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Respiratory syncytial virus and influenza virus infection in adult primary care patients: Association of age with prevalence, diagnostic features and illness course



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ARTICLE INFO

Article history:

Received 8 December 2019

Received in revised form 6 April 2020

Accepted 7 April 2020

Keywords:

Respiratory syncytial virus

Influenza virus

Primary care

Acute cough

ABSTRACT

Objectives: To better target new vaccines and treatments being developed for respiratory syncytial virus (RSV) and influenza virus (influenza), we studied the association of age with prevalence, diagnostic features and course of illness of these infections in primary care patients.

Methods: Secondary analysis of observational data on the aetiology, diagnosis and prognosis in adults presenting to primary care with acute cough in 12 European countries (2007–2010) using regression analyses corrected for clustering of patients within countries. Age groups were 18–59 years, 60–74 years, and 75 years and older (75+).

Results: Nasopharyngeal swabs for 144 (4.6%), 169 (5.4%) and 104 (3.4%) out of 3104 patients were polymerase chain reaction (PCR) positive for RSV, influenza A and influenza B, respectively. RSV prevalence in patients 75+ (8.5%) was twice the prevalence in those under 60 years (4.2%). Influenza prevalence was not associated with age. Diagnostic features for these viruses were not associated with age. Symptom duration was associated with age for RSV and influenza B, but not for influenza A. The odds of unresolved symptoms after 28 days were associated with age for RSV only. Illness deterioration was associated with age for RSV, with patients 75+ at increased risk, but not for influenza.

Conclusion: In adults presenting to primary care with acute cough, the diagnostic features of RSV or influenza infection are not associated with age. For RSV both the prevalence and illness course are significantly worse at higher age, for influenza only the illness course is.

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1. Introduction

Viral respiratory tract infections (RTIs) are a major public health problem due to their ease of transmission, substantial morbidity and wide occurrence. Their higher incidence and severity during

winter months increases the burden of RTIs. Associated pathogens confined to winter months, with often overlapping epidemics, are respiratory syncytial virus (RSV) and influenza virus (influenza) (Eccles, 2002; Griffin et al., 2002; Mourtoukou and Falagas, 2007). Although RTIs in patients presenting to primary care are usually self-limiting, infections in individuals at the extremes of the age spectrum are typically more severe, with prolonged symptoms and an increased risk of complications (Thompson et al., 2003; Falsey et al., 2005; Amand et al., 2018; Belongia et al., 2018). Also in individuals between the ends of the age spectrum (mostly working

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adults), RSV and influenza are considered important pathogens (Hashem and Hall, 2003; Hall et al., 2009).

With new vaccines and treatments under development, identifying phenotypic features and risk groups that can be targeted with these potential vaccines and treatments for RSV and influenza is becoming increasingly relevant. A promising example of targeted treatment is the use of different treatment strategies across age groups. However, the association of age with prevalence, diagnostic features and illness course of RSV and influenza infection in adults is not well described. Several international studies reported on the prevalence of RSV among adults with cough in primary care. However, these studies recruited from a single country, mostly the US (Dowell et al., 1996; Hall et al., 2001; O'Shea et al., 2005; Volling et al., 2014). Epidemiological studies suggested that the illness course of RSV approaches that of influenza, with the elderly at higher risk of serious illness (Haber, 2018). Despite the increase in awareness of a possible association with age, our understanding of the illness course of RSV and influenza across different age groups is poor. Therefore, we set out to assess the association of age with prevalence, diagnostic features and illness course of RSV and influenza infection in adults presenting to primary care with acute cough.

2. Methods

2.1. Data

The data used in this study were part of the prospective GRACE (Genomics to combat Resistance against Antimicrobials in Community-acquired lower respiratory tract infection (LRTI) in Europe; www.grace-lrti.org) study. A detailed description of the original study can be found elsewhere (Ieven et al., 2018). In summary, general practitioners (GPs) from 16 primary care research networks included 3104 adults that consulted with acute cough for the first time between October 2007 and April 2010. Primary care research networks were located in 12 European countries (Belgium, England, France, Germany, Italy, the Netherlands, Poland, Spain, Slovakia, Slovenia, Sweden and Wales). Exclusion criteria were pregnancy, consumption of antibiotics in the previous month and any condition associated with immunodeficiency. For this secondary analysis, patients without aetiology results were excluded.

GPs reported the patient's symptoms and comorbidities in a case report form on the day of consultation. For each patient, two nasopharyngeal swabs (NPS) were taken, which were transported to the central lab at the Antwerp University Hospital (Belgium). Presence of bacterial pathogens (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Bordetella pertussis* and *Legionella pneumoniae*) and viral pathogens (RSV and influenza, but also rhinovirus, coronavirus, metapneumovirus, parainfluenza, adenovirus, polyomavirus and bocavirus) was assessed using bacterial cultures, serology and/or in-house polymerase chain reactions (PCRs) as described before (Ieven et al., 2018). The presence of pneumonia was assessed in all patients using chest radiography (van Vugt et al., 2013).

In addition, patients filled out a symptom diary each day until their symptoms cleared, up to a maximum of 28 days. Among other features, they rated the severity of cough, shortness of breath, wheezing, runny nose, chest pain, fever, disturbed sleep and interference with normal activities or work. Each symptom received a daily score from 0 (indicating no problem) to 6 (indicating that the problem is as bad as it could be). A review of their primary care medical records was performed to extract information on re-consultation with new or worsened symptoms or admission to hospital within four weeks of the initial consultation.

2.2. Analysis

We assessed the association of age with prevalence, diagnostic features and illness course of RSV and influenza infection. The data were categorized in three age groups: 18–59 years, 60–74 years and 75 years and older. Prevalence of RSV and influenza was defined as the number of positive cases out of the total number of patients with available PCR results for RSV and influenza, respectively. For the country-specific prevalence, England and Wales were combined into 'UK'. Because patients were clustered within countries, virus-specific association of age with prevalence was assessed using a hierarchical generalized linear model (HGLM) (Verbeke and Molenberghs, 2009). A Tukey multiple comparisons correction was used to compare prevalence between age groups (Tukey, 1991).

Diagnosis of RSV and influenza infection was defined as a PCR positive NPS result for the respective virus. Virus-specific association of age with diagnostic features, i.e. patient characteristics, presenting symptoms and additional test results, was evaluated using an HGLM. Included patient characteristics were gender (male/female), current smoker (yes/no), history of pulmonary comorbidities (asthma and/or chronic obstructive pulmonary disease and/or other chronic lung disease; yes/no) and history of cardiac comorbidities (heart failure and/or ischemic heart disease and/or other heart disease; yes/no). Selected symptoms related to RSV or influenza infection were runny nose (yes/no), fever (yes/no), wheeze (yes/no) and interference with normal activities or work (yes/no). In addition, virus-specific association of age with the presence of pneumonia on a chest radiograph (yes/no), and detection of bacteria (yes/no) and viruses (yes/no) on an NPS was assessed.

Virus-specific association of age with the illness course of RSV and influenza was examined after exclusion of patients that did not return their diary and was defined using three outcomes: duration of symptoms, unresolved symptoms at day 28 and illness deterioration defined as either re-consultation with new or worsened complaints or admission to a hospital. Included symptoms were cough, shortness of breath, wheeze, runny nose, chest pain, fever, disturbed sleep and interference with normal activities or work. Duration of symptoms was defined as the number of days until the patients rated their symptoms as 'no problem' (score = 0). For each symptom, virus-specific association of age with duration of the symptom was studied using an accelerated failure time model with Weibull distributed error terms that accounts for clustering of patients within countries. Patients who were still experiencing symptoms at day 28 were labelled as patients with unresolved symptoms. The odds of unresolved symptoms was compared using a Firth-adjusted HGLM for each symptom (Firth, 1993). The odds of illness deterioration were compared using an additional Firth-adjusted HGLM.

Due to data sparseness, the analyses were adjusted for significant covariates only (univariate p -value <0.10). Covariates that were considered include gender (male/female), history of pulmonary comorbidities (yes/no), history of cardiac comorbidities (yes/no), current smoker (yes/no), received influenza vaccination (yes/no), number of days coughing before consultation, detection of bacteria (yes/no) and detection of viruses other than the studied virus (yes/no). The average symptom severity (as assessed by the GP at consultation) was considered as an additional covariate in the analyses of illness course.

3. Results

3.1. Prevalence of illness

A total of 3104 patients were included in the original study. Patients that did not have a PCR result available (90/3104) were

excluded from this secondary analysis. In this patient subset, 144 patients (4.8%) tested positive for RSV and 307 patients (10.2%) tested positive for influenza (169 influenza A, 104 influenza B, 34 type not determined). Six patients tested positive for both viruses (0.2% of analysed samples; 3 influenza A, 2 influenza B, 1 type not determined). Other baseline characteristics are reported in Table 1.

The prevalence of RSV infection differed between the three age groups under study ($p=0.0255$): 84 out of 1999 patients aged 18–59 years (4.2%), 41 out of 791 patients aged 60–74 years (5.2%) and 19 out of 224 patients aged 75 years and older (8.5%) tested positive. Patients aged 75 years and older were significantly more likely to test positive for RSV when compared to those aged 18–59 years (odds ratio (OR): 2.11, 95% confidence interval (CI): [1.14–3.91]). After accounting for significant covariates, the prevalence of RSV remained associated with age ($p=0.0264$, OR: 2.27, 95% CI: [1.12–4.64]). Odds ratios and 95% confidence intervals are reported in Table 2.

The prevalence of influenza infection also differed between the three age groups ($p<0.0001$): 243 patients aged 18–59 years (12.2%: 136 influenza A, 82 influenza B, 25 type not determined), 52 patients aged 60–74 years (6.6%: 28 influenza A, 17 influenza B, 7 type not determined) and 12 patients aged 75 years and older (5.4%: 5 influenza A, 5 influenza B, 2 type not determined) tested positive. The patients aged 60 years and older were significantly less likely to test positive for influenza A when compared to patients aged 18–59 years (OR: 0.51, 95% CI: [0.31–0.83] for 60–74 years and OR: 0.33, 95% CI: [0.11–0.95] for 75 years and older). Patients aged 60–74 years were significantly less likely to test positive for influenza B when compared to patients aged 18–59 years (OR: 0.53, 95% CI: [0.28–0.99]). After accounting for significant covariates, the odds of influenza were not associated with age anymore ($p=0.2179$ for influenza A and $p=0.7330$ for influenza B). Odds ratios and 95% confidence intervals are reported in Table 2.

3.2. Diagnostic value of patient characteristics

The odds of RSV was significantly lower when the patient was a current smoker (OR: 0.66, 95% CI: [0.44–0.99]). After accounting for significant covariates, the odds of RSV was no longer associated with smoking status ($p=0.3534$; Table 3).

The odds of influenza A was significantly lower when the patient was a current smoker (OR: 0.68, 95% CI: [0.47–0.99] or had a history of cardiac comorbidities (OR: 0.41, 95% CI: [0.19–0.87]). The odds of influenza B was significantly lower when the patient had a history of pulmonary comorbidities (OR: 0.48, 95% CI: [0.24–0.95]). After accounting for significant covariates, the odds of Influenza was no longer associated with a history of pulmonary ($p=0.1026$) or cardiac ($p=0.2798$) comorbidities (Table 3). The association between the odds of influenza A and smoking status

remained significant (OR: 0.60, 95% CI: [0.40–0.89]). However, this association was not associated with age ($p=0.0799$).

3.3. Diagnostic value of presenting symptoms

The odds of RSV was significantly higher when the patient presented with a runny nose (OR: 1.95, 95% CI: [1.25–3.02]). After accounting for significant covariates, the association between the odds of RSV and the presence of a runny nose remained significant (OR: 2.42, 95% CI: [1.54–3.78]; Table 3). However, this association was not associated with age ($p=0.2508$).

The odds of influenza A was significantly higher when the patient presented with fever (OR: 4.79, 95% CI: [3.41–6.74]) or interference with normal activities or work (OR: 2.03, 95% CI: [1.40–2.94]). The odds of influenza B was significantly higher when the patient presented with fever (OR: 4.17, 95% CI: [2.74–6.35]), without wheezing (OR: 1.76, 95% CI: [1.13–2.74]) or with interference with normal activities or work (OR: 3.18, 95% CI: [1.87–5.40]). After accounting for significant covariates, the association with presenting with fever (OR: 4.23, 95% CI: [2.95–6.07] for influenza A, OR: 3.71, 95% CI: [2.37–5.79] for influenza B) and interference with normal activities or work (OR: 1.65, 95% CI: [1.12–2.44] for influenza A, OR: 2.76, 95% CI: [1.59–4.78] for influenza B) remained significant (Table 3). However, neither the association with fever ($p=0.4816$ for influenza A and $p=0.3638$ for influenza B) nor the association with interference with normal activities or work ($p=0.7193$ for influenza A and $p=0.0732$ for influenza B) was associated with age.

3.4. Diagnostic value of additional testing

The odds of both RSV and influenza were significantly lower when another virus was detected (OR: 0.23, 95% CI: [0.14–0.35] for RSV, OR: 0.23, 95% CI: [0.15–0.35] for influenza A and OR: 0.16, 95% CI: [0.09–0.28] for influenza B). After accounting for significant covariates, the association between the odds of both RSV and influenza and the presence of another virus remained significant (OR: 0.18, 95% CI: [0.12–0.29] for RSV, OR: 0.17, 95% CI: [0.11–0.26] for influenza A and OR: 0.10, 95% CI: [0.06–0.19] for influenza B; Table 3). However, these associations were not associated with age ($p=0.3087$, $p=0.9828$ and $p=0.6462$, respectively).

3.5. Illness course: duration of symptoms

Out of the patients that tested positive for RSV, 123 (85.4%) completed their diary. Among patients that tested positive for influenza A or B, 138 (82.6%) and 89 (86.4%), respectively, completed their diary. Four patients that returned their diary tested positive for both RSV and influenza (two influenza A and two influenza B).

Table 1
Baseline characteristics for adult acute cough patients in primary care.

	All adults (N = 3104) – N (%)	18–59 years (N = 1999) – N (%)	60–74 years (N = 791) – N (%)	75 years and older (N = 224) – N (%)
Gender: male	1215 (40.3)	760 (38.0)	344 (43.5)	111 (49.6)
History of pulmonary comorbidities ^a	514 (17.1)	301 (15.1)	156 (19.7)	57 (25.4)
History of cardiac comorbidities ^b	277 (9.2)	75 (3.8)	127 (16.1)	75 (33.5)
Received influenza vaccination	720 (23.9)	229 (11.5)	338 (42.8)	153 (68.3)
Current smoker	845 (28.1)	696 (34.9)	139 (17.6)	10 (4.5)
Bacteria detected	652 (21.6)	429 (21.5)	179 (22.6)	44 (19.6)
Viruses detected	1494 (49.6)	1033 (51.7)	358 (45.3)	103 (46.0)
Days coughing prior to consultation ^c	7 [3–14]	5 [3–10]	7 [4–14]	8 [5–15]

^a Pulmonary comorbidities include asthma, chronic obstructive pulmonary disease and other chronic lung diseases.

^b Cardiac comorbidities include heart failure, ischemic heart disease and other heart diseases.

^c Median and interquartile range are reported here.

Table 2

Association of age with the prevalence of respiratory syncytial virus (RSV) and influenza virus infection among adult acute cough patients in primary care.

	RSV		Influenza A		Influenza B	
	Univariate OR (95% CI)	Multivariate OR (95% CI)	Univariate OR (95% CI)	Multivariate OR (95% CI)	Univariate OR (95% CI)	Multivariate OR (95% CI)
60–74 years versus 18–59 years	1.25 [0.79–1.97]	1.26 [0.76–2.08]	0.51 [0.31–0.83]	0.69 [0.41–1.18]	0.53 [0.28–0.99]	0.82 [0.42–1.60]
75 years and older versus 18–59 years	2.11 [1.14–3.91]	2.27 [1.12–4.64]	0.33 [0.11–0.95]	0.62 [0.20–1.95]	0.57 [0.19–1.67]	1.14 [0.35–3.73]
75 years and older versus 60–74 years	1.70 [0.87–3.32]	1.81 [0.89–3.66]	0.64 [0.21–2.00]	0.89 [0.28–2.90]	1.07 [0.33–3.51]	1.39 [0.40–4.83]
Gender: male	0.86 [0.61–1.21]	–	0.88 [0.64–1.21]	–	1.24 [0.83–1.83]	–
History of pulmonary comorbidities ^a	1.24 [0.82–1.88]	–	0.96 [0.63–1.47]	–	0.48 [0.24–0.95]	0.55 [0.27–1.13]
History of cardiac comorbidities ^b	1.34 [0.80–2.26]	–	0.41 [0.19–0.87]	0.64 [0.29–1.44]	0.80 [0.39–1.66]	–
Received influenza vaccination	1.38 [0.95–1.99]	0.98 [0.64–1.51]	0.42 [0.26–0.68]	0.52 [0.31–0.87]	0.46 [0.26–0.84]	0.52 [0.27–0.99]
Current smoker	0.66 [0.44–0.99]	0.82 [0.53–1.25]	0.68 [0.47–0.99]	0.60 [0.40–0.89]	0.88 [0.56–1.38]	–
Bacteria detected	0.91 [0.60–1.38]	–	1.07 [0.74–1.55]	–	1.37 [0.88–2.13]	–
Other viruses detected	0.23 [0.14–0.35]	0.19 [0.12–0.29]	0.23 [0.15–0.35]	0.17 [0.11–0.26]	0.16 [0.09–0.28]	0.10 [0.06–0.19]
Days coughing prior to consultation	0.95 [0.92–0.98]	0.92 [0.89–0.95]	0.90 [0.86–0.93]	0.87 [0.84–0.91]	0.84 [0.79–0.89]	0.80 [0.75–0.86]

OR: odds ratio; CI: (Wald) confidence interval; –: covariate was not included in the multivariate analysis because of insignificant *p*-value (*p* < 0.10) in the univariate analysis. Numbers printed in bold indicate significance in the multivariate model (*p* < 0.05).

^a Pulmonary comorbidities include asthma, chronic obstructive pulmonary disease and other chronic lung diseases.

^b Cardiac comorbidities include heart failure, ischemic heart disease and other heart diseases.

Table 3

Diagnostic value of patient characteristics, presenting symptoms and additional testing in adult acute cough patients in primary care that tested positive for respiratory syncytial virus (RSV) or influenza virus.

	RSV – adjusted OR (95% CI)	Influenza A – adjusted OR (95% CI)	Influenza B – adjusted OR (95% CI)
Gender: male	0.78 [0.54–1.12]	0.96 [0.68–1.34]	1.28 [0.85–1.94]
Current smoker	0.82 [0.53–1.25]	0.60 [0.40–0.89]	0.80 [0.50–1.30]
History of pulmonary comorbidities ^a	1.14 [0.73–1.78]	1.16 [0.74–1.82]	0.55 [0.27–1.13]
History of cardiac comorbidities ^b	0.94 [0.52–1.71]	0.64 [0.29–1.44]	1.24 [0.55–2.78]
Presence of runny nose	2.42 [1.54–3.78]	1.36 [0.93–1.98]	1.35 [0.85–2.16]
Presence of fever	0.93 [0.64–1.36]	4.23 [2.95–6.07]	3.71 [2.37–5.79]
Presence of wheezing	1.24 [0.87–1.75]	1.21 [0.85–1.73]	0.72 [0.44–1.16]
Interference with normal activities or work	1.10 [0.76–1.58]	1.65 [1.12–2.44]	2.76 [1.59–4.78]
Pneumonia detected	0.50 [0.18–1.39]	0.85 [0.38–1.91]	0.34 [0.08–1.42]
Bacteria detected	0.89 [0.58–1.37]	1.05 [0.71–1.56]	1.36 [0.85–2.16]
Other viruses detected	0.18 [0.12–0.29]	0.17 [0.11–0.26]	0.10 [0.06–0.19]

OR: odds ratio; CI: (Wald) confidence interval; numbers printed in bold indicate significance: models accounted for significant covariates (influenza vaccination, smoking status, days coughing prior to consultation and presence of other viruses for RSV; history of cardiac comorbidities, influenza vaccination, smoking status, days coughing prior to consultation and presence of other viruses for influenza A; history of pulmonary comorbidities, influenza vaccination, days coughing prior to consultation and presence of other viruses for influenza B).

^a Pulmonary comorbidities include asthma, chronic obstructive pulmonary disease and other chronic lung diseases.

^b Cardiac comorbidities include heart failure, ischemic heart disease and other heart diseases.

For RSV, the time until resolution of symptoms was associated with age: the median time until the patient no longer experienced shortness of breath was 70.9% (95% CI: [6.9%–173%]) longer in the patients aged 75 years and older when compared to patients aged 18–59 years. Also, the median time until the patient no longer

experienced a runny nose was 52.2% (95% CI: [9.5%–143.5%]) longer in patients aged 60–74 years when compared to patients aged 18–59 years.

For influenza A, the time until resolution of symptoms was not associated with age (Table 4). For influenza B, the time until

Table 4

Duration of symptoms after the initial consultation (days) in adult acute cough patients that tested positive for respiratory syncytial virus (RSV) or influenza virus in primary care.

	N (%)	RSV – median [IQR]			N (%)	Influenza A – median [IQR]			N (%)	Influenza B – median [IQR]		
		18–59 years	60–74 years	75 years and older		18–59 years	60–74 years	75 years and older		18–59 years	60–74 years	75 years and older
Cough	121 (98.4)	12 [7–16]	14 [9–19]	14 [9–20]	137 (99.3)	11 [7–19]	13 [10–23]	15 [12–19]	86 (96.6)	11 [7–15]	16 [8–28]	12 [10–15]
Shortness of breath	88 (71.5)	7 [5–16]	9 [5–14]	11 [8–17]	95 (68.8)	7 [5–12]	11 [7–19]	7 [5–18]	53 (59.6)	6 [4–8]	7 [5–12]	11 [7–12]
Wheeze	64 (52.0)	8 [4–13]	7 [3–10]	9 [6–11]	73 (52.9)	7 [4–9]	10 [10–13]	9 [8–10]	37 (41.6)	5 [4–8]	8 [4–15]	8 [6–9]
Runny nose	106 (86.2)	8 [5–14]	9 [6–20]	7 [7–19]	117 (84.8)	7 [5–12]	8 [6–12]	7 [6–14]	74 (83.1)	7 [4–13]	11 [9–14]	12 [12–13]
Chest pain	58 (47.2)	7 [4–12]	6 [4–15]	7 [5–12]	86 (62.3)	6 [4–8]	5 [5–8]	8 [7–9]	50 (56.2)	5 [4–7]	6 [5–7]	4 [4–4]
Fever	34 (27.6)	5 [3–8]	4 [3–6]	3 [3–4]	77 (55.8)	4 [3–5]	4 [3–5]	2 [2–2]	51 (57.3)	4 [3–6]	6 [5–7]	9 [9–9]
Disturbed sleep	87 (70.7)	7 [4–10]	7 [4–10]	7 [5–11]	102 (73.9)	7 [4–9]	7 [3–10]	8 [7–8]	61 (68.5)	6 [3–8]	9 [3–16]	11 [8–13]
Interference with normal activities or work	89 (72.4)	7 [5–11]	9 [6–14]	8 [7–12]	116 (84.1)	7 [5–10]	8 [6–15]	8 [7–9]	76 (85.4)	7 [5–9]	8 [4–12]	5 [4–6]

N: number of patients; IQR: interquartile range. Numbers printed in italic indicate that significance testing was not conducted because at least one of the age groups contained no variation (i.e. all patients have the same resolution time). Number printed in bold indicate significance: models accounted for significant covariates (days coughing prior to consultation, smoking status, presence of a bacteria, presence of other viruses and average symptom severity at consultation for RSV; gender, history of cardiac comorbidities, influenza vaccination, days coughing prior to consultation, presence of a bacteria, presence of other viruses and average symptom severity at consultation for influenza A; gender, history of pulmonary comorbidities, history of cardiac comorbidities, smoking status, influenza vaccination, days coughing prior to consultation, presence of other viruses and average symptom severity at consultation for influenza B).

Table 5
Unresolved symptoms after 28 days in adult acute cough patients that tested positive for respiratory syncytial virus (RSV) or influenza virus in primary care.

	RSV – adjusted OR (95% CI)		Influenza A – adjusted OR (95% CI)		Influenza B – adjusted OR (95% CI)	
	60–74 years and older versus 18–59 years	75 years and older versus 60–74 years	60–74 years and older versus 18–59 years	75 years and older versus 60–74 years	60–74 years and older versus 18–59 years	75 years and older versus 60–74 years
Cough	1.72 [0.66–3.54]	0.99 [0.27–2.06]	1.41 [0.59–2.52]	2.38 [0.58–11.74]	1.69 [0.39–8.36]	8 (9.3)
Shortness of breath	2.34 [1.04–4.30]	1.24 [0.45–2.84]	1.73 [0.95–4.04]	4.49 [0.97–29.68]	2.59 [0.39–13.34]	0 (0.0)
Wheeze	1.79 [0.76–3.76]	1.00 [0.35–3.24]	1.80 [0.89–4.16]	60–74: 1/13	75+0/2	1 (2.7)
Runny nose	2.44 [1.09–4.49]	1.84 [0.63–4.74]	1.85 [0.94–3.94]	60–74: 0/20	75+0/3	4 (5.4)
Chest pain	1.31 [0.66–2.76]	1.73 [0.76–3.89]	NA	NA	NA	0 (0.0)
Fever	NA	NA	NA	NA	NA	0 (0.0)
Disturbed sleep	1.85 [0.76–3.89]	75+0/12	1.85 [0.94–3.94]	60–74: 2/21	75+0/2	1 (1.6)
Interference with normal activities or work	2.56 [1.08–5.39]	1.66 [0.67–3.12]	1.85 [0.94–3.94]	60–74: 3/20	75+0/3	0 (0.0)
Illness deterioration	1.08 [0.49–1.64]	1.82 [0.98–5.64]	1.16 [0.53–2.86]	3.13 [0.59–16.81]	2.71 [0.42–18.85]	17 (19.5)

OR: odds ratio; CI: (bootstrap-based) confidence interval; numbers printed in italic report number of events/number of patients instead of odds ratios which indicates that significance testing was not conducted because at least one of the age groups contained no variation (i.e. no patients with unresolved symptoms). Numbers printed in bold indicate significance; models accounted for significant covariates (smoking status and presence of other viruses for RSV; days coughing prior to consultation and presence of other viruses for influenza A; presence of other viruses for influenza B).

resolution of symptoms was associated with age: the median time until the patient no longer experienced cough was 72.9% (95% CI: [20.7%–147.8%]) longer in patients aged 60–74 when compared to patients aged 18–59 years (Table 4).

3.6. Illness course: unresolved symptoms after 28 days

For RSV, the odds of unresolved shortness of breath was significantly higher in patients aged 60–74 years (OR: 2.34, 95% CI: [1.04–4.30]) and patients aged 75 years and older (OR: 2.90, 95% CI: [1.31–6.44]) when compared to patients aged 18–59 years (Table 5). Also the odds of an unresolved runny nose (OR: 2.44, 95% CI: [1.09–4.49]) and interference with normal activities or work (OR: 2.56, 95% CI: [1.08–5.39]) was significantly higher in patients aged 60–74 years when compared to patients aged 18–59 years. For influenza A, the odds of unresolved symptoms was not associated with age. Data were too sparse to draw conclusions for the association between age and the odds of unresolved symptoms for influenza B.

3.7. Illness course: illness deterioration

For RSV, 22.1% ($N=27$) experienced illness deterioration, which was defined as re-consultation with new or worsened complaints ($N=27$) or admission to hospital ($N=1$) within 28 days of the initial consultation. Patients aged 75 years and older were at increased risk of illness deterioration when compared to patients aged 18–59 years (OR: 1.98, 95% CI: [1.04–4.64]). For influenza A, 17.4% ($N=22$) experienced illness deterioration (re-consultation with new or worsened complaints). For influenza B, 19.5% ($N=17$) experienced illness deterioration (re-consultation with new or worsened complaints ($N=16$) or admission to hospital ($N=1$)). The odds of illness deterioration for influenza was not associated with age.

4. Discussion

We demonstrated that the prevalence of RSV was associated with age, while the prevalence of influenza was not. The diagnostic features of neither RSV nor influenza were associated with age. However, whenever another virus was detected, presence of RSV or influenza was less likely. The duration of symptoms of RSV and influenza B, but not influenza A, was associated with age. Symptom resolution after 28 days and illness deterioration were both associated with age for RSV, but not for influenza.

The prevalence of RSV among patients aged 18–59 years (4.2%) was low when compared to the prevalence reported by Hall et al. when focussing on symptomatic cases (6%). However, while we focused on adults presenting to primary care with acute respiratory infection (ARI)-like complaints, Hall et al. sampled individuals that were included in their study weekly, with RSV positive individuals eligible who would not usually consult their GP (Hall et al., 2001). The prevalence of influenza among patients aged 18–59 years (12.2%) was close to the prevalence reported by Chlibek et al. (11.5%).

The prevalence of RSV among patients aged 60 years and older (5.9%) was high when compared to the prevalence reported by Nicholson et al. (3.4% of illness episodes). Also the prevalence of influenza among patients aged 60 years and older (6.3%) was high when compared to the prevalence reported by Nicholson et al. (4.4% of illness episodes). However, while we included adults with acute cough or other signs of LRTI, Nicholson et al. also included patients with symptoms such as earache, face ache and gritty eyes, which are less common in RSV or influenza infection (Nicholson et al., 1997). Falsey et al. reported a higher prevalence of RSV (8.9% of illness cases) and influenza (6.0% of illness cases). This is not unexpected, as Falsey et al. contacted participating individuals weekly, hence also including RSV and influenza positive patients

that might not have visited their GP on their own initiative. While the influenza prevalence reported by Falsey et al. approaches ours, the prevalence of RSV is dissimilar, suggesting that influenza positive patients are more likely to consult their GP compared to RSV positive patients, a finding which is corroborated by the importance of interference with normal activities of work in influenza but not RSV (Table 3). In addition to health care system accessibility characteristics, any in-depth cross-country comparison of influenza prevalence would need to carefully consider differences arising from different intensities of included influenza seasons, different vaccine efficacies for these seasons and different vaccination coverage rates by age.

The most recent estimates for patients aged 60 years and older we could find in the current literature are those reported by Belongia et al. Both for RSV (10.8%) and for influenza (23.0%), their reported prevalence was higher than the prevalence we reported. However, even though both studies focused on patients presenting with ARI-like complaints, we included only outpatients while Belongia et al. included both in- and outpatients, making a direct comparison invalid (Belongia et al., 2018).

Diagnosing RSV or influenza was significantly less likely when another virus was detected. This corresponds with findings by other authors. Shinjoh et al. showed that the growth of RSV is blocked by coinfection with influenza *in vitro* (Shinjoh et al., 2000). Also *in vivo*, RSV epidemics have been known to be interrupted by influenza epidemics (Anestad, 1982, 1987; Nishimura et al., 2005). Other interferences have also been observed, e.g. RSV can reduce infections with rhinovirus, rhinovirus can reduce infections with adenovirus, parainfluenza and influenza, . . . (Greer et al., 2009; Casalegno et al., 2010; Achten et al., 2017).

4.1. Strengths and limitations

To our knowledge, this is the first large European study assessing the association of age with prevalence, diagnostic features and illness course of RSV and influenza in adults presenting to primary care with acute cough. Strengths of this study include the participation of adults from different age groups across 12 European countries. A limitation is that only adults with acute cough or adults suspected of an LRTI that presented to primary care were included in the study.

4.2. Implications for practice and research

While the diagnostic features of both RSV and influenza are not associated with the patient's age, the prevalence of RSV and the illness course of both viruses are, making it reasonable to believe that these viruses hit the elderly harder. For this reason, GPs should take age into account when following up their patients, and further research on the management of RSV or influenza infections should at least distinguish between patients under and over 60 years of age.

Funding

RB is funded as a postdoctoral researcher by the Research Foundation – Flanders (FWO). SC, CB, NH, PB and HG are members of the Respiratory Syncytial Virus Consortium in Europe (RESCUE). RESCUE has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement no. 116019. NH acknowledges support from the University of Antwerp scientific chair in Evidence-Based Vaccinology, financed in 2009–2020 by a gift from Pfizer and in 2016–2019 from GSK.

The GRACE project was funded by the European Community's Sixth Framework Programme (grant agreement 518226). Work in the UK was also supported by the National Institute for Health

Research. Work in Barcelona was also supported by 2009 SGR 911 Ciber de Enfermedades Respiratorias (Ciberes CB06/06/0028). Work in Belgium was also supported by the Methusalem financing programme of the Flemish Government and by FWO (G.0274.08N). This work was also supported through the European Science Foundation (ESF), in the framework of the Research Networking Programme TRACE (www.esf.org/trace).

Conflict of interest

None declared.

Acknowledgements

We thank all the clinicians and patients who consented to be part of GRACE, without whom this study would not have been possible. We are grateful to key members of the GRACE project group whose hard work has made this study possible, including Niels Adriaenssens, Jordi Almirall, Curt Brugman, Slawomir Chlabicz, An De Sutter, Mel Davies, Maciek Godycki-Cwirko, Patricia Fernandez, Iris Hering, Kerenza Hood, Greet Ieven, Tom Schaberg, Antoni Torres, Anna Kowalczyk, Christine Lammens, Marieke Lemiengre, Frank Leus, Katherine Loens, Artur Mierzecki, Michael Moore, Magdalena Muras, Gilly O'Reilly, Nuria Sanchez Romano, Matteu Serra Prat, Jackie Swain, Robert Veen, and Tricia Worby.

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