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

TITLE PAGE

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

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Take home message

Respiratory syncytial virus (RSV) infection in older adults is recognized, 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.

ABSTRACT

Background Respiratory syncytial virus (RSV) infection in older adults is recognized 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 REspiratory Syncytial virus Consortium in EUrope (RESCEU). Participants were recruited before two independent RSV-seasons through general practitioner's offices. 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, 513 in season 2018-2019) with a median age of 75 years (range 60-100). 1023 (99%) lived independently at home at baseline. RSV-illness incidence was 4.2% (22/527) and 7.2% (37/513) in the respective seasons. RSV-illness did not affect frailty or cardiopulmonary status during the course of the study. No patients were hospitalized 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 11/36 (31%) of cases. RSV-ARTI could not clinically be differentiated from all other ARTI 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.

INTRODUCTION

Respiratory Syncytial Virus (RSV) is responsible for a significant burden of disease among 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 industrialized countries occurs in those that are above 65 years of age [2, 4]. Studies in hospitalized patients and nursing home residents showed that severe RSV infection occurs in those who are older, have an immunodeficiency or 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-center studies were conducted 15 years ago and only the study by Falsey and colleagues [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 the value of these therapeutics in community-dwelling older adults is urgently required. To address this gap in 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 1st – May 1st) an independent cohort of participants was recruited from 17 general practitioner's 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 less than a 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 Clinicaltrials.gov, identifier: NCT03621930 and in the study protocol [Supplemental file]. Eligible patients received an initial invitation letter by their general practitioner after which they were contacted by the study team for study recruitment [Supplemental file].

Study procedures

Between August and September a pre-season baseline home visit was performed during which patient characteristics were obtained and sampling was performed (amongst others, 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 one 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 hours after notification. RSV and influenza were tested within 24 hours after the home visit from the nasopharyngeal sample using a molecular point-of-case test (the Xpert® Xpress Flu/RSV assay (Cepheid, Sunnyvale, CA, USA)[9]. A second nasopharyngeal swab was collected for validation of RSV by qPCR. RSV-antibody titers (pre-F, post-F and neutralizing antibodies) were determined before and after the RSV-season [Supplemental file]. Vital signs (heart rate, respiratory rate, SpO_2 and temperature) were measured during the home visit and patients were instructed to complete a daily symptom log [Supplemental file], and noted doctors' visits and used medication during 28 days or for as long as symptoms were present. A post-season home visit was performed within two months after the RSV-season during which clinical data and samples were collected similar to the baseline visit. Reported pneumonia and hospitalizations were verified by medical notes review.

Definitions

The primary outcome, RSV-illness, was defined as either a PCR-confirmed RSV-ARTI or a ≥4-fold increase in any RSV antibody titer post-season compared to baseline [Statistical Analysis Plan]. 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 whereas the cut-off for frail is at ≥4. We classified ARTI for severity. Severe disease included hospitalization within 28 days after ARTI onset while moderate disease included any medical-attendance (except hospitalization) or new or increased used 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 were calculated using the Exact Clopper-Pearson method. Sensitivity analysis of the 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 seven days of symptom onset) if serology was not available. Subsequently, patients with a ≥2 to <4-fold rise in serum RSV antibodies (probable RSV) were added as cases to obtain the sensitivity estimates [Statistical Analysis Plan].

Second, patient characteristics, symptoms and vital signs, severity, and changes in frailty and cardiopulmonary status were compared between ARTI with different viral aetiology. We only compared PCR-confirmed ARTI since these could be directly linked to respiratory illness. Multivariable logistic regression analysis was performed to evaluate the prognostic performance (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 version 4.0.1 and the mice package was used for multiple imputation.

RESULTS

Study population

Out of 6398 invitations sent out by the general practitioners, we included 1040 participants (16%) [Figure 1]. 527 participated during the 2017-2018 season, and 513 participated during the 2018-2019 RSV-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 participants who died during the study [Figure 1]. 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 616/1040 participants (59%, range 1-5 episodes). Study team visits were performed in 95% (805/844) of ARTIs. Median time between onset of symptoms and the study visit was four days (range 0-33) days and 88% of tested ARTIs were visited within one week after onset of symptoms (78% in the first, 97% in the second season). 39/844 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 ≥4-fold seroconversion, was diagnosed in 59/1040 participants. We diagnosed 22/527 participants (4.2%, 95% CI 2.6-6.3%) in the first, and 37/513 (7.2%, 95% CI 5.5-10.2%) in the second RSV-season [Table 2]. RSV-illness was detected by PCR (20 cases), serology (23 cases) or both (16 cases) [Table 2]. Most RSV-illnesses identified only by serology did experience an ARTI during follow-up (16/23, 70%) which was either PCR-negative (20 ARTI in 13 patients) or

were from a missed visit (3 patients) [Table S1-S3]. RSV-ARTI, based on PCR only, was diagnosed in 11/527 patients (2.1%, 95% CI 1.0-3.7%) in the first, and 25/513 (4.9%, 95% CI 3.2-7.1%) in the second RSV-season [Table 2]. Medically-attended RSV (MA-RSV) was seen in 4/527 (0.8%) patients in the first, and 7/513 (1.4%) patients in the second RSV-season. RSV B was most often detected (26/32 subtyped RSV-ARTI) during both seasons [Table S1]. No RSV reinfection or coinfections with influenza occurred. Sensitivity analyses showed an incidence of 8.0% (5.8–10.6%) in the first, and 9.9% (7.5-12.8%) in the second RSV-season [Supplemental file].

Influenza-ARTI, based on PCR only, was detected in 59 participants [Table S1]. Influenza A incidence was 2.7% (14/527) in the first season and 3.3% (17/513) in the second season. Influenza B was only detected in the first season in 5.5% (28/527) participants. 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%) [Table S1]. Baseline characteristics were similar for patients with ARTI by different viral aetiologies [Table 3, Table S3].

Severity of infection

Severity was compared between 805 PCR-confirmed ARTI [Table 4]. Four ARTI episodes required hospitalization. All were PCR-negative for RSV (one was PCR-positive for influenza). There was no ARTI-related mortality. RSV-ARTI required less medical attendance (31% vs 60%, p=0.006) and fewer antibiotic prescriptions (6% vs 31%, p=0.004) compared to influenza-ARTI. Symptom duration for RSV-ARTI averaged 19 days and was significantly longer compared to other infections (19 vs 12 days, p=0.006), but similar to influenza-ARTI (19 versus 18 days, p=0.53). 22% of RSV-ARTI still had symptoms after 28 days. Similar results were observed for A and B subtypes of RSV and influenza [Table S4]. Another four patients were hospitalized from the 39 missed visits and had therefore no molecular test. No evidence of RSV infection was seen in three of these hospitalized patients of whom serology was available.

Frailty and comorbidity

Groningen Frailty Indicator (GFI) scores were significantly higher at baseline in those with older age (p=0.001), with comorbidity (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 [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 in 750/805 (93%) of ARTIs. Patients with RSV and influenza generally reported more symptoms compared to other ARTI [Table 4]. 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% in community-dwelling older adults in Europe. While prevalent, our study shows that most RSV infections were mild and did not require hospitalization or led 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, 11-13]. Most comparable is the study by Falsey and colleagues [1]. Amongst other groups, they studied 608 older adults aged ≥65 years without disabling comorbidity during four RSV-seasons from 1999-2003. RSV incidence ranged from 3-7% between the seasons based on viral culture, PCR and serology. Nicholson and colleagues

followed a cohort of 533 community-dwelling older adults and found an incidence of 3.2% although RSV diagnosis was solely based on serology [7]. This is in line with our serology-based incidences (2.8% and 4.7%). RSV vaccine trials typically showed lower estimates ranging from 1.6-3.4% in published [12, 13], and 1.97-4.9% in unpublished studies [11]. However, estimates were often based on single seasons, with different ARTI definitions, different participation criteria, and generally did not include serology.

RSV incidence in our study varied substantially per season although confidence intervals overlapped. Several factors may explain this difference. National surveillance indicated a higher RSV-peak in 2018-2019 in Belgium and the United Kingdom compared to 2017-2018 [14-18]. Second, delayed sampling was more common in our first season which might have resulted in misclassification by PCR [19]. Third, viral interference between RSV and influenza is suggested [20, 21]. The large 2017-2018 influenza B outbreak may have influenced the RSV-epidemic. Fourth, RSV incidence was higher in the second season when the cohort was significantly older and had more comorbidity compared to the first season. Although severity is associated with older age and comorbidity [1, 3, 22-24], RSV incidence was not associated with these factors in ours and other studies [22, 25].

RSV severity

While in-hospital RSV infections are associated with high morbidity and mortality [1, 6, 26], 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], non-existent to very low hospitalization rates [1, 2] and a lower rate of doctor's visits and antibiotic prescriptions compared to influenza in this population was observed before [1]. Symptoms and duration of illness was comparable with influenza-ARTI, except for fever, which was more often seen in influenza-ARTI. This could have attributed to more doctor's visits and antibiotic prescriptions in our study. 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 case of suspected RSV infection in the

community. Careful monitoring of patients with an increased risk of severe disease like those with cardiopulmonary comorbidity 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 from 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 general practitioners offices made it possible to study a generalizable community population. 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 one week after onset of symptoms.

Regarding limitations, first, testing early in the course of infection is crucial in diagnosing RSV in older adults [19]. Delayed testing did occur, most often during the first season (22% versus 3% in the second season). More serology-confirmed cases were identified compared to PCR-confirmed cases in this first season which could reflect misclassification by PCR. Three patients had detectable RSV by qPCR but were below the predefined limits of detection excluding them as cases in our analyses. This could have underestimated RSV incidence. Second, 39 ARTI-episodes, including four hospitalizations, were missed and therefore not sampled. Three of these missed ARTI showed seroconversion of RSV-antibodies but none of the hospitalized patients did. Third, without acute and convalescent serum flanking illnesses we could not determine the fraction of symptomatic RSV because we were unable to directly link serologic responses to illnesses. Symptom and severity analyses were therefore limited to PCR-confirmed ARTI limiting the power of these analyses. Fourth, since we collected convalescent serum after the season, antibody decay could have occurred between acute RSV infection and convalescent sampling [27]. This could have underestimated the incidence and could explain why 87% (27/31) of PCR-confirmed cases had a ≥2-fold increase in serum antibodies but just 52% (16/31) showed a ≥4-fold increase. Sensitivity analysis including cases with

probable seroconversion showed a total incidence of 8.0% (+3.8%) in the first, and 9.9% (+2.7%) in the second season. These estimates provide the upper limit of RSV incidence that could have occurred in our study although this is speculative. Fifth, influenza was only confirmed with PCR and not serology. This has underestimated the incidence of influenza in our study [28] and limited comparisons between influenza and RSV to PCR-confirmed ARTI. Sixth, the cohort was too small and perhaps 'too healthy' to provide estimates about more severe complications such as hospitalizations or death although the fact that we did not observed any for RSV is reassuring. Seventh, 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. Eight, 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]. Last, 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 organized and were not excluded based on unwillingness to participate or 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 emphasizes the variability between seasons and importance of using different methods of RSV detection. This should help patient management in family practice when RSV is suspected, but also aid efforts to develop vaccines and therapeutics against RSV and guide implementation of preventive strategies, when RSV vaccines become available.

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Contributors: KK designed the study, collected the data, drafted the analysis plan, performed the analyses and drafted the manuscript. NA, BR, HR and JA were involved in the acquisition of data. SC, CCB, TV, JYP, GI, VS and ARF advised about the analysis plan and interpretation of the data. OG, VP, CV, SSBJ, DÖ and JAe provided the lab analyses of biomaterials. JGW and LJB designed the study, drafted the analysis plan, interpreted the data and led the study. All authors were involved in the analysis plan and critically reviewed the manuscript. All authors contributed to and approved the final manuscript.

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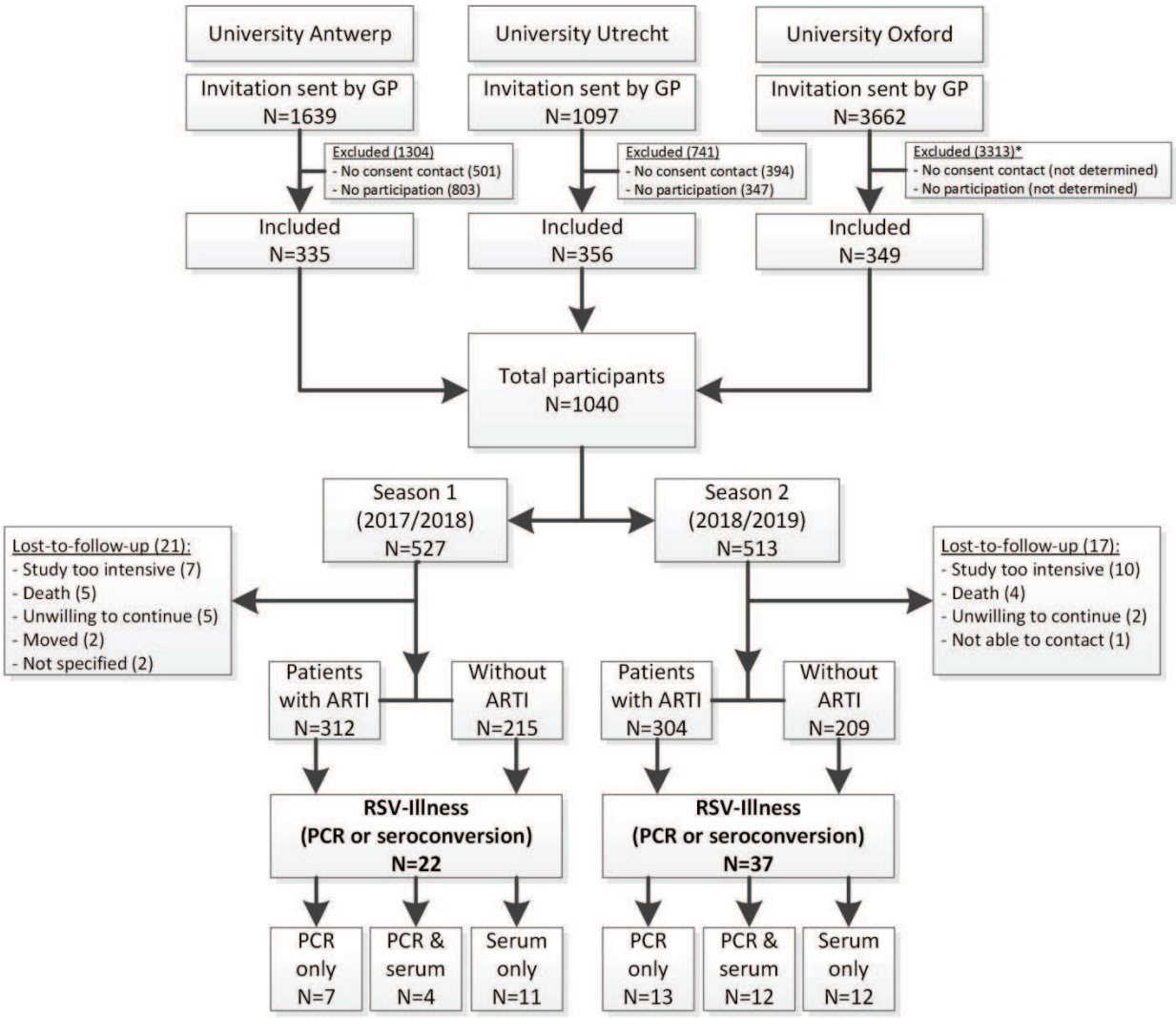
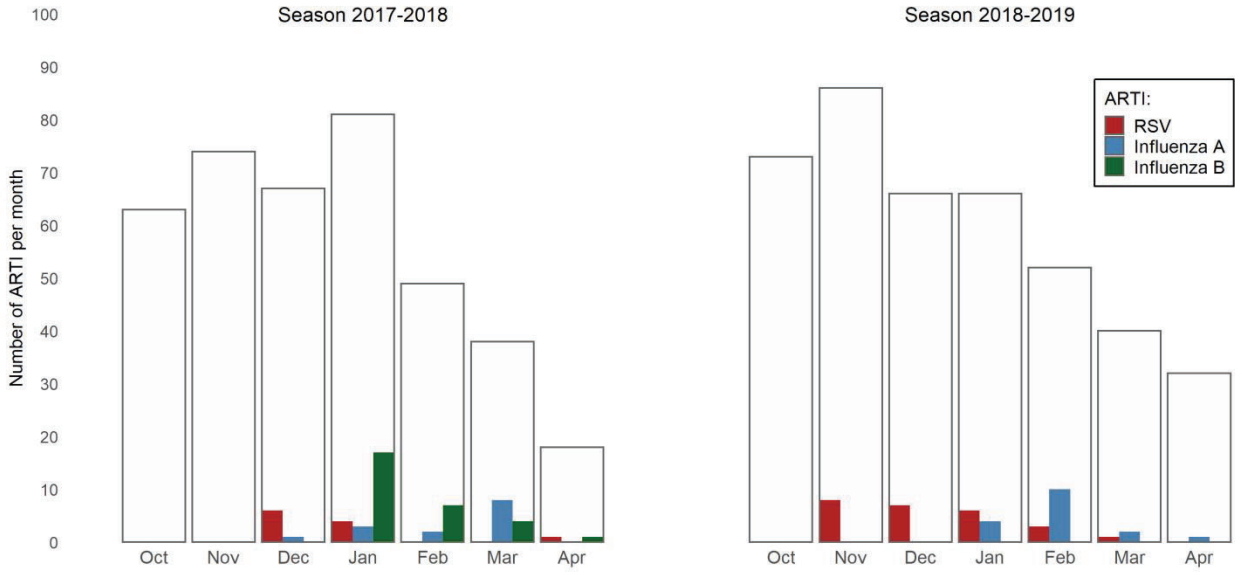


Figure 1. Recruitment, flow and outcomes in the older adult cohort study

ARTI: Acute Respiratory Tract Infection, PCR: Polymerase Chain Reaction. *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 (opt-in procedure).



ARTI Type	Oct-17	Nov-17	Dec-17	Jan-18	Feb-18	Mar-18	Apr-18	-	Oct-18	Nov-18	Dec-18	Jan-19	Feb-19	Mar-19	Apr-19	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

ARTI: Acute Respiratory Tract Infection. ARTI are ordered based on the date of the positive test. Only those with a result from molecular testing on nasopharyngeal swab are included in this figure and table. The white columns represent the total number of ARTI. Unknown RSV (n=4) were not subtyped since these cases were not tested by qPCR

Table 1. Characteristics of study participants

	Total study population N = 1040	Season 2017-2018 N = 527	Season 2018-2019 N = 513
Study site:			
Belgium	335 (32%)	204 (39%)	131 (25%)
Netherlands	356 (34%)	148 (28%)	208 (41%)
United Kingdom	349 (34%)	175 (33%)	174 (34%)
Age:			
Years; median (range)	75 (60-100)	70 (60-95)	78 (60-100)
Age above 75	562 (54%)	174 (33%)	388 (76%)
Female sex	554 (54%)	268 (51%)	286 (56%)
Northwest European[a]	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[b]	394 (38%)	217 (41%)	177 (35%)
Comorbidity (any)	697 (67%)	316 (60%)	381 (75%)
Cardiovascular disease[c]	212 (21%)	78 (15%)	134 (26%)
Congestive Heart disease	11 (1%)	5 (1%)	6 (1%)
Lung disease[c]	120 (12%)	55 (10%)	65 (13%)
Asthma	54 (5%)	29 (6%)	25 (5%)
COPD	54 (5%)	22 (4%)	32 (6%)
Cardiovascular or lung disease[c]	307 (30%)	121 (23%)	186 (37%)
Diabetes[c]	80 (8%)	35 (7%)	45 (9%)
Allergies (any)[1]	276 (27%)	131 (25%)	145 (29%)
Hay fever	59 (6%)	23 (4%)	36 (7%)
House dust mite	32 (3%)	21 (4%)	11 (2%)
Polypharmacy (>4 medicines)	372 (36%)	165 (31%)	207 (40%)
Respiratory medication	174 (17%)	88 (17%)	86 (17%)
Pneumococcal vaccination[2]	118 (13%)	75 (16%)	43 (9%)
Influenza vaccination[3]	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 (≥1 unit per week)	666 (64%)	349 (66%)	317 (62%)
Average consumption	1-7 units/week	1-7 units/week	1-7 units/week
Frailty[4]			
GFI score; median (range)	2 (0-12)	2 (0-12)	2 (0-12)
Frail (GFI score ≥4 points)	148 (15%)	70 (14%)	78 (17%)

Abbreviations: COPD = Chronic Obstructive Pulmonary Disease; GFI = Groningen Frailty indicator. [a] Born in one of the three participating countries or directly surrounding countries. [b] Defined as university of applied sciences or higher. [c] Cardiovascular comorbidity included all arrhythmias, structural heart diseases, 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 one or two or unspecified diabetes. Missing data <1% is not shown, if more than 1% is missing, the percentages are added as footnote. [1]missing N=20 (2%), [2]Missing N=95 (9%), [3]missing N=52 (5%), [4]missing N=78 (8%)

Table 2. RSV infection

	2017-2018 N = 527		2018-2019 N = 513	
	Cases	% (95% CI)	Cases	% (95% CI)
RSV-illness[a]	22	4.2% (2.6- 6.3)	37	7.2% (5.5 - 10.2)
PCR positive[b]	11	2.1% (1.0-3.7)	25	4.9% (3.2-7.1)
Seroconversion[c]	15	2.8% (1.6-4.7)	24	4.7% (3.0-6.9)

[a] Either positive PCR or evidence of seroconversion [b] Based on positive PCR or POCT [c] based on ≥4-fold increase in any antibody titer.

Table 3. Characteristics of patients with PCR-confirmed ARTI

	RSV-ARTI patients N= 36	Influenza-ARTI patients N= 59	Other ARTI patients N= 477	Patients without ARTI N= 417
Age; median years [IQR]	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[a]	17 (47%)	28 (48%)	183 (38%)	154 (37%)
Comorbidity (any)	23 (64%)	37 (63%)	338 (71%)	268 (65%)
Cardiac disease[b]	7 (19%)	10 (17%)	103 (22%)	84 (20%)
Congestive heart disease	1 (3%)	1 (2%)	4 (1%)	5 (1%)
Lung disease[b]	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[b]	2 (6%)	5 (9%)	51 (11%)	19 (5%)
Polypharmacy (≥4)	12 (33%)	17 (29%)	187 (39%)	136 (33%)
Respiratory medication	6 (17%)	13 (22%)	92 (19%)	48 (12%)
Previous influenza vaccination[1]	30 (86%)	46 (78%)	359 (78%)	278 (72%)
Previous pneumococcal vaccination[2]	4 (12%)	10 (20%)	55 (13%)	41 (10%)
Current smoker	3 (8%)	3 (5%)	29 (6%)	39 (9%)
Former smoker	14 (39%)	17 (29%)	206 (43%)	153 (37%)
Frailty[3]				
Frail baseline[c]	2 (6%)	6 (11%)	71 (16%)	60 (16%)
GFI score baseline; median [IQR]	1.5 [1-3]	2 [1-3]	2 [1-4]	2 [1-4]
GFI change over season; median [IQR]	0 [-1 – 1]	0 [-1 – 1]	0 [-1 – 1]	0 [-1 – 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[4]				
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%)

Abbreviations: IQR=interquartile range; GFI = Groningen Frailty indicator. 23 patients with only serologic evidence of RSV infection and 28 patients with a missed visit were excluded from this table. 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 [a] Defined as university of applied sciences or higher. [b] Cardiovascular comorbidity included all arrhythmias, structural heart diseases, 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 one or two or unspecified diabetes. [c] GFI score of ≥4 points. Missing data <1% is not shown, if more than 1% is missing, the percentages are added as footnote. [1]missing N=52 (5%), [2]missing N=95 (9%), [3]missing baseline N=78 (8%), missing end-of-season N=114 (11%), missing either N=180 (17%) [4]missing N=62.

Table 4. Clinical symptoms of respiratory episodes

Patient reported symptoms [a]	RSV-ARTI episodes N= 36	Influenza-ARTI episodes N= 57	Other ARTI Episodes [b] 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%)**
Dyspnea	24 (67%)	42 (74%)	309 (47%)*
Fever (measured ≥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 [c]			
Fever (measured ≥38°C)	2 (6%)	9 (16%)	13 (2%)
Respiratory rate >20/min	6 (17%)	8 (14%)	63 (10%)
Saturation SpO_2 < 95%	5 (14%)	10 (18%)	39 (6%)

Numbers represent respiratory episodes unless stated otherwise. Abbreviations: ARTI = acute respiratory tract infection. Statistical significance compared to RSV-ARTI is indicated by the asterisks: *P<0.05 **P<0.01 ***P<0.001 (not indicated if non-significant). [a] At least once during the respiratory infection based on the symptom diary [b] RSV and influenza negative infections based on PCR. [c] Measured by the study team.

Table 5. Severity of PCR-confirmed ARTI episodes

	RSV-ARTI episodes N= 36	Influenza-ARTI episodes N= 60	Other ARTI episodes N= 690[a]
Median duration of symptoms [IQR]	19 [13-27]	18 [14- 22]	12 [8-21]**
Unresolved illness[b]	8 (22%)	9 (16%)	105 (17%)
Medication[c]	10 (28%)	26 (44%)	99 (15%)
Respiratory medication	9 (25%)	13 (22%)	68 (10%)*
Antibiotics	2 (6%)	18 (31%)**	49 (7%)
Antivirals	0 (0%)	2 (3%)	0 (0%)
Corticosteroids	0 (0%)	2 (3%)	9 (1%)
Medical attendance	11 (31%)	36 (60%)**	138 (20%)
Hospitalization	0 (0%)	1 (2%)	3 (0.4%)
Emergency department	0 (0%)	0 (0%)	1 (0.2%)
General practitioner visit	10 (28%)	32 (55%)*	122 (18%)
Telephone call to doctor	2 (6%)	3 (5%)	7 (1%)
LRTI[d]	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%)

Abbreviations: IQR=interquartile range; LRTI = Lower respiratory tract infection. Statistical significance compared to RSV-ARTI is indicated by the asterisks: *p-value<0.05 **p<0.01 ***p<0.001 (not indicated if non-significant). [a] 19 episodes with other infection but positive seroconversion for RSV and 39 missed visits were excluded from this table [b] Illness that persisted beyond the 28 diary days. [c] Enhanced use or newly prescribed inhaled respiratory medication, antibiotics, antivirals or corticosteroids. [d] clinically diagnosed or radiologically confirmed pneumonia.