for fever which was more often seen in influenza ARTI. This could have attributed to more doctor visits and antibiotic prescriptions in our study. However, none of the clinical symptoms could distinguish RSV from all other ARTI without viral testing. Our findings suggest that watchful waiting, using a continuity of care approach to identify those who do need more intensive care, is justified in cases of suspected RSV infection in the community. Careful monitoring of patients with an increased risk of severe disease, such as those with cardiopulmonary comorbidities, should be part of this approach.

Strengths and limitations

The main strength of this study is that we are the first to provide burden estimates of RSV infection using both PCR and serology based on a large community cohort of older adults in multiple European countries. Crucial in the study design was premorbid recruitment and prospective follow-up of a representative community population. Recruitment from GPs offices made it possible to study a generalisable community population. Furthermore, without the need of medical attendance to trigger an ARTI home visit, there was no selection bias for viral testing based on disease severity. With intensive surveillance, during multiple RSV seasons, we managed to visit 88% of infections within 1 week of symptom onset.

Some limitations should also be mentioned. First, testing early in the course of infection is crucial in diagnosing RSV in older adults [20]; however, delayed testing did occur, most often during the first season (22% *versus* 3% in the second season). In addition, more serology-confirmed cases were identified compared to PCR-confirmed cases in this first season, which could reflect misclassification by PCR. Notably, three patients had detectable RSV by quantitative PCR but were below the predefined limits of detection, excluding them as cases in our analyses. As such, this could have underestimated RSV



ARTI type	Oct 2017	Nov 2017	Dec 2017	Jan 2018	Feb 2018	Mar 2018	Apr 2018	–	Oct 2018	Nov 2018	Dec 2018	Jan 2019	Feb 2019	Mar 2019	Apr 2019	Total
RSV A	0	0	2	3	0	0	0	–	0	0	1	0	0	0	0	6
RSV B	0	0	3	1	0	0	1	–	0	7	4	6	3	1	0	26
RSV unknown	0	0	1	0	0	0	0	–	0	1	2	0	0	0	0	4
Influenza A	0	0	1	3	2	8	0	–	0	0	0	4	10	2	1	31
Influenza B	0	0	0	17	7	4	1	–	0	0	0	0	0	0	0	29
Other ARTI	63	74	60	57	40	26	16	–	73	78	59	56	39	37	31	709
Total	63	74	67	81	49	38	18	–	73	86	66	66	52	40	32	805

FIGURE 2 Observed respiratory infections per study season. Acute respiratory tract infections (ARTIs) are ordered based on the date of the positive test. Only those with a result from molecular testing on a nasopharyngeal swab are included. The white columns represent the total number of ARTIs. Unknown respiratory syncytial virus (RSV) cases (n=4) were not subtyped, since these cases were not tested by quantitative PCR.

incidence. Secondly, 39 ARTI episodes, including four hospitalisations, were missed and therefore not sampled. Three of these missed ARTIs showed seroconversion of RSV antibodies but none of the hospitalised patients did. Thirdly, without acute and convalescent serum flanking illness we could not determine the fraction of symptomatic RSV, as we were unable to directly link serologic responses to illness. Symptom and severity analyses were therefore limited to PCR-confirmed ARTI, limiting the power of these analyses. Fourthly, since we collected convalescent serum after the season, antibody decay could have occurred between acute RSV infection and convalescent sampling [28]. This could have underestimated the incidence and could explain why 27 out of 31 PCR-confirmed cases (87%) had a two-fold or greater increase in serum antibodies but just 16 out of 31 (52%) showed a four-fold or greater increase. Sensitivity analysis including cases with probable seroconversion showed a total incidence of 8.0% (+3.8% compared to the primary analysis) in the first season and 9.9% (+2.7% compared to the primary analysis) in the second season. These estimates provide the upper limit of RSV incidence that could have occurred in our study, although this is speculative. Fifthly, influenza was only confirmed with PCR and not serology and this has underestimated the incidence of influenza in our study [29] while limiting comparisons between influenza and RSV to PCR-confirmed ARTI. Sixthly, the cohort was too small and perhaps "too healthy" to provide estimates about more severe complications, such as hospitalisations or death, although the fact that we did not observed any such complications for RSV is reassuring. Seventhly, we might have missed progression of frailty in any group due to the relatively healthy study population at the start of follow-up. Also, measurement at baseline and after the season could be too long to assess the short-term impact of respiratory infection, or too short to assess long-lasting increases in frailty. Eighthly, study visits and testing for RSV could have influenced health-care seeking behaviour. The proportion of MA-RSV was 31%,which is in line with the 17%–45% observed in similar studies [1, 7]. Finally, selection bias could have occurred since 16% of those invited by their GP participated. However, the majority of non-inclusions were never contacted by the study team because of the way recruitment was organised and these candidates were not excluded based on unwillingness to participate or any predefined criteria.

Conclusion

This well-powered, prospective, European cohort study showed that RSV is prevalent in community-dwelling older adults but rarely causes severe disease. This study confirms and updates estimates from earlier studies but also emphasises the variability between seasons and the importance of using different methods of RSV detection. This should help patient management in family practice when RSV is suspected, but should also aid efforts to develop vaccines and therapeutics against RSV and, when RSV vaccines become available, guide implementation of preventive strategies.

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Author contributions: K. Korsten designed the study, collected the data, drafted the analysis plan, performed the analyses and drafted the manuscript. N. Adriaenssens, B. Ravanfar, H. Rutter and J. Allen were involved in the acquisition of data. S. Coenen, C. Butler, T. Verheij, J-Y. Pirçon, G. Ispas, V. Shinde and A. Falsey advised about the analysis plan and interpretation of the data. O. Gruselle, V. Pavot, C. Vernhes, S. Balla-Jhagjhoorsingh, D. Öner and J. Aerssens provided the laboratory analyses of biomaterials. J. Wildenbeest and L. Bont designed the study, drafted the analysis plan, interpreted the data and led the study. All authors were involved in the analysis plan, critically reviewed the manuscript, and contributed to and approved the final version.

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