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Clinical Microbiology and Infection

DOI: 10.1016/j.cmi.2019.01.014

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Abstract

Objectives

We aimed to identify patients' clinical characteristics associated with respiratory viruses identified among patients presenting with influenza-like illness (ILI).

Methods

A sample of patients of all ages presenting with ILI was included by physicians of the French *Sentinelles* network during two seasons (2015/16 and 2016/17). Nasopharyngeal samples were tested for the presence of influenza virus (IV), respiratory syncytial virus (RSV), rhinovirus (HRV), and metapneumovirus (HMPV). Patients' characteristics associated with each of the four virus classes were studied using multivariate logistic regressions.

Results

A total of 5859 patients were included in the study: 48.0% tested positive for IV, 7.9% for HRV, 7.5% for RSV, and 4.1% for HMPV. Cough was associated with IV (OR 2.14 95%CI [1.81;2.52], RSV (2.52 [1.75;3.74]) and HMPV detection (2.15 [1.40;3.45]). Rhinorrhoea was associated mainly with HRV detection (1.75 [1.34;2.32]). Headache was associated with IV detection (1.75 [1.34;2.32]), whereas absence of headache was associated with RSV and HMPV detection. Dyspnoea was associated with RSV detection (2.33 [1.73;3.12]) and absence of dyspnoea with IV detection. Conjunctivitis was associated with IV detection (1.27 [1.08;1.50]). Some associations were observed only in children: dyspnoea and cough with RSV detection (<5 y), conjunctivitis with IV detection (<15 y). Period of onset of symptoms differed among aetiological diagnoses. Seasonal influenza vaccination decreased the risk of IV detection (0.67 [0.51;0.86]).

Conclusions

This study allowed the identification of symptoms associated with several viral aetiologies in patients with ILI. A proper knowledge and understanding of these clinical signs may improve the medical management of patients.

Keywords

Influenza-like illness; respiratory viruses; respiratory infections; influenza; surveillance; Primary care

Introduction

Precise aetiological diagnoses of respiratory infections require virological analyses as none of the common respiratory viruses provide a pathognomonic clinical picture [1, 2]. Clinical symptoms and impact according to patient characteristics differ depending on the virus responsible for the infection, and seasonal dynamics vary according to the virus as well as across seasons [1, 3, 4]. Knowledge of factors associated with the virological status might improve treatment decisions and medical care proposed by the physician at the time of diagnosis, especially for influenza, for which antivirals are recommended for the at-risk population [1, 5, 6].

In France, in primary care, since 1984, the *Sentinelles* network has been conducting surveillance of patients with influenza-like illness, with a specific definition for the purpose of influenza surveillance (called thereafter Sentinelles influenza-like illness (S-ILI)) [7, 8]. Since 2014, this surveillance has been linked to virological analyses to detect and characterize respiratory viruses circulating [9]. This surveillance is based on general practitioners (GPs) and paediatricians who collect nasopharyngeal swabs among patients with S-ILI. These are routinely tested for four common respiratory virus classes: influenza virus (IV), respiratory syncytial virus (RSV), human metapneumovirus (HMPV), and human rhinovirus (HRV).

As improved characterization of community-acquired respiratory infections could help healthcare professionals in the management of these infections, the aim of this study was to identify the clinical characteristics collected by the physician in patients with S-ILI that were associated with each of the four tested viruses (IV, RSV, HRV and HMPV). Primary analyses were conducted by comparing patients positive for one virus to the rest of the cohort. Secondary analyses were performed considering only patients who tested positive for any of the virus classes, and considering different age groups.

Methods

Study design and data collection

Virological surveillance of respiratory viruses in France involves 250 GPs and 100 paediatricians of the French *Sentinelles* network with a nationwide coverage [9]. The surveillance uses a specific definition of S-ILI for patients' recruitment: sudden onset of fever >39°C with myalgia and respiratory signs, diagnosed by the physician. This definition was chosen for its high predictive value for influenza infection [7]. The study period covered two surveillance seasons: 2015/16 (week 2015w40 to 2016w17) and 2016/17 (week 2016w40 to 2017w15) (Figure 1).

During the virological surveillance period, sentinel physicians collected nasopharyngeal swabs along with clinical data in a systematically selected sample of their patients presenting with S-ILI [9]. The sample consisted of the first two S-ILI patients of the week, unrelated to one another, consulting within less than 48 hours since symptom onset and consenting to provide a nasopharyngeal specimen. Each patient could be included only once a year. During the 2016/17 influenza epidemic, GPs were allowed to include one additional patient aged 65 years (y) or older presenting with S-ILI, to improve influenza surveillance among the elderly. The study population consisted of all S-ILI patients swabbed, with exclusion of co-infected patients, of patients that were not tested for the presence of the four virus classes and of patients swabbed more than seven days after symptom onset.

Virological analyses were performed by the French National Reference Centre for respiratory viruses (CNR, in Paris and Lyon) and the Laboratory of Virology at the University of Corsica. The three laboratories performed real-time reverse-transcriptase polymerase chain reaction (RT-PCR) tests for the detection of IV (A and B), RSV, HMPV, and HRV.

Outcomes and explanatory variables

For each patient, the outcome corresponded to the virological result: positive for IV, RSV, HMPV, HRV, positive for several virus classes – called "co-infected", or negative for all viruses tested – called "negative". Based on a previous study reporting no differences between IVA and IVB symptoms [2], we did not discriminate IVA and IVB patients.

Explanatory variables studied were those identifiable by the physician during the consultation: age (eight groups: <5 y, 5-14 y, 15-29 y, 30-44 y, 45-64 y, and ≥65 y), influenza vaccination for current season (received at least 14 days before onset of symptoms), period of onset of symptoms (before, during or after the influenza epidemic as published by the Sentinelles network for France [8] - reported in Figure 1), cough, rhinorrhoea, dyspnoea, sore throat, conjunctivitis, headache, malaise, vomiting, and diarrhoea.

To identify which of these explanatory variables were associated with the viral infection, we performed the following analyses:

- four independent analyses with the virological result as outcome (IV, RSV, HMPV or HRV), considering the whole study population (i.e. whatever the virological result, positive or negative);
- four independent analyses with the virological result as outcome (IV, RSV, HMPV or HRV), considering independently three age groups belonging to the study population: young children (<5 y), older children (5-14 y) and adults (≥15 y);
- IV detection as outcome, considering a subgroup of the study population with the patients positive for IV or negative for all four virus classes;
- IV detection as outcome, considering a subgroup of the study population with the patients positive for any of the four virus classes;
- any virus detection as outcome, considering the whole study population.

Statistical analyses

Multivariate logistic regressions were performed to identify factors associated with the outcomes of interest. Starting with all explanatory variables in the model (see above), we used a backward process based on likelihood-ratio test to remove the least significant variables from the model step-by-step (p-value level of 0.05).

Ethical statement

The protocol was conducted in agreement with the Helsinki declaration. We obtained authorization from the French Data Protection Agency (CNIL#471393) and the French ethical research committee (*Comité de protection des personnes*). All participating physicians consent to publication of the results from the surveillance.

Results

During the 2015/16 and 2016/17 surveillance seasons, sentinel physicians swabbed 6997 patients with S-ILI. Among them, 5859 (83.7%) were included in the study (Figure 2): 3003 collected during the 2015/16 season (from September 29, 2015 to May 1, 2016) and 2856 during the 2016/17 season (from October 3, 2016 to April 16, 2017). Laboratory analysis allowed the identification of 2815 (48.0%) patients positive for IV, 462 (7.9%) for HRV, 437 (7.5%) for RSV, 242 (4.1%) for HMPV and 1903 (32.5%) patients negative for all virus classes tested (Table 1). A total of 192 patients co-infected were excluded from the analysis (Figure 2, Table 1). These patients were always positive for IV and for one or two other virus classes (57.3% for HRV, 26.6% for RSV and 18.8% for HMPV).

Characteristics of the patients included are reported in Table 1. Among the study population, 32.9% (n=1917) were aged less than 5 y, 18.8% (n=1098) were between 5 and 14 y and 48.2% (n=2811) were 15 or older. The median age of the adults (≥15 y) was 39 y (inter-quartile range: 28 to 53 y). The period of onset of symptoms was during the influenza epidemic in 64.8% of

patients (n=3794), before the epidemic in 26.3% (n=1539) and after the epidemic in 9.0% (n=526) (Figure 1). Among the study population, 12.8% (n=722) had at least one chronic disease, and 6.3% (n=363) were vaccinated with the seasonal influenza vaccine.

Symptoms and baseline patient characteristics associated with laboratory confirmation of each of the four virus classes are reported in Table 2. Results of age-subgroup analyses are reported in Supplementary Table S1.

Symptoms associated with detection of IV were cough, absence of dyspnoea, conjunctivitis, headache, and rhinorrhoea. Patients were more likely to be IV-positive during the epidemic period. Compared to the middle-age group (30-44 y), school-aged children (5-14 y) had a higher risk to be IV-positive, and the youngest (<5 y) had a lower risk. Seasonal influenza vaccination was associated with a lower risk of IV detection. Among the youngest (<5 y), headache was associated with IV detection while cough and rhinorrhoea were not. Conjunctivitis was associated with IV detection among children (<15 y). The complementary analysis comparing IV-positive patients to two other groups (all negative patients or patients positive for another respiratory virus) provided results consistent with the primary analysis for IV (Supplementary Table S2, Table 2).

Detection of RSV was associated with cough, dyspnoea, absence of headache and rhinorrhoea. RSV was more frequently identified before the influenza epidemic period. The youngest (<5 y) had the highest risk to be RSV-positive, the 5-14 y, the 45-64 y and the elderly (≥65 y) had an increased risk compared to the middle-age group (30-44 y). In age-subgroup analyses, some differences should be noted: cough and dyspnoea were associated with RSV detection in the <5 y while sore throat was identified for adults (≥15 y).

Laboratory confirmation of HMPV was associated with cough and absence of headache. Patients were more likely to be HPMV-positive outside of the influenza epidemic period.

Compared to the 30-44 y, the <5 y, the 45-64 y and the ≥65 y had a higher risk to be HMPV-positive. Concerning age-subgroup analyses, cough were associated with confirmation of HMPV for children (<15 y) and absence of headache was associated with HMPV detection for the <5 y.

Only rhinorrhoea was associated with HRV detection. Patients were more likely to be HRV-positive outside the influenza epidemic and particularly before this period. The youngest (<5 y) had a higher risk and the 5-14 y a lower risk to be HRV-positive, compared to the 30-44 y. Among age groups, rhinorrhoea was associated with HRV detection for the <5 y and the ≥15 y, whereas only absence of headache was associated with HRV detection for the 5-14 y.

Lastly, when comparing patients positive for any of the four virus classes to patients negative, we highlighted two symptoms (cough and rhinorrhoea) associated with virus detection along with extreme age groups (<15 y or ≥45 y, compared to the 30-44 y) (Supplementary Table S2).

Discussion

During the two surveillance seasons analysed, an aetiological agent was detected in more than two thirds of patients with S-ILI (defined as a sudden onset of fever >39°C with myalgia and respiratory signs) seen by physicians of the *Sentinelles* network. We found that three baseline characteristics (age, period of symptom onset, seasonal influenza vaccination) and five symptoms (cough, rhinorrhoea, headache, conjunctivitis, and dyspnoea) were associated with an increased or decreased risk of detection of at least one of the four virus classes. These factors are identifiable by the physician at the time of S-ILI diagnosis (Table 3).

All four respiratory virus classes co-circulated to various extent during the winter period in France (December to March). However, their intensity of circulation varied over the months, consistent with previous studies [4, 10-12]: HRV circulated mostly during autumn and could reappear in spring, RSV had higher activity in late autumn to early winter, IV predominated

mainly during winter. As expected, we showed that the risk of IV detection was higher during the influenza epidemic period, which supports the use of this S-ILI definition and the influenza epidemic detection method [13]. However, the proportion of S-ILI patients positive for IV was 48.0% over the study period and never higher than 76.0% by week (Figure 1). Laboratory confirmation of virus infection by RT-PCR is costly and is not feasible in real time at the physician's office. Although an accurate aetiological diagnosis will require laboratory analysis, knowledge of combined observable factors predictive of viruses responsible for infection among S-ILI patients, might help to improve the rapid management of these infections. Analyses provided here are comparisons in relative terms, which should not be interpreted as patterns of incidence.

Compared to middle-age adults (30-44 y), youngest children (<5 y) had an increased risk to be positive for HRV, HMPV, and especially for RSV which affects more commonly this age group [14-16]. Moreover, the 45-64 y and ≥65 y age groups had a higher risk to be positive for RSV and HMPV compared to the 30-44 y - in line with a previous study [3]. The clinical signs associated with detection of a virus among patients with S-ILI varied among age groups. However, differences in age-related clinical symptoms should be interpreted cautiously, as the frequency of the four isolated viruses differed markedly among children and adults [4, 16]. Consequently, the limited number of individuals for some age-subgroups analyses could explain in part the age-related differences in clinical signs highlighted.

Cough was the most frequently reported symptom, associated with IV, RSV and HMPV detections, as expected [1, 3, 17]. Presence of dyspnoea was associated with RSV infection while absence of dyspnoea was related to IV detection, as previously reported [16]. This is consistent with the biology of these viruses: typically, IV infections predominantly involve the upper respiratory tract and trachea [18, 19], as human strains of IV primarily target cells of the upper airway [20], unlike RSV which are more commonly associated with lower respiratory

tract infections such as bronchiolitis and pneumonia [21, 22]. Headache was associated with an increased risk of IV detection and a lower risk of RSV and HMPV detection, consistent with previous studies [7, 16, 23]. Association between conjunctivitis and IV detection was mainly reported among the youngest [7, 19]. HRV detection was associated with one symptom – rhinorrhoea, in line with less severe illness caused by HRV compared to other viruses [4].

Influenza vaccination was associated with a lower risk to be IV-positive, in concordance with the influenza vaccine effectiveness estimated for these two seasons in Europe (33% 95%CI[10;51] against A(H1N1)pdm09 viruses in 2015/16; 20% [-14;43] against B viruses in 2015/16; 21% [6;34] against A(H3N2) viruses in 2016/17) [24].

Our study is based on data collected by a longstanding surveillance system with a standardized protocol, allowing the inclusion of a large number of patients during two surveillance seasons. However, some limitations should be noted. First, patients were included using a fever definition of >39°C, resulting in a high proportion of IV-positive patients (48.0%). This did not allow studying milder respiratory infections nor the impact of symptoms included in the definition. Second, we highlighted symptoms associated with IV detection without type/sub-type/lineage distinction. This choice was based on previous studies in France [2] although others reported that symptoms may differ with influenza types and subtypes [7]. In France, the 2015/16 influenza season was dominated by influenza type B viruses (among IVs detected 72% were type B and 27% subtype A(H1N1)pdm09) [9 #100], while the 2016/17 season was dominated by subtype A(H3N2) (98%) [25]. Thirdly, only four virus classes were studied – others such as adenoviruses or coronaviruses were not investigated. Fourthly, we excluded the 192 co-infected patients (2.7%) from the analyses. As all of them were infected by IV, we compared these co-infected patients with those positive for IV only: we found that the co-infected were younger and presented similar symptoms, with slight differences: more dyspnoea, less malaise and less headache. Fifthly, data collected did neither allow the analysis of the

intensity, nor the severity of the infection in terms of duration of symptoms or risk for hospitalization.

This study allowed the identification of symptoms associated with several viral aetiologies in patients presenting with S-ILI in primary care. As patients are not routinely virologically tested, a proper knowledge and understanding of clinical signs of these respiratory illnesses may contribute to improve decision-making and medical care of patients.

Competing interests

Dr. Lina received travel grants to attend meetings from GSK and Sanofi Pasteur. Dr. Lina is a member of the scientific boards of the GII and GHISN. All personal remuneration stopped in September 2010. Dr. van der Werf reports grants from Santé publique France, during the conduct of the study; other from ESWI, outside the submitted work.

Funding

This project has received funding from the European Union's Horizon 2020 Research and Innovation Program under grant agreement No 634446 to conduct the study in individuals aged 65 years or older and from Santé publique France, the national public health agency in France.

Acknowledgments

We thank all GPs and paediatricians participating in the French Sentinelles network. We also thank the European Centre for Disease Prevention and Control, which contributed to the funding of the study.

Authors' contributions

TH, TB, and CS designed the study. SM, CP, CT, LC, AF, BL, SvdW, IB, AMV, MV and SB participated in data collection and analysis. CS performed the statistical analysis. CS, SM, and TH drafted the manuscript. All the authors contributed and approved the final version of the manuscript.

Figures

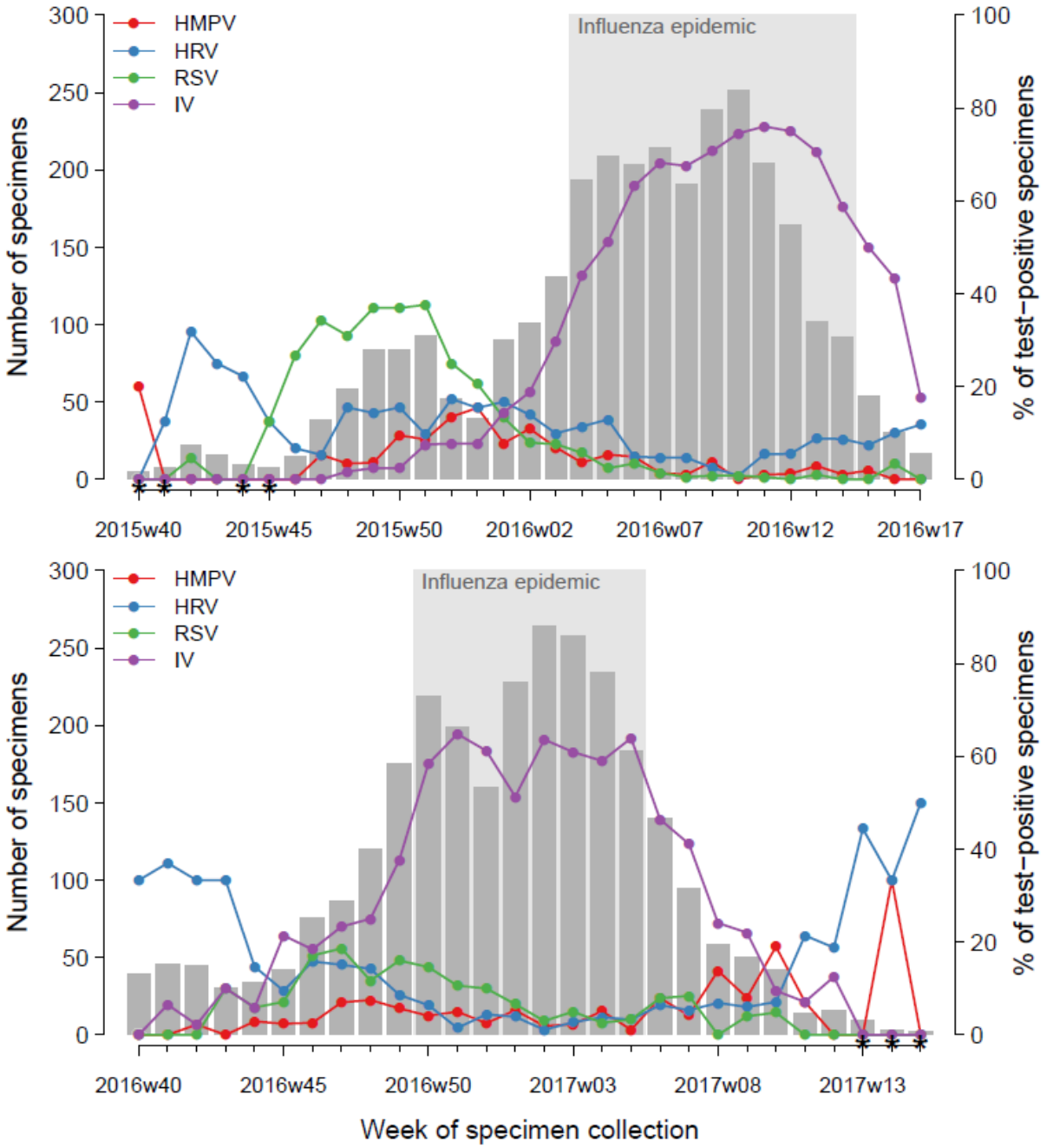

Figure 1. Size of study population and percentage of patients tested positive for the four virus classes studied: influenza viruses (IV), respiratory syncytial viruses (RSV), human rhinoviruses (HRV), and human metapneumoviruses (HMPV) by week, seasons 2015/16 and 2016/17, France. (* Number of samples for the week was less than 10)

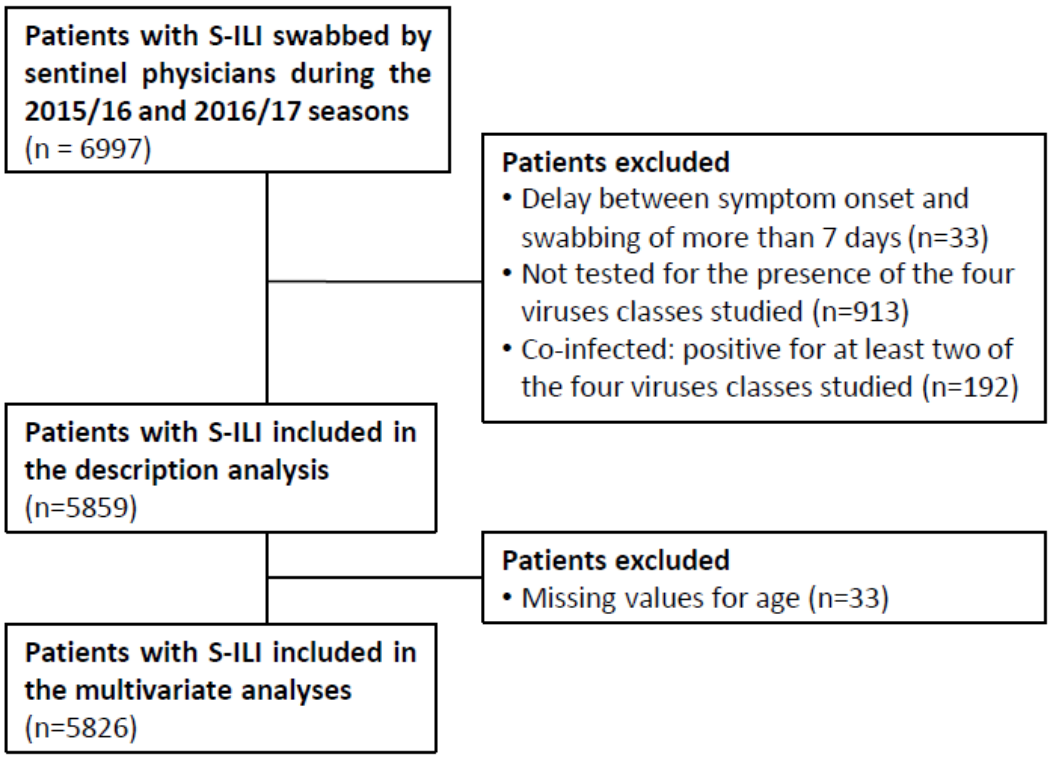

Figure 2. Flowchart of data exclusion of study population, seasons 2015/16 and 2016/17, France.

Tables

Table 1. Description of study population according to viral aetiology, seasons 2015/16 and 2016/17, France.

		Influenza virus (n=2815)	Respiratory syncytal virus (n=437)	Human metapneumo-virus (n=242)	Human rhinovirus (n=462)	Co-infected (n=192)	No virus (n=1903)	Total included in the study[¥] (n=5859)
Season	2015/16	1483 (52.7%)	218 (49.9%)	115 (47.5%)	249 (53.9%)	94 (49%)	938 (49.3%)	3003 (51.3%)
	2016/17	1332 (47.3%)	219 (50.1%)	127 (52.5%)	213 (46.1%)	98 (51%)	965 (50.7%)	2856 (48.7%)
Clinical presentation								
Period onset of symptoms	Before influenza epidemic	238 (8.5%)	263 (60.2%)	94 (38.8%)	238 (51.5%)	30 (15.6%)	706 (37.1%)	1539 (26.3%)
	During influenza epidemic	2399 (85.2%)	150 (34.3%)	110 (45.5%)	180 (39%)	155 (80.7%)	955 (50.2%)	3794 (64.8%)
	After influenza epidemic	178 (6.3%)	24 (5.5%)	38 (15.7%)	44 (9.5%)	7 (3.6%)	242 (12.7%)	526 (9%)
Cough		2477 (88%)	403 (92.2%)	220 (90.9%)	382 (82.7%)	170 (88.5%)	1408 (74%)	4890 (83.5%)
Rhinorrhoea		2150 (76.4%)	382 (87.4%)	191 (78.9%)	394 (85.3%)	156 (81.2%)	1305 (68.6%)	4422 (75.5%)
Headache		1881 (66.8%)	120 (27.5%)	95 (39.3%)	218 (47.2%)	85 (44.3%)	1157 (60.8%)	3471 (59.2%)
Sore throat		1447 (51.4%)	171 (39.1%)	104 (43%)	221 (47.8%)	87 (45.3%)	918 (48.2%)	2861 (48.8%)
Conjunctivitis		479 (17%)	65 (14.9%)	29 (12%)	75 (16.2%)	35 (18.2%)	256 (13.5%)	904 (15.4%)
Malaise		366 (13%)	24 (5.5%)	15 (6.2%)	50 (10.8%)	12 (6.2%)	252 (13.2%)	707 (12.1%)
Dyspnea		205 (7.3%)	81 (18.5%)	27 (11.2%)	54 (11.7%)	22 (11.5%)	184 (9.7%)	551 (9.4%)
Vomiting		300 (10.7%)	52 (11.9%)	23 (9.5%)	54 (11.7%)	24 (12.5%)	237 (12.5%)	666 (11.4%)
Diarrhoea		172 (6.1%)	40 (9.2%)	18 (7.4%)	30 (6.5%)	15 (7.8%)	145 (7.6%)	405 (6.9%)
Baseline characteristics								
Sex	F	1329 (48.1%)	214 (50%)	110 (46.2%)	222 (49.2%)	82 (43.2%)	913 (49.3%)	2788 (48.7%)
	M	1432 (51.9%)	214 (50%)	128 (53.8%)	229 (50.8%)	108 (56.8%)	939 (50.7%)	2942 (51.3%)
	Missing values[*]	54 (1.9%)	9 (2.1%)	4 (1.7%)	11 (2.4%)	2 (1%)	51 (2.7%)	129 (2.2%)
Age groups (years)	0 - 4	641 (22.9%)	323 (74.3%)	125 (52.1%)	239 (52%)	107 (55.7%)	589 (31.1%)	1917 (32.9%)
	5 - 14	675 (24.1%)	33 (7.6%)	31 (12.9%)	44 (9.6%)	44 (22.9%)	315 (16.6%)	1098 (18.8%)
	15 - 29	447 (16%)	17 (3.9%)	21 (8.8%)	52 (11.3%)	14 (7.3%)	299 (15.8%)	836 (14.3%)
	30 - 44	442 (15.8%)	11 (2.5%)	14 (5.8%)	54 (11.7%)	15 (7.8%)	335 (17.7%)	856 (14.7%)
	45 - 64	410 (14.7%)	37 (8.5%)	27 (11.2%)	51 (11.1%)	7 (3.6%)	257 (13.6%)	782 (13.4%)
	>= 65	182 (6.5%)	14 (3.2%)	22 (9.2%)	20 (4.3%)	5 (2.6%)	99 (5.2%)	337 (5.8%)
	Missing values[*]	18 (0.6%)	2 (0.5%)	2 (0.8%)	2 (0.4%)	0 (0%)	9 (0.5%)	33 (0.6%)
Chronic condition		316 (11.7%)	60 (14.3%)	39 (16.9%)	60 (13.7%)	26 (13.8%)	247 (13.6%)	722 (12.8%)
	Missing values[*]	104 (3.7%)	18 (4.1%)	11 (4.5%)	25 (5.4%)	4 (2.1%)	81 (4.3%)	239 (4.1%)
Influenza vaccination (for current season)		178 (6.4%)	19 (4.4%)	16 (6.7%)	21 (4.6%)	129 (6.9%)	7 (3.7%)	129 (6.9%)
	Missing values[*]	39 (1.4%)	6 (1.4%)	4 (1.7%)	6 (1.3%)	4 (2.1%)	25 (1.3%)	80 (1.4%)

[¥]Excluding co-infected individuals; [*]Missing values were not included in percentage calculations

Table 2. Clinical characteristics associated with four respiratory virus classes among patients seen by physicians of the *Sentinelles* network for influenza-like illness, multivariate analyses, seasons 2015/16 and 2016/17, France

	Influenza virus		**Respiratory syncytial virus**		**Human metapneumovirus**		**Human rhinovirus**	
	OR [95%CI]	p-value	OR [95%CI]	p-value	OR [95%CI]	p-value	OR [95%CI]	p-value
Cough	2.14 [1.81;2.52]	$<10^{-5}$	2.52 [1.75;3.74]	$<10^{-5}$	2.15 [1.40;3.45]	$<10^{-3}$	NS	
Headache	1.19 [1.03;1.37]	0.016	0.60 [0.46;0.78]	$<10^{-3}$	0.62 [0.45;0.85]	0.003	NS	
Rhinorrhoea	1.21 [1.05;1.39]	0.009	1.43 [1.06;1.97]	0.018	NS		1.75 [1.34;2.32]	$<10^{-4}$
Dyspnoea	0.56 [0.46;0.70]	$<10^{-5}$	2.33 [1.73;3.12]	$<10^{-5}$	NS		NS	
Conjunctivitis	1.27 [1.08;1.50]	0.004	NS		NS		NS	
Period of onset of symptoms		$<10^{-5}$		$<10^{-5}$		$<10^{-5}$		$<10^{-5}$
Before influenza epidemic	0.11 [0.09;0.13]		3.72 [2.98;4.66]		1.89 [1.41;2.52]		3.30 [2.68;4.06]	
During influenza epidemic	-*		-*		-*		-*	
After influenza epidemic	0.30 [0.24;0.36]		1.19 [0.74;1.84]		2.74 [1.84;3.99]		1.80 [1.26;2.53]	
Age group (years)		$<10^{-5}$		$<10^{-5}$		$<10^{-3}$		$<10^{-5}$
< 5	0.59 [0.48;0.72]		10.6 [5.89;21.12]		3.05 [1.75;5.73]		1.67 [1.23;2.31]	
5-14	1.59 [1.29;1.95]		2.83 [1.46;5.94]		1.82 [0.98;3.55]		0.64 [0.42;0.97]	
15-29	1.05 [0.85;1.30]		1.69 [0.79;3.77]		1.61 [0.82;3.27]		0.98 [0.66;1.46]	
30-44	-*		-*		-*		-*	
45-64	1.1 [0.88;1.36]		3.74 [1.95;7.79]		2.02 [1.07;4.00]		1.02 [0.68;1.53]	
>=65	1.34 [0.99;1.82]		3.1 [1.38;7.14]		3.78 [1.92;7.70]		1.00 [0.57;1.68]	
Influenza vaccination (for current season)	0.67 [0.51;0.86]	0.002	NS		NS		NS	

*Reference group, NS: non significant, OR: odd ratio, 95%CI: 95% confidence interval
For each virus, an independent multivariate regression analysis was performed considering the whole study population (i.e. whatever the virological result, positive or negative).

Table 3. Clinical and epidemiological characteristics associated with different viruses responsible of *Sentinelles* influenza-like illnesses (defined as a sudden onset of fever over 39°C with myalgia and respiratory signs)

	Influenza virus	**Respiratory syncytial virus**	**Human metapneumo-virus**	**Human rhinovirus**
Cough	+ +	+ +	+ +	
Headache	+	-	-	
Rhinorrhoea	+	+		+
Dyspnoea	-	+ +		
Conjunctivitis	+			
Period of onset of symptoms				
Before influenza epidemic	- - -	+ + +	+	+ + +
During influenza epidemic	*	*	*	*
After influenza epidemic	- - -		+ +	+
Age group (years)				
< 5	-	+ + +	+ + +	+
5-14	+	+		-
15-29				
30-44	*	*	*	*
45-64		+ + +	+ +	
>=65		+ + +	+ + +	
Influenza vaccination (for current season)	-			

*Reference group

Adjusted OR significantly higher than 1:

"+" for $1 < OR < 2$

"+ +" for $2 \leq OR < 3$

"+ + +" for $OR \geq 3$

Adjusted OR significantly lower than 1:

"-" for $0.5 < OR < 1$

"- -" for $0.3 < OR \leq 0.5$

"- - -" for $OR \leq 0.3$

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