In-hospital and midterm post-discharge complications of adults hospitalised with respiratory syncytial virus infection in France, 2017–2019: an observational study

Alexandre Descamps[1], Nezha Lenzi[2], Florence Galtier[2,3], Fabrice Lainé[2,4], Zineb Lesieur[2], Philippe Vanhems[2,5,6], Sélilah Amour[5,6], Anne-Sophie L'Honneur[7], Nadhira Fidouh[8], Vincent Foulongne[9], Gisèle Lagathu[10], Xavier Duval[2,11,12], Corinne Merle[13], Bruno Lina[14], Fabrice Carrat[15], Odile Launay[1,2,17] and Paul Loubet[2,16,17], on behalf of the FLUVAC study group

[1]Université de Paris, Inserm CIC 1417, Assistance Publique Hôpitaux de Paris, Hôpital Cochin, CIC Cochin Pasteur, Paris, France. [2]Inserm, F-CRIN, Innovative Clinical Research Network in Vaccinology (I-REIVAC), Paris, France. [3]Inserm CIC 1411, Montpellier University Hospital, Montpellier, France. [4]Inserm CIC 1414, CHU Rennes, Rennes, France. [5]Service Hygiène, Epidémiologie, Infectiovigilance et Prévention, Centre Hospitalier Edouard Herriot, Hospices Civils de Lyon, Lyon, France. [6]CIRI, Centre International de Recherche en Infectiologie (Equipe Laboratoire des Pathogènes Emergents), Université Lyon, Inserm, U1111, Université Claude Bernard Lyon 1, CNRS, UMR5308, Lyon, France. [7]Service de Virologie, Hôpital Cochin, Paris, France. [8]Laboratoire de Virologie, Hôpital Bichat, Paris, France. [9]Service de Virologie, CHU Montpellier, Hôpital Saint Eloi, Montpellier, France. [10]Laboratoire de Virologie, Pôle Micro-organismes, CHU Rennes, Rennes, France. [11]Assistance Publique Hôpitaux de Paris, Hôpital Bichat, Centre d'Investigation Clinique, Inserm CIC 1425, Paris, France. [12]Université de Paris, IAME, Inserm, Paris, France. [13]Infectious Diseases Dept, Montpellier University Hospital, Montpellier, France. [14]Hospices Civils de Lyon, Laboratoire de Virologie, Institut des Agents Infectieux (IAI), Centre National de Référence des Virus Respiratoires France Sud, Hôpital de la Croix-Rousse, Lyon, France. [15]Sorbonne Université, Inserm, Institut Pierre Louis d'Épidémiologie et de Santé Publique (IPLESP), Assistance Publique Hôpitaux de Paris, Hôpital Saint Antoine, Paris, France. [16]VBMI, Inserm U1047, Dept of Infectious and Tropical Disease, CHU Nîmes, Université de Montpellier, Nîmes, France. [17]Last authors contributed equally to this article.

Corresponding author: Paul Loubet (Paul.LOUBET@chu-nimes.fr)

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Respiratory syncytial virus infection in hospitalised adults with influenza-like illness was associated with poor in-hospital and midterm post-discharge outcomes, which may be worse than or similar to those of patients with influenza virus infection https://bit.ly/2VAsMhh

Cite this article as: Descamps A, Lenzi N, Galtier F, *et al*. In-hospital and midterm post-discharge complications of adults hospitalised with respiratory syncytial virus infection in France, 2017–2019: an observational study. *Eur Respir J* 2022; 59: 2100651 [DOI: 10.1183/13993003.00651-2021].

Received: 3 March 2021
Accepted: 6 July 2021

Abstract

Objectives The purpose of this study was to describe the clinical characteristics and in-hospital and post-discharge outcomes of respiratory syncytial virus (RSV) infection among adults hospitalised with influenza-like illness (ILI) and compared against patients admitted for influenza.

Methods Adults hospitalised with ILI were prospectively included from five French university hospitals over two consecutive winter seasons (2017/2018 and 2018/2019). RSV and influenza virus were detected by multiplex reverse transcription PCR on nasopharyngeal swabs. RSV-positive patients were compared to RSV-negative and influenza-positive hospitalised patients. Poisson regression models were used to estimate the adjusted prevalence ratio (aPR) associated with in-hospital and post-discharge outcomes between RSV and influenza infections. The in-hospital outcome was a composite of the occurrence of at least one complication, length of stay ⩾7 days, intensive care unit admission, use of mechanical ventilation and in-hospital death. Post-discharge outcome included 30- and 90-day all-cause mortality and 90-day readmission rates.

Results Overall, 1428 hospitalised adults with ILI were included. RSV was detected in 8% (114 of 1428) and influenza virus in 31% (437 of 1428). Patients hospitalised with RSV were older than those with influenza (mean age 73.0 *versus* 68.8 years, p=0.015) with a higher frequency of chronic respiratory or cardiac disease (52% *versus* 39%, p=0.012, and 52% *versus* 41%, p=0.039, respectively) and longer hospitalisation duration (median stay 8 *versus* 6 days, p<0.001). Anti-influenza therapies were less prescribed among RSV patients than influenza patients (20% *versus* 66%, p<0.001). In-hospital composite

outcome was poorer in RSV patients (aPR 1.5, 95% CI 1.1–2.1) than in those hospitalised with influenza. No difference was observed for the post-discharge composite outcome (aPR 1.1, 95% CI 0.8–1.6).
Conclusion RSV infection results in serious respiratory illness, with worse in-hospital outcomes than influenza and with similar midterm post-discharge outcomes.

Introduction

Before the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, respiratory syncytial virus (RSV) was one of the three most common causes of respiratory illness among older adults, along with influenza and rhinovirus [1]. It is responsible for a significant burden in those with comorbidities, who are at increased risk for serious pulmonary complications and long-term complications of respiratory infections [2–4]. In 2015, an estimated 1.5 million episodes of acute lower respiratory infections, involving 214 000 hospitalisations and up to 14 000 in-hospital deaths, were attributable to RSV in older adults in industrialised countries [5]. RSV was estimated to infect ∼4−10% of high-risk adults and 16% of those hospitalised with acute respiratory illness [6].

Nevertheless, the occurrence of RSV infections in adults is difficult to assess and it remains clinically under-diagnosed [7]. In addition, owing to the cost and lack of specific antiviral drugs, adults hospitalised for acute respiratory illness are often not tested for RSV (or other respiratory viruses), but only for influenza virus. However, the development of more sensitive molecular methods, such as multiplex reverse transcription PCR (RT-PCR), has improved the detection of respiratory viruses and thus provides new epidemiological information [8].

Although data on RSV infection are available in several European countries [9], post-infection outcomes are still poorly studied [10]. Yet understanding of these outcomes, at both community and hospital levels, is critical to increase awareness of the real burden of RSV infections and to justify the need for specific RSV vaccines and drugs [11].

The objectives of this study were to describe the clinical characteristics and the in-hospital and post-discharge outcomes of adult patients hospitalised with RSV and to compare them to those of patients hospitalised with influenza during the same time period.

Methods

Study design and participants

We used data from the FLUVAC study, a prospective, multicentre case–control study of influenza vaccine effectiveness conducted since the 2012/2013 season in five French university hospitals (Cochin Hospital, Paris; Bichat Hospital, Paris; Pontchaillou Hospital, Rennes; University Hospital, Montpellier; Edouard Herriot Hospital, Lyon) [12, 13]. Here, we performed a *post hoc* analysis of laboratory-confirmed RSV and influenza virus infections over two consecutive winter seasons (2017/2018 and 2018/2019) for which follow-up data after hospital discharge were available.

Enrolments took place during periods of influenza and RSV circulation (from late October to mid-April) for the two seasons. All adults hospitalised for at least 24 h for influenza-like illness (ILI) with symptom onset <7 days before swabbing were included in the study. Study staff actively reviewed daily hospital admissions to identify eligible patients according to the following European Centre for Disease Prevention and Control (ECDC) definition for ILI cases: 1) at least one of the systemic symptoms of fever or feverishness, malaise, headache, myalgia or deterioration of general condition (asthenia or loss of weight or anorexia or confusion or dizziness); and 2) at least one of the respiratory symptoms of cough, sore throat or shortness of breath [14]. After informed consent, participants were interviewed, and nasopharyngeal samples obtained at enrolment. Samples were restricted to adults with ILI onset ⩽48 h after admission to exclude nosocomial infections. Patients with contraindications for influenza vaccine or who previously tested positive for any influenza virus in the current season were not enrolled.

Electronic medical records and interviews with patients or families were used to collect socio-demographic and baseline characteristics at admission including chronic underlying conditions, ILI episode presentation and subsequent in-hospital treatments, length of stay and clinical outcomes. The details of the definitions are displayed in supplementary table S1. Patients or their relatives and general practitioners were contacted by phone to collect follow-up data at 1 and 3 months after hospital discharge.

In-hospital and post-discharge outcomes

Two composite outcomes, including hospital utilisation and clinical outcomes, were defined: 1) in-hospital outcome, which was a composite of the occurrence of at least one complication (pneumonia, respiratory

failure, acute respiratory distress syndrome or acute heart failure) or length of stay ⩾7 days or intensive care unit (ICU) admission or use of invasive mechanical ventilation for support or in-hospital death; and 2) post-discharge outcome, which was a composite of 30- and 90-day all-cause mortality or 90-day readmission after discharge.

Respiratory virus identification

RSV, influenza virus and other respiratory viruses (adenovirus; bocavirus 1–4; coronavirus 229E, OC43 and NL63; human metapneumovirus; parainfluenza virus 1–4; and picornavirus) were detected by multiplex RT-PCR in nasopharyngeal swabs using Allplex Respiratory Panels 1, 2 and 3 or an Anyplex II RV 16 detection kit (Seegene, Seoul, South Korea). Any available bronchoalveolar lavage fluid samples or tracheal aspirates were also tested. Samples were tested in the virology laboratory of each participating hospital.

Statistical analysis

We first compared baseline characteristics, clinical presentation and in-hospital and post-discharge outcomes of all adult patients hospitalised with ILI during the two influenza seasons. Adults hospitalised with RSV–influenza co-infections were excluded from the analysis. Univariate analyses were used to compare RSV-positive patients to two different comparison groups: 1) all RSV-negative patients (including influenza-positive patients, patients infected by other respiratory viruses and patients with no respiratory virus detected) and 2) influenza-positive patients. Descriptive data are presented as median (IQR), mean±SD or frequencies with proportions. Pearson's Chi-squared test, Fisher's exact test, t-test or the Wilcoxon rank-sum test were used for univariate comparisons as appropriate. Missing data for each variable were excluded from the denominator.

Multivariable analyses were then conducted using robust Poisson regression with a robust error variance to estimate the prevalence ratio (PR) associated with in-hospital and post-discharge outcomes between RSV-positive and influenza-positive patients after adjustment for selected cofounders of clinical relevance [15]. Covariates in the regression models included age (considered as a binary variable <65 and ⩾65 years), sex, history of seasonal influenza and pneumococcal vaccination, chronic respiratory and cardiac disease, hospitalisation in the previous 12 months, prior corticosteroid medication and any hospital use of anti-influenza therapies or antibiotics. Missing values from covariates included in regression models were imputed with chained equations. Data were assumed to be missing at random. All statistical analyses were performed with Stata/IC v15.0 (StataCorp LP, College Station, TX, USA). A p-value <0.05 was considered statistically significant. PRs are displayed with their 95% confidence intervals.

Ethics

The FLUVAC study (ClinicalTrials.gov NCT02027233) followed Good Epidemiological and Clinical Practices in Clinical Research, and the Declaration of Helsinki, and was approved by the regional ethics committees. During each season, all study participants gave their informed consent for respiratory virus testing.

Results

Study population

Overall, 1428 adults hospitalised with ILI were included in the FLUVAC study: 712 during the 2017/2018 season and 716 during the 2018/2019 season (figure 1). Their mean age was 68 years (range 19–98 years) and 55% were male. Most patients (87%) had at least one underlying condition, mainly chronic respiratory or cardiac disease (47% and 40%, respectively). The proportion with a seasonal influenza vaccination was 52%, and 48% of patients had been hospitalised within the last 12 months.

At least one respiratory virus was detected in 53% of adults hospitalised with ILI symptoms (supplementary table S2). In total, 114 individuals tested positive for RSV (52 and 62 patients for the 2017/2018 and 2018/2019 seasons, respectively), representing 8% of the total population and 15% of those positive for at least one respiratory virus. The most frequently detected virus was influenza (31%, n=437) followed by picornavirus (9%, n=125), RSV (8%, n=114), coronavirus (3%, n=44) and metapneumovirus (3%, n=40). After exclusion of RSV–influenza co-infections (n=6), data for 1422 patients were further analysed (709 and 713 patients for the 2017/2018 and 2018/2019 seasons, respectively).

Characteristics and outcomes of RSV-positive patients

Among patients with laboratory-confirmed RSV infection (n=108 after excluding the six co-infections with influenza virus), 52% were female and their mean age was 73 years (range 30–97 years, table 1). The majority had at least one chronic condition (90%), mostly chronic respiratory (52%) and cardiac (52%)

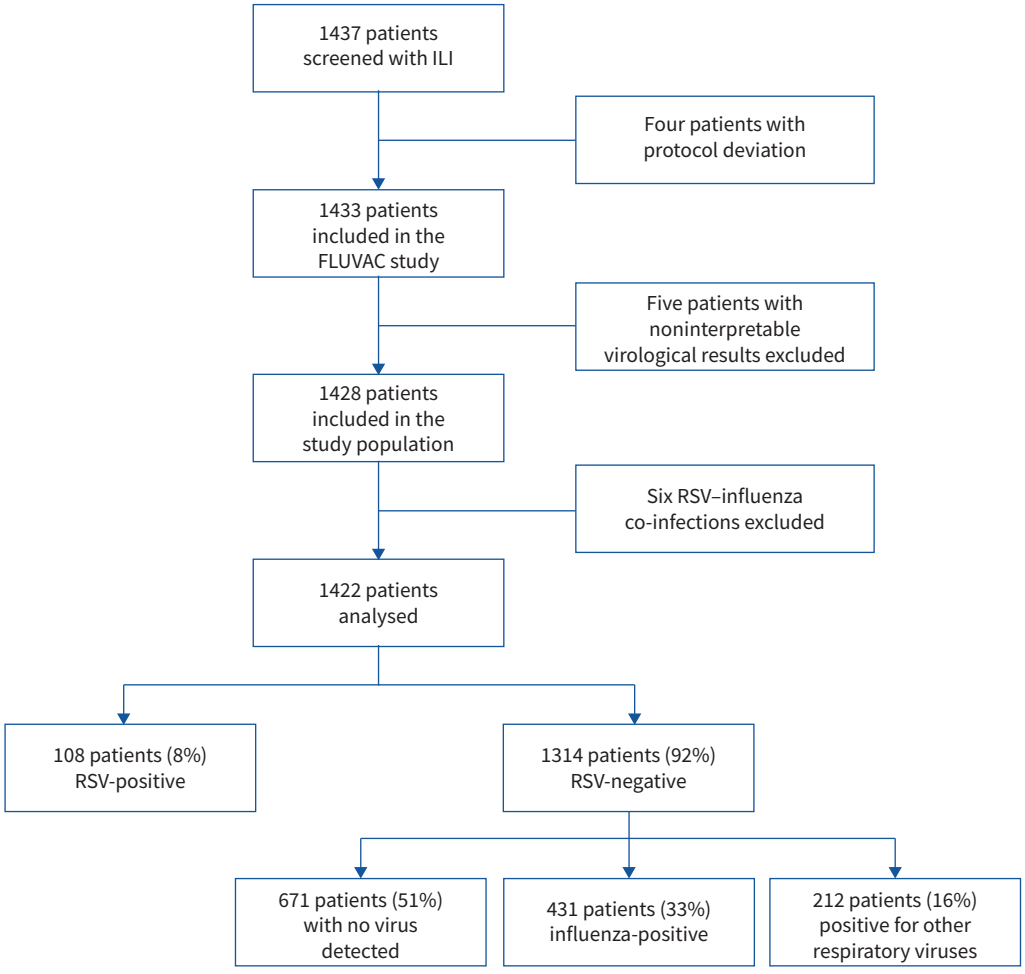

FIGURE 1 FLUVAC study flowchart, winter seasons 2017/2018 and 2018/2019. ILI: influenza-like illness; RSV: respiratory syncytial virus.

diseases, or diabetes mellitus (24%). On admission, RSV-positive patients were more likely to have a chronic cardiac disease than RSV-negative patients (52% *versus* 39%, p=0.008). Patients with RSV had a longer hospital stay than those without (table 2), with a higher median length of stay (8 *versus* 6 days, p=0.005) and a greater frequency of stays ⩾7 days (64% *versus* 49%, p=0.003). During hospitalisation, 58% of patients with RSV had at least one complication, mainly respiratory failure (31%), pneumonia (31%) or heart failure (15%). Among those with a complication, the median length of stay for RSV-positive patients was 9 days (IQR 5–16 days). A total of 26 RSV-positive patients (24%) were admitted to ICU. All-cause mortality during hospitalisation was 3% (table 2), and the cumulative mortality within 30 and 90 days after hospital discharge was 9% and 13%, respectively (table 3).

Comparison of RSV-positive and influenza-positive patients

In univariate analysis, adults hospitalised with RSV were older (mean age 73.0 *versus* 68.8 years, p=0.015), more likely to have a chronic respiratory or cardiac disease (52% *versus* 39%, p=0.012 and 52% *versus* 41%, p=0.039, respectively) and more likely to be vaccinated against seasonal influenza (59% *versus* 48%, p=0.037) compared to those with influenza (table 1). Use of corticosteroids therapy was more prevalent among patients with RSV than those with influenza (20% *versus* 12%, p=0.026 for systemic and 30% *versus* 21%, p=0.048 for inhaled corticosteroids therapy). RSV-positive patients reported significantly more dyspnoea (91% *versus* 71%) but less headache (21% *versus* 35%) and myalgia (18% *versus* 31%) than influenza-positive patients.

In-hospital characteristics and outcomes for patients with RSV and influenza are described in table 2. The median length of stay was greater among RSV-positive than influenza-positive patients (8 days, IQR 5–13 days

TABLE 1 Baseline characteristics and clinical presentation of adults hospitalised with RSV or influenza virus, winter seasons 2017/2018 and 2018/2019 (excluding co-infections)

	RSV-positive	All RSV-negative	p-value[#]	Influenza-positive	p-value[¶]
Subjects, N	108	1314		431	
Baseline characteristics					
Mean±SD age at admission (range), years	73.0±12.9 (30–97)	68.8±17.5 (19–98)	0.016	68.8±16.7 (19–96)	0.015
Male sex	52/108 (48)	734/1314 (56)		243/431 (56)	
Median BMI (IQR), kg·m^{-2}	25.0 (22.2–30.9)	24.6 (21.3–29.0)	0.107	25.0 (21.9–29.5)	0.500
Current smokers	18/108 (17)	270/1305 (21)	0.319	86/429 (20)	0.427
Comorbidity					
At least one	97/108 (90)	1147/1314 (87)	0.446	368/431 (85)	0.231
Chronic respiratory disease	56/108 (52)	610/1314 (46)	0.277	166/431 (39)	0.012
Chronic heart disease	56/108 (52)	509/1313 (39)	0.008	176/431 (41)	0.039
Diabetes mellitus	26/108 (24)	271/1314 (21)	0.397	90/431 (21)	0.470
Chronic renal disease	20/108 (19)	193/1314 (15)	0.284	60/431 (14)	0.229
Cancer (solid tumour and haematological malignancy)	25/107 (23)	228/1313 (18)	0.166	72/431 (17)	0.109
Other immunodeficiency	9/108 (8)	94/1314 (7)	0.649	33/431 (8)	0.815
Cirrhosis	3/108 (3)	72/1314 (5)	0.227	20/431 (5)	0.392
Current season influenza vaccination	63/106 (59)	665/1307 (51)	0.090	206/428 (48)	0.037
Presence of children <5 years old in household	10/108 (9)	86/1313 (7)	0.281	27/430 (6)	0.274
Pre-hospital medication					
Immunosuppressive therapy	10/108 (9)	119/1309 (9)	0.953	34/429 (8)	0.651
Systemic corticosteroids	22/108 (20)	182/1309 (14)	0.066	52/429 (12)	0.026
Inhaled corticosteroids	32/108 (30)	267/1309 (20)	0.024	89/429 (21)	0.048
Hospitalisation in the previous 12 months	46/108 (43)	623/1308 (48)	0.314	180/429 (42)	0.905
Clinical presentation					
Median time from symptom onset to admission (IQR), days	2 (1–4)	2 (1–3)	0.620	2 (1–3)	0.627
Symptoms					
Fever	94/108 (87)	1127/1313 (86)	0.730	381/431 (88)	0.696
Cough	93/108 (86)	1026/1313 (78)	0.052	380/430 (88)	0.519
Dyspnoea	98/108 (91)	1049/1314 (80)	0.006	306/431 (71)	<0.001
Sudden symptom onset	33/105 (31)	416/1293 (32)	0.875	156/426 (37)	0.320
Weakness/malaise	25/105 (24)	286/1306 (22)	0.650	105/428 (25)	0.877
Headache	22/107 (21)	368/1310 (28)	0.094	148/429 (35)	0.006
Myalgia	19/106 (18)	335/1310 (26)	0.080	133/429 (31)	0.008
Sore throat	18/107 (17)	207/1311 (16)	0.779	83/429 (19)	0.550

Data are presented as n/N (%), unless otherwise indicated, where n is the number of patients and N the total number of cases. The value of N may change due to missing data. p-value from Pearson's Chi-squared test, Fisher's exact test, t-test or Wilcoxon rank-sum test, as appropriate. RSV: respiratory syncytial virus; BMI: body mass index; IQR: interquartile range. [#]: comparison between RSV-positive and RSV-negative patients; [¶]: comparison between RSV-positive and influenza-positive patients.

versus 6 days, IQR 3–10 days; p<0.001). Similarly, prolonged hospitalisations (⩾7 days) were more frequent (64% *versus* 44%, p<0.001). They were also more likely to present with at least one complication during their hospitalisation (58% *versus* 47%, p=0.030), in particular respiratory failure (31% *versus* 16%, p<0.001). As expected, the use of anti-influenza therapies was significantly different between RSV and influenza patients (20% *versus* 66%), representing 31% in the whole cohort, 98% of which was oseltamivir. ICU admission, in-hospital mortality and post-discharge follow-up did not differ between adults infected with RSV or influenza (tables 2 and 3).

In multivariate analysis, the adjusted PR (aPR) of in-hospital composite outcome was significantly higher among adults hospitalised with RSV than among those hospitalised with influenza (aPR 1.5, 95% CI 1.1–2.1, table 4). The occurrence of respiratory complications during hospitalisation was more common in RSV-infected adults, including respiratory failure (aPR 1.6, 95% CI 1.1–2.3) and acute respiratory distress syndrome (aPR 2.0, 95% CI 1.3–3.1). ICU admission (aPR 2.0, 95% CI 1.4–2.9) and use of invasive mechanical ventilation (aPR 1.7, 95% CI 1.1–2.4) were greater among those infected with RSV than with influenza. Readmission within 90 days of hospital discharge (aPR 1.0, 95% CI 0.7–1.4), cumulative mortality within 30 and 90 days after hospital discharge (aPR 1.4, 95% CI 0.9–2.2 and aPR 1.5, 95% CI 1.0–2.3, respectively) and post-discharge composite outcome (aPR 1.1, 95% CI 0.8–1.6) did not differ between patients with RSV and those with influenza. aPRs did not vary according to influenza vaccination status when compared to vaccinated and non-vaccinated influenza-positive patients (supplementary table S3).

TABLE 2 In-hospital characteristics and outcomes of adults hospitalised with RSV or influenza virus, winter seasons 2017/2018 and 2018/2019 (excluding co-infections)

	RSV-positive	All RSV-negative	p-value[#]	Influenza-positive	p-value[¶]
Subjects, N	108	1314		431	
At least one complication during the hospital stay	63/108 (58)	683/1311 (52)	0.212	201/431 (47)	0.030
Pneumonia	33/108 (31)	348/1311 (27)	0.366	98/431 (23)	0.090
Bacterial infection	11/108 (10)	238/1311 (18)	0.036	56/431 (13)	0.429
Respiratory failure	34/108 (31)	285/1311 (22)	0.020	69/431 (16)	<0.001
Acute heart failure	16/108 (15)	143/1311 (11)	0.216	36/431 (8)	0.042
ARDS	10/108 (9)	93/1311 (7)	0.404	30/431 (7)	0.415
Acute renal failure	14/108 (13)	145/1311 (11)	0.547	47/431 (11)	0.546
Length of stay ⩾7 days	69/108 (64)	643/1314 (49)	0.003	189/431 (44)	<0.001
Median length of stay (IQR), days	8 (5–13)	6 (4–11)	0.005	6 (3–10)	<0.001
Any antibiotic drug use during hospitalisation	70/108 (65)	829/1294 (64)	0.876	294/422 (70)	0.332
Any antiviral drug use during hospitalisation	21/108 (20)	424/1313 (32)	0.006	284/431 (66)	<0.001
ICU admission	26/108 (24)	275/1312 (21)	0.447	72/431 (17)	0.076
Invasive mechanical ventilation support	17/108 (16)	157/1312 (12)	0.250	53/431 (12)	0.341
In-hospital mortality	3/108 (3)	59/1314 (4)	0.621	15/431 (3)	1.000

Data are presented as n/N (%), unless otherwise indicated, where n is the number of patients and N the total number of cases. The value of N may change due to missing data. p-values from Pearson's Chi-squared test, Fisher's exact test or Wilcoxon rank-sum test, as appropriate. RSV: respiratory syncytial virus; ARDS: acute respiratory distress syndrome; IQR: interquartile range; ICU: intensive care unit. [#]: comparison between RSV-positive and RSV-negative patients; [¶]: comparison between RSV-positive and influenza-positive patients.

Discussion

In this *post hoc* analysis of a prospective multicentre study, including 1428 adults hospitalised in France with ILI during two consecutive winter seasons before the SARS-CoV-2 pandemic, RSV was the third most frequently found respiratory virus (8%, 95% CI 6–9%). Adults hospitalised with RSV were slightly older with frequent chronic conditions and frequently presented with complications. In-hospital outcomes were more severe compared to those of influenza-positive patients. Midterm post-discharge outcomes, including 30- and 90-day all-cause mortality or 90-day readmission after discharge, were similar in RSV- and influenza-positive patients.

The rate of RSV infection is consistent with previous estimates from a retrospective cohort of hospitalised adults aged ⩾18 years over three seasons and among adults aged ⩾65 years with moderate-to-severe ILI episodes over four consecutive winters, all reporting RSV rates in hospitalised patients of 6–12% [1, 16]. Several factors can influence the detection of RSV infection. First, the age at recruitment: several reports focused on older adults [10, 17], whereas we included all adults aged ⩾18 years, a population in which RSV infections are less prevalent [18]. Second, the recruitment period in our study was the same for both the 2017/2018 and 2018/2019

TABLE 3 Post-discharge outcomes of adults hospitalised with RSV or influenza virus, winter seasons 2017/2018 and 2018/2019 (excluding co-infections)

	RSV-positive	All RSV-negative	p-value[#]	Influenza-positive	p-value[¶]
Subjects, n	108	1314	0.349	431	0.676
Discharge setting after hospitalisation					
Home	84/105 (80)	954/1256 (76)		325/416 (78)	
Other setting[+]	21/105 (20)	302/1256 (24)		91/416 (22)	
Cumulative mortality					
Within 30 days after hospital discharge[§]	10/107 (9)	98/1302 (8)	0.497	26/429 (6)	0.225
Within 90 days after hospital discharge[f]	14/107 (13)	136/1293 (11)	0.410	36/426 (8)	0.142
Readmission within 90 days of hospital discharge	28/91 (31)	323/1050 (31)	1.000	90/346 (26)	0.363

Data are presented as n/N (%), unless otherwise indicated, where n is the number of patients and N the total number of cases. The value of N may change due to missing data. p-value from Pearson's Chi-squared test or Fisher's exact test, as appropriate. RSV: respiratory syncytial virus. [#]: comparison between RSV-positive and RSV-negative patients; [¶]: comparison between RSV-positive and influenza-positive patients; [+]: discharge to rehabilitation facility, nursing facility, hospice or transfer to another hospital; [§]: 13 patients declined to answer or were lost to follow-up; [f]: nine additional patients declined to answer or were lost to follow-up.

TABLE 4 Composite outcomes and selected complications among adults hospitalised with RSV or influenza, winter seasons 2017/2018 and 2018/2019 (excluding co-infections)

	RSV-positive	Influenza-positive	aPR[#] (95% CI)	p-value
Subjects, N	108	431		
In-hospital				
In-hospital composite outcome[¶]	68/108 (63)	215/431 (50)	1.5 (1.1–2.1)	0.018
Complication during hospitalisation (at least one)				
Pneumonia	33/108 (31)	98/431 (23)	1.1 (0.8–1.6)	0.511
Respiratory failure	34/108 (31)	69/431 (16)	1.6 (1.1–2.3)	0.011
Acute heart failure	16/108 (15)	36/431 (8)	1.5 (0.9–2.3)	0.079
ARDS	10/108 (9)	30/431 (7)	2.0 (1.3–3.1)	0.002
Acute renal failure	14/108 (13)	47/431 (11)	1.0 (0.7–1.5)	0.997
Length of stay ⩾7 days	69/108 (64)	189/431 (44)	1.9 (1.4–2.7)	<0.001
ICU admission	26/108 (24)	72/431 (17)	2.0 (1.4–2.9)	<0.001
Invasive mechanical ventilation support	17/108 (16)	53/431 (12)	1.7 (1.1–2.4)	0.010
Post-discharge				
Post-discharge composite outcome[+]	41/101 (41)	119/370 (32)	1.1 (0.8–1.6)	0.438
Cumulative mortality				
Within 30 days after hospital discharge	10/107 (9)	26/429 (6)	1.4 (0.9–2.2)	0.157
Within 90 days after hospital discharge	14/107 (13)	36/426 (8)	1.5 (1.0–2.3)	0.059
Readmission within 90 days of hospital discharge	28/91 (31)	90/346 (26)	1.0 (0.7–1.4)	0.914

Data are presented as n/N (%), unless otherwise indicated, where n is the number of patients and N the total number of cases. The value of N may change due to missing data. RSV: respiratory syncytial virus; aPR: adjusted prevalence ratio; ARDS: acute respiratory distress syndrome; ICU: intensive care unit. [#]: aPR for age ⩾65 years, sex, chronic respiratory and cardiac diseases, seasonal influenza and pneumococcal vaccination, hospitalisation (in previous 12 months), antibiotic, antiviral, immunosuppressive therapy or prior corticosteroids receipt (oral or inhaled); [¶]: defined as in-hospital complications (at least one), length of stay ⩾7 days, ICU admission, invasive mechanical ventilation support or death; [+]: defined as mortality within 30 and 90 days or readmission within 90 days after hospital discharge.

winter seasons and was planned to cover RSV and influenza epidemic periods (November to mid-April) according to the national surveillance data published by the French public health agency (supplementary figures S4 and S5). Third, the syndromic case definition may vary across studies and influenza seasons.

We reported a high proportion of underlying conditions among RSV-positive patients, particularly chronic respiratory or cardiac diseases, which may put them at increased risk of severe disease and morbidity due to RSV infection [6, 19, 20]. Furthermore, we found poor in-hospital outcomes among patients hospitalised with RSV: 58% developed at least one complication during the hospital stay, >20% were admitted to ICU and 16% of RSV hospitalisations involved mechanical ventilation. A similar percentage of adult RSV patients receiving assisted ventilation were reported in a retrospective study from a large national sample of hospital inpatients [21].

Overall, in-hospital outcomes were significantly more severe in RSV-positive compared to influenza-positive patients after adjustment for comorbidities, mainly due to the higher rate of respiratory complications and use of intensive care or invasive mechanical ventilation and the longer hospitalisation. These results confirm earlier studies in which patients with RSV infections were at higher risk of serious clinical outcomes than those with influenza [10, 18, 22].

In our study, the two groups were not significantly different for post-discharge outcomes, including hospital readmission (31% *versus* 26%) and cumulative mortality within 30 and 90 days after discharge (9% *versus* 6% and 13% *versus* 8%, respectively). Ackerson *et al*. [10] reported a greater mortality within 1 year of admission (OR 1.3, 95% CI 1.0–1.6) with a significantly lower 1-year survival rate among RSV-positive compared to influenza-positive patients (74% *versus* 81%). Similar mortality rates in adults hospitalised with RSV infection were reported by Lee *et al.* [16] within 30 and 60 days of RSV hospitalisation (9% and 12%, respectively), and by Tseng *et al.* [23] within 30 and 90 days (9% and 12%, respectively) in a large cohort of older adults hospitalised with RSV infection in the USA.

RSV and influenza patients in our study did not differ in terms of pneumonia, including radiologically confirmed pneumonia and exacerbation of asthma/chronic obstructive pulmonary disease, while previous studies reported a higher occurrence of severe lower respiratory complications among those infected with RSV [20, 24]. Although immunocompromised adults with cancer, especially haematopoietic stem cell

transplant patients or those under intensive chemotherapy for solid cancer, are at risk of severe RSV infection [25], no significant differences were observed between RSV-positive patients and RSV- or influenza-negative patients. Furthermore, antibiotics were commonly prescribed in our study, as reported in previous studies among patients hospitalised with RSV, highlighting the need for optimal use of antibiotics in early management of viral respiratory infections, especially among patients with comorbidities and at risk of complications [6, 18, 26].

The strengths of this study include the detailed in-hospital clinical characteristics and post-discharge outcomes of adults hospitalised with ILI in a prospective multicentre design over two consecutive winter seasons. Moreover, the standardised patient screening and enrolment among long-term participating centres and laboratories minimised information bias. This study also has some limitations. First, despite the large number of included patients, the study was probably underpowered to show statistical differences in midterm post-discharge outcomes. Second, although RSV infections share similar symptoms with influenza [27] and are more likely to be symptomatic among adults [28], the case definition used to include ILI patients in the influenza vaccine effectiveness study probably underestimated the occurrence of RSV hospital admissions and may not reflect the relative incidence of RSV infections with different clinical manifestations [29]. Third, the use of antivirals may improve influenza but not RSV infection, for which targeted therapies are still lacking [30]. The observed differences between RSV and influenza patients probably reflect the antiviral therapy discontinuation after confirmation of RSV infection, and the inverse with influenza infection. This may influence outcomes of influenza patients, notably in the case of influenza pneumonia in which oseltamivir may improve the survival of patients with severe forms [31]. In sensitivity analyses, PRs comparing outcomes among RSV-positive patients to those among influenza-positive patients without antiviral therapy were consistent with previous estimates (supplementary table S6). Finally, other pathogens such as bacterial respiratory pathogens may have been involved in the symptoms reported among adults hospitalised with ILI and the role of bacterial concomitant infection is not fully understood as a result of imprecise or no diagnostic testing. The absence of data on bacteriological results at the time of presentation prevents us from addressing this issue.

The results of this study illustrate the increasing recognition of RSV infection as a common aetiology of severe respiratory infection among hospitalised adults. However, RSV is still clinically under-recognised by healthcare providers despite the progressive introduction of new diagnostic testing, and patients are not routinely tested in all settings [32]. Because severe cases are more likely to be diagnosed, incidence and burden of RSV among adults are difficult to measure. Therefore, further data are needed to describe the severity and long-term outcomes of RSV infections in various settings. In addition to preventing influenza, prevention and early diagnosis of RSV infections could reduce the occurrence of severe forms in these populations at increased risk of complications in parallel with measures to prevent nosocomial transmission. This study highlights the need for effective RSV-specific therapies, especially new vaccines under development for which criteria for vaccination policy need to be defined [33].

The findings from this study indicate that RSV is an important cause of serious respiratory infection among hospitalised adults associated with severe hospital outcomes. Further studies with a larger sample and a longer follow-up will allow a more accurate assessment of the post-discharge outcomes of RSV infection among older adults and those with comorbidities. In addition, increased recognition among healthcare providers and early identification of RSV with standardised screening recommendations will be important once vaccines or specific antiviral treatments become available.

Acknowledgments: The authors acknowledge the FLUVAC study group and all the study staff for their significant contribution to the FLUVAC study over the seasons: CHU Rennes: S. Jouneau and P. Tattevin. CHU Montpellier: P. Géraud, L. Crantelle, V. Driss, E. Nyiramigisha, C. Agostini, C. Serrand, A. Bourdin, A. Konaté, X. Capdevilla, G. Du Cailar, A. Terminet, H. Blain, M-S. Leglise, P. Corne, L. Landreau, K. Klouche, A. Bourgeois, M. Sebbane, G. Mourad, H. Leray, M. Le Quintrec-Donnette, M-S. Duc and N. Tombou. Hospices Civils de Lyon: K. Tazarourte, L. Argaud, M. Valette and R. Bouslama. Hôpital Bichat: B. Celestin, J-F. Alexandra, T. Goulenock, R. Bertinchamp, T. Papo, C. Rioux, V. Joly, M. Dubret, X. Lescure, S. Lariven, Y. Yazdanpanah, M-C. Dombret, S. Brossen, B. Crestani, N. Faucher, C. Lamaye, A. Raynaud-Simon, L. Peirera, E. Dupeyrat, M. Ranaivoson, A. Leleu, C. Choquet, E. Casalino, L-B. Luong Nguyen, B. Mollo, C-A. Agbessi, P. Leguen, M. Ghanem, G. Mourin and C. Lahaye. Hôpital Cochin: L. Belarbi, F. Chau, M. Lachatre, P. Grange, S. Momcilovic, K. Cheref, L. Fernandes, M-S. Cisse, R. Kanaan, D. Dusser, M. Jerbi, N. Roche, J. Chapron, I. Honore, N. Chaabane, N. Carlier, C. Martin, I. Zaien, C. Hamard, S. Chelabi, J. Marey, A-C. Sainte-Marie, C. Lejeunne, P. Legendre, T-A. Szwebel, A. Regent, G. Venturelli, C. Jamart, F. Dumas, B. Doumenc, T. Duchenoy, S. Ayllon-Milla, A-S. Lopes, A. Najafi, D. Pereira, T. Pinto, S. Neraal, A. Chevalier, F. Lecomte, M. Buffo, C. Magne, R. Ranerison, N. Marin, J. Kansao, J. Charpentier, J-P. Mira, J-D. Chiche, J. Rondy,

A. Gavaud, P. Dupland, E. Baron, G. Savary, A. Cao, P. Jaubert, D. Duboc, M. Sochala, M. Jozwiak and F. Labouree. The authors also thank the department heads who agreed to perform the study in their unit, the investigators and all the patients who agreed to participate. We thank Sarah Kabani for proofreading the manuscript.

Author contributions: A. Descamps, P. Loubet and O. Launay conceptualised the original study. A. Descamps, P. Loubet and O. Launay developed the methodology. A. Descamps performed the analysis. A. Descamps and P. Loubet wrote the original manuscript. N. Lenzi, F. Galtier, F. Lainé, Z. Lesieur, P. Vanhems, S. Amour, A-S. L'Honneur, N. Fidouh, V. Foulongne, G. Lagathu, X. Duval, C. Merle, B. Lina, F. Carrat and O. Launay critically reviewed the manuscript and agreed to be accountable for all aspects of the work. P. Loubet and O. Launay supervised the research.

Conflict of interest: N. Lenzi has nothing to disclose. F. Galtier has nothing to disclose. F. Lainé has nothing to disclose. Z. Lesieur has nothing to disclose. P. Vanhems reports grants from Pfizer, Sanofi, Anios, MSD and Astellas, outside the submitted work. S. Amour has nothing to disclose. A-S. L'Honneur has nothing to disclose. N. Fidouh has nothing to disclose. V. Foulongne has nothing to disclose. G. Lagathu has nothing to disclose. X. Duval has nothing to disclose. C. Merle has nothing to disclose. B. Lina has nothing to disclose. F. Carrat has nothing to disclose. O. Launay is principal investigator for clinical trials sponsored by Janssen, GSK, Pfizer, Sanofi Pasteur and MSD, outside the submitted work. P. Loubet reports personal fees from Pfizer and non-financial support from Sanofi Pasteur, outside the submitted work. A. Descamps has nothing to disclose.

Support statement: The current work received no funding. However, the study sites received funding from Janssen and Sanofi Pasteur for the FLUVAC study. The funders had no role in considering the choice of research project, design of the study, analyses and interpretation of the data, writing of the report or decision to publish.

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