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Early and tardive extra-respiratory manifestations of Influenza and HRSV in hospitalized adults.

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Liste des abréviations

AGGIR	Autonomie Gérontologie Groupe IsoRessource
A(H1N1)pdm09	A(H1N1) pandemic (2009)
AIC	Akaike Interaction Criterion.
ALT	Alanine transaminase
ALP	Alcaline phosphatase
AST	Aspartate transaminase
BMI	Body Mass Index
CHU	Centre Hospitalier Universitaire
COPD	Chronic obstructive pulmonary disease
Covid-19	Coronavirus disease (2019 pandemic)
CPK	Creatine phosphokinase
CRP	C-Reactive Protein
ER	Emergency Room
GGT	Gamma-glutamyltranspeptidase
GIR	Groupe IsoRessource
HIV	Human Immunodeficiency Virus
HRSV	Human Respiratory Syncytial Virus
MDRD	Modification of diet in renal disease study equation
NA	Not applicable
ND	Not done
n.s.	non significant
PaO_2	Partial pressure of oxygen in arterial blood
PCR	Polymerase Chain Reaction
qSOFA score	Quick Sepsis Organ Failure Assessment score
SD	Standard deviation
SpO_2	Peripheral capillary oxygen saturation
TSH	Thyroid stimulating hormone

Early and tardive extra-respiratory manifestations of Influenza and HRSV in hospitalized adults

Authors

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Authors' contributions

Etienne Mériglier, Guillaume Béraud, Mélanie Catroux, France Cazenave-Roblot and Blandine Rammaert designed the study and the protocol.

Etienne Mériglier and Blandine Rammaert submitted the study design to local ethics committee's approbation.

Gaëtan Motillon and Nicolas Leveque screened the patients for the study.

Gaëtan Motillon, Mélanie Catroux, Thomas Brunet, Florence Boissier, Vanessa Bironneau, Pierre Poupin, Anne Keller and Mickaël Martin included patients, received their non-opposition, and collected their medical information.

Gaëtan Motillon recorded data for analysis.

Guillaume Béraud performed statistical analysis.

Gaëtan Motillon and Mickaël Martin wrote the manuscript.

All authors revised the manuscript and gave their full agreement for submission.

Abstract

Extra-respiratory manifestations of Influenza and Human Respiratory Syncytial Virus (HRSV) are barely known in adults. This study aimed to describe extra-respiratory manifestations of Influenza (and its subtypes) and HRSV in adults. Two hundred and forty-eight hospitalized patients, with positive polymerase chain reaction or molecular detection nasal test for Influenza or HRSV were prospectively included during winter 2018-2019. Hundred and eighteen (87.9%) patients had at least one extra-respiratory manifestation or more. The main extra-respiratory signs were cardiac, neurologic and urinary/digestive (41.6%, 33.7% and 59.0% for Influenza and 52.3%, 23.2% and 57.3% for HRSV, respectively). Muscular injury was infrequent in HRSV, compared to influenza ($p<0.001$). A(H1N1) Influenza infected fewer elderly patients ($p<0.001$), with fewer medical conditions, and expressed fewer cardiac disorders compared to A(H3N2) Influenza and HRSV-infected patients ($p=0.046$). In multivariate analysis, C-reactive protein (CRP) level at admission was the only variable significantly associated with the developpement of one overall extra-respiratory manifestation ($p=0.018$).

Key-words : Influenza, Human ; Respiratory Syncytial Virus, Human

Introduction

Influenza viruses and Human Respiratory Syncytial Virus (HRSV) are circulating around the world in seasonal epidemics, causing acute respiratory illnesses. Worldwide, according to recent estimations, more than 500.000 patients die of seasonal influenza infections each year, mostly due to pulmonary complications[1-3]. In Europe, HRSV causes early winter outbreaks, often preceding influenza[4], with similar morbidity and mortality[5-10].

Although early respiratory manifestations of Influenza and HRSV are well described in literature[1-10], there is a lack of evidence concerning extra-respiratory manifestations of both viruses, especially after decline of early signs of infection.

Extra-respiratory expressions of influenza and HRSV have been predominantly reported in children[11-16], especially in neurological and cardiologic forms. In adults, among systemic non-respiratory manifestations of A(H1N1) influenza reported since the 2009 pandemic, cardiac affections are the most widely documented[17-18], particularly myocarditis and pericarditis[19]. Many case reports of hepatic, neurologic, hematologic, renal affections have also been described[20-22], but there is a lack of evidence concerning their frequency and associated risk factors. For HRSV, no data exists on adults.

The aim of this study was to describe the early and tardive extra-respiratory manifestations of Influenza and HRSV in adults. Associated risk factors were also assessed.

Methods

Study design and patient recruitment

All the consecutive patients aged 18 years or older with positive nasal Polymerase Chain Reaction (PCR) test (Allplex™ PCR Multiplex Seegene Eurobio; BioFire® FilmArray® Biomérieux) or molecular detection (Xpert® Xpress Flu Cepheid), for Influenza or HRSV from December 2018 to May 2020 and hospitalized in the French tertiary center of Poitiers University Hospital or Montmorillon Hospital were asked to participate in the study. Patients who did not speak French or were unable to understand the rules and implications of the study, patients with a documented nasal PCR viral coinfection, outpatients and end-of-life care patients were excluded as well as those who accepted to participate over 14 days after the positive PCR test to avoid memory biases.

The study was approved by the local ethics committee. All patients provided written non-opposition. When non-opposition consent was impossible to obtain (i.e. neurologic conditions, respiratory distress or shock), agreement was first obtained via a designated reliable person, until the patient itself was able to fully approve the inclusion, otherwise the patient was excluded.

Data collection

Patients were given a first questionnaire containing 15 items in order to describe early symptoms appeared within 7 days before test positivity (Appendix 1).

Patient data were collected during hospital stay: demographic values (age, sex, body mass index [BMI]); medical history; vaccinal status about Influenza; autonomy of patients over 65 years old using the French classification Autonomie Gérontologie Groupe IsoRessource (AGGIR) (ranging from 6 (full autonomy) to 1 (totally dependent)); Influenza subtype; severity at admission, assessed with the quick Sepsis Organ Failure Assessment score (qSOFA score) (containing 3 criteria: respiratory rate ≥22 cycles per minute, systolic blood pressure ≤100 mmHg, or altered mental status); oseltamivir treatment; respiratory and extra-respiratory manifestations during hospitalization along with biological and radiological results (Appendix 2).

At day 30, patients were asked to answer another questionnaire to describe tardive symptoms experienced within 1 month after viral detection, either directly if the patient was still in hospital, or

by phone call (Appendix 3), and evolution data were assessed (date of release, new hospitalization, death) from patient or general practitionner, and medical records.

Outcome measures

The primary outcome was the frequency and the type of each in-hospital extra-respiratory manifestation related to influenza or HRSV. The secondary outcomes included early and tardive extra-respiratory manifestations, patient's outcome, number of extra-respiratory manifestations and identification of associated risk factors.

Statistics

Sample size was estimated using formula $n = [z^2 * p (1-p)] / e^2$, where z stands for normal standard deviation (1.96 for an alpha risk of 5%), p is the predicted proportion of extra-respiratory manifestations (according to cardiac complications that are the most widely described in the literature, ranging from 0.4 to 22%[18], and neurologic complications estimated around 11%[21], an approximation of 15% extra-respiratory manifestations was retained), and e stands for margin error, set at 0.05. Indeed, the sample size n was 196 patients. Accepting a risk of 10% of participation refusals, a minimal number of 216 patients was considered necessary.

Qualitative variables were compared with χ^2 test or Fischer's exact test. Quantitative variables following normal distribution were compared using the Student's t-test. Non-normally distributed quantitative values were compared with the Mann-Whitney/Wilcoxon test. Simple linear regression was performed to identify factors associated with each extra-respiratory manifestation. Automated step-by-step regression was used to select parameters for multiple linear regression for multivariate models. Models were selected by lowest Akaike Information Criterion[23], for better compromise between parsimony and likelihood.

Statistical analysis was performed using R. 4.0.4 software (2021-02-15) (R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

Results

Inclusion

From December 3rd, 2018 to March 14th, 2019, 538 patients aged 18 years and older with positive nasal PCR test for Influenza or HRSV were screened. Among them, 290 were excluded due to the following: inability to consent (n=48) (dementia or mental illness [n=40], end-of-life care [n=2] and not speaking French [n=6]); death before inclusion (n=30); outpatients (n=96); discharge from the hospital before inclusion in the study (n=43); viral coinfection (n=25); refusals (n=8); missing data (n=8); over the 14-day limit (n=14); duplicates (n=18). Finally, 248 patients were included in the study (figure 1).

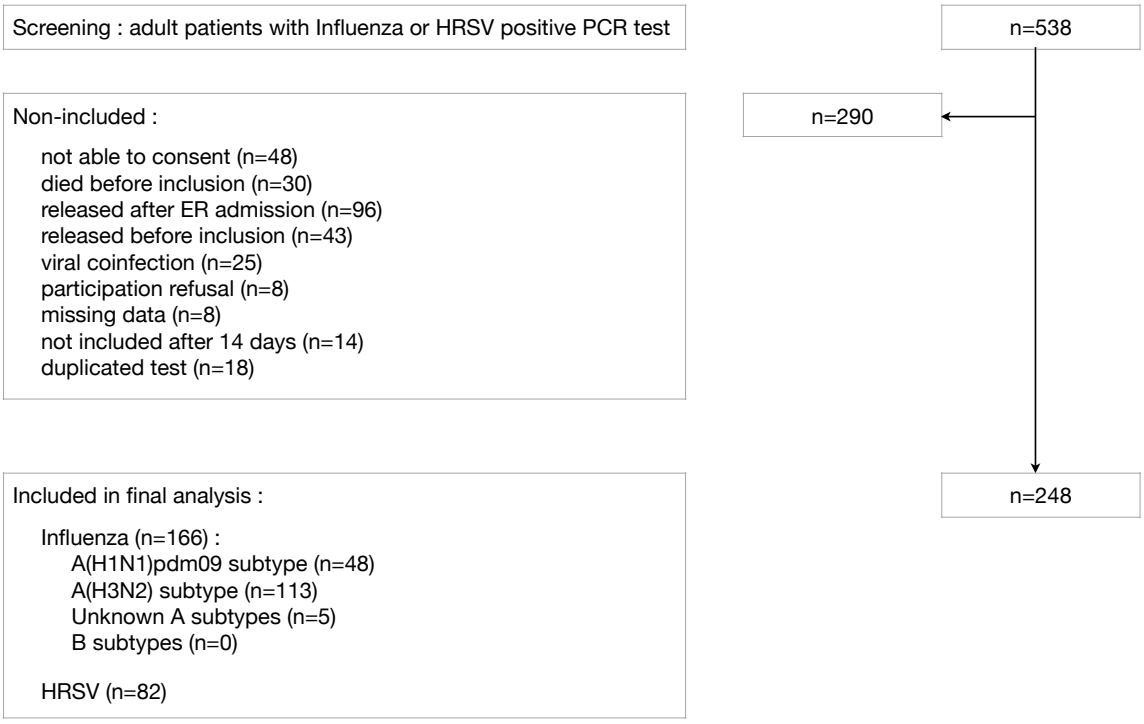

Figure 1. Flowchart

HRSV: Human Respiratory Syncytial Virus. PCR: Polymerase Chain Reaction. ER: emergency room.

Virologic subtypes

Among the 248 patients included, 166 were infected with Influenza and 82 with HRSV. Subtypes of Influenza were recorded for 161 patients: 48 A(H1N1)pdm09 and 133 A(H3N2), with no B influenza detected. Five patients had positive rapid molecular detection for Influenza (using Xpert® Xpress Flu Cepheid method), that could not inform about the Influenza subtype. They were therefore included in the full cohort as Influenza-infected patients but were not considered in subgroup analysis.

Baseline characteristics

Clinical characteristics at admission are depicted in table 1. The mean age was 74±16.2 years with 74.6% over 65 years, and 54.8% female. Arterial hypertension was the main comorbidity (63.3%). Fifteen percent were active smokers. Forty percent of patients had been vaccinated against Influenza.

Baseline clinical characteristics were similar between Influenza and HRSV groups, except for stroke and cardiac arrythmia history, more frequent for HRSV (20.7% *vs* 10.2%, p=0.031 and 46.3% *vs* 31.3%, p=0.025, respectively). In contrast, the clinical characteristics differed significantly between Influenza subtypes. Indeed, compared to A(H3N2) and HRSV, A(H1N1)pdm09 was less frequent in patients over 65 years (p<0.001), and A(H1N1) patients had less arterial hypertension (p=0.005), fewer cardiovascular diseases (p=0.004), less cardiac arrythmia (p=0.006) and less neurological disease (p=0.023). On the other hand, A(H3N2)-infected patients more frequently had chronic kidney diseases (p<0.001) (Table 1).

Early symptoms

The first questionnaire given at admission was fulfilled by 196 patients (79.0% of total cohort). The main early symptoms acquired within 7 days before viral diagnosis were cough (81.6%), dyspnea (69.5%), fever (50.5%) and diverse neurological signs (45.5%) such as headache and motor weakness. Compared to HRSV, Influenza infected patients reported more frequently fever (58.3% *vs* 34.4%, p=0.003), muscular pain (39.1% *vs* 15.4%, p=0.001) and red eye (56.5% *vs* 10%, p=0.021), globally equally distributed between A(H1N1) and A(H3N2) expect for confusion/ behavior disorder which were more frequent in the A(H3N2) sub-group (p=0.042) (Table 2).

Table 1. Baseline clinical characteristics

Baseline characteristics [a]	All (n=248)[b]	Influenza (n=166)	HRSV (n=82)	p	A(H1N1) (n=48)	A(H3N2) (n=113)	HRSV (n=82)	p
Age (in years) - mean (SD)	74.0 (16.2)	73.0 (17.0)	76.0 (14.3)	0.148	62.4 (18.6)	78.2 (13.5)	76.0 (14.3)	0.254
Age>65 years	185 (74.6%)	121 (72.9%)	64 (78.0%)	0.470	23 (47.9%)	95 (84.1%)	64 (78.0%)	<0.001*
Dependant elderly people[c]	26 (14.3%)	18 (14.9%)	8 (13.1%)	0.826	1 (4.0%)	17 (18.3%)	8 (13.1%)	0.206
Male sex	112 (45.2%)	80 (48.2%)	32 (39.0%)	0.219	24 (50.0%)	56 (49.6%)	32 (39.0%)	0.291
Weight (in kilogram) - mean (SD)	72.9 (19.3)	72.8 (18.3)	73.2 (21.3)	0.883	75.8 (20.3)	71.2 (16.6)	73.2 (21.3)	0.389
Overweight/obesity	126 (51.6%)	87 (53.0%)	39 (47.6%)	0.621	22 (46.8%)	62 (55.4%)	39 (47.6%)	0.516
Diabetes	53 (21.4%)	34 (20.5%)	19 (23.2%)	0.748	5 (10.4%)	28 (24.8%)	19 (23.2%)	0.753
Hypertension	157 (63.3%)	101 (60.8%)	56 (68.3%)	0.315	21 (43.8%)	79 (69.9%)	56 (68.3%)	0.005*
Cardiovascular disease	134 (54.0%)	87 (52.4%)	47 (57.3%)	0.552	16 (33.3%)	69 (61.1%)	47 (57.3%)	0.004*
Cardiac arrythmia	90 (36.3%)	52 (31.3%)	38 (46.3%)	0.025*	9 (18.8%)	42 (37.2%)	38 (46.3%)	0.006*
Active smoker	38 (15.4%)	25 (15.2%)	13 (15.9%)	1.000	10 (21.3%)	14 (12.4%)	13 (15.9%)	0.336
Chronic respiratory disease	96 (38.7%)	60 (36.1%)	36 (43.9%)	0.269	14 (29.2%)	44 (38.9%)	36 (43.9%)	0.249
Neurological condition	43 (17.3%)	32 (19.3%)	11 (13.4%)	0.288	4 (8.3%)	28 (24.8%)	11 (13.4%)	0.023*
Stroke	34 (13.7%)	17 (10.2%)	17 (20.7%)	0.031*	5 (10.4%)	12 (10.6%)	17 (20.7%)	0.113
Chronic kidney disease	101 (40.7%)	75 (45.2%)	26 (31.7%)	0.054	13 (27.1%)	61 (54.0%)	26 (31.7%)	<0.001*
Hepatic underlying condition	12 (4.8%)	7 (4.2%)	5 (6.1%)	0.538	3 (6.2%)	4 (3.5%)	5 (6.1%)	0.586
Solid organ transplant	7 (2.8%)	6 (3.6%)	1 (1.2%)	0.431	3 (6.2%)	3 (2.7%)	1 (1.2%)	0.228
Bone marrow transplant	3 (1.2%)	2 (1.2%)	1 (1.2%)	1.000	2 (4.2%)	0 (0.0%)	1 (1.2%)	0.084
HIV-positive patients	1 (0.4%)	1 (0.6%)	0 (0.0%)	1.000	0 (0.0%)	1 (0.9%)	0 (0.0%)	1.000
Sickle cell anemia	1 (0.4%)	1 (0.6%)	0 (0.0%)	1.000	1 (2.1%)	0 (0.0%)	0 (0.0%)	0.198
Primary immune deficiency	4 (1.6%)	4 (2.4%)	0 (0.0%)	0.305	2 (4.2%)	2 (1.8%)	0 (0.0%)	0.190
History of cancer	49 (19.8%)	31 (18.7%)	18 (22.0%)	0.612	9 (18.8%)	22 (19.5%)	18 (22.0%)	0.912
Hematological malignancy	23 (9.3%)	18 (10.8%)	5 (6.1%)	0.255	7 (14.6%)	11 (9.7%)	5 (6.1%)	0.261
Auto-immune disease	26 (10.5%)	15 (9.0%)	11 (13.4%)	0.378	9 (18.8%)	6 (5.3%)	11 (13.4%)	0.020*
Influenza-vaccinated	83 (39.9%)	61 (42.1%)	22 (34.9%)	0.359	12 (27.3%)	48 (49.5%)	22 (34.9%)	0.027*
Pregnancy	2 (0.8%)	1 (1.2%)	1 (2.0%)	1.000	0 (0.0%)	0 (0.0%)	1 (2.0%)	0.562

HRSV: Human Respiratory Syncytial Virus. SD: standard deviation. HIV: Human Immunodeficiency virus.

[a] Unless otherwise specified, all values are expressed in n (%).

[b] Subtype of Influenza was unknown for 5 patients. They were included in analysis in « Influenza » group but excluded from subgroup analysis.

[c] Groupe IsoRessource (GIR) 1 and GIR2 patients among patients over 65 years old.

* Considered as significant.

Table 2. Early symptoms.

Early symptoms[a]	All (n=196)[b]	Influenza (n=132)	HRSV (n=64)	p	A(H1N1) (n=38)	A(H3N2) (n=89)	HRSV (n=64)	p
Fever	99 (50.5%)	77 (58.3%)	22 (34.4%)	0.003*	23 (60.5%)	50 (56.2%)	22 (34.4%)	0.009*
Pharyngeal pain	66 (33.7%)	45 (34.1%)	21 (32.8%)	0.987	18 (47.4%)	27 (30.3%)	21 (32.8%)	0.186
Associated with odynophagia	39 (44.8%)	27 (47.4%)	12 (40.0%)	0.667	9 (39.1%)	18 (54.5%)	12 (40.0%)	0.396
Cough	160 (81.6%)	108 (82.4%)	52 (80.0%)	0.826	32 (84.2%)	71 (80.7%)	52 (80.0%)	0.914
Productive cough	97 (60.2%)	65 (60.2%)	32 (60.4%)	1.000	19 (61.3%)	43 (59.7%)	32 (60.4%)	1.000
Dyspnea	137 (69.5%)	88 (66.7%)	49 (75.4%)	0.278	25 (67.6%)	59 (65.6%)	49 (75.4%)	0.433
Palpitation	52 (26.3%)	34 (25.6%)	18 (27.7%)	0.883	11 (28.9%)	21 (23.3%)	18 (27.7%)	0.731
Chest pain	36 (18.2%)	27 (20.3%)	9 (13.8%)	0.363	9 (23.7%)	18 (20.0%)	9 (13.8%)	0.424
Muscular pain	62 (31.3%)	52 (39.1%)	10 (15.4%)	0.001*	16 (42.1%)	32 (35.6%)	10 (15.4%)	0.004*
Neurological signs	85 (45.5%)	58 (46.0%)	27 (44.3%)	0.943	20 (54.1%)	34 (40.5%)	27 (44.3%)	0.381
Headache	59 (53.2%)	40 (55.6%)	19 (48.7%)	0.624	16 (69.6%)	21 (46.7%)	19 (48.7%)	0.186
Associated with fever	35 (45.5%)	29 (64.4%)	6 (18.8%)	<0.001*	10 (62.5%)	18 (69.2%)	6 (18.8%)	<0.001*
Associated with photophobia	14 (17.9%)	11 (24.4%)	3 (9.1%)	0.148	1 (5.9%)	9 (36.0%)	3 (9.1%)	0.014*
Vision disturbance	16 (13.6%)	11 (14.3%)	5 (12.2%)	0.973	2 (8.0%)	8 (16.7%)	5 (12.2%)	0.598
Neuropathic pain	11 (8.8%)	10 (12.5%)	1 (2.2%)	0.096	2 (8.0%)	7 (13.7%)	1 (2.2%)	0.117
Paresthesia	28 (21.9%)	20 (24.1%)	8 (17.8%)	0.547	3 (11.1%)	17 (32.7%)	8 (17.8%)	0.067
Motor weakness	38 (30.6%)	25 (31.2%)	13 (29.5%)	1.000	5 (20.0%)	18 (35.3%)	13 (29.5%)	0.423
Confusion/behaviour disorder	26 (22.8%)	20 (27.4%)	6 (14.6%)	0.185	3 (12.5%)	16 (35.6%)	6 (14.6%)	0.042*
Digestive symptoms	63 (33.0%)	44 (34.1%)	19 (30.6%)	0.755	15 (40.5%)	26 (29.5%)	19 (30.6%)	0.473
Abdominal pain	34 (45.3%)	24 (46.2%)	10 (43.5%)	1.000	7 (41.2%)	15 (48.4%)	10 (43.5%)	0.867
Nausea/vomiting	36 (48.0%)	26 (51.0%)	10 (41.7%)	0.613	7 (46.7%)	16 (50.0%)	10 (41.7%)	0.867
Diarrhea	42 (53.2%)	30 (55.6%)	12 (48.0%)	0.701	13 (68.4%)	14 (45.2%)	12 (48.0%)	0.251
Arthralgia	30 (15.2%)	21 (15.8%)	9 (13.8%)	0.883	7 (18.4%)	13 (14.4%)	9 (13.8%)	0.806
Associated with joint swelling	8 (22.9%)	5 (20.0%)	3 (30.0%)	0.661	1 (14.3%)	4 (23.5%)	3 (30.0%)	0.876
Ophthalmic signs	20 (10.3%)	14 (10.8%)	6 (9.4%)	0.961	4 (10.8%)	9 (10.1%)	6 (9.4%)	1.000
Red eye	14 (42.4%)	13 (56.5%)	1 (10.0%)	0.021*	5 (62.5%)	7 (53.8%)	1 (10.0%)	0.048*
Ocular pain	14 (42.4%)	11 (47.8%)	3 (30.0%)	0.455	2 (28.6%)	8 (57.1%)	3 (30.0%)	0.369
Visual loss	11 (34.4%)	8 (34.8%)	3 (33.3%)	1.000	2 (28.6%)	6 (42.9%)	3 (33.3%)	0.892
Rash	13 (6.6%)	8 (6.0%)	5 (7.7%)	0.761	2 (5.3%)	6 (6.7%)	5 (7.7%)	1.000
Testiular pain	1 (1.0%)	0 (0.0%)	1 (3.8%)	0.271	0 (0.0%)	0 (0.0%)	1 (3.8%)	0.490
Neck pain/swelling	10 (5.1%)	7 (5.3%)	3 (4.6%)	1.000	1 (2.6%)	6 (6.7%)	3 (4.6%)	0.763
Facial edema	9 (4.6%)	7 (5.3%)	2 (3.1%)	0.721	3 (7.9%)	4 (4.5%)	2 (3.1%)	0.545

HRSV: Human Respiratory Syncytial Virus. All values are expressed in n (%).

[a] Appeared within 7 days before viral diagnosis.

[b] Subtype of Influenza was unknown for 5 patients. They were included in analysis in « Influenza » group but excluded from subgroup analysis.

* Considered as significant.

Biological data

All patients had a biology within 48 hours after admission. The only difference was a lower neutrophilic count in the influenza group (5.7 *vs* 7.1 G/L, p=0.014). In subgroup analysis, compared to A(H1N1)pdm09 and HRSV, A(H3N2) had lower neutrophil and platelet counts (p=0.006 and p=0.009 respectively). There was no difference on hemoglobin, lymphocytes, and CRP levels or on liver markers between viral subtypes (Table 3).

Table 3. Baseline biological characteristics

Biological characteristics [a]	All (n=248)[b]	Influenza (n=166)	HRSV (n=82)	p	A(H1N1) (n=48)	A(H3N2) (n=113)	HRSV (n=82)	p
Hemoglobin (g/dL)	12.9 [11.6 - 14.0]	12.7 [11.6 - 14.0]	13.0 [11.6 - 13.9]	0.511	12.7 [11.0 - 14.5]	12.8 [11.8 - 14.0]	13.0 [11.6 - 13.9]	0.806
Leucocytes (G/L)	8.1 [6.0 - 10.9]	7.6 [5.6 - 10.4]	9.4 [6.8 - 12.0]	0.294	7.8 [5.9 - 9.7]	7.5 [5.5 - 10.3]	9.4 [6.8 - 12.0]	0.150
Neutrophils (G/L)	6.1 [4.3 - 8.9]	5.7 [4.1 - 8.0]	7.1 [4.8 - 10.2]	0.014*	6.3 [4.6 - 7.5]	5.3 [3.7 - 7.9]	7.1 [4.8 - 10.2]	0.006*
Lymphocytes (G/L)	0.9 [0.6 - 1.3]	0.9 [0.6 - 1.3]	1.0 [0.6 - 1.5]	0.320	0.9 [0.6 - 1.2]	0.8 [0.6 - 1.3]	1.0 [0.6 - 1.5]	0.173
Platelets (G/L)	201.5 [160.3 - 254.0]	195.5 [149.8 - 252.5]	214.5 [174.0 - 258.3]	0.105	215.5 [166.8 - 266.3]	187.0 [143.5 - 235.0]	214.5 [174.0 - 258.3]	0.009*
Serum creatinine (µmol/L)	83.0 [67.5 - 113.0]	85.0 [70.0 - 113.0]	78.0 [61.3 - 115.0]	0.229	76.5 [57.8 - 100.0]	87.0 [71.8 - 119.0]	78.0 [61.3 - 115.0]	0.342
MDRD (mL/min/1.73m²)	63.0 [48.0 - 90.0]	63.5 [47.0 - 91.3]	62.0 [49.0 - 88.8]	0.367	76.0 [54.5 - 99.3]	59.0 [47.0 - 84.0]	62.0 [49.0 - 88.8]	0.097
AST (IU/L)	27.0 [18.0 - 40.0]	30.5 [19.0 - 45.8]	22.5 [17.3 - 32.5]	0.878	32.0 [23.0 - 65.0]	29.0 [18.0 - 37.0]	22.5 [17.3 - 32.5]	0.983
ALT (IU/L)	20.0 [13.0 - 33.0]	20.0 [14.0 - 33.0]	20.0 [13.0 - 32.0]	0.980	23.0 [16.8 - 39.0]	17.0 [13.0 - 26.8]	20.0 [13.0 - 32.0]	0.355
GGT (IU/L)	49.5 [26.5 - 99.8]	53.0 [29.5 - 100.5]	39.5 [23.3 - 95.0]	0.996	60.0 [34.5 - 115.5]	47.5 [23.3 - 94.3]	39.5 [23.3 - 95.0]	0.733
ALP (IU/L)	78.0 [64.0 - 99.5]	78.0 [63.5 - 99.0]	80.0 [64.0 - 100.8]	0.596	70.5 [58.8 - 90.8]	79.5 [64.8 - 101.0]	80.0 [64.0 - 100.8]	0.913
CRP (mg/L)	51.0 [22.0 - 96.5]	56.0 [26.0 - 94.3]	43.5 [15.8 - 116.0]	0.780	65.0 [33.5 - 163.0]	50.0 [25.0 - 80.0]	43.5 [15.8 - 116.0]	0.092
TSH (mIU/L)	1.4 [0.8 - 2.3]	1.4 [0.9 - 2.3]	1.4 [0.6 - 2.4]	0.351	1.5 [0.9 - 3.1]	1.4 [0.9 - 2.3]	1.4 [0.6 - 2.4]	0.361

HRSV: Human Respiratory Syncytial Virus. MDRD: Modification of Diet in Renal Disease study equation. AST: Aspartate transaminase. ALT: Alanine transaminase. GGT: gamma-glutamyltranspeptidase. ALP: alcaline phosphatase. CRP: C-reactive protein. TSH: thyroid-stimulating hormone.

[a] All variables are expressed as median [Q1-Q3].

[b] Subtype of Influenza was unknown for 5 patients. They were included in analysis in « Influenza » group but excluded from subgroup analysis.

* Considered as significant.

In-hospital extra-respiratory manifestations

General condition

The median delay from first symptom to hospital admission was 3 days for both Influenza and HRSV groups. This time was longer in the A(H1N1)pdm09 subgroup compared to other subgroups (p=0.015). Fever was more frequent in the Influenza group (91.0% *vs* 58.5%, p<0.001), especially for A(H1N1) subtype (p<0.001). The rate of severe infection (qSOFA≥1) was similar between the two groups (63.3% and 69.5%, p=0.405) and subtypes (Table 4).

Respiratory manifestations

The rates of overall respiratory signs and complications were similar between Influenza (96.4%) and HRSV (96.3%) group. Pneumonia was observed in half of both groups, pleural effusion in 16.3% and other respiratory signs (bronchitis, asthma attack, COPD exacerbations) in 87.4%. In subtype analysis, A(H1N1) was associated with fewer respiratory signs (p=0.011) with fewer other respiratory signs (p=0.018) (Table 4).

Cardiac manifestations

Cardiac manifestations were more frequent in the HRSV group (57.3%, *vs* 41.6%, p=0.028) with an over-representation of *de novo* arrythmia in this group (42.6% *vs* 17.4%, p=0.006). However, subtype analysis interestingly revealed that A(H3N2) was associated with a higher rate of cardiac insufficiency (p=0.009) and A(H1N1) with more frequent pericarditis (p=0.012) and other cardiac signs as hemodynamic failure (p=0.027) (Table 4).

Neurological signs

Neurological signs occurred in 33.7% of Influenza cases and in 23.2% of HRSV cases (n.s.). In both groups, non-specific signs such as confusion were the most represented (86.8%). Meningitis was biologically confirmed in 3 cases (1 in the influenza group and 2 in the HRSV group) as was objective encephalitis for 2 patients (1 in the influenza group and 1 in the HRSV group). There was no difference according to virus subtypes (Table 4).

Table 4. In-hospital clinical manifestations.

Clinical manifestations [a]	All (n=248)[b]	Influenza (n=166)	HRSV (n=82)	p	A(H1N1) (n=48)	A(H3N2) (n=113)	HRSV (n=82)	p
Delay 1st symptom to diagnosis (days)[c]	3.0 [2.0 - 6.0]	3.0 [2.0 - 6.0]	3.0 [2.0 - 7.0]	0.227	5.0 [2.0 - 7.0]	3.0 [2.0 - 4.5]	3.0 [2.0 - 7.0]	0.015*
General condition								
Fever	199 (80.2%)	151 (91.0%)	48 (58.5%)	<0.001*	47 (97.9%)	101 (89.4%)	48 (58.5%)	<0.001*
qSOFA ≥1 at admission	162 (65.3%)	105 (63.3%)	57 (69.5%)	0.405	31 (64.6%)	71 (62.8%)	57 (69.5%)	0.613
Oseltamivir treatment	51 (20.6%)	51 (30.7%)	NA	NA	18 (37.5%)	30 (26.5%)	NA	NA
Respiratory signs	239 (96.4%)	160 (96.4%)	79 (96.3%)	1.000	43 (89.6%)	112 (99.1%)	79 (96.3%)	0.011*
SpO_2 (%)[c]	93.0 [90.0 - 95.0]	93.0 [90.0 - 95.0]	93.0 [90.0 - 95.0]	0.628	93.0 [85.8 - 94.3]	94.0 [92.0 - 95.0]	93.0 [90.0 - 95.0]	0.088
Respiratory rate (cycles/min)[c]	26.0 [22.0 - 32.0]	26.0 [22.3 - 32.0]	26.5 [22.3 - 32.0]	0.933	26.0 [23.5 - 35.0]	26.0 [22.0 - 30.0]	26.5 [22.3 - 32.0]	0.573
PaO_2 (mmHg)[c]	70.0 [60.0 - 82.0]	69.0 [60.0 - 80.3]	72.0 [61.0 - 83.0]	0.758	63.0 [56.0 - 73.8]	70.5 [64.5 - 80.0]	72.0 [61.0 - 83.0]	0.094
Pneumonia	124 (51.9%)	79 (49.4%)	45 (57.0%)	0.334	27 (62.8%)	50 (44.6%)	45 (57.0%)	0.070
Pleural effusion	39 (16.3%)	26 (16.2%)	13 (16.5%)	1.000	8 (18.6%)	17 (15.2%)	13 (16.5%)	0.843
Other respiratory signs	209 (87.4%)	142 (88.8%)	67 (84.8%)	0.511	33 (76.7%)	104 (92.9%)	67 (84.8%)	0.018*
Cardiac signs	116 (46.8%)	69 (41.6%)	47 (57.3%)	0.028*	17 (35.4%)	51 (45.1%)	47 (57.3%)	0.046*
Cardiac insufficiency	90 (77.6%)	56 (81.2%)	34 (72.3%)	0.373	10 (58.8%)	46 (90.2%)	34 (72.3%)	0.009*
New arrythmia	32 (27.6%)	12 (17.4%)	20 (42.6%)	0.006*	3 (17.6%)	8 (15.7%)	20 (42.6%)	0.008*
Acute coronary syndrome	12 (10.4%)	7 (10.1%)	5 (10.9%)	1.000	0 (0.0%)	6 (11.8%)	5 (10.9%)	0.434
Pericarditis	6 (5.2%)	3 (4.3%)	3 (6.4%)	0.685	3 (17.6%)	0 (0.0%)	3 (6.4%)	0.012*
Other cardiac signs	19 (16.4%)	11 (15.9%)	8 (17.0%)	1.000	6 (35.3%)	4 (7.8%)	8 (17.0%)	0.027*
Serum troponin (ng/L)[c]	40.0 [24.5 - 111.0]	52.0 [27.0 - 102.0]	32.5 [19.3 - 115.3]	0.547	48.5 [31.0 - 111.0]	46.0 [26.5 - 73.8]	32.5 [19.3 - 115.3]	0.125
Performed echocardiography	40 (33.1%)	22 (31.0%)	18 (36.0%)	0.695	9 (52.9%)	12 (22.6%)	18 (36.0%)	0.057
Normal	11 (27.5%)	8 (36.4%)	3 (16.7%)		4 (44.4%)	4 (33.3%)	3 (16.7%)	
Ancient abnormalities	6 (15.0%)	3 (13.6%)	3 (16.7%)	0.450	1 (11.1%)	2 (16.7%)	3 (16.7%)	0.640
Recent abnormalities	23 (57.5%)	11 (50.0%)	12 (66.7%)		4 (44.4%)	6 (50.0%)	12 (66.7%)	
Neurological signs	75 (30.2%)	56 (33.7%)	19 (23.2%)	0.106	12 (25.0%)	42 (37.2%)	19 (23.2%)	0.087
Clinical signs of meningitis	5 (6.6%)	3 (5.4%)	2 (10.0%)	0.602	2 (16.7%)	1 (2.4%)	2 (10.0%)	0.082
Biological signs of meningitis	3 (3.9%)	1 (1.8%)	2 (10.0%)	0.168	0 (0.0%)	1 (2.4%)	2 (10.0%)	0.242
Clinical signs of encephalitis	6 (7.9%)	4 (7.1%)	2 (10.0%)	0.651	2 (16.7%)	1 (2.4%)	2 (10.0%)	0.082
Radiologic signs of encephalitis	1 (1.3%)	1 (1.8%)	0 (0.0%)	1.000	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
Electrical signs of encephalitis	2 (2.6%)	1 (1.8%)	1 (5.0%)	0.460	0 (0.0%)	0 (0.0%)	1 (5.0%)	0.432
Paresthesia	4 (5.3%)	2 (3.6%)	2 (10.0%)	0.282	0 (0.0%)	2 (4.8%)	2 (10.0%)	0.621
Motor or sensory dysfunction	6 (7.9%)	4 (7.1%)	2 (10.0%)	0.651	1 (8.3%)	3 (7.1%)	2 (10.0%)	0.855
Stroke	1 (1.3%)	1 (1.8%)	0 (0.0%)	1.000	0 (0.0%)	1 (2.4%)	0 (0.0%)	1.000
Other neurological signs	66 (86.8%)	49 (87.5%)	17 (85.0%)	0.717	10 (83.3%)	38 (90.5%)	17 (85.0%)	0.690
Muscle damage	52 (21.0%)	46 (27.7%)	6 (7.3%)	<0.001*	16 (33.3%)	28 (24.8%)	6 (7.3%)	<0.001*
CPK levels (IU/L)[c]	324.0 [66.0 - 1034.0]	324.0 [66.0 - 1034.0]	ND	NA	53.0 [39.0 - 167.0]	630.0 [269.0 - 1148.0]	ND	NA
Rheumatologic signs	33 (13.3%)	24 (14.5%)	9 (11.0%)	0.553	8 (16.7%)	15 (13.3%)	9 (11.0%)	0.618
Arthralgia	30 (90.9%)	23 (95.8%)	7 (77.8%)	0.174	7 (87.5%)	15 (100%)	7 (77.8%)	0.137
Arthritis	6 (18.2%)	3 (12.5%)	3 (33.3%)	0.309	0 (0.0%)	3 (20.0%)	3 (33.3%)	0.313
Other rheumatologic signs	3 (9.1%)	1 (4.2%)	2 (22.2%)	0.174	1 (12.5%)	0 (0.0%)	2 (22.2%)	0.137
Urinary and/or digestive disorders	145 (58.5%)	98 (59.0%)	47 (57.3%)	0.891	31 (64.6%)	62 (54.9%)	47 (57.3%)	0.530
Abdominal pain	19 (13.1%)	14 (14.3%)	5 (10.6%)	0.610	5 (16.1%)	8 (12.9%)	5 (10.6%)	0.722
Diarrhea	37 (25.5%)	28 (28.6%)	9 (19.1%)	0.309	12 (38.7%)	15 (24.2%)	9 (19.1%)	0.162
Dysuria/burning sensation	3 (2.1%)	2 (2.0%)	1 (2.1%)	1.000	0 (0.0%)	2 (3.2%)	1 (2.1%)	0.798
Acute urinary retention	10 (6.9%)	10 (10.2%)	0 (0.0%)	0.031*	2 (6.5%)	8 (12.9%)	0 (0.0%)	0.020*
Other urinary/digestive signs	131 (90.3%)	90 (91.8%)	41 (87.2%)	0.383	26 (83.9%)	59 (95.2%)	41 (87.2%)	0.141
Genital signs	2 (0.8%)	2 (1.2%)	0 (0.0%)	1.000	0 (0.0%)	1 (0.9%)	0 (0.0%)	1.000
Ophthalmologic signs	9 (3.6%)	7 (4.2%)	2 (2.4%)	0.722	2 (4.2%)	4 (3.5%)	2 (2.4%)	0.898
Skin involvement	18 (7.3%)	14 (8.4%)	4 (4.9%)	0.437	3 (6.2%)	10 (8.8%)	4 (4.9%)	0.608
Others	38 (15.3%)	23 (13.9%)	15 (18.3%)	0.356	5 (10.4%)	16 (14.2%)	15 (18.3%)	0.482

HRSV: Human Respiratory Syncytial Virus. qSOFA: quick sepsis organ failure assessment score. SpO_2: peripheral capillary oxygen saturation. PaO_2: partial pressure of oxygen in arterial blood. CPK: Creatine phosphokinase. ND: not done. NA: non applicable.

[a] Unless otherwise specified, all values are expressed in n (%).

[b] Subtype of Influenza was unknown for 5 patients. They were included in analysis in « Influenza » group but excluded from subgroup analysis.

[c] Quantitative values are expressed as median [Q1-Q3].

* Considered as significant.

Other affections

Muscular injury affected 27.7% and 7.3% of the Influenza and HRSV groups respectively ($p<0.001$). Arthralgia was the main rheumatologic sign in both Influenza and HRSV groups (95.8% and 77.8% respectively, n.s.). Six cases of arthritis were reported, equally distributed between the two groups.

Urinary and digestive disorders were common in both groups (59.0% and 57.3%, n.s.) with a high rate of renal insufficiency and liver abnormalities (cholestasis and/or cytolysis) (nearly 90% of cases). The second disorder was diarrhea (28.6% and 19.1%, n.s.), followed by abdominal pain (14.3% and 10.6%, n.s.). Ten (10.2%) patients in the Influenza group presented acute urinary retention and none in the HRSV group ($p=0.031$), especially in the A(H3N2) subtype ($p=0.020$).

Skin involvement occurred in 8.4% of Influenza cases and in 4.9% of HRSV cases (n.s.). Genital and ophthalmic signs were infrequent (< 5% in both groups).

Except for acute urinary retention, there were not any discrepancies between viral subtypes (Table 4; Appendix 4: figures S1, S2).

Tardive symptoms

One hundred and fifty-four patients (62.1%) answered the second questionnaire detailing symptoms occurred within 1 month after viral diagnosis. The most frequently reported were cough (62.3%), neurological signs (50.3%), dyspnea (42.9%) and muscular pain (38.3%), with no significant differences between viral subgroups (Table 5).

Evolution at 1 month

At 1 month, 203 patients (81.9% of total cohort) were released from hospital. Thirty-seven (14.9%) were still hospitalized, in link with the viral infection for 22 of them (59.4%). Ten patients (4.0%) died before follow-up, with an estimation of imputability of viral infection or its complications of 80%. There were no differences in evolution between virus subtypes (Table 6).

Table 5. Tardive symptoms

Tardive symptoms[a]	All (n=154)[b]	Influenza (n=94)	HRSV (n=60)	p	A(H1N1) (n=27)	A(H3N2) (n=64)	HRSV (n=60)	p
Fever	38 (24.7%)	27 (28.7%)	11 (18.3%)	0.181	10 (37.0%)	15 (23.4%)	11 (18.3%)	0.161
Pharyngeal pain	26 (16.9%)	13 (13.8%)	13 (21.7%)	0.296	4 (14.8%)	9 (14.1%)	13 (21.7%)	0.533
Associated with odynophagia	9 (33.3%)	5 (38.5%)	4 (28.6%)	0.695	1 (25.0%)	4 (44.4%)	4 (28.6%)	0.857
Cough	96 (62.3%)	58 (61.7%)	38 (63.3%)	0.974	21 (77.8%)	35 (54.7%)	38 (63.3%)	0.115
Productive cough	53 (55.2%)	31 (52.5%)	22 (59.5%)	0.651	11 (52.4%)	20 (55.6%)	22 (59.5%)	0.896
Dyspnea	66 (42.9%)	37 (39.4%)	29 (48.3%)	0.352	14 (51.9%)	20 (31.2%)	29 (48.3%)	0.079
Palpitation	19 (12.3%)	13 (13.8%)	6 (10.0%)	0.650	6 (22.2%)	7 (10.9%)	6 (10.0%)	0.287
Chest pain	22 (14.3%)	13 (13.8%)	9 (15.0%)	1.000	6 (22.2%)	7 (10.9%)	9 (15.0%)	0.346
Muscular pain	59 (38.3%)	35 (37.2%)	24 (40.0%)	0.862	13 (48.1%)	21 (32.8%)	24 (40.0%)	0.372
Neurological signs	77 (50.3%)	45 (48.4%)	32 (53.3%)	0.666	14 (51.9%)	30 (47.6%)	32 (53.3%)	0.825
Headache	34 (43.0%)	19 (41.3%)	15 (45.5%)	0.891	6 (42.9%)	13(41.9%)	15 (45.5%)	0.955
Associated with fever	5 (13.9%)	5 (25.0%)	0 (0.0%)	0.053	0 (0.0%)	5 (35.7%)	0 (0.0%)	0.011*
Associated with photophobia	3 (8.6%)	1 (5.0%)	2 (13.3%)	0.565	1 (16.7%)	0 (0.0%)	2 (13.3%)	0.374
Vision disturbance	17 (21.5%)	12 (26.1%)	5 (15.2%)	0.374	4 (28.6%)	8 (25.8%)	5 (15.2%)	0.477
Neuropathic pain	9 (11.7%)	5 (11.1%)	4 (12.5%)	1.000	3 (21.4%)	2 (6.7%)	4 (12.5%)	0.421
Paresthesia	19 (24.1%)	12 (26.1%)	7 (21.2%)	0.816	4 (28.6%)	8 (25.8%)	7 (21.2%)	0.831
Motor weakness	40 (50.6%)	23 (50.0%)	17 (51.5%)	1.000	6 (42.9%)	16 (51.6%)	17 (51.5%)	0.912
Confusion/behaviour disorder	23 (28.7%)	13 (28.3%)	10 (29.4%)	1.000	7 (50.0%)	6 (19.4%)	10 (29.4%)	0.110
Digestive symptoms	44 (28.6%)	26 (27.7%)	18 (30.0%)	0.896	11 (40.7%)	13 (20.3%)	18 (30.0%)	0.124
Abdominal pain	18 (40.9%)	11 (42.3%)	7 (38.9%)	1.000	5 (45.5%)	5 (38.5%)	7 (38.9%)	1.000
Nausea/vomiting	13 (29.5%)	7 (26.9%)	6 (33.3%)	0.903	4 (36.4%)	3 (23.1%)	6 (33.3%)	0.764
Diarrhea	24 (54.5%)	15 (57.7%)	9 (50.0%)	0.845	6 (54.5%)	7 (53.8%)	9 (50.0%)	1.000
Arthralgia	23 (14.9%)	16 (17.0%)	7 (11.7%)	0.498	7 (25.9%)	8 (12.5%)	7 (11.7%)	0.223
Associated with joint swelling	4 (17.4%)	3 (18.8%)	1 (14.3%)	1.000	1 (14.3%)	1 (12.5%)	1 (14.3%)	1.000
Ophthalmic signs	21 (13.6%)	13 (13.8%)	8 (13.3%)	1.000	6 (22.2%)	7 (10.9%)	8 (13.3%)	0.369
Red eye	12 (60.0%)	8 (66.7%)	4 (50.0%)	0.648	3 (60.0%)	5 (71.4%)	4 (50.0%)	0.844
Ocular pain	12 (60.0%)	7 (58.3%)	5 (62.5%)	1.000	3 (60.0%)	5 (71.4%)	5 (62.5%)	0.631
Visual loss	8 (40.0%)	4 (33.3%)	4 (50.0%)	0.648	2 (40.0%)	2 (28.6%)	4 (50.0%)	0.844
Rash	21 (13.6%)	13 (13.8%)	8 (13.3%)	1.000	6 (22.2%)	7 (10.9%)	8 (13.3%)	0.369
Testiular pain	2 (2.6%)	0 (0.0%)	2 (7.1%)	0.129	0 (0.0%)	0 (0.0%)	2 (7.1%)	0.267
Neck pain/swelling	4 (2.6%)	3 (3.2%)	1 (1.7%)	1.000	1 (3.7%)	2 (3.1%)	1 (1.7%)	0.829
Facial edema	2 (1.3%)	1 (1.1%)	1 (1.7%)	1.000	1 (3.7%)	0 (0.0%)	1 (1.7%)	0.174

HRSV: Human Respiratory Syncytial Virus. All values are expressed in n (%).

[a] Appeared within 30 days after viral diagnosis.

[b] Subtype of Influenza was unknown for 5 patients. They were included in analysis in « Influenza » group but excluded from subgroup analysis.

* Considered as significant.

Table 6. Evolution at 1 month

Evolution	All (n=248)[a]	Influenza (n=166)	HRSV (n=82)	p	A(H1N1) (n=48)	A(H3N2) (n=113)	HRSV (n=82)	p
Definitive release from Hospital	203 (81.9%)	137 (82.5%)	66 (80.5%)	0.828	40 (83.3%)	93 (82.3%)	66 (80.5%)	0.928
Prolonged or new hospitalization								
Still hospitalized at 1 month	15 (6.0%)	8 (4.8%)	7 (8.5%)	0.266	3 (6.3%)	5 (4.4%)	7 (8.5%)	0.536
Second hospitalization after 1st release	22 (8.9%)	17 (10.2%)	5 (6.1%)	0.400	5 (10.4%)	12 (10.6%)	5 (6.1%)	0.539
Total of both groups	37 (14.9%)	25 (15.1%)	12 (14.6%)	1.000	8 (16.7%)	17 (15.0%)	12 (14.6%)	0.952
Imputability of viral infection	22 (59.4%)	13 (52.0%)	9 (75.0%)	0.294	4 (50.0%)	9/17 (52.9%)	9 (75.0%)	0.468
Death	10 (4.0%)	6 (3.6%)	4 (4.9%)	0.734	1 (2.1%)	4 (3.5%)	4 (4.9%)	0.823
After first admission	8 (80.0%)	4 (66.7%)	4 (100.0%)	0.4667	1 (100.0%)	3 (75.0%)	4 (100.0%)	1.000
Occurred after 2nd hospitalization	2 (20.0%)	2 (33.3%)	0 (0.0%)	-	0 (0.0%)	1 (25.0%)	0 (0.0%)	-
Imputability of viral infection	8 (80.0%)	5 (83.3%)	3 (75.0%)	1.000	0 (0.0%)	4 (100.0%)	3 (75.0%)	0.222

HRSV: Human Respiratory Syncytial Virus. All values are expressed in n (%).

[a] Subtype of Influenza was unknown for 5 patients. They were included in analysis in « Influenza » group but excluded from subgroup analysis.

Frequency of appearance

Among all patients, 218 (87.9%) developed at least one extra-respiratory manifestation, with a mean of 1.97±1.28 per patient. No differences were observed between subgroups (Appendix 5: Table S1).

Factors associated with development of extra-respiratory manifestations

Multivariate analysis, performed on the baseline clinical and biological characteristics at admission, revealed that CRP level was the only variable associated with the appearance of one overall extra-respiratory manifestation (p=0.018).

On further specific analyses, cardiac arrythmia (p=0.003), recent (<1 year) or actively treated cancer (p=0.008), or non-recent history of cancer (p=0.046), non-treated auto-immune disease (p=0.025) and MDRD at admission (p=0.010) were associated with cardiovascular manifestations. Previous neurological conditions (p=0.007) were associated with appearance of neurological disorders, whereas MDRD and AST abnormalities at admission were significantly associated with uro-digestive disorders (p<0.001 and p=0.002, respectively) (Appendix 6: Tables S2-S11).

Discussion

This study provides original data about extra-respiratory manifestations of Influenza and HRSV in hospitalized adults during winter 2018-2019.

In this cohort of mostly old and comorbid patients, severe infections represented 65.3% of cases and were similar between Influenza and HRSV patients.

Cardiac manifestations were frequent (41.6% and 57.3% for Influenza and HRSV cases respectively), such as cardiac failure, new arrythmia, or acute coronary syndrome, at higher rates than in previous retrospective cohorts studying Influenza[1,2], probably due to an old, comorbid, and severely ill population. Pericarditis was more frequent in A(H1N1) subgroup, but interpretation is limited by the low sample size. Multivariate analysis tends to identify possible risk factors of developing cardiac manifestations, such as previous cardiac arrythmia, chronic renal insufficiency and markers of immune dysfunction (cancer history, auto-immune disease), but with low evidence.

Neurological signs were present in 33.7% of Influenza and in 23.2% of HRSV infections, containing many non-specific disorders, and only a few cases of acute cerebral or meningeal inflammation. The same phenomenon was reported in the A(H1N1)pdm09 pediatric population, at lower rates[11-13], however it remains unclear whether the virus directly infects the central nervous system, or whether encephalopathy is caused secondary by cardiovascular or respiratory dysfunction in children; our results in adults could provide more evidence in favor to the second hypothesis.

Non-specific urinary and digestive symptoms such as abdominal pain, diarrhea, and dysuria were frequent in our study. Renal failures were also frequent, associated with a substantial number of cardiovascular and renal conditions. Hepatic disorders occurred frequently, early at admission for a fourth of the cohort, possibly partially linked with a direct tropism of HRSV and Influenza. However, many cases of secondary hepatic impairment occurred during hospitalization, reinforcing the hypothesis of side effects of antibiotic therapy rather than extra-respiratory manifestations of Influenza or HRSV.

The higher gap between Influenza and HRSV concerned muscle injury, rarely expressed in HRSV cases (7.3% *vs* 27.7%, $p<0.001$). We found no evidence in previous literature that could elucidate this phenomenon.

This study has several strengths. To the best of our knowledge, it is the first to exhaustively assess all extra-respiratory manifestations of Influenza subtypes and HRSV. Second, the bicentric systematic screening and the prospective design of the cohort limited selection and memory biases respectively.

The first limitation of our study is due to the selection of hospitalized patients, leading to a recruitment of older, more severe, and frail patients, reducing generalization of our study to the overall population. Another limit is the lack of data about the rate of secondary bacterial infections that could have interfered with viral symptoms. Antibiotic therapy was frequently administered, leading to possible confusion with virologic clinical and biological phenotype itself, and could explain that CRP level was significantly independently associated with appearance of extra-respiratory manifestations of all type.

The physiopathogeny of systemic manifestations of both viruses remains unclear. To et al.[24] found in a fatal ARDS group of A(H1N1)-infected patients, compared to patients with mild infections, a higher proportion of myocarditis (21.7%) as well as immune-mediated disorders such as reactive hemophagocytosis, thrombotic phenomena, lymphoid atrophy, diffuse alveolar damage, and multiorgan dysfunction similar to fatal avian influenza A H5N1 infection; cytokinic storm described in ARDS due to Influenza, especially via IL-6, CXCL8/IL-8, CCL2/MCP1, and TNFα, is associated with disease severity[5, 26-27], and altered innate and adaptative immunity has been reported in severe or fatal influenza infections[25, 28]. Thus, extra-respiratory manifestations could be linked to inadequate immune response, as suggests the higher CRP levels found in patients with extra-respiratory affections, leading to a more severe disease. Further analysis is still in process in order to assess if systemic expression is associated with a higher severity of infection.

Interestingly, multivariate analysis did not find a strong link between previous immune disorders (cancer, hemopathy, auto-immune disease) and extra-respiratory signs. Furthermore, specific organ affliction was not strongly associated with the previous dysfunction of the organ itself. Viral expression could then be mostly independent from host factors, and explain why, as for the recent coronavirus disease 2019 (Covid-19) pandemic, our models fail to predict patients' evolution from previous host condition.

Conclusion

Extra-respiratory manifestations of Influenza or HRSV infection are frequent and mostly represented by cardiac, neurological, and urinary/digestive signs (46.8%, 30.2%, and 58.5%, respectively). A(H1N1) Influenza infected fewer elderly patients ($p<0.001$), with fewer medical conditions, and expressed fewer cardiac disorders compared to A(H3N2) Influenza and HRSV-infected patients ($p=0.046$). In multivariate analysis, C-reactive protein (CRP) level at admission was the only variable significantly associated with the development of an extra-respiratory manifestation of all type ($p=0.018$).

Conflict of interest

Nicolas Lévêque received hospitality advantages from BioMérieux Company. Gaëtan Motillon, Etienne Mériglier, France Cazenave-Roblot, Guillaume Béraud, Mélanie Catroux, Thomas Brunet, Florence Boissier, Vanessa Bironneau, Pierre Poupin, Anne Keller, Pascal Roblot, Mickaël Martin, and Blandine Rammaert declared no conflict of interest in connection with this publication.

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Supplemental data

Appendix 1: Questionnaire at admission (symptoms appeared within 7 days before diagnosis)

Questionnaire 1
Grippe et VRS Patient

Initiale Nom/ Prénom : ____ / ____ Date de naissance : ____ ____ / 19___ ___
mm aaaa

Date du remplissage : ____ ____ / ____ ____ /201____

Service d'hospitalisation : _____

Sexe : Femme ❑ 0 Homme ❑

Madame, Monsieur,

Dans les **7 JOURS AVANT** votre hospitalisation, quelles ont été les manifestations **INHABITUELLES** que vous avez constatées (qu'elles continuent ou non actuellement) ?

1. Avez-vous eu de la fièvre (>38°C)	Oui ❑1	Non ❑0
2. Avez-vous eu des maux de gorge ?	Oui ❑1	Non ❑0
2a Si oui, vous gênaient-ils pour avaler les aliments ?	Oui ❑1	Non ❑0
3. Avez-vous eu de la toux ?	Oui ❑1	Non ❑0
3a Si oui, était-elle productive (émission de crachats) ?	Oui ❑1	Non ❑0
4. Avez-vous eu des difficultés à respirer ?	Oui ❑1	Non ❑0
5. Avez-vous eu des troubles neurologiques (faiblesse musculaire, douleurs intenses, invalidantes dans les bras, les jambes, des maux de tête, comportement inhabituel etc.) ?	Oui ❑1	Non ❑0
Si oui, avez-vous présenté :		
▪ 5a des maux de tête ?	Oui ❑1	Non ❑0
Si oui, étaient-ils associés à : 5b de la fièvre ?	Oui ❑1	Non ❑0
5c une gêne à la lumière ?	Oui ❑1	Non ❑0
▪ 5d des troubles de la vision inhabituels ?	Oui ❑1	Non ❑0
○ 5e Combien de temps ont-ils duré ?	I__ __I mn ou I__ __I heures ou I__ __I jours	

▪ 5f des douleurs à type de brûlure ou de décharge électrique?		Oui ❑1	Non ❑0
Si oui, où étaient-elles localisées ?	5f1 les bras	Oui ❑1	Non ❑0
	5f2 les mains	Oui ❑1	Non ❑0
	5f3 les jambes	Oui ❑1	Non ❑0
	5f4 les pieds	Oui ❑1	Non ❑0
	5f5 le dos	Oui ❑1	Non ❑0
décrivez ces douleurs :			
○ 5g Combien de temps ont-elles duré ?		I__ __I mn ou I__ __I heures ou I__ __I jours	
○ 5h Quelle était leur intensité sur une échelle de 1 (très faible) à 10 (maximale) ?		I__ __I	
▪ 5i des fourmillements ou un engourdissement d'un ou plusieurs membres ?		Oui ❑1	Non ❑0
5j Si oui, où étaient-elles localisées ?	5j1 les bras	Oui ❑1	Non ❑0
	5j2 les mains	Oui ❑1	Non ❑0
	5j3 les jambes	Oui ❑1	Non ❑0
	5j4 les pieds	Oui ❑1	Non ❑0
	5j5 le dos	Oui ❑1	Non ❑0
décrivez ces fourmillements ou engourdissements :			
○ 5k Combien de temps ont-ils duré ?		I__ __I mn ou I__ __I heures ou I__ __I jours	
○ 5l Quelle était leur intensité sur une échelle de 1 (très faible) à 10 (maximale) ?		I__ __I	
▪ 5m une faiblesse d'un ou plusieurs membres ?		Oui ❑1	Non ❑0
5n Si oui, où était-elle localisée ?	5n1 les bras	Oui ❑1	Non ❑0
	5n2 les mains	Oui ❑1	Non ❑0
	5n3 les jambes	Oui ❑1	Non ❑0
	5n4 les pieds	Oui ❑1	Non ❑0
	5n5 le dos	Oui ❑1	Non ❑0
▪ 5o un comportement inhabituel constaté par l'un de vos proche (confusion) ?		Oui ❑1	Non ❑0

6. Avez-vous eu des troubles digestifs ?	Oui ❑1	Non ❑0
Si oui, avez vous présenté :		
▪ 6a Des douleurs abdominales ?	Oui ❑1	Non ❑0
▪ 6b Des nausées ou vomissements ?	Oui ❑1	Non ❑0
▪ 6c Des diarrhées ?	Oui ❑1	Non ❑0

7. Avez-vous eu des palpitations ?	Oui ❑1	Non ❑0

8. Avez-vous eu des douleurs dans la poitrine ?	Oui ❑1	Non ❑0
Si oui, décrivez-les :		
▪ 8a Combien de temps ont-elles duré ?	I__ __I mn ou I__ __I heures ou I__ __I jours	
▪ 8b Quelle était leur intensité sur une échelle de 1 (très faible) à 10 (maximale) ?	I__ __I	

9. Avez-vous eu des douleurs dans les muscles ?	Oui ❑1	Non ❑0

10. Avez-vous eu des douleurs dans les articulations inhabituelles ?		Oui ❑1	Non ❑0
10a Si oui, avez-vous présenté un gonflement d'une ou plusieurs articulations ?		Oui ❑1	Non ❑0
10b Si oui, où étaient-il(s) localisé(s) ?	10b1 les épaules	Oui ❑1	Non ❑0
	10b2 les coudes	Oui ❑1	Non ❑0
	10b3 les poignets	Oui ❑1	Non ❑0
	10b4 les doigts	Oui ❑1	Non ❑0
	10b5 les hanches	Oui ❑1	Non ❑0
	10b6 les genoux	Oui ❑1	Non ❑0
	10b7 les chevilles	Oui ❑1	Non ❑0
	10b8 les orteils	Oui ❑1	Non ❑0

11. Avez-vous eu des plaques rouges ou des boutons sur la peau ?	Oui ❑1	Non ❑0

12. Avez- vous eu des signes visuels ?	Oui ❑1	Non ❑0
Si oui, avez-vous présenté ?		
▪ 12a un/des yeux rouges	Oui ❑1	Non ❑0
▪ 12b des douleurs à l'oeil	Oui ❑1	Non ❑0
▪ 12c une diminution très récente de la vue	Oui ❑1	Non ❑0

13. Avez-vous eu des douleurs testiculaires ?	Oui ❑1	Non ❑0

14. Avez-vous eu des douleurs ou gonflement du cou ?	Oui ❑$_1$	Non ❑$_0$

15. Avez-vous eu des douleurs ou gonflement des joues ?	Oui ❑$_1$	Non ❑$_0$

Si les signes décrits dans ce questionnaire surviennent dans le mois suivant votre hospitalisation, merci de contacter le médecin qui vous a pris en charge pendant votre hospitalisation ou le Dr MERIGLIER.

Merci de remettre ce questionnaire au médecin de votre service.

Appendix 2: Medical data from Day 0 to Day 30 from diagnosis

GIVRE – CRF PATIENTS

1. DONNEES ADMINISTRATIVES

Date d'inclusion (= date de signature de non-opposition)	|__|__|/|__|__|/|__|__|__|__| J J / M M / A A A A
Initiales patient |__|__| N P	**N° inclusion du patient** |__|__|__|

2. INCLUSION

Date du recueil de la non opposition	|__|__|/|__|__|/|__|__|__|__| J J / M M / A A A A

- **Critères d'inclusion**

Age ≥ 18 ans	❑ Oui	❑ Non
Ayant donné sa non opposition	❑ Oui	❑ Non
Patient hospitalisé au CHU de Poitiers en service conventionnel ou en réanimation et avec des prélèvements nasopharyngés positifs pour la grippe ou le VRS	❑ Oui	❑ Non

- **Critères de non-inclusion**

Patient présentant une co-infection virale	❑ Oui	❑ Non
Patient non affilié à un régime de sécurité sociale	❑ Oui	❑ Non
Patient hospitalisé ou soigné sans son consentement	❑ Oui	❑ Non

3. ANTECEDENTS

- **Caractéristiques démographiques**

Date de naissance |__|__|/|__|__|__|__| M M / A A A A	**Sexe** ❑ Masculin ❑ Féminin
Poids	|__|__|__| kg
Taille	|__|__|__| cm

- **Comorbidités et antécédents**

Diabète	❑ Oui	❑ Non	**Si oui :** ❑ Type I ❑ Type II Insulinotraité : ❑ Oui ❑ Non
Hypertension artérielle	❑ Oui	❑ Non	
Maladie cardio-vasculaire	❑ Oui	❑ Non	**Si oui** : cardiopathie congénitale : ❑ Oui ❑ Non insuffisance cardiaque : ❑ Oui ❑ Non valvulopathie : ❑ Oui ❑ Non angor : ❑ Oui ❑ Non syndrome coronarien aigu : ❑ Oui ❑ Non Autres : ❑ Oui ❑ Non ***Si oui***, préciser : _
Arythmie cardiaque	❑ Oui	❑ Non	**Si oui**, préciser quel type d'arythmie : _
Tabagisme actif ou sevré depuis moins de 3ans	❑ Oui	❑ Non	
Pathologie respiratoire chronique	❑ Oui	❑ Non	**Si oui**, BPCO : ❑ Oui ❑ Non Autres : ❑ Oui ❑ Non Si autres, préciser : _
Surpoids	❑ Oui	❑ Non	**Si oui** : ❑ IMC entre 25 et 30 ❑ IMC entre 30 et 40 ❑ IMC supérieur à 40

Maladie neurologique	❑ Oui	❑ Non	**Si oui :** Démence type Alzheimer : ❑ Oui ❑ Non Autres démences : ❑ Oui ❑ Non Sclérose en plaques : ❑ Oui ❑ Non Para/Tétraplégie : ❑ Oui ❑ Non Autres : ❑ Oui ❑ Non ***Si oui***, préciser : _
Accident vasculaire cérébral	❑ Oui	❑ Non	**Si oui :** Ischémique : ❑ Oui ❑ Non Hémorragique : ❑ Oui ❑ Non Séquellaire : ❑ Oui ❑ Non
Insuffisance rénale chronique **(DFG < 90mL/min/1,73m²)**	❑ Oui	❑ Non	**Si oui** : ❑ DFG entre 60-89 ❑ DFG entre 30 -59 ❑ DFG entre 15-29 ❑ DFG < 15 ❑ Dialyse
Pathologie hépatique chronique	❑ Oui	❑ Non	**Si oui** , préciser : _
Transplantation d'organe	❑ Oui	❑ Non	**Si oui** , préciser quel organe : _
Transplantation de moelle osseuse	❑ Oui	❑ Non	**Si oui :** Autogreffe : ❑ Oui ❑ Non Allogreffe : ❑ Oui ❑ Non
Infection par le VIH	❑ Oui	❑ Non	**Si oui,** préciser le dernier compte de CD4+ : _ _ _ _ _ /mm3
Drépanocytose	❑ Oui	❑ Non	
Déficit immunitaire primitif	❑ Oui	❑ Non	
Cancer solide	❑ Oui, en cours de traitement ou traitement arrêté depuis <1 an	❑ Oui, non traité ou traitement arrêté depuis ≥ 1 an	❑ Non
Hémopathie maligne	❑ Oui, en cours de traitement ou traitement arrêté depuis <1 an	❑ Oui, non traité ou traitement arrêté depuis ≥ 1 an	❑ Non
Maladie auto-immune ou inflammatoire	❑ Oui, et traitement par corticoïdes uniquement ❑ Oui, et traitement immunosuppresseur/immunomodulateur hors corticoïdes uniquement ❑ Oui, et traitement par corticoïdes + traitement immunosuppresseur/modulateur ❑ Oui, sans traitement ❑ Non		

- **Autres caractéristiques**

Patient vacciné contre la grippe	❑ Oui	❑ Non
Si femme, enceinte ?	❑ Oui	❑ Non
Si patient ≥ 65ans	**Statut GIR :**	❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6

4. CARACTERISTIQUES CLINIQUES

Diagnostic virologique = jour de réalisation du prélèvement viral

Durée des symptômes avant le diagnostic virologique			_ _ _ jours
Traitement par Oseltamivir	❑ Oui	❑ Non	Si oui, durée : _ _ _ jours
Fièvre >38°C ≤7j du diagnostic virologique	❑ Oui	❑ Non	
Signes de gravité le jour du diagnostic virologique	❑ Oui	❑ Non	quickSOFA score : ❑ **1** ❑ **2** ❑ **3**
Signes respiratoires	❑ Oui	❑ Non	**Si oui,** Saturation en oxygène : _ _ _ % Fréquence respiratoire : _ _ _/min PaO2 : _ _ _ _ _ mm Hg Pneumonie : ❑ Oui ❑ Non Pleurésie : ❑ Oui ❑ Non Autre diagnostic : ❑ Oui ❑ Non **Si oui**, préciser : _

5. MANIFESTATIONS EXTRA-RESPIRATOIRES SURVENUES ENTRE J-7 ET J+30 DU DIAGNOSTIC VIROLOGIQUE

<table>
<tr><td rowspan="3">Signes cardiaques</td><td>❑ Oui</td><td>❑ Non</td><td rowspan="2">Si oui,

Décompensation cardiaque :
❑ Oui ❑ Non

Modification récente de l'ECG /Trouble du rythme : ❑ Oui ❑ Non

Si oui, préciser lequel : _ _ _ _ _ _ _
_ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _
_ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

Syndrome coronarien aigu :
❑ Oui ❑ Non

Péricardite : ❑ Oui ❑ Non

Autres signes cardiaques :
❑ Oui ❑ Non
Si oui , préciser : _ _ _ _ _ _ _ _ _ _
_ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _
_ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

Dosage de la troponine :
❑ Oui ❑ Non
Si oui, Valeur : |__|__|__|__| ng/L</td></tr>
<tr><td colspan="2">Si oui, date de survenue :

|__|__|/|__|__|/|__|__|__|__|
J J / M M / A A A A</td></tr>
<tr><td>Echographie cardiaque :

Si oui,
date de réalisation :

|__|__|/|__|__|/|__|__|__|__|
J J / M M / A A A A</td><td colspan="2">❑ Oui ❑ Non

Si oui,
❑ Normale
❑ Anomalies anciennes connues
❑ Anomalies récentes
si Anomalies récentes, préciser lesquelles : _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _
_ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _
_ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _
_ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _</td></tr>
</table>

Signes neurologiques	❑ Oui	❑ Non	**Si oui,** Signes de méningite clinique : ❑ Oui ❑ Non Signes de méningite biologique : ❑ Oui ❑ Non Signes d'encéphalite clinique : ❑ Oui ❑ Non Signes d'encéphalite radiologique : ❑ Oui ❑ Non Signes d'encéphalite à l'EEG : ❑ Oui ❑ Non Paresthésies : ❑ Oui ❑ Non Déficit sensitivo-moteur : ❑ Oui ❑ Non ***Si oui**, préciser lequel* : _ AVC ou AIT : ❑ Oui ❑ Non Autres : ❑ Oui ❑ Non ***Si oui**, préciser lequel* : _
Myalgies	❑ Oui	❑ Non	Dosage des CPK : ❑ Oui ❑ Non **Si oui**, Valeur : |__|__|__| mg/L
Signes rhumatologiques	❑ Oui	❑ Non	**Si oui,** Arthralgies : ❑ Oui ❑ Non ***Si oui**, précisez les articulations* : : _ Arthrites : ❑ Oui ❑ Non ***Si oui**, précisez les articulations : _* _ Autres : ❑ Oui ❑ Non ***Si oui**, préciser lequel* : _

Signes digestifs et urinaires	❑ Oui	❑ Non	**Si oui,** Douleurs abdominales : ❑ Oui ❑ Non Diarrhées : ❑ Oui ❑ Non Brûlures mictionnelles : ❑ Oui ❑ Non Rétention aigue d'urine : ❑ Oui ❑ Non Autres : ❑ Oui ❑ Non ***Si oui**, préciser lequel* : _
Atteintes des organes génitaux externes	❑ Oui	❑ Non	**Si oui**, préciser : _
Signes ophtalmologiques	❑ Oui	❑ Non	**Si oui**, préciser : _
Signes cutanés	❑ Oui	❑ Non	**Si oui**, préciser : _
Autres	❑ Oui	❑ Non	**Si oui**, préciser : _

6. CARACTERISTIQUES BIOLOGIQUES ET RADIOLOGIQUES ENTRE J-7 ET J+30 DU DIAGNOSTIC VIROLOGIQUE

Prélèvements naso-pharyngés		
Grippe	❑ Positif ❑ Négatif |__|__|/|__|__|/|__|__|__|__| J J / M M / A A A A	**Si positif :** H1N1 : ❑ Oui ❑ Non H3N2 : ❑ Oui ❑ Non Grippe B : ❑ Oui ❑ Non Autres : ❑ Oui ❑ Non ***Si oui,*** préciser : _
VRS	❑ Positif ❑ Négatif |__|__|/|__|__|/|__|__|__|__| J J / M M / A A A A	

Biologie à l'admission +/- 48h / Date |__|__|/|__|__|/|__|__|__|__|

Hémoglobine	**Valeur :** |__|__| , |__| g/dL
Globules blancs	**Valeur :** |__|__|__|__|__| /mm^3 PNN |__|__|__|__|__| /mm^3 Lymphocytes |__|__|__|__|/mm^3
Plaquettes	**Valeur :** |__|__|__|__|__|__|__| /mm^3
Créatinine	**Valeur :** |__|__|__|__| µmol/L **Soit Cl selon MDRD** : |__|__|__| ml/min/1,73m²
Bilan hépatique	**ASAT Valeur :** |__|__|__|__| UI/L **ALAT Valeur :** |__|__|__|__| UI/L **GammaGT Valeur :** |__|__|__|__| UI/L **PAL Valeur :** |__|__|__|__| UI/L
CRP	**Valeur :** |__|__|__| mg/L
TSH	|__|__| , |__| mUI/L

7. EVOLUTION à J+30 SUIVANT L'INCLUSION

Données obtenues par	❑ contact téléphonique du patient ❑ contact du médecin généraliste

Sortie d'hospitalisation	❑ Sorti définitivement	***Si oui,*** date de sortie : |__|__|/|__|__|/|__|__|__|__|
	❑ Encore hospitalisé à 1 mois	
	❑ Sorti puis réhospitalisé	***Si oui,*** date de sortie : |__|__|/|__|__|/|__|__|__|__| Date de réadmission : |__|__|/|__|__|/|__|__|__|__| Service de réadmission : _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _
	Raisons du prolongement de l'hospitalisation ou de la réhospitalisation	_ _
	Dossier revu par le comité scientifique : ❑ Imputable à l'infection virale ou à ses complications ❑ Non imputable	
Décès	❑ Oui ❑ Non	**Si oui,** date : |__|__|/|__|__|/|__|__|__|__|
	Cause du décès : _	
	Dossier revu par le comité scientifique : ❑ Décès imputable à l'infection virale ou à ses complications ❑ Non imputable	

Commentaires :

Appendix 3: Questionnaire at 1 month (symptoms appeared within 1 month after diagnosis)

Questionnaire 2
Grippe et VRS Patient

1 MOIS APRES LE DIAGNOSTIC JOURS, quelles sont les manifestations **INHABITUELLES** que vous avez constatées (qu'elles continuent ou non actuellement) ?

Initiale Nom/ Prénom : ____ / ____ Date de naissance : ____ ____ / 19___ ___
mm aaaa

Date du remplissage : ____ ____ / ____ ____ /201____

Service d'hospitalisation : _____

Sexe : Femme ❑ 0 Homme ❑ 1

1. Avez-vous eu de la fièvre (>38°C)	Oui ❑1	Non ❑0
2. Avez-vous eu des maux de gorge ?	Oui ❑1	Non ❑0
2a Si oui, vous gênaient-ils pour avaler les aliments ?	Oui ❑1	Non ❑0
3. Avez-vous eu de la toux ?	Oui ❑1	Non ❑0
3a Si oui, était-elle productive (émission de crachats) ?	Oui ❑1	Non ❑0
4. Avez-vous eu des difficultés à respirer ?	Oui ❑1	Non ❑0
5. Avez-vous eu des troubles neurologiques (faiblesse musculaire, douleurs intenses, invalidantes dans les bras, les jambes, des maux de tête, comportement inhabituel etc.) ?	Oui ❑1	Non ❑0
Si oui, avez-vous présenté :		
▪ 5a des maux de tête ?	Oui ❑1	Non ❑0
Si oui, étaient-ils associés à : 5b de la fièvre ?	Oui ❑1	Non ❑0
5c une gêne à la lumière ?	Oui ❑1	Non ❑0
▪ 5d des troubles de la vision inhabituels ?	Oui ❑1	Non ❑0
○ 5e Combien de temps ont-ils duré ?	I__ __I mn ou I__ __I heures ou I__ __I jours	
▪ 5f des douleurs à type de brûlure ou de décharge électrique?	Oui ❑1	Non ❑0

Si oui, où étaient-elles localisées ?	5f1 les bras	Oui ❑1	Non ❑0
	5f2 les mains	Oui ❑1	Non ❑0
	5f3 les jambes	Oui ❑1	Non ❑0
	5f4 les pieds	Oui ❑1	Non ❑0
	5f5 le dos	Oui ❑1	Non ❑0
décrivez ces douleurs :			
○ 5g Combien de temps ont-elles duré ?		l__ __l mn ou l__ __l heures ou l__ __l jours	
○ 5h Quelle était leur intensité sur une échelle de 1 (très faible) à 10 (maximale) ?		l__ __l	
▪ 5i des fourmillements ou un engourdissement d'un ou plusieurs membres ?		Oui ❑1	Non ❑0
5j Si oui, où étaient-elles localisées ?	5j1 les bras	Oui ❑1	Non ❑0
	5j2 les mains	Oui ❑1	Non ❑0
	5j3 les jambes	Oui ❑1	Non ❑0
	5j4 les pieds	Oui ❑1	Non ❑0
	5j5 le dos	Oui ❑1	Non ❑0
décrivez ces fourmillements ou engourdissements :			
○ 5k Combien de temps ont-ils duré ?		l__ __l mn ou l__ __l heures ou l__ __l jours	
○ 5l Quelle était leur intensité sur une échelle de 1 (très faible) à 10 (maximale) ?		l__ __l	
▪ 5m une faiblesse d'un ou plusieurs membres ?		Oui ❑1	Non ❑0
5n Si oui, où était-elle localisée ?	5n1 les bras	Oui ❑1	Non ❑0
	5n2 les mains	Oui ❑1	Non ❑0
	5n3 les jambes	Oui ❑1	Non ❑0
	5n4 les pieds	Oui ❑1	Non ❑0
	5n5 le dos	Oui ❑1	Non ❑0
▪ 5o un comportement inhabituel constaté par l'un de vos proche (confusion) ?		Oui ❑1	Non ❑0

6. Avez-vous eu des troubles digestifs ?	Oui ❑1	Non ❑0
Si oui, avez vous présenté :		
▪ 6a Des douleurs abdominales ?	Oui ❑1	Non ❑0
▪ 6b Des nausées ou vomissements ?	Oui ❑1	Non ❑0
▪ 6c Des diarrhées ?	Oui ❑1	Non ❑0

7. Avez-vous eu des palpitations ?	Oui ❑1	Non ❑0

8. Avez-vous eu des douleurs dans la poitrine ?	Oui ❑1	Non ❑0
Si oui, décrivez-les :		
▪ 8a Combien de temps ont-elles duré ?	I__ __I mn ou I__ __I heures ou I__ __I jours	
▪ 8b Quelle était leur intensité sur une échelle de 1 (très faible) à 10 (maximale) ?	I__ __I	

9. Avez-vous eu des douleurs dans les muscles ?	Oui ❑1	Non ❑0

10. Avez-vous eu des douleurs dans les articulations inhabituelles ?		Oui ❑1	Non ❑0
10a Si oui, avez-vous présenté un gonflement d'une ou plusieurs articulations ?		Oui ❑1	Non ❑0
10b Si oui, où étaient-il(s) localisé(s) ?	10b1 les épaules	Oui ❑1	Non ❑0
	10b2 les coudes	Oui ❑1	Non ❑0
	10b3 les poignets	Oui ❑1	Non ❑0
	10b4 les doigts	Oui ❑1	Non ❑0
	10b5 les hanches	Oui ❑1	Non ❑0
	10b6 les genoux	Oui ❑1	Non ❑0
	10b7 les chevilles	Oui ❑1	Non ❑0
	10b8 les orteils	Oui ❑1	Non ❑0

11. Avez-vous eu des plaques rouges ou des boutons sur la peau ?	Oui ❑1	Non ❑0

12. Avez- vous eu des signes visuels ?	Oui ❑1	Non ❑0
Si oui, avez-vous présenté ?		
▪ 12a un/des yeux rouges	Oui ❑1	Non ❑0
▪ 12b des douleurs à l'oeil	Oui ❑1	Non ❑0
▪ 12c une diminution très récente de la vue	Oui ❑1	Non ❑0

13. Avez-vous eu des douleurs testiculaires ?	Oui ❑1	Non ❑0

14. Avez-vous eu des douleurs ou gonflement du cou ?	Oui ❑1	Non ❑0

15. Avez-vous eu des douleurs ou gonflement des joues ?	Oui ❑$_1$	Non ❑$_0$

Appendix 4: Supplemental data: frequency of extra-respiratory manifestations and comparison between subgroups.

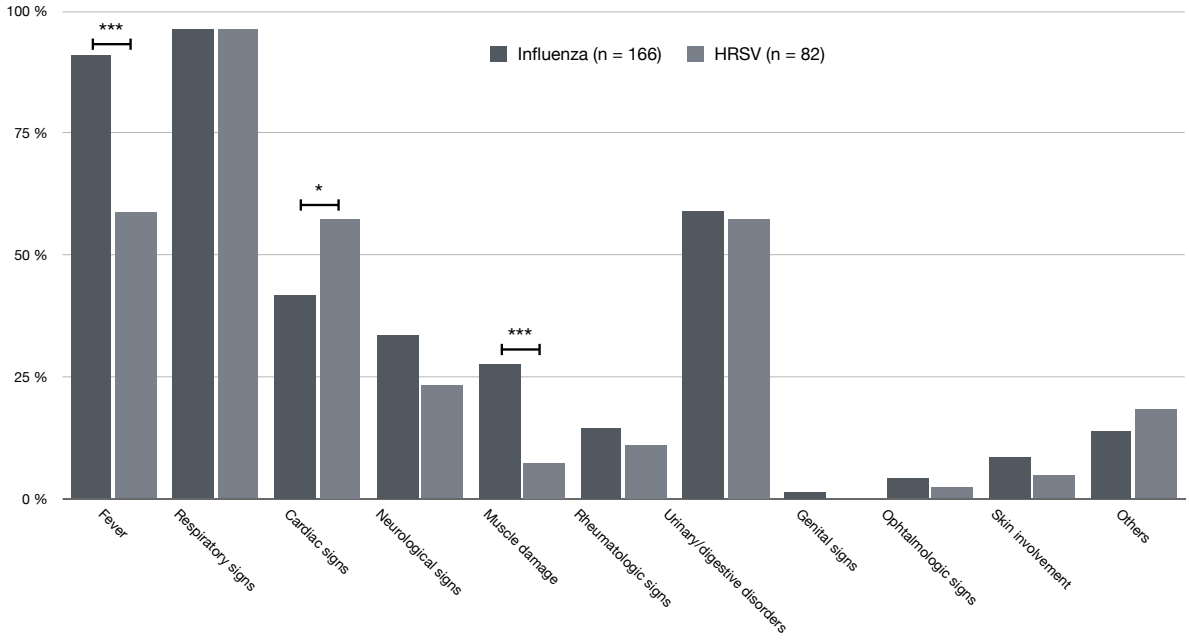

Figure S1. Frequency of each manifestation of Influenza and HRSV

HRSV: Human Respiratoy Syncytial Virus.

* p<0.05. ** p<0,01. *** p<0.001. Not specified: considered as non significant.

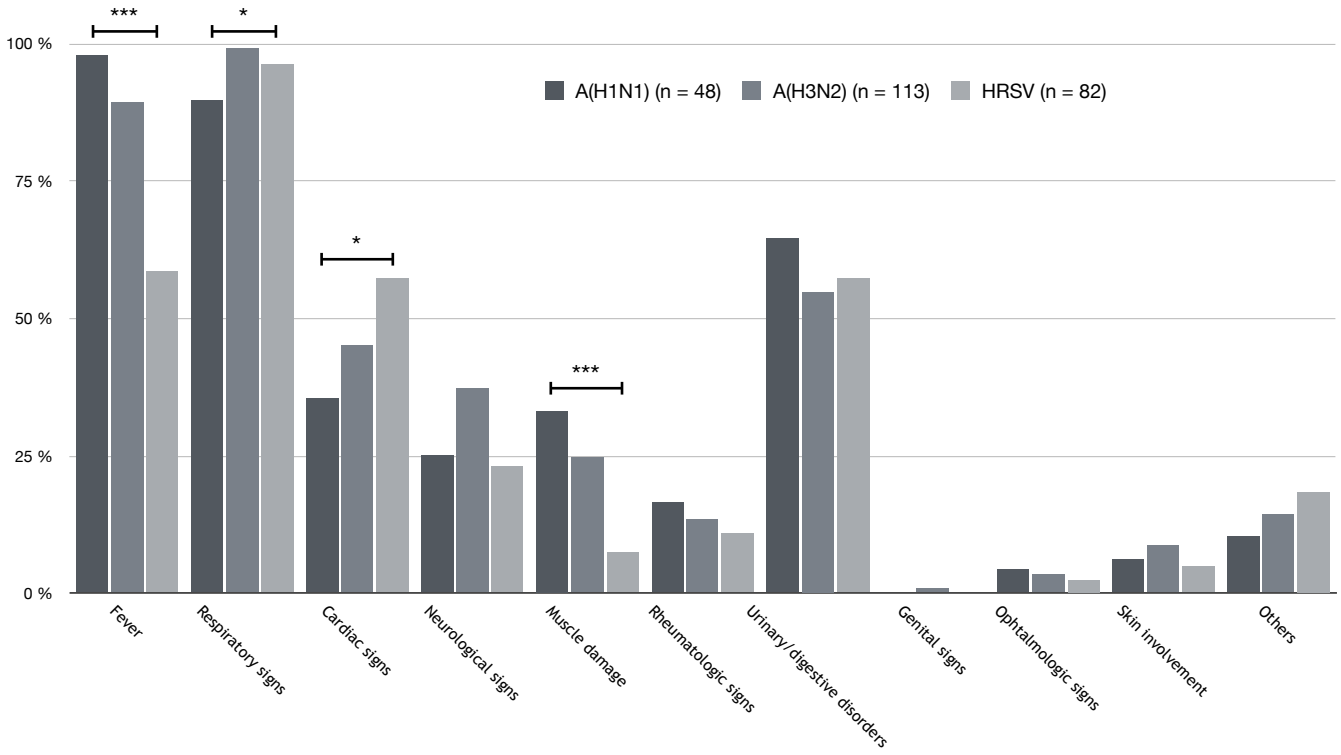

Figure S2. Frequency of each manifestation in A(H1N1), A(H3N2) and HRSV subgroups

HRSV: Human Respiratoy Syncytial Virus.

* p<0.05. ** p<0.01. *** p< 0.001. Not specified: considered as non significant.

Appendix 5: Supplemental data: Number of extra-respiratory manifestations and comparison between subgroups.

Table S1. Number of extra-respiratory manifestations

Number of extra-respiratory manifestations	All (n=248)[a]	Influenza (n=166)	HRSV (n=82)	p	A(H1N1) (n=48)	A(H3N2) (n=113)	HRSV (n=82)	p
Per patient - Mean (SD)	1.97 (1.28)	2.04 (1.35)	1.82 (1.10)	0.163	1.96 (1.34)	2.03 (1.32)	1.82 (1.10)	0.514
Repartition - Number (%)								
0	30 (12.1%)	21 (12.7%)	9 (11.0%)		6 (12.5%)	15 (13.3%)	9 (11.0%)	
1	66 (26.6%)	42 (25.3%)	24 (29.3%)		15 (31.3%)	25 (22.1%)	24 (29.3%)	
2	74 (29.8%)	46 (27.7%)	28 (34.1%)		10 (20.8%)	36 (31.9%)	28 (34.1%)	
3	48 (19.4%)	32 (19.3%)	16 (19.5%)		11 (22.9%)	21 (18.6%)	16 (19.5%)	
4	20 (8.1%)	16 (9.6%)	4 (4.9%)		4 (8.3%)	11 (9.7%)	4 (4.9%)	
5 or more	10 (4.0%)	9 (5.4%)	1 (1.2%)		2 (4.2%)	5 (4.4%)	1 (1.2%)	

HRSV: Human Respiratory Synctitial Virus. SD: Standard deviation.
[a] Subtype of Influenza was unknown for 5 patients. They were included in analysis in « Influenza » group but excluded from subgroup analysis.

Appendix 6: Multiple linear regression.

Table S2. Factors associated with extra-respiratory manifestation of all type

Multiple linear regression	Estimate	Standard error	p
All manifestations (best AIC: 483.72)			
Height	0.014	0.010	0.146
Cardiac arrythmia	0.313	0.202	0.124
HIV-positive	2.013	1.170	0.088
Primary immune deficiency	-1.153	0.691	0.097
Lymphocyte count	$1.518x10^{-5}$	$1.032x10^{-5}$	0.144
MDRD	0.005	0.003	0.143
CRP	0.002	0.001	0.018 *

AIC: Akaike Interaction Criterion. HIV: Human Immunodeficiency Virus. MDRD: Modification of diet in renal disease study equation. CRP: C-reactive protein.

* Considered as significant.

Table S3. Factors associated with cardiac manifestations

Multiple linear regression	Estimate	Standard error	p
Cardiac manifestations (best AIC: 192.10)			
Hypertension	-0.903	0.527	0.086
Cardiac arrythmia	1.354	0.456	0.003 *
Overweight/obesity	0.735	0.473	0.120
Hepatic underlying condition	-2.317	1.420	0.103
Solid organ transplant	2.179	1.370	0.112
Bone marrow transplant	0.346	6939	0.996
Primary immune deficiency	0.339	3350	0.992
History of cancer < 1 year	4.878	1.832	0.008 *
History of cancer (non treated or > 1 year)	2.499	1.252	0.046 *
Auto-immune dis. (immunosupp. Non-steroid therapy)	-0.472	4305	0.991
Auto-immune dis. (immunosupp. + steroid therapy)	-0.136	2369	0.995
Auto-immune dis. (steroid therapy)	0.650	1.250	0.603
Auto-immune dis. (no treatment)	3.592	1.606	0.025 *
Age	0.032	0.019	0.090
H3N2	0.526	0.673	0.435
HRSV	1.314	0.714	0.066
Cancer/Hemopathy/auto-immune disease	-2.047	1.281	0.110
Haemoglobin	0.228	0.136	0.094
Leucocyte count	3.372×10^{-5}	2.517×10^{-5}	0.180
MDRD	-0.020	0.008	0.010 *

AIC: Akaike Interaction Criterion. HRSV: Human Respiratory Syncytial Virus. MDRD: Modification of diet in renal disease study equation.

* Considered as significant.

Table S4. Factors associated with neurological manifestations

Multiple linear regression	Estimate	Standard error	p
Neurological manifestations (best AIC: 182.05)			
Height	0.047	0.022	0.033 *
Neurological condition	1.352	0.500	0.007 *
Hepatic underlying condition	1.524	1.082	0.159
Solid organ transplant	-0.190	2597	0.994
History of cancer < 1 year	-1.778	1.223	0.146
History of cancer (non treated or > 1 year)	-0.806	0.562	0.151
Auto-immune dis. (immunosupp. Non-steroid therapy)	-0.198	3533	0.996
Auto-immune dis. (immunosupp. + steroid therapy)	-0.176	3761	0.996
Auto-immune dis. (steroid therapy)	-0.182	2420	0.994
Auto-immune dis. (no treatment)	0.560	0.931	0.548
CRP	0.004	0.002	0.022 *

AIC: Akaike Interaction Criterion. CRP: C-reactive protein.

* Considered as significant.

Table S5. Factors associated with myalgia

Multiple linear regression	Estimate	Standard error	p
Myalgia (best AIC: 153.26)			
Male sex	-1.325	0.795	0.095
Height	0.081	0.046	0.080
Hypertension	1.155	0.705	0.102
Cardiac arrythmia	-1.116	0.624	0.074
Active smoker	-1.547	0.886	0.081
Neurological condition	-1.676	0.854	0.081
HIV-positive	0.210	6523	0.050 *
History of cancer < 1 year	-0.181	2261	0.998
History of cancer (non treated or > 1 year)	-0.194	2261	0.994
Hematological malignancy < 1 year	-0.193	2261	0.993
Hematological malignancy (non treated or > 1 year)	-0.236	1695	0.993
Auto-immune dis. (immunosupp. Non-steroid therapy)	-0.354	3916	0.989
Auto-immune dis. (immunosupp. + steroid therapy)	-0.369	3869	0.993
Auto-immune dis. (steroid therapy)	-0.187	2261	0.992
Auto-immune dis. (no treatment)	-0.160	2261	0.993
Age	-0.039	0.021	0.060
Cancer/Hemopathy/auto-immune disease	0.196	2261	0.993
Biology at admission	0.032	0.014	0.024 *
Lymphocyte count	-1.952×10^{-4}	1.441×10^{-4}	0.176
Platelet count	-4.718×10^{-6}	3.103×10^{-6}	0.128
Creatinine level	-0.011	0.008	0.159
CRP	-0.004	0.003	0.115

AIC: Akaike Interaction Criterion. HIV: Human Immunodeficiency Virus. CRP: C-reactive protein.

* Considered as significant.

Table S6. Factors associated with rheumatologic signs

Multiple linear regression	Estimate	Standard error	p
Rheumatologic signs (best AIC: 48.00)			
Height	63.19	799.4	0.937
Diabetes	-791.4	1.044×10^4	0.940
Cardiovascular disease	-1445	1.845×10^4	0.938
Overweight/obesity	684.4	8993	0.939
Neurological condition	-320.3	4362	0.941
Stroke	3255	4.187×10^4	0.938
Chronic kidney disease	-7.132×10^2	9465	0.940
Hepatic underlying condition	4828	6.161×10^5	0.938
Solid organ transplant	-4040	5.136×10^5	0.937
HIV-positive	5768	3.634×10^5	0.987
Primary immune deficiency	-820.3	8.452×10^4	0.992
History of cancer < 1 year	-6666	1.118×10^5	0.952
History of cancer (non treated or > 1 year)	-1.769×10^4	2.272×10^5	0.938
Age	20.40	265.3	0.939
Cancer/Hemopathy/auto-immune disease	1745	2.248×10^4	0.938
Biology date	48.54	619.7	0.938
Neutrophil count	0.092	1.226	0.940
Platelet count	-0.001	0.018	0.950
Serum creatinine	-46.04	583.9	0.937
MDRD	-26.95	342.9	0.937
AST	-71.52	905.8	0.937
ALT	-34.59	464.2	0.941
CRP	-4.252	54.65	0.938

AIC: Akaike Interaction Criterion. HIV: Human Immunodeficiency Virus. MDRD: Modification of diet in renal disease study equation. AST: asparagine transferase. ALT: alanine transferase. CRP: C-reactive protein.

* Considered as significant.

Table S7. Factors associated with uro-digestive signs

Multiple linear regression	Estimate	Standard error	p
Uro-digestive signs (best AIC: 175.39)			
Primary immune deficiency	-16.15	1340	0.990
Platelet count	4.185×10^{-6}	2.373×10^{-6}	0.078
MDRD	-0.025	0.007	<0.001 *
AST	0.040	0.013	0.002 *
HRSV	0.581	0.406	0.152

AIC: Akaike Interaction Criterion. MDRD: Modification of diet in renal disease study equation. AST: asparagine transferase. HRSV: Human Respiratory Syncytial Virus.
* Considered as significant.

Table S8. Factors associated with genital signs

Multiple linear regression	Estimate	Standard error	p
Genital signs (best AIC: 8.00)			
Diabetes	44.21	3.628×10^{4}	0.999
Hepatic underlying condition	46.06	3.578×10^{4}	0.999
Solid organ transplant	-45.76	1.204×10^{5}	1.000

AIC: Akaike Interaction Criterion.
* Considered as significant.

Table S9. Factors associated with ophthalmic signs

Multiple linear regression	Estimate	Standard error	p
Ophthalmic signs (best AIC: 28.00)			
Male sex	542.7	$3.463x10^4$	0.987
Weight	-22.48	1412	0.987
Diabetes	-1757	$1.053x10^5$	0.987
Cardiac arrythmia	-335.6	$2.084x10^4$	0.987
Chronic respiratory disease	-299.0	$1.935x10^4$	0.988
Overweight/obesity	474.8	$2.854x10^4$	0.987
Neurological condition	266.7	$1.634x10^4$	0.987
Leucocyte count	-0.539	29.98	0.986
Neutrophil count	0.517	28.99	0.986
Lymphocyte count	0.564	31.33	0.986
Serum creatinine	1.775	97.26	0.985
AST	-13.75	757.7	0.986
ALT	12.63	738.2	0.986

AIC: Akaike Interaction Criterion. AST: asparagine transferase. ALT: alanine transferase.

* Considered as significant.

Table S10. Factors associated with cutaneous signs

Multiple linear regression	Estimate	Standard error	p
Cutaneous signs (best AIC: 40.00)			
Male sex	-1312	$4.416x10^4$	0.976
Weight	20.60	714.3	0.977
Height	62.28	2135	0.977
Diabetes	1270	$4.300x10^4$	0.976
Hypertension	739.2	$2.511x10^4$	0.977
Active smoker	1644	$5.611x10^4$	0.977
Chronic respiratory disease	-931.0	$3.252x10^4$	0.977
Overweight/obesity	-1906	$6.442x10^4$	0.976
Neurological condition	-1686	$6.873x10^4$	0.980
Chronicc kidney disease	2077	$7.022x10^4$	0.976
Hepatic underlying condition	-2234	$1.101x10^5$	0.984
Solid organ transplant	1412	$4.803x10^4$	0.977
Age	11.46	400.6	0.977
Cancer/Hemopathy/auto-immune disease	938.3	$3.195x10^4$	0.977
Biology date	-8.930	305.1	0.977
Lymphocyte count	0.249	8.625	0.977
Platelet count	-0.008	0.257	0.976
MDRD	41.20	1396	0.976
ALT	-11.88	408.6	0.977

AIC: Akaike Interaction Criterion. MDRD: Modification of diet in renal disease study equation. ALT: alanine transferase.

* Considered as significant.

Table S11. Factors associated with other signs

Multiple linear regression	Estimate	Standard error	p
Other signs (best AIC 128.00)			
Height	0.050	0.030	0.096
Neurological condition	-2.310	1.268	0.068
Primary immune deficciency	-22.24	4449	0.996
History of cancer < 1 year	-42.02	4462	0.992
History of cancer (non treated or > 1 year)	-22.79	3009	0.994
Hematological malignancy < 1 year	-22.36	3009	0.994
Hematological malignancy (non treated or > 1 year)	2.750	1.848	0.138
Auto-immune dis. (immunosupp. Non-steroid therapy)	-17.75	3009	0.995
Auto-immune dis. (immunosupp. + steroid therapy)	-39.54	5984	0.995
Auto-immune dis. (steroid therapy)	-39.22	4385	0.993
Auto-immune dis. (no treatment)	-16.23	3009	0.996
H3N2	1.957	1.062	0.065
HRSV	0.797	1.080	0.460
Cancer/Hemopathy/auto-immune disease	22.59	3009	0.994
Serum creatinine	-0.013	0.008	0.084
MDRD	-0.042	0.020	0.036 *
AST	-0.042	0.018	0.016 *
CRP	0.008	0.003	0.007 *

AIC: Akaike Interaction Criterion. HRSV: Human Respiratory Syncytial Virus. MDRD: Modification of diet in renal disease study equation. AST: asparagine transferase. CRP: C-reactive protein.
* Considered as significant.

SERMENT

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En présence des Maîtres de cette école, de mes chers condisciples et devant l'effigie d'Hippocrate, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la médecine. Je donnerai mes soins gratuits à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail. Admis dans l'intérieur des maisons mes yeux ne verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés, et mon état ne servira pas à corrompre les mœurs ni à favoriser le crime. Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses ! Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque !

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Résumé

Les manifestations extra-respiratoires liées à l'infection à Influenza ou au VRS sont peu connues chez l'adulte. L'objectif de cette étude était de décrire la fréquence et le type de ces manifestations chez des patients adultes hospitalisés pour une infection à Influenza ou au VRS. Deux-cent quarante-huit patients ayant eu un test nasal par technique de polymerase chain reaction (PCR) ou par détection moléculaire, positif à Influenza ou à VRS ont été inclus de manière prospective durant l'hiver 2018-2019. Les principales manifestations extra-respiratoires étaient cardiaques, neurologiques et uro-digestives (41,6 %, 33,7 % et 59,0 % pour Influenza et 52,3 %, 23,2 % et 57,3 % pour le VRS, respectivement). L'atteinte musculaire était rare parmi les infections à VRS en comparaison à Influenza ($p<0,001$). Le sous-type A(H1N1)pdm09 touchait une population moins souvent âgée ($p<0,001$), et présentant moins de comorbidités, et était responsable de signes cardiaques plus rares que le sous-type A(H3N2) et le VRS ($p=0,046$). En analyse multivariée, le taux de CRP à l'admission était le seul paramètre significativement associé à l'apparition d'une manifestation extra-respiratoire de tout type ($p=0,018$).

Mots-clés : Influenza, Human ; Respiratory Syncytial Virus, Human