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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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1 Abstract

2 *Objectives:* To describe the clinical characteristics and in/out-hospital outcomes of
3 respiratory syncytial virus (RSV) infection among adults hospitalised with influenza-like
4 illness (ILI) and compared against patients admitted for influenza.

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

15 *Results:* Overall, 1,428 hospitalised adults with ILI were included. RSV was detected in 8%
16 (114/1428) and influenza virus in 31% (437/1428). Patients hospitalised with RSV were older
17 than those with influenza (mean age, 73.0 vs 68.8 years; $p=0.015$) with a higher frequency of
18 respiratory (52% vs 39%, $p=0.012$) or cardiac chronic diseases (52% vs 41%, $p=0.039$) and
19 longer hospitalisation duration (median stay 8 vs 6 days, $p<0.001$). Anti-influenza therapies
20 were less prescribed among RSV than influenza patients (20% vs 66%, $p<0.001$). In-hospital
21 composite outcome was poorer in RSV patients (adjusted prevalence ratio (aPR)=1.5; 95%
22 Confidence Interval (95% CI) 1.1-2.1) than in those hospitalised with influenza. No difference
23 was observed for the post-discharge composite outcome (aPR=1.1; 95% CI 0.8-1.6).

24 *Conclusion:* RSV infection results in serious respiratory illness with in-hospital outcomes
25 worse than influenza and with similar midterm post-discharge outcomes.

1 **In-hospital and midterm out-hospital complications of adults hospitalised with** 2 **respiratory syncytial virus infection in France, 2017-2019: an observational study**

3

4 **Introduction**

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

14 Nevertheless, the occurrence of RSV infections in adults is difficult to assess and it
15 remains clinically under-diagnosed (7). In addition, due to cost and lack of specific antiviral
16 drugs, adults hospitalised for acute respiratory illness are often not tested for RSV (or other
17 respiratory viruses), but only for influenza virus. However, the development of more sensitive
18 molecular methods, such as multiplex reverse transcription polymerase chain reaction (RT-
19 PCR), has improved the detection of respiratory viruses providing new epidemiological
20 information (8).

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

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

1

2 Methods

3 *Study design and participants*

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

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

24 Electronic medical records and interviews with patients or families were used to
25 collect socio-demographic and baseline characteristics at admission including chronic
26 underlying conditions, ILI episode presentation and subsequent in-hospital treatments, length
27 of stay and clinical outcomes. The details of the definitions are displayed in **Supplementary**

1 **tables S1.** Patients or their relatives and general practitioners were contacted by phone to
2 collect follow-up data at 1 and 3 months after hospital discharge.

3

4 *In-hospital and post-discharge outcomes*

5 Two composite outcomes including hospital utilization and clinical outcomes were defined as
6 follows: (i) in-hospital outcome which was a composite of the occurrence of at least one
7 complication (pneumonia, respiratory failure, acute respiratory distress syndrome or acute
8 heart failure) or length of stay ≥ 7 days or intensive care unit (ICU) admission or use of
9 invasive mechanical ventilation for support or in-hospital death, and (ii) post-discharge
10 outcome which was a composite of 30- and 90-day all-cause mortality or 90-day readmission
11 after discharge.

12

13 *Respiratory virus identification*

14 RSV, influenza virus, and other respiratory viruses (adenovirus, bocavirus 1-4, coronavirus
15 229E, OC43 and NL63, human metapneumovirus, parainfluenza virus 1-4 and picornavirus)
16 were detected by multiplex RT-PCR in nasopharyngeal swabs using Allplex™ Respiratory
17 Panels 1, 2, 3 or Anyplex™ II RV 16 detection kit (Seegene, South Korea). Any available
18 bronchoalveolar lavage fluid samples or tracheal aspirates were also tested. Samples were
19 tested in the virology laboratory of each participating hospital.

20

21 *Statistical analysis*

22 We first compared baseline characteristics, clinical presentation and in-hospital and post-
23 discharge outcomes of all adult patients hospitalised with ILI during the two influenza
24 seasons. Adults hospitalised with RSV-influenza co-infections were excluded from the
25 analysis. Univariate analyses were used to compare RSV-positive patients to two different
26 comparison groups: (a) all RSV-negative patients (including influenza-positive patients,
27 patients infected by other respiratory viruses and patients with no respiratory virus detected)
28 and (b) influenza-positive patients. Descriptive data are presented as medians with

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

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

17

18 *Ethics*

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

23

24 *Results*

25 *Study population*

26 Overall, 1428 adults hospitalised with ILI were included in the FLUVAC study: 712 during the
27 2017-18 season and 716 during the 2018-19 season (**Figure 1**). Their mean age was 68

1 years (range 19-98) and 55% were male. Most patients (87%) had at least one underlying
2 condition, mainly respiratory (47%) or cardiac chronic disease (40%). The proportion of
3 seasonal influenza vaccination was 52%, and 48% of patients had been hospitalised within
4 the last 12 months.

5 At least one respiratory virus was detected in 53% of adults hospitalised with ILI
6 symptoms (**Supplementary table S2**). In total, 114 individuals tested positive for RSV (52
7 and 62 patients for the 2017-18 and 2018-19 seasons, respectively), representing 8% of the
8 total population and 15% of those positive for at least one respiratory virus. The most
9 frequently detected virus was influenza (31%, n = 437) followed by picornavirus (9%, n =
10 125), RSV (8%, n = 114), coronavirus (3%, n = 44) and metapneumovirus (3%, n = 40). After
11 exclusion of RSV-influenza co-infections (n = 6), 1422 patients were further analysed (709
12 and 713 patients for the 2017-18 and 2018-19 seasons, respectively).

13

14 *Characteristics and outcomes of RSV-positive patients*

15 Among patients with laboratory-confirmed RSV infection (n = 108 after excluding the 6 co-
16 infections with influenza virus), 52% were female and their mean age was 73 years (range
17 30-97, **Table 1**). The majority had at least one chronic condition (90%), mostly respiratory
18 (52%) and cardiac chronic diseases (52%), or diabetes mellitus (24%). At admission, RSV-
19 positive patients were more likely to have a chronic cardiac disease than RSV-negative
20 patients (52% vs 39%, p = 0.008). Patients with RSV had a longer hospital stay than those
21 without (**Table 2**), with a higher median length of stay (8 vs 6 days, p = 0.005) and a greater
22 frequency of stays longer than 7 days (64% vs 49%, p = 0.003). During hospitalisation, 58%
23 of patients with RSV had at least one complication, mainly respiratory failure (31%),
24 pneumonia (31%) or heart failure (15%). Among those with a complication, the median
25 length of stay for RSV-positive patients was 9 days (IQR, 5-16). A total of 26 RSV-positive
26 patients (24%) were admitted to ICU. All-cause mortality during hospitalisation was 3%
27 (**Table 2**), and the cumulative mortality within 30- and 90-days after hospital discharge was
28 9% and 13%, respectively (**Table 3**).

1

2 *Comparison of RSV-positive and influenza-positive patients*

3 In univariate analysis, adults hospitalised with RSV were older (mean age, 73.0 vs 68.8
4 years; $p = 0.015$), and more likely to have a chronic respiratory or cardiac disease (52% vs
5 39%, $p = 0.012$ and 52% vs 41%, $p = 0.039$, respectively), and to be vaccinated against
6 seasonal influenza (59% vs 48%, $p = 0.037$) compared to those with influenza (**Table 1**). Use
7 of corticosteroids therapy was more prevalent among patients with RSV than those with
8 influenza (20% vs 12%, $p = 0.026$ for systemic and 30% vs 21%, $p = 0.048$ for inhaled
9 corticosteroids therapy). RSV-positive patients reported significantly more dyspnoea (91% vs
10 71%) but less headache (21% vs 35%) and myalgia (18% vs 31%) than influenza-positive
11 patients.

12 In-hospital characteristics and outcomes for patients with RSV and influenza are
13 described in **Table 2**. The median length of stay was greater among RSV positive compared
14 to influenza-positive patients (8 days (IQR, 5-13) vs 6 days (IQR, 3-10), $p < 0.001$). Similarly,
15 prolonged hospitalisations (≥ 7 days) were more frequent (64% vs 44%, $p < 0.001$). They
16 were also more likely to present at least one complication during their hospitalisation (58% vs
17 47%, $p = 0.030$), in particular respiratory failure (31% vs 16%, $p < 0.001$). As expected, the
18 use of anti-influenza therapies was significantly different between RSV and influenza patients
19 (20% vs 66%), representing 31% in the whole cohort, 98% of which was oseltamivir. ICU
20 admission, in-hospital mortality and post-discharge follow-up did not differ between adults
21 infected with RSV or influenza (**Tables 2 and 3**).

22 In multivariate analysis, the prevalence ratio of in-hospital composite outcome was
23 significantly higher among adults hospitalised with RSV compared to those hospitalised with
24 influenza (aPR = 1.5; 95% CI 1.1-2.1, **Table 4**). The occurrence of respiratory complications
25 during hospitalisation was more common in RSV-infected adults, including respiratory failure
26 (aPR = 1.6; 95% CI 1.1-2.3) and acute respiratory distress syndrome (aPR = 2.0; 95% CI
27 1.3-3.1). Intensive care unit admission (aPR = 2.0; 95% CI 1.4-2.9) and use of invasive
28 mechanical ventilation (aPR = 1.7; 95% CI 1.1-2.4) were greater among those infected with

1 RSV than with influenza. Readmission within 90 days of hospital discharge (aPR = 1.0; 95%
2 CI 0.7-1.4), cumulative mortality within 30- and 90-days after hospital discharge (aPR = 1.4;
3 95% CI 0.9-2.2 and aPR = 1.5; 95% CI 1.0-2.3) and post-discharge composite outcome
4 (aPR = 1.1; 95% CI 0.8-1.6) did not differ between patients with RSV and those with
5 influenza. Adjusted prevalence ratios did not vary according to influenza vaccination status
6 when compared to vaccinated and non-vaccinated influenza-positive patients
7 **(Supplementary table S3).**

8

9 Discussion

10 In this post-hoc analysis of a prospective, multicentre study, including 1428 adults
11 hospitalised in France with ILI during two consecutive winter seasons before the SARS-CoV-
12 2 pandemic, RSV was the third most frequently found respiratory virus (8%, 95%CI 6-9).
13 Adults hospitalised with RSV were slightly older, with frequent chronic conditions, and
14 frequently presented complications. In-hospital outcomes were more severe compared to
15 those of influenza-positive patients. Midterm post-discharge outcomes, including 30- and 90-
16 day all-cause mortality or 90-day readmission after discharge, were similar in RSV- and
17 influenza-positive patients.

18 The rate of RSV infection is consistent with previous estimates, from a retrospective
19 cohort of hospitalised adults aged ≥ 18 years over three seasons, and among adults aged
20 ≥ 65 years with moderate-to-severe ILI episodes over four consecutive winters, all reporting
21 RSV rates in hospitalised patients ranging from 6 to 12% (1,16). Several factors may
22 influence the detection of RSV infection. First, the age at recruitment; several reports focused
23 on older adults (10,17), whereas we included all adults aged ≥ 18 years, a population in which
24 RSV infections are less prevalent (18). Second, the recruitment period in our study was the
25 same for both 2017-18 and 2018-19 winter seasons and was planned to cover RSV and
26 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

1 hospitalised with ILI and the role of bacterial concomitant infection is not fully understood as
2 a result of imprecise or no diagnostic testing. The absence of data on bacteriological results
3 at the time of presentation prevents us from addressing this issue.

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

16

17 Conclusion

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

25

26 Authors' contributions

1 A.D., P.L. and O.L. conceptualized the original study. A.D., P.L. and O.L. developed the
2 methodology. A.D. performed the analysis. A.D. and P.L. wrote the original manuscript. N.L.,
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4 reviewed the manuscript and agreed to be accountable for all aspects of the work. P.L and
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12

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14 The authors declare no conflict of interest related to the study. O.L. is principal investigator
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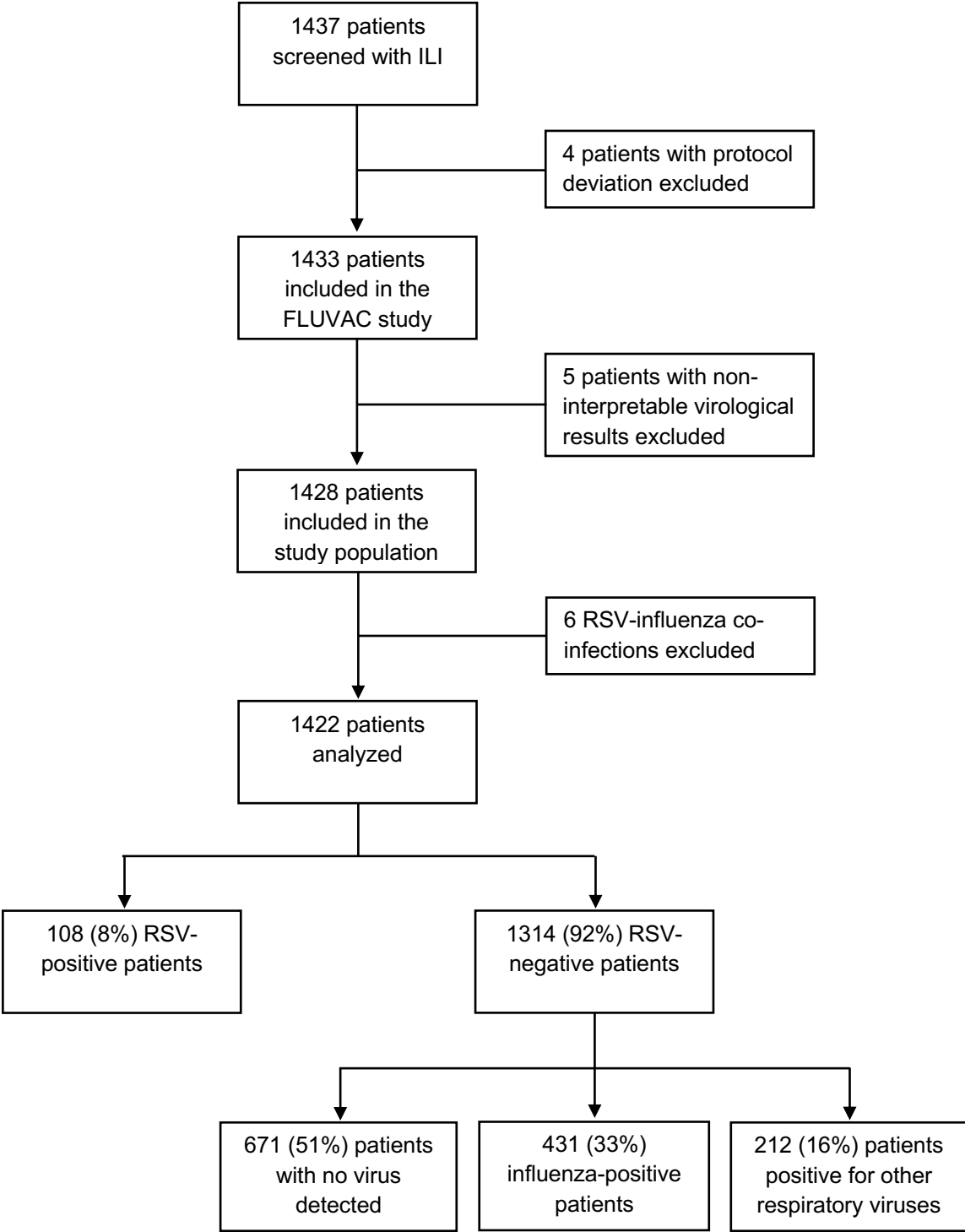
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2

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)

Baseline characteristics	RSV + (n = 108)	All RSV - (n = 1314)	p^a	Influenza + (n = 431)	p^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 ²)					
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^a	Influenza + (n = 431)	p^b
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
Clinical presentation					
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.

^a Comparison between RSV (+) and RSV (-) patients.

^b 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^a	Influenza + (n = 431)	p^b
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.

^a Comparison between RSV (+) and RSV (-) patients.

^b 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^a	Influenza + (n = 431)	p^b
Discharge setting after hospitalisation, n (%)			0.349		0.676
Home	84/105 (80)	954/1256 (76)		325/416 (78)	
Other setting ^c	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.

^a Comparison between RSV (+) and RSV (-) patients.

^b Comparison between RSV (+) and influenza (+) patients.

^c 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”

Contents:

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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

Category (and ICD-10 codes)	Underlying medical conditions ^a
<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
^a Chronic disease grouping followed national recommendations on influenza vaccination: https://solidarites-sante.gouv.fr/IMG/pdf/calendrier_vaccinal_300421.pdf	

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 ¹ and ATS/IDSA 2007/2019 guidelines ²
Respiratory failure	Defined as acute or chronic impairment of gas exchange causing hypoxia (PaO ₂ ≤60 mmHg) with or without hypercapnia (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) ³
Acute respiratory distress syndrome (ARDS)	According to Berlin criteria ⁴
Acute renal failure	According to KDIGO criteria ⁵
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 ⁶

¹ SPILF/AFSSAPS/SPLF, Antibiothérapie par voie générale dans les infections respiratoires basses de l'adulte, juillet 2010. Available from :

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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)

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

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

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

^b 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

In-hospital composite outcome	All RSV (+) vs. Influenza (+) unvaccinated ^a		All RSV (+) vs. Influenza (+) vaccinated ^b	
	aPR [*]	(95% CI)	aPR [*]	(95% CI)
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 (≥ 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)
Post-discharge composite outcome				
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.

^a Excluding only influenza (+) patients with current and prior season vaccination.

^b 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 ≥ 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)

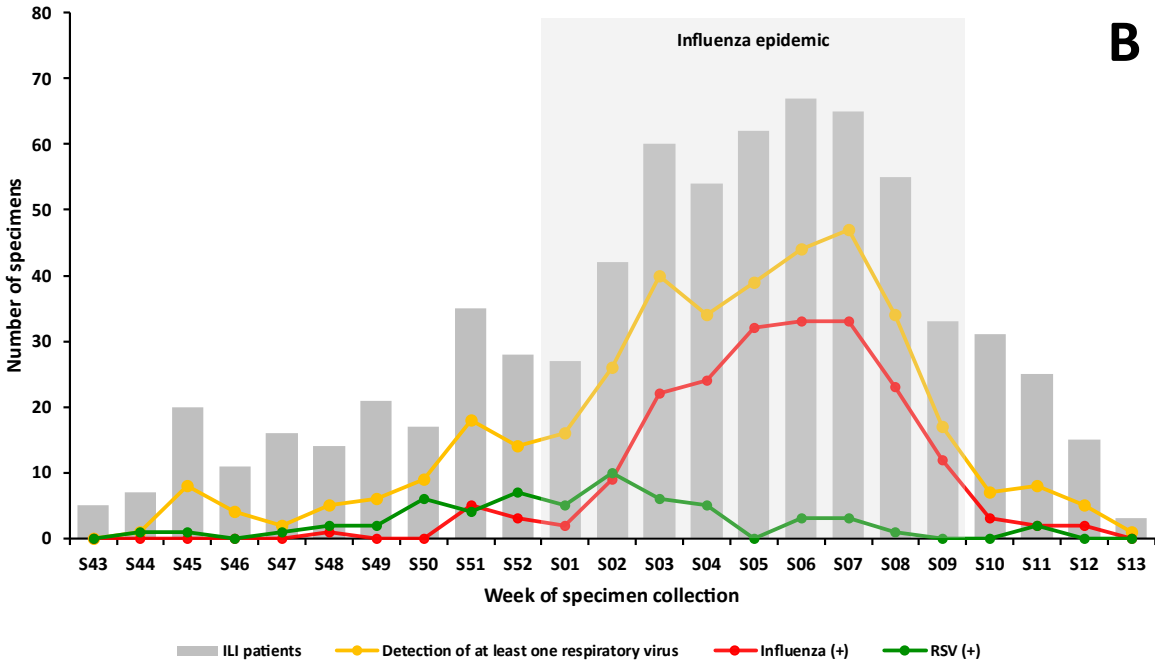
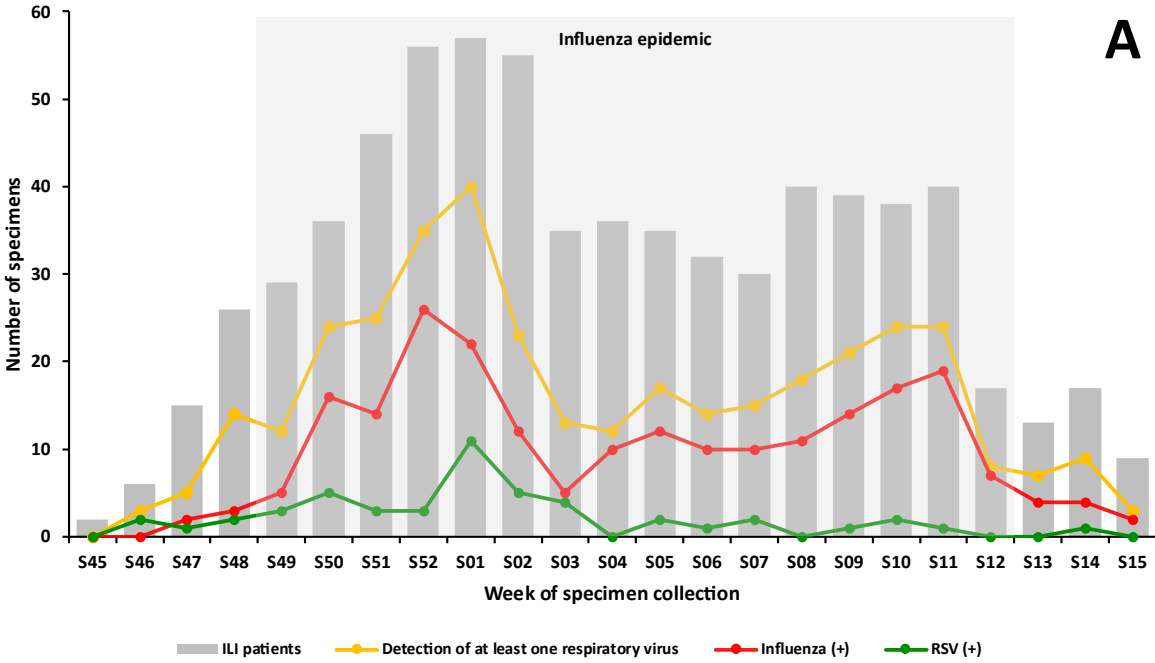
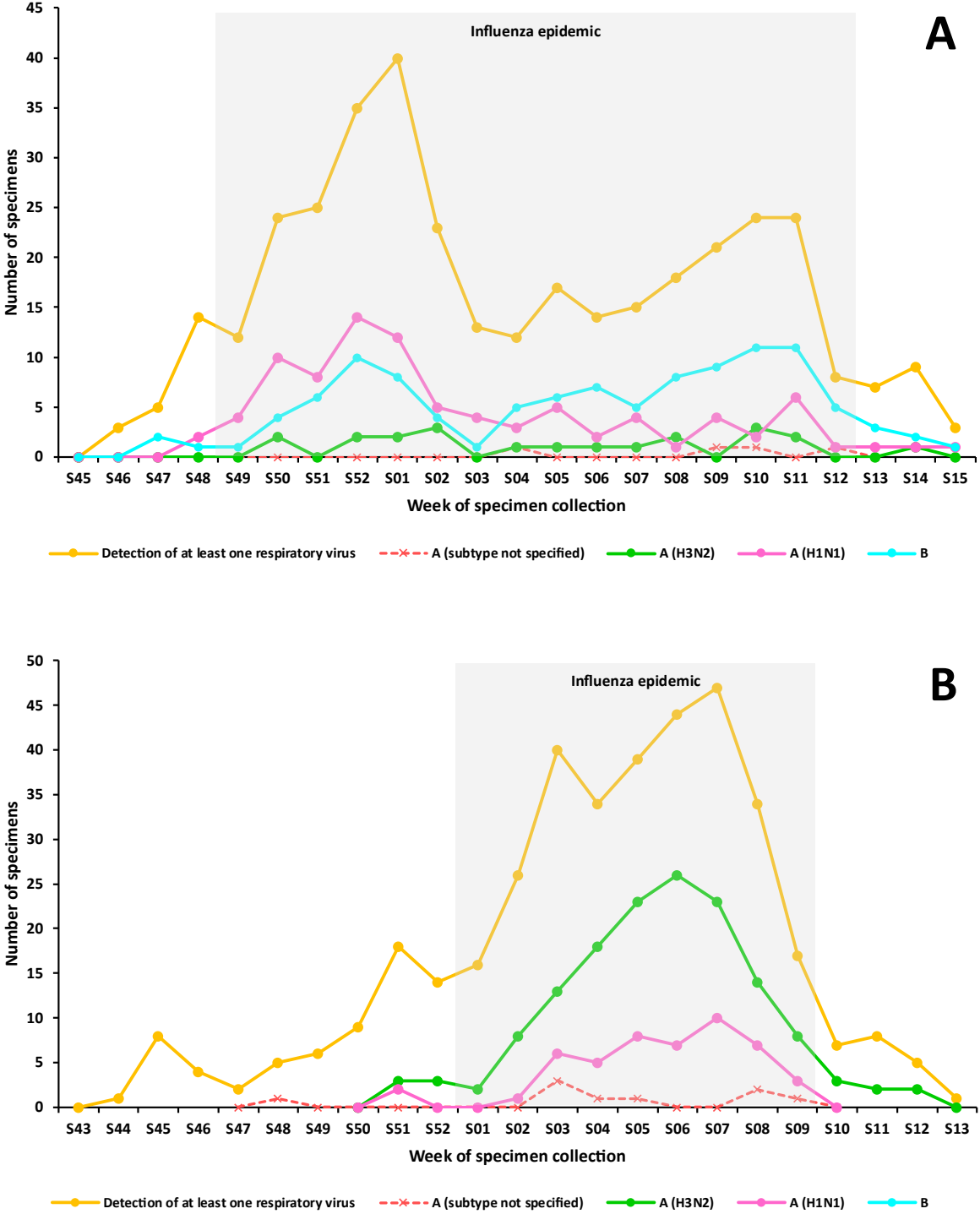


Figure S5. Distribution of influenza virus type and subtype among adults hospitalised with ILI in the FLUVAC study, by week, during A) winter season 2017-18 and B) winter season 2018-19 (the grey shaded areas correspond to the start and end of the influenza season)



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	
In-hospital composite outcome^a	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)
Post-discharge composite outcome^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).

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

^b 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
In-hospital composite outcome^a	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
Post-discharge composite outcome^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).

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

^b Defined as mortality within 30 and 90 days or readmission within 90 days after hospital discharge.