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## **Title page**

# **In-hospital and midterm out-hospital complications of adults hospitalised with respiratory syncytial virus infection in France, 2017-2019: an observational study**

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**Take-Home Message (247 characters):**

Respiratory syncytial virus infection in hospitalised adults with influenza-like illness was associated with poor in-hospital and midterm post-discharge outcomes, that may be worse or similar than those of patients with influenza virus infection.

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## Abstract

*Objectives:* To describe the clinical characteristics and in/out-hospital 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 RT-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  $\geq 7$  days, intensive care unit (ICU) admission, use of mechanical ventilation and in-hospital death. Post-discharge outcome included 30/90-day all-cause mortality and 90-day readmission rates.

*Results:* Overall, 1,428 hospitalised adults with ILI were included. RSV was detected in 8% (114/1428) and influenza virus in 31% (437/1428). Patients hospitalised with RSV were older than those with influenza (mean age, 73.0 vs 68.8 years;  $p=0.015$ ) with a higher frequency of respiratory (52% vs 39%,  $p=0.012$ ) or cardiac chronic diseases (52% vs 41%,  $p=0.039$ ) and longer hospitalisation duration (median stay 8 vs 6 days,  $p<0.001$ ). Anti-influenza therapies were less prescribed among RSV than influenza patients (20% vs 66%,  $p<0.001$ ). In-hospital composite outcome was poorer in RSV patients (adjusted prevalence ratio (aPR)=1.5; 95% Confidence Interval (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 in-hospital outcomes worse than influenza and with similar midterm post-discharge outcomes.

# **In-hospital and midterm out-hospital complications of adults hospitalised with respiratory syncytial virus infection in France, 2017-2019: an observational study**

## **Introduction**

Before the 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 co-morbidities, 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 approximately 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, due to 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 polymerase chain reaction (RT-PCR), has improved the detection of respiratory viruses providing 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, 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 2012-13 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 24h 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 European Centre for Disease Prevention and Control (ECDC) definition for ILI cases: (i) at least one of the following systemic symptoms – fever or feverishness, malaise, headache, myalgia or deterioration of general condition (asthenia or loss of weight or anorexia or confusion or dizziness) – and (ii) at least one of the following respiratory symptoms – 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  $\leq 48$ h after admission to exclude nosocomial infections. Patients with contra-indication for influenza vaccine or 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**

**tables 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 utilization and clinical outcomes were defined as follows: (i) 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  $\geq 7$  days or intensive care unit (ICU) admission or use of invasive mechanical ventilation for support or in-hospital death, and (ii) 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, 3 or Anyplex™ II RV 16 detection kit (Seegene, 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: (a) all RSV-negative patients (including influenza-positive patients, patients infected by other respiratory viruses and patients with no respiratory virus detected) and (b) influenza-positive patients. Descriptive data are presented as medians with

interquartile range (IQR), mean and standard deviation (SD) or frequencies with proportions. Pearson chi-square test, Fisher exact test, *t* test or Wilcoxon rank-sum test were used for univariate comparisons as appropriate. Missing data for each variable were excluded from the denominator.

Then, multivariable analyses were 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). A p-value < 0.05 was considered statistically significant. PRs are displayed with their 95% confidence intervals (95% CIs).

## *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 2017-18 season and 716 during the 2018-19 season (**Figure 1**). Their mean age was 68



years (range 19-98) and 55% were male. Most patients (87%) had at least one underlying condition, mainly respiratory (47%) or cardiac chronic disease (40%). The proportion of 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 2017-18 and 2018-19 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), 1422 patients were further analysed (709 and 713 patients for the 2017-18 and 2018-19 seasons, respectively).

#### *Characteristics and outcomes of RSV-positive patients*

Among patients with laboratory-confirmed RSV infection (n = 108 after excluding the 6 co-infections with influenza virus), 52% were female and their mean age was 73 years (range 30-97, **Table 1**). The majority had at least one chronic condition (90%), mostly respiratory (52%) and cardiac chronic diseases (52%), or diabetes mellitus (24%). At admission, RSV-positive patients were more likely to have a chronic cardiac disease than RSV-negative patients (52% vs 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 vs 6 days, p = 0.005) and a greater frequency of stays longer than 7 days (64% vs 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). 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 vs 68.8 years;  $p = 0.015$ ), and more likely to have a chronic respiratory or cardiac disease (52% vs 39%,  $p = 0.012$  and 52% vs 41%,  $p = 0.039$ , respectively), and to be vaccinated against seasonal influenza (59% vs 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% vs 12%,  $p = 0.026$  for systemic and 30% vs 21%,  $p = 0.048$  for inhaled corticosteroids therapy). RSV-positive patients reported significantly more dyspnoea (91% vs 71%) but less headache (21% vs 35%) and myalgia (18% vs 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 compared to influenza-positive patients (8 days (IQR, 5-13) vs 6 days (IQR, 3-10),  $p < 0.001$ ). Similarly, prolonged hospitalisations ( $\geq 7$  days) were more frequent (64% vs 44%,  $p < 0.001$ ). They were also more likely to present at least one complication during their hospitalisation (58% vs 47%,  $p = 0.030$ ), in particular respiratory failure (31% vs 16%,  $p < 0.001$ ). As expected, the use of anti-influenza therapies was significantly different between RSV and influenza patients (20% vs 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 prevalence ratio of in-hospital composite outcome was significantly higher among adults hospitalised with RSV compared to 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). Intensive care unit 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) 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. Adjusted prevalence ratios did not vary according to influenza vaccination status when compared to vaccinated and non-vaccinated influenza-positive patients (**Supplementary table S3**).

## 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 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  $\geq 18$  years over three seasons, and among adults aged  $\geq 65$  years with moderate-to-severe ILI episodes over four consecutive winters, all reporting RSV rates in hospitalised patients ranging from 6 to 12% (1,16). Several factors may 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  $\geq 18$  years, a population in which RSV infections are less prevalent (18). Second, the recruitment period in our study was the same for both 2017-18 and 2018-19 winter seasons and was planned to cover RSV and influenza epidemic periods – November to mid-April – according to the national surveillance

1 data published by the French public health agency (**Supplementary figures S4 and S5**). In  
2 addition, the syndromic case definition may vary across studies and influenza seasons.

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

11 Overall, in-hospital outcomes were significantly more severe in RSV-positive  
12 compared to influenza-positive patients after adjustment for comorbidities, mainly due to the  
13 higher rate of respiratory complications and use of intensive care or invasive mechanical  
14 ventilation and the longer hospitalisation. These results confirm earlier studies where patients  
15 with RSV infections were at higher risk of serious clinical outcomes than those with influenza  
16 (10,18,22).

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

26 Interestingly, RSV and influenza patients in our study did not differ in terms of  
27 pneumonia, including radiologically confirmed pneumonia and exacerbation of  
28 asthma/COPD, while previous studies reported higher occurrence of severe lower respiratory

1 complications among those infected with RSV (20,24). Although immunocompromised adults  
2 with cancer, especially haematopoietic stem cell transplant patients or those under intensive  
3 chemotherapy for solid cancer, are at risk of severe RSV infection (25), no significant  
4 differences were observed between RSV-positive patients and RSV- or influenza-negative  
5 patients. Furthermore, antibiotics were commonly prescribed in our study, as reported in  
6 previous studies among patients hospitalized with RSV, highlighting the need for optimal use  
7 of antibiotics in early management of viral respiratory infections especially among patients  
8 with comorbidities and at risk of complications (6,18,26).

9         The strengths of this study include the detailed in-hospital clinical characteristics and  
10 post-discharge outcomes of adults hospitalised with ILI in a prospective multicentre design  
11 over two consecutive winter seasons. Moreover, the standardised patient screening and  
12 enrolment among long-term participating centres and laboratories minimised information  
13 bias. This study also has some limitations. First, despite the large number of included  
14 patients, the study was probably underpowered to show statistical differences in midterm  
15 post-discharge outcomes. Second, although RSV infections share similar symptoms with  
16 influenza (27) and are more likely to be symptomatic among adults (28), the case definition  
17 used to include ILI patients in the influenza vaccine effectiveness study probably  
18 underestimated the occurrence of RSV hospital admissions and may not reflect the relative  
19 incidence of RSV infections with different clinical manifestations (29). Furthermore, the use of  
20 antivirals may improve influenza but not RSV infection, for which targeted therapies are still  
21 lacking (30). The observed differences between RSV and influenza patients probably reflect  
22 the antiviral therapy discontinuation after confirmation of RSV infection, and the inverse with  
23 influenza infection. This may influence outcomes of influenza patients, notably in the case of  
24 influenza pneumonia where oseltamivir may improve the survival of patients with severe  
25 forms (31). In sensitivity analyses, prevalence ratios comparing outcomes among RSV  
26 positive patients to those with influenza without antiviral therapy were consistent with  
27 previous estimates (**Supplementary table S6**). Finally, other pathogens such as bacterial  
28 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 health care providers despite the progressive introduction of new diagnostic testing, and patients are not routinely tested in all settings (32). As 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 highlighted the need for effective RSV-specific therapies, especially new vaccines under development for whom criteria for vaccination policy need to be defined (33).

## Conclusion

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 health care providers and early identification of RSV with standardised screening recommendations will be important once vaccines or specific antiviral treatments become available.

## Authors' contributions

A.D., P.L. and O.L. conceptualized the original study. A.D., P.L. and O.L. developed the methodology. A.D. performed the analysis. A.D. and P.L. wrote the original manuscript. N.L., F.G., F.L., Z.L., P.V., S.A., A-S.L., N.F., V.F., G.L., X.D., C.M., B.L., F.C. and O.L. critically reviewed the manuscript and agreed to be accountable for all aspects of the work. P.L and O.L. supervised the research.

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## **Transparency declaration**

The authors declare no conflict of interest related to the study. O.L. is principal investigator for clinical trials sponsored by Janssen, GSK, Pfizer, Sanofi Pasteur and MSD. P.L. has received personal fees and non-financial support from Pfizer and Sanofi Pasteur.

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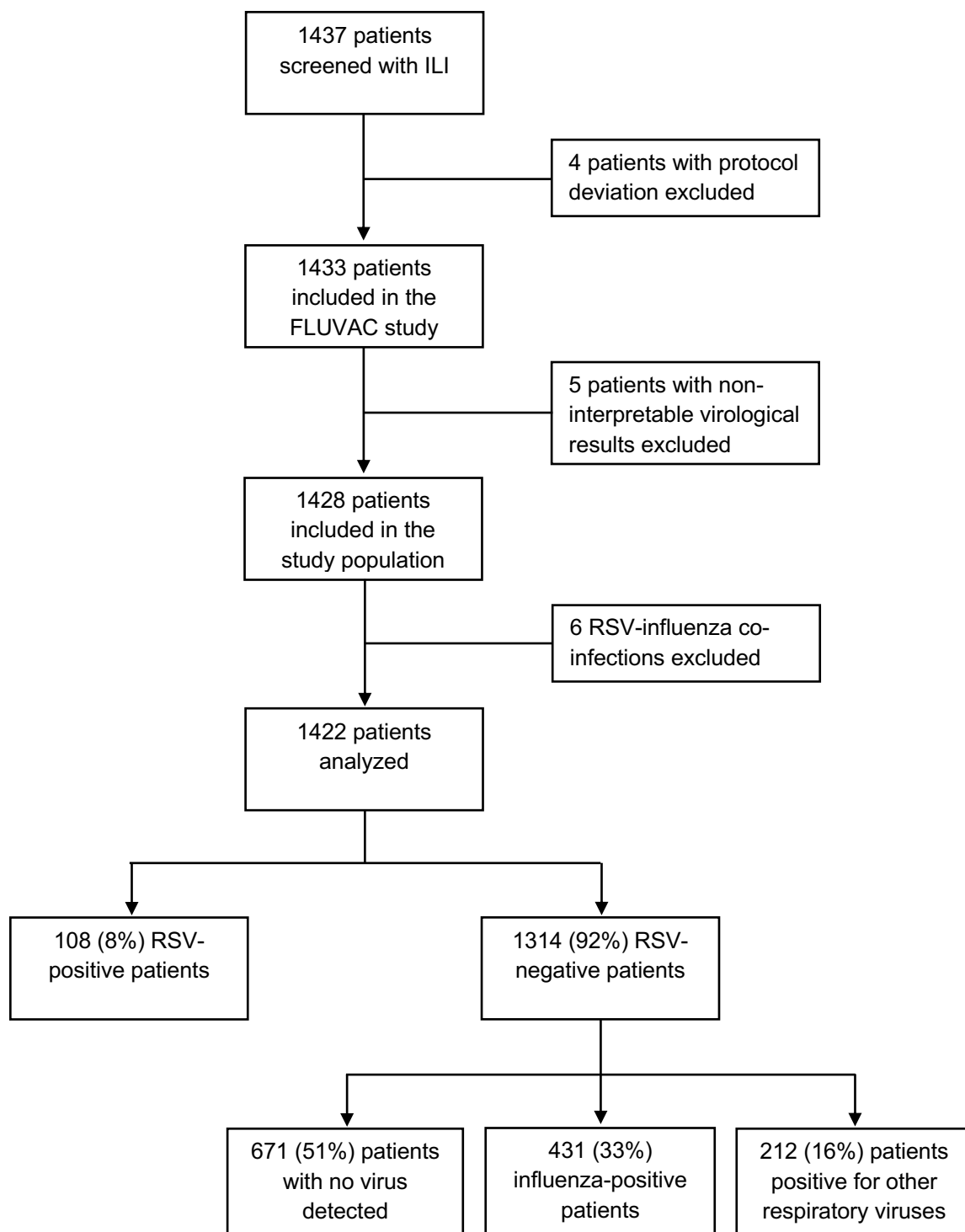
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2

**Figure 1.** FLUVAC study flowchart, winter seasons 2017-18 and 2018-19



**Abbreviations:** ILI, influenza-like illness; RSV, respiratory syncytial virus.

**Table 1.** Baseline characteristics and clinical presentation of adults hospitalised with respiratory syncytial virus or influenza virus, winter seasons 2017-18 and 2018-19 (excluding co-infections)

	RSV + (n = 108)	All RSV - (n = 1314)	p <sup>a</sup>	Influenza + (n = 431)	p <sup>b</sup>
<b>Baseline characteristics</b>					
Age at admission (years)					
Mean age (SD, range)	73.0 (12.9, 30-97)	68.8 (17.5, 19-98)	0.016	68.8 (16.7, 19-96)	0.015
Sex, n (%)					
Male	52/108 (48)	734/1314 (56)		243/431 (56)	
Body Mass Index (kg/m <sup>2</sup> )					
Median BMI (IQR)	25.0 (22.2-30.9)	24.6 (21.3-29.0)	0.107	25.0 (21.9-29.5)	0.500
Smoking status, n (%)					
Current smokers	18/108 (17)	270/1305 (21)	0.319	86/429 (20)	0.427
Comorbidity, n (%)					
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, n (%)	63/106 (59)	665/1307 (51)	0.090	206/428 (48)	0.037

**Table 1.** (continued from previous section)

	RSV + (n = 108)	All RSV - (n = 1314)	p <sup>a</sup>	Influenza + (n = 431)	p <sup>b</sup>
Presence of children <5 years old in household, n (%)	10/108 (9)	86/1313 (7)	0.281	27/430 (6)	0.274
Prehospital medication, n (%)					
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, n (%)	46/108 (43)	623/1308 (48)	0.314	180/429 (42)	0.905
<b>Clinical presentation</b>					
Median time from symptom onset to admission, days (IQR)	2 (1-4)	2 (1-3)	0.620	2 (1-3)	0.627
Symptoms, n (%)					
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

Values are n/N (%), where n is the number of patients and N the total number of cases. The value of N may change due to missing data.

Abbreviations: IQR, interquartile range; RSV, respiratory syncytial virus; SD, standard deviation.

<sup>a</sup> Comparison between RSV (+) and RSV (-) patients.

<sup>b</sup> Comparison between RSV (+) and influenza (+) patients.

P-value from Pearson chi-square test, Fisher exact test, *t* test or Wilcoxon rank-sum test, as appropriate.

**Table 2.** In-hospital characteristics and outcomes of adults hospitalised with respiratory syncytial virus or influenza virus, winter seasons 2017-18 and 2018-19 (excluding co-infections)

	RSV + (n = 108)	All RSV - (n = 1314)	p <sup>a</sup>	Influenza + (n = 431)	p <sup>b</sup>
At least one complication during the hospital stay, n (%)	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
Acute respiratory distress syndrome (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), n (%)	69/108 (64)	643/1314 (49)	0.003	189/431 (44)	<0.001
Median length of stay, days (IQR)	8 (5-13)	6 (4-11)	0.005	6 (3-10)	<0.001
Any antibiotic drug use during hospitalisation, n (%)	70/108 (65)	829/1294 (64)	0.876	294/422 (70)	0.332
Any antiviral drug use during hospitalisation, n (%)	21/108 (20)	424/1313 (32)	0.006	284/431 (66)	<0.001
Intensive care unit (ICU) admission, n (%)	26/108 (24)	275/1312 (21)	0.447	72/431 (17)	0.076
Invasive mechanical ventilation support, n (%)	17/108 (16)	157/1312 (12)	0.250	53/431 (12)	0.341
In-hospital mortality, n (%)	3/108 (3)	59/1314 (4)	0.621	15/431 (3)	1.000

Values are n/N (%), where n is the number of patients and N the total number of cases. The value of N may change due to missing data.

Abbreviations: IQR, interquartile range; RSV, respiratory syncytial virus.

<sup>a</sup> Comparison between RSV (+) and RSV (-) patients.

<sup>b</sup> Comparison between RSV (+) and influenza (+) patients.

P-value from Pearson chi-square test, Fisher exact test, or Wilcoxon rank-sum test, as appropriate.



**Table 3.** Post-discharge outcomes of adults hospitalised with respiratory syncytial virus or influenza virus, winter seasons 2017-18 and 2018-19 (excluding co-infections)

	RSV + (n = 108)	All RSV - (n = 1314)	p <sup>a</sup>	Influenza + (n = 431)	p <sup>b</sup>
Discharge setting after hospitalisation, n (%)			0.349		0.676
Home	84/105 (80)	954/1256 (76)		325/416 (78)	
Other setting <sup>c</sup>	21/105 (20)	302/1256 (24)		91/416 (22)	
Cumulative mortality, n (%)					
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	14/107 (13)	136/1293 (11)	0.410	36/426 (8)	0.142
Readmission within 90 days of hospital discharge, n (%)	28/91 (31)	323/1050 (31)	1.000	90/346 (26)	0.363

Values are n/N (%), where n is the number of patients and N the total number of cases. The value of N may change due to missing data. Within 30 days after discharge, 13 patients declined to answer or were lost to follow-up, and 9 additional patients within 90 days.

Abbreviations: IQR, interquartile range; RSV, respiratory syncytial virus.

<sup>a</sup> Comparison between RSV (+) and RSV (-) patients.

<sup>b</sup> Comparison between RSV (+) and influenza (+) patients.

<sup>c</sup> Discharge to rehabilitation facility, nursing facility, hospice or transfer to another hospital.

P-value from Pearson chi-square test or Fisher exact test, as appropriate.

**Supplementary material for “In-hospital and midterm out-hospital complications of adults hospitalised with respiratory syncytial virus infection in France, 2017-2019: an observational study”**

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Figure S4. Distribution of respiratory syncytial virus (RSV) and influenza virus among adults hospitalised with ILI in the FLUVAC study, by week, during A) winter season 2017-18 and B) winter season 2018-19 (the grey shaded areas correspond to the start and end of the influenza season)

Figure S5. Distribution of influenza virus type and subtype among adults hospitalised with ILI in the FLUVAC study, by week, during A) winter season 2017-18 and B) winter season 2018-19 (the grey shaded areas correspond to the start and end of the influenza season)

Table S6. Composite outcomes and selected complications among adults hospitalised with respiratory syncytial virus or influenza with or without use of antiviral therapy, winter seasons 2017-18 and 2018-19

**Table S1a.** Definition of comorbidities at hospital admission considered in the FLUVAC study

<b>Category (and ICD-10 codes)</b>	<b>Underlying medical conditions<sup>a</sup></b>
<i>Chronic respiratory disease</i> (ICD-10: A15-16, A19, E84.0, J40-47, J60-94, J95-99)	INCLUDING: respiratory tuberculosis (pulmonary, miliary but not that of other systems), asthma, chronic obstructive pulmonary disease, cystic fibrosis, bronchiectasis and other chronic sequelae of infections, emphysema, chronic lung diseases due to external agents, interstitial lung diseases, pleural diseases, respiratory failure
<i>Chronic cardiac disease</i> (ICD-10: A52.0, B37.6, I05-09, I11, I13, I20-25, I26-28, I30-51, I97.0-1, R00.1, T81.718A, T81.72XA, T82.817A, T82.818A, Q20-28, Q87.4, R01.1-2)	INCLUDING: ischemic heart diseases, hypertensive heart, cardiomyopathies and most conduction disorders, congenital malformations, pulmonary heart diseases, diseases of pulmonary vessels, other forms of heart disease (including nonrheumatic valve disorders, pericarditis, endocarditis, myocarditis, heart failure), complication of other artery/vein following a procedure, embolism of cardiac/vascular prosthetic devices, implants and grafts
<i>Chronic renal disease</i> (ICD-10: M10.30, N00-19, N20.0, N28.9)	INCLUDING: glomerulonephritis, interstitial nephritis/pyelonephritis, acute kidney failure and chronic kidney disease, calculus of kidney, disorder of kidney and ureter and other miscellaneous conditions
<i>Diabetes mellitus</i> (ICD-10: E10-11)	INCLUDING: type 1 and type 2 diabetes
<i>Cancer</i> (ICD-10: C00-97, D37-48, Z85, Z92.3, Z92.6)	INCLUDING: all malignant neoplasms (both solid and haematologic), neuroendocrine tumours, either in treatment, active follow-up, or <5 years post curative treatment
<i>Other Immunodeficiency</i> (ICD-10: B20-B24, D80-84, D89, Z94)	INCLUDING: HIV, immunity deficiency, organ or tissue replaced by transplant
<i>Cirrhosis</i> (ICD-10: K70, K72, K74.6)	INCLUDING: alcoholic liver disease, hepatic failure, other and unspecified cirrhosis of liver
<sup>a</sup> Chronic disease grouping followed national recommendations on influenza vaccination: <a href="https://solidarites-sante.gouv.fr/IMG/pdf/calendrier_vaccinal_300421.pdf">https://solidarites-sante.gouv.fr/IMG/pdf/calendrier_vaccinal_300421.pdf</a>	

**Table S2b.** Definition of in-hospital outcomes considered in the FLUVAC study

	Definition and classification
Pneumonia	Defined as the presence of suggestive signs and symptoms and ground-glass opacities on chest radiographs or computed tomographic scans (confirmed by radiologists) according to SPILF/AFSSAPS/SPLF 2010 <sup>1</sup> and ATS/IDSA 2007/2019 guidelines <sup>2</sup>
Respiratory failure	Defined as acute or chronic impairment of gas exchange causing hypoxia ( $\text{PaO}_2 \leq 60$ mmHg) with or without hypercapnia ( $\text{PaCO}_2 > 45$ mmHg))
Acute heart failure	<i>De novo</i> or acute decompensation of chronic heart failure defined by ESC Guidelines (e.g. acute myocardial dysfunction, acute valve insufficiency, hypertensive emergency, severe rhythm disturbance, acute coronary events, excluding non-cardiac causes) <sup>3</sup>
Acute respiratory distress syndrome (ARDS)	According to Berlin criteria <sup>4</sup>
Acute renal failure	According to KDIGO criteria <sup>5</sup>
ICU admission	Defined as the presence of at least 2 organ failures with a risk of death according to the French Society of Anaesthesiology and Intensive Care Medicine <sup>6</sup>

<sup>1</sup> SPILF/AFSSAPS/SPLF, Antibiothérapie par voie générale dans les infections respiratoires basses de l'adulte, juillet 2010. Available from : [https://www.infectiologie.com/UserFiles/File/medias/\\_documents/consensus/2010-infVRB-spilf-afssaps.pdf](https://www.infectiologie.com/UserFiles/File/medias/_documents/consensus/2010-infVRB-spilf-afssaps.pdf)

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**Table S2.** Virus distribution associated with influenza-like illness (ILI) in the FLUVAC study, winter seasons 2017-2019 (including co-infections)

<b>Seasons</b>	<b>Total (N = 1428)</b>	<b>2017-18 (n = 712)</b>	<b>2018-19 (n = 716)</b>
Detection of at least one respiratory virus	<b>757 (53%)</b>	369 (52%)	388 (54%)
Influenza virus	<b>437 (31%)</b>	228 (32%)	209 (29%)
Type A	<b>325 (23%)</b>	116 (16%)	209 (29%)
A(H1N1)	<b>140 (10%)</b>	91 (13%)	49 (7%)
A(H3N2)	<b>172 (12%)</b>	21 (3%)	151 (21%)
Not determined	<b>13 (1%)</b>	4 (1%)	9 (1%)
Type B	<b>112 (8%)</b>	112 (16%)	– –
B Yamagata	<b>100 (7%)</b>	100 (14%)	– –
B Victoria	<b>0 (0%)</b>	0 (0%)	– –
Not determined	<b>12 (1%)</b>	12 (2%)	– –
Picornavirus	<b>125 (9%)</b>	50 (7%)	75 (10%)
Respiratory Syncytial Virus	<b>114 (8%)</b>	52 (7%)	62 (9%)
Coronavirus <sup>a</sup>	<b>44 (3%)</b>	17 (2%)	27 (4%)
Human Metapneumovirus	<b>40 (3%)</b>	21 (3%)	19 (3%)
Other respiratory viruses <sup>b</sup>	<b>37 (2%)</b>	18 (3%)	19 (3%)

No detection of influenza B virus for the 2018-19 season.

<sup>a</sup> Multiplex PCR panel detect 229E/NL63/OC43 coronaviruses (HKU1 not included).

<sup>b</sup> Including adenovirus, bocavirus and human parainfluenza virus 1-4 (HPIVs).

**Table S3.** Composite outcomes and selected complications among adults hospitalised with respiratory syncytial virus or influenza with or without current and prior influenza season vaccination, winter seasons 2017-18 and 2018-19

	All RSV (+) vs. Influenza (+) unvaccinated <sup>a</sup>		All RSV (+) vs. Influenza (+) vaccinated <sup>b</sup>	
	aPR <sup>*</sup>	(95% CI)	aPR <sup>*</sup>	(95% CI)
<b>In-hospital composite outcome</b>				
Complication during hospitalisation (at least one), n (%)	1.3	(0.9-1.8)	1.4	(1.0-1.9)
Pneumonia	0.8	(0.6-1.7)	1.1	(0.8-1.6)
Respiratory failure	1.2	(1.0-1.6)	1.5	(1.1-2.2)
Acute heart failure	1.4	(0.9-2.1)	1.4	(0.9-2.1)
Acute respiratory distress syndrome (ARDS)	1.5	(1.0-2.3)	1.9	(1.3-2.8)
Acute renal failure	0.8	(0.5-1.2)	1.0	(0.7-1.6)
Length of stay ( $\geq 7$ days), n (%)	1.7	(1.3-2.3)	1.5	(1.1-2.1)
Intensive care unit (ICU) admission, n (%)	1.7	(1.2-2.4)	1.8	(1.2-2.5)
Invasive mechanical ventilation support, n (%)	1.4	(0.9-1.9)	1.6	(1.2-2.3)
<b>Post-discharge composite outcome</b>				
Cumulative mortality, n (%)	1.3	(1.0-1.7)	1.2	(0.9-1.6)
Within 30 days after hospital discharge	1.1	(0.7-1.6)	1.4	(1.0-2.0)
Within 90 days after hospital discharge	1.2	(0.8-1.8)	1.6	(1.2-2.3)
Readmission within 90 days of hospital discharge, n (%)	1.4	(1.0-1.9)	1.0	(0.7-1.4)

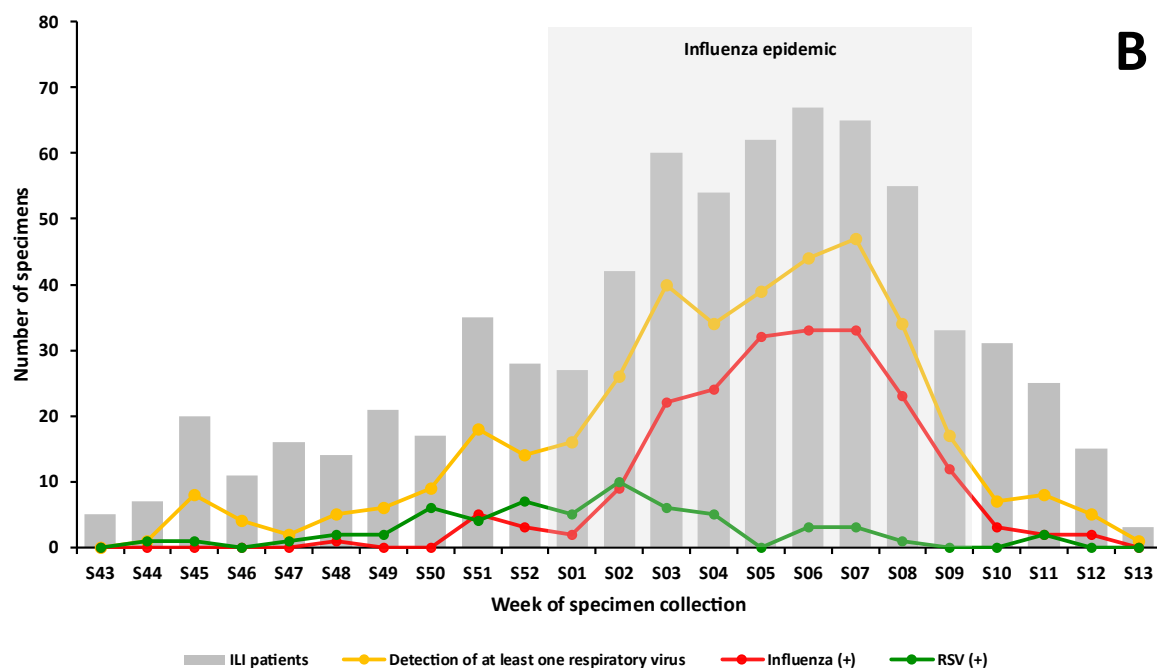
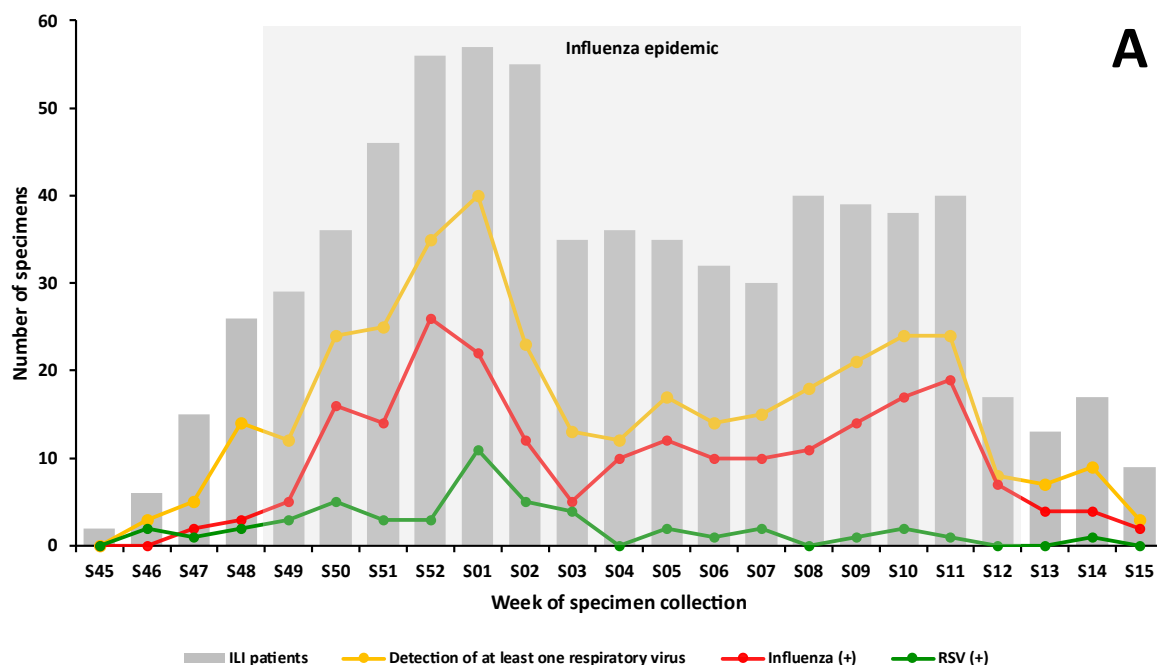
Abbreviations: aPR, adjusted prevalence ratio; 95% CI, 95% confidence interval.

<sup>a</sup> Excluding only influenza (+) patients with current and prior season vaccination.

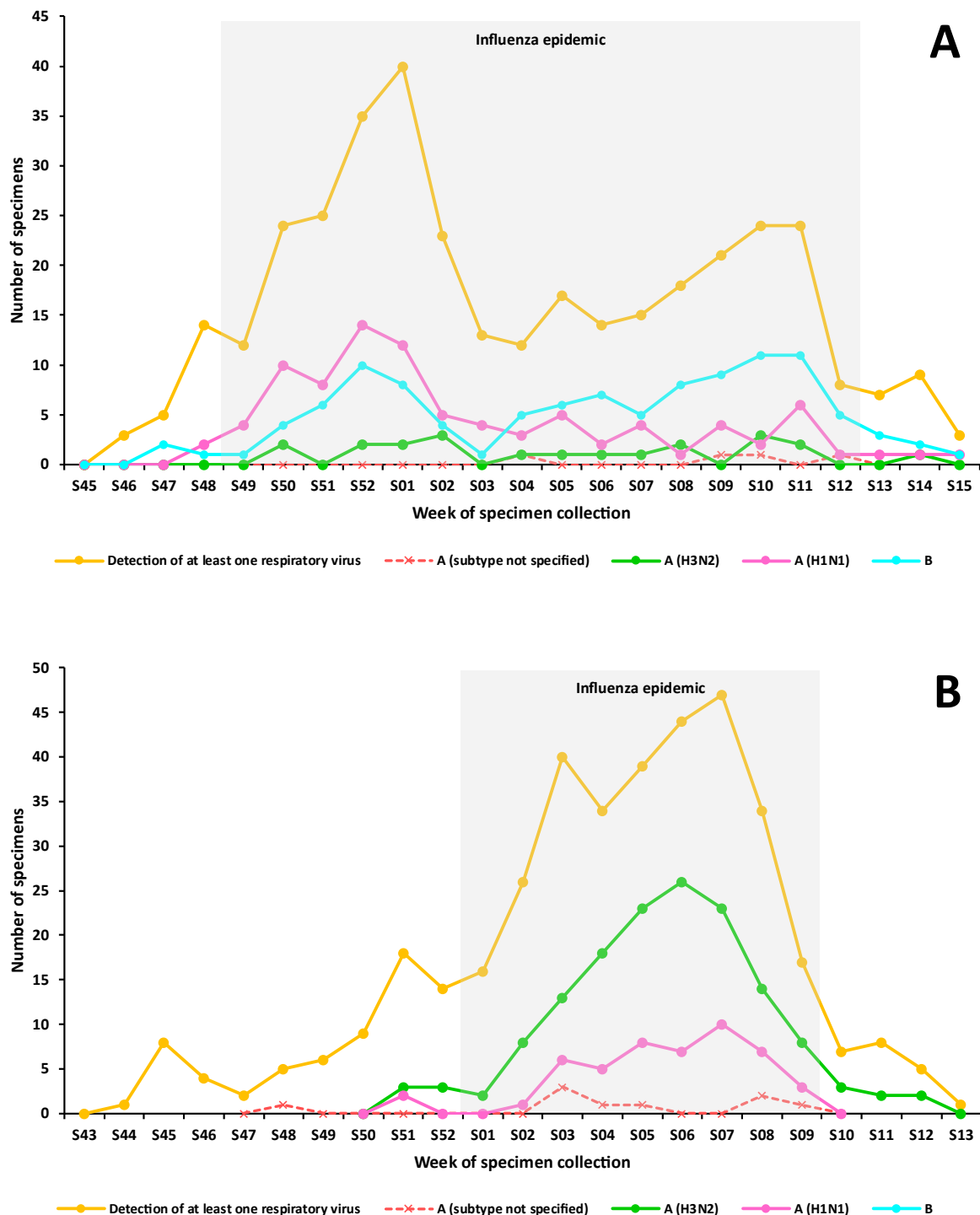
<sup>b</sup> Excluding only influenza (+) patients without current and prior season vaccination. Note that combination of current and prior vaccination included patients vaccinated in the current season only, prior season only and both current/prior seasons.

\*Adjusted PR for: age  $\geq 65$  years, sex, chronic respiratory and cardiac diseases, pneumococcal vaccination, hospitalisation (in previous 12 months), antibiotic, antiviral, immunosuppressive therapy or prior corticosteroids receipt (oral or inhaled).

**Figure S4.** Distribution of respiratory syncytial virus (RSV) and influenza virus among adults hospitalised with ILI in the FLUVAC study, by week, during A) winter season 2017-18 and B) winter season 2018-19 (the grey shaded areas correspond to the start and end of the influenza season)



**Figure S5.** Distribution of influenza virus type and subtype among adults hospitalised with ILI in the FLUVAC study, by week, during A) winter season 2017-18 and B) winter season 2018-19 (the grey shaded areas correspond to the start and end of the influenza season)



According to national surveillance data, both influenza A and B co-circulated in the 2017/18 season with an atypical dynamic – two consecutive waves due to the circulation of A(H1N1)pdm09 followed by B/Yamagata lineage – whereas the 2018/19 season was dominated by subtype A(H3N2) with almost no detection of type B viruses.



Available from:

- Surveillance de la grippe en France, saison 2017-2018 (French)  
<https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-et-infections-respiratoires/grippe/documents/article/surveillance-de-la-grippe-en-france-saison-2017-2018>
- Surveillance de la grippe en France, saison 2018-2019 (French)  
<https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-et-infections-respiratoires/grippe/documents/article/surveillance-de-la-grippe-en-france-saison-2018-2019>

**Table S6.** Composite outcomes and selected complications among adults hospitalised with respiratory syncytial virus or influenza with or without use of antiviral therapy, winter seasons 2017-18 and 2018-19

	aPR (95% CI)*			
	All RSV (+) vs Influenza (+) with or without use of antiviral therapy		All RSV (+) vs Influenza (+) without use of antiviral therapy	
<b>In-hospital composite outcome<sup>a</sup></b>	1.49	(1.08-2.11)	1.35	(1.04-1.81)
Complication during hospitalisation (at least one), n (%)				
Pneumonia	1.10	(0.77-1.58)	1.19	(0.88-1.60)
Respiratory failure	1.58	(1.11-2.25)	1.38	(1.09-1.78)
Acute heart failure	1.48	(0.92-2.28)	1.37	(0.92-2.05)
Acute respiratory distress syndrome (ARDS)	2.00	(1.29-3.11)	1.85	(1.36-2.51)
Acute renal failure	1.00	(0.65-1.53)	1.18	(0.78-1.80)
Length of stay (≥7 days), n (%)	1.91	(1.38-2.65)	1.67	(1.24-2.24)
Intensive care unit (ICU) admission, n (%)	2.03	(1.41-2.93)	1.51	(1.16-2.15)
Invasive mechanical ventilation support, n (%)	1.65	(1.13-2.41)	1.52	(1.13-2.05)
<b>Post-discharge composite outcome<sup>b</sup></b>	1.14	(0.82-1.60)	0.99	(0.75-1.32)
Cumulative mortality, n (%)				
Within 30 days after hospital discharge	1.39	(0.88-2.19)	1.66	(1.06-2.59)
Within 90 days after hospital discharge	1.51	(0.98-2.31)	1.39	(0.94-2.06)
Readmission within 90 days of hospital discharge, n (%)	1.01	(0.67-1.43)	0.98	(0.67-1.43)

Abbreviations: aPR, adjusted prevalence ratio; 95% CI, 95% confidence interval.

\*Adjusted PR 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).

<sup>a</sup> Defined as in-hospital complications (at least one), length of stay (≥7 days), ICU admission, invasive mechanical ventilation support or death.

<sup>b</sup> Defined as mortality within 30 and 90 days or readmission within 90 days after hospital discharge.

**Table 4.** Composite outcomes and selected complications among adults hospitalised with respiratory syncytial virus or influenza, winter seasons 2017-18 and 2018-19 (excluding co-infections)

	RSV + (n = 108)	Influenza + (n = 431)	aPR* (95% CI)	p
<b>In-hospital composite outcome<sup>a</sup></b>	68/108 (63)	215/431 (50)	1.5 (1.1-2.1)	0.018
Complication during hospitalisation (at least one), n (%)				
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
Acute respiratory distress syndrome (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), n (%)	69/108 (64)	189/431 (44)	1.9 (1.4-2.7)	<0.001
Intensive care unit (ICU) admission, n (%)	26/108 (24)	72/431 (17)	2.0 (1.4-2.9)	<0.001
Invasive mechanical ventilation support, n (%)	17/108 (16)	53/431 (12)	1.7 (1.1-2.4)	0.010
<b>Post-discharge composite outcome<sup>b</sup></b>	41/101 (41)	119/370 (32)	1.1 (0.8-1.6)	0.438
Cumulative mortality, n (%)				
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, n (%)	28/91 (31)	90/346 (26)	1.0 (0.7-1.4)	0.914

Abbreviations: aPR, adjusted prevalence ratio; 95% CI, 95% confidence interval.

\*Adjusted PR 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).

<sup>a</sup> Defined as in-hospital complications (at least one), length of stay (≥7 days), ICU admission, invasive mechanical ventilation support or death.

<sup>b</sup> Defined as mortality within 30 and 90 days or readmission within 90 days after hospital discharge.