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Abstract

Objectives. To describe the prevalence, clinical features and complications of human metapneumovirus (hMPV) infections in a population of adults hospitalized with influenza-like illness (ILI).

Methods. This was a retrospective, observational, multicenter cohort study using prospectively collected data from adult patients hospitalized during influenza virus circulation, for at least 24h, for community-acquired ILI (with symptom onset <7 days). Data were collected from five French teaching hospitals over six consecutive winters (2012-2018). Respiratory viruses were identified by multiplex RT-PCR on nasopharyngeal specimens. hMPV+ patients were compared to hMPV– patients, influenza+ and respiratory syncytial virus (RSV)+ patients using multivariate logistic regressions. Primary outcome was the prevalence of hMPV in patients hospitalized for ILI.

Results. Among the 3148 patients included (1449 (46%) women, 1988 (63%) aged 65 and over; 2508 (80%) with chronic disease), at least one respiratory virus was detected in 1604 (51%, 95%CI [49-53]), including 100 cases of hMPV (100/3148, 3% 95%CI [3-4]), of which 10 (10%) were viral co-infection. In the hMPV+ patients, mean length of stay was 7 days, 62% (56/90) developed a complication, 21% (14/68) were admitted to intensive care unit and 4% (4/90) died during hospitalization. In comparison with influenza+ patients, hMPV+ patients were more frequently > 65 years old (aOR=3.3, 95%CI[1.9-6.3]) and presented more acute heart failure during hospitalization (aOR=1.8, 95%CI[1.0-2.9]). Compared to RSV+ patients, hMPV+ patients had less cancer (aOR=0.4, 95%CI[0.2-0.9]) and were less likely to smoke (aOR=0.5, 95%CI[0.2-0.9]) but had similar outcomes especially high rate of respiratory and cardiovascular complications.

Conclusions. Adult hMPV infections mainly affect the elderly and patients with chronic conditions and are responsible for frequent cardiac and pulmonary complications similar to

those of RSV infections. At-risk populations would benefit from the development of antivirals and vaccines targeting hMPV.

Key words: human Metapneumovirus; Influenza; Respiratory Syncytial Virus; Adults

Introduction

During winter, community-acquired influenza-like illness (ILI), mostly caused by respiratory viruses, is very common. The most frequent viruses seen in primary care are influenza viruses A/B, rhinovirus, coronavirus, respiratory syncytial virus (RSV) and human metapneumovirus (hMPV) [1,2]. In the hospital setting, adults with ILI are commonly tested only for influenza, resulting in limited data concerning other respiratory viruses. The use of multiplex RT-PCR allows identification of multiple viruses simultaneously but remains a second-line test in non-immunocompromised patients in emergency departments because of its cost and the limited therapeutic options [3].

Human MPV, discovered in 2001, is phylogenetically similar to RSV and has been frequently found associated with respiratory tract illnesses [1,4,5]. Its circulation occurs with a seasonal distribution from January to March in the Northern hemisphere, often overlapping or following RSV infection season [6,7]. Human MPV is a major pediatric respiratory pathogen [8] but can affect all age groups, especially persons with chronic conditions [9], leading to diverse clinical presentation from upper respiratory tract symptoms to severe pneumonia [10,11] .

While hMPV is known to contribute substantially to the burden of wintertime respiratory illnesses in adults [12], data on its frequency and comparison to other respiratory viruses in large adult populations are scarce.

We aimed to (i) describe the clinical characteristics and outcome of hMPV infection and (ii) compare hMPV to influenza and RSV infections in adults hospitalized for community-acquired ILI in France in winter between 2012 and 2018.

Methods

Study design

We performed a post-hoc, retrospective analysis of the FLUVAC study. FLUVAC is a French prospective case-test negative design study evaluating influenza vaccine effectiveness on influenza-associated hospitalization conducted in five (2012/13, 2015/16 to 2017/18) or six (2013/14 to 2014/15) teaching hospitals. All adults hospitalized for at least 24 h for ILI during influenza circulation period, with symptom onset <7 days before screening, were included in FLUVAC. ILI was defined according to the European Centre for Disease Prevention and Control (ECDC) definition [13] as a combination of the following: (a) at least one of the following systemic symptoms: fever or feverishness, headache, myalgia or malaise, and (b) at least one of the following respiratory symptoms: cough, sore throat or dyspnea. Patient with contra-indication for influenza immunization, those who had previously tested positive for influenza virus in the same season and those without French social security affiliation were excluded. Each participant was interviewed, and nasopharyngeal samples were obtained at enrolment to screen for influenza and other respiratory viruses.

In the present study, we included all the patients from the first six FLUVAC seasons (2012/13, 2013/14, 2014/15, 2015/16, 2016/17, 2017/18) for whom virologic results on respiratory viruses were available (Figure 1).

Outcomes

The primary outcome was the prevalence of confirmed hMPV infection in patients hospitalized with ILI. Secondary outcomes were the demographic characteristics, chronic underlying diseases and treatments, clinical presentation of the ILI episode and complications, intensive care unit admission or death in patients with hMPV infections.

Microbiological data

Respiratory viruses were identified using multiplex RT-PCR performed on nasopharyngeal swabs. Clinical bronchoalveolar lavage fluid samples and tracheal aspirates were also tested. Samples were first tested in the virology laboratory of each participating hospital using real-time (RT) influenza A and B PCR after manual nucleic acid extraction. All samples were then sent to the French National Influenza Reference Centre (CNR-Lyon) for influenza confirmation and screening for other respiratory viruses (adenoviruses, bocaviruses, hMPV, picornavirus, RSV, coronaviruses, parainfluenza viruses (since 2013)) by RT-PCR using the Respiratory Multiwell System r-gene® on an ABI 7300 analyzer between 2012/13 and 2014/15. Since 2015/16, all the virology laboratories of the five sites used the same Eurobio kit and only B lineage was provided by the CNR-Lyon.

Statistical analysis

Quantitative variables were expressed as mean and standard deviation (SD) or median and interquartile range (IQR), and qualitative variables as number and percentage. Qualitative variables were compared using the χ^2 and Fisher's exact tests, as appropriate. Quantitative variables were compared by Wilcoxon rank sum test. Missing data for each variable were excluded from the denominator.

Patients with multiple viral infections were excluded from the analyses. Univariate analysis was used to asses risk factors for the detection of hMPV infection, influenza infection, RSV infection and acute heart failure. We performed two multivariate analyses using a backward stepwise logistic regression model using hMPV test result (positive/negative) and acute heart failure (yes/no) as the dependent variable in the first and second model respectively. Covariates with a p-value <0.2 in univariate analysis were tested in the multivariate model. Results from regression models are expressed as crude odds ratios (OR) and adjusted ORs (aOR) with 95% CI. A p-value of <0.05 was considered statistically significant. Analyses were performed using R software (Version 1.1.463).

Ethics

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

Results

Comparison of hMPV+ and hMPV- patients

Of the 3148 patients included in the FLUVAC study, 1604 (51%, 95%CI [49-53]) tested positive for at least one respiratory virus. Most had influenza (1123/1604, 70%, 95%CI [68-72]), while 167 had picornavirus (10%, 95%CI [9-12]), 145 had RSV (9%, 95%CI [8-10]), 100 had hMPV (6%, 95%CI [5-7]), 38 had adenovirus (2%, 95%CI [2-3]) and 23 had bocavirus (1%, 95%CI [1-2]) (Figure 1 and Table S1). Ten of the 100 hMPV infections (10%) were co-infection cases with at least one other virus: 3 with influenza A virus, 1 with coronavirus, 1 with both influenza A virus and coronavirus, 2 with picornavirus, 1 with parainfluenza virus, 1 with adenovirus and 1 with RSV.

Overall, 3% (95%CI[3-4]) of people with ILI symptoms (90/3148) tested positive for hMPV. Peak hMPV detection occurred between mid-January and mid-February (Supplementary Figure 1 & 2). While patients with hMPV infections were generally older than those without (median age 78 years [IQR 70-86] versus 71 years [IQR 57-83], p<.001), other demographic characteristics were similar. Most patients with hMPV presented at least one chronic condition (81%, 73/90), mostly cardiac (50%, 45/90) and respiratory (44%, 40/90) chronic diseases, 17% under immunosuppressive treatment (15/90), 14% active smokers (12/87) and 41% (37/90) hospitalized in the 12 months preceding the study (Table 1).

The median time from symptom onset to admission was similar between hMPV+ and hMPV- patients (2 days (IQR, 1-3)) as well as the main symptoms at inclusion except for weakness/malaise that was less frequent in hMPV+ patients (13/90 (14%) vs 27%, p<.007).

There was no difference between hMPV+ and hMPV- groups in terms of median length of stay, number of complications during hospitalization, intensive care unit (ICU) admission and death. However, hMPV+ patients were more likely to have an acute heart failure during hospitalization (25% (22/89) vs 14% (377/2722), p<.004).

There was no difference in sociodemographic characteristics, clinical presentation or outcomes between hMPV and viral coinfection and patients with hMPV infections alone.

In the multivariate analysis, when comparing hMPV+ patients to all hMPV- patients, age > 65 years (aOR 95% CI 3.3 [1.9;6.1], p<0.001) was significantly associated with hMPV detection. In contrast, the sudden onset of symptoms, defined as the occurrence of malaise/weakness, was associated with the absence of hMPV infection (aOR 95% CI 0.4 [0.2;0.8], p=0.008) (**Table 1**).

After adjustment for chronic heart disease, age, gender, smoking status and influenza vaccination, hMPV infection was significantly associated with occurrence of acute heart failure during hospitalization (aOR 95% CI 1.8 [1.1;3.0], p=0.02).

Comparison of hMPV and influenza+ patients

In univariate analysis, in comparison to influenza+ patients, hMPV+ patients were older (median age 78 IQR [70-86] versus 69 IQR [54-82] years old, respectively, p<0.001), more vaccinated against influenza (58% versus 39% respectively, p<0.001), presented more dyspnea at inclusion (p=0.05) but less weakness (p=0.01), headache (p=0.01) and sore throat (p=0.008). They were more likely to present acute heart failure during the hospital stay (p=0.002). Other outcomes were not significantly different (**Table 2**).

In the final model from multivariate analysis, in comparison with influenza+ patients, hMPV+ patients were more frequently > 65 years old (aOR 3.3 [1.9-6.3], p<0.001).

Comparison of hMPV+ and RSV+ patients

In univariate analysis, hMPV+ patients had less chronic disease (p=0.04), including chronic renal failure (p=0.04) and cancer (p=0.05) and were less likely to smoke (p=0.05) than RSV+ patients.

In the final multivariate model, in comparison with RSV+ patients, hMPV+ patients had less cancer (aOR=0.4 [0.2-0.9], p=0.02) and were less likely to smoke (aOR=0.5 [0.2-0.9], p=0.04). Clinical presentation and outcomes were similar between the two groups (**Table 2**).

Discussion

In our post-hoc analysis of 3148 hospitalized adult patients with community-acquired ILI, hMPV was found in 3% of the samples. These patients were older, had chronic conditions, frequent respiratory and cardiac chronic diseases, and frequently presented complications. This prevalence is consistent with several studies that found hMPV in 3 to 6% of adult patients with lower respiratory tract infection in primary care [1,14–16] and in 6% of patients hospitalized for acute respiratory infection (ARI) [17]. This frequency may vary according to the inclusion criteria, especially temperature cut-off, as hMPV infection frequently causes non-febrile illness [5].

Our hospitalized hMPV+ adults were mostly older and/or high risk patients as previously described in the literature [5,10,18–20]. Complications were frequent (62%), as well as ICU admission (17%) and death (4%). These rates were similar to those of the 91 hospitalized patients with hMPV from the Walsh *et al.* study in 2008 in the USA [10], but lower than those of the 128 critically ill adults with hMPV infection (31% required ICU admission and 8% died) from the Hasvold *et al.* study in 2016 [20].

The majority of hMPV+ patients presented several respiratory signs (cough, dyspnea), whereas sudden onset of symptoms was associated with the absence of hMPV infection. There were differences in clinical presentation between hMPV+ patients and influenza+ patients (less frequent constitutional symptoms (headache, weakness, myalgia) but more dyspnea) but not between hMPV+ patients and RSV+ patients. These points emphasize the difficulty of distinguishing respiratory viruses based on clinical signs alone and question the relevance of the current ILI definition to detect hMPV infection.

Interestingly, we also found that hMPV+ patients were older and presented more chronic cardiac conditions and acute heart failure during the hospitalization than influenza+ patients. Although, influenza [21] and RSV [22] are known to worsen heart failure, no study has specifically assessed hMPV [21,22]. In our study, hMPV infection was independently associated with the occurrence of acute heart failure.

Several limitations should be acknowledged. First, we enrolled patients during influenza virus circulation whereas hMPV circulation does not always match that of influenza. Second, we had no data to support causality between the detection of hMPV in nasopharyngeal samples and the ILI hospital admission. Other pathogens such as respiratory bacteria may have been involved and hMPV may been a concomitant infectious agent with no role in the symptoms reported. The absence of data on bacteriological results prevents us from addressing this issue. Finally, although asymptomatic carriage of hMPV appears to be uncommon [26], we had no control population (i.e. hospitalized adults without ILI symptoms) to help evaluate hMPV pathogenicity.

In conclusion, adult hMPV infections concerned 3% of patients hospitalized with ILI in tertiary care hospitals over six consecutive influenza seasons in France. Most of the patients were older, had associated chronic conditions and developed pulmonary and cardiac complications. The relation between hMPV infection and worsening of heart failure needs further investigation. These at-risk populations would benefit from the development of antivirals and vaccines targeting hMPV.

Transparency declaration

The authors declare no competing interest related to the study. P Loubet has received personal fees and non-financial support from Pfizer and Sanofi Pasteur. O Launay is an investigator for clinical trials sponsored by Janssen, GSK, Pfizer, Sanofi Pasteur and MSD and received travel support to attend scientific meetings from pharmaceutical companies.

Authors' Contributions

PL and OL conceptualized the study. PL developed the methodology. PM did the analysis. PL and PM wrote the original manuscript. NL, FG, FL, ZL, PV, XD, DP, SA, SR, GL, ASL, VF, NH, BL and FC critically reviewed the manuscript. OL supervised the research.

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TABLES

Table 1. Clinical characteristics and outcomes of hospitalized patients infected with human Metapneumovirus compared to patient without human Metapneumovirus, 2012-2018

	hMPV- (n=3048)	hMPV+ (n=90)	Univariate analysis	Multivariate analysis				
				Crude OR		p-value	Adjusted OR	p-value
Baseline characteristics								
Gender								
Women, n (%)	1390/3048 (46%)	50/90 (56%)	0.06	1.5	[1.0;2.3]	0.08		
Men, n (%)	1658/3048 (54%)	40/90 (44%)						
Age								
Median age, years (IQR)	71 (56-82)	78 (70-86)	<0.001					
Age > 65, n (%)	1904/3048 (62%)	76/90 (84%)	<0.001	2.9	[1.6;5.7]	0.001	3.3 [1.9;6.1]	<0.001
Median BMI, kg/m2 (IQR)	24.8 (21.5 - 28.5)	24.8 (21.5 -28.5)						
Smoking status								
Smoker, n (%)	641/2938	12/87(14%)	0.07	0.9	[0.5;1.7]	0.84		
Ex-smoker, n (%)	973/2938	28/87 (32%)	0.93					
Non-smoker, n (%)	1324/2938	47/87 (54%)	0.12					
Chronic diseases (at least one), n (%)	2428/3048 (80%)	73/90 (81%)	0.74					
Chronic respiratory disease, n (%)	1361/3048 (45%)	40/90 (44%)	0.96					
Chronic heart disease, n (%)	1267/3048 (42%)	45/90 (50%)	0.12	1.1	[0.7;1.8]	0.57		
Diabetes, n (%)	714/3048 (23%)	18/90 (20%)	0.52					
Chronic renal failure, n (%)	468/3048 (15%)	9/90 (10%)	0.17	0.5	[0.2;1.0]	0.08		
Cancer, n (%)	515/3048 (17%)	13/90 (14%)	0.45					
Cirrhosis, n (%)	109/3035 (4%)	4/90 (4%)	0.55					
Immunosuppressive treatment, n (%)	514/3043 (17%)	15/90 (17%)	0.85					
Pregnancy, n (% of women of childbearing age)	28/339 (8%)	0	1					
Influenza vaccination, n (%)	1418/3011 (47%)	52/90 (58%)	0.03	1.1	[0.7;1.7]	0.69		
Hospitalization in the previous 12 months, n (%)	1405/3031 (46%)	37/90 (41%)	0.33					
Presence of child/children <5 in the household, n (%)	182/3025 (6%)	5/90 (6%)	0.80					
Clinical presentation								
Median time from symptom onset to hospitalization, days (IQR)	2 (1-3)	2 (1-3)	0.7					
Symptoms								
Fever or feverishness, n (%)	2562/3045 (84%)	79/90 (88%)	0.40					
Cough, n (%)	2360/3045 (78%)	75/90 (83%)	0.18	1.5	[0.9;2.7]	0.18		
Dyspnea, n (%)	1739/2199 (79%)	76/90 (84%)	0.54					
Weakness/malaise, n (%)	821/3041 (27%)	13/90 (14%)	0.007	0.5	[0.2;0.8]	0.01	0.4 [0.2;0.8]	0.008
Headache, n (%)	755/3032 (25%)	16/90 (18%)	0.08	0.8	[0.4;1.4]	0.44		
Myalgia, n (%)	734/3029 (24%)	19/90 (21%)	0.45					
Sore throat, n (%)	439/3024 (15%)	8/90 (9%)	0.10	0.8	[0.3;1.5]	0.48		
Outcome								
At least one complication during the hospital stay, n (%)	1648/3148 (52%)	56/90 (62%)	0.13					
Pneumonia*, n (%)	918/3124 (29%)	32/89 (36%)	0.27					
Respiratory failure, n (%)	873/3124 (28%)	32/89 (36%)	0.17					
Acute heart failure, n (%)	420/3122 (13%)	22/89 (25%)	0.004					
Acute respiratory distress syndrome, n (%)	257/3123 (8%)	8/89 (9%)	0.85					
Median length of stay, days (IQR)	5 (3-9)	7 (4-13)	0.50					
ICU admission after hospitalization in acute care, n (%)	543/2283 (24%)	15/90 (17%)	0.60					
Death, n (%)	137/3131 (4%)	4/90 (4%)	1					

Table 2. Sociodemographic, clinical characteristics and outcome of hospitalized patients infected with human Metapneumovirus, compared to RSV and influenza virus infected patients, 2012-2018

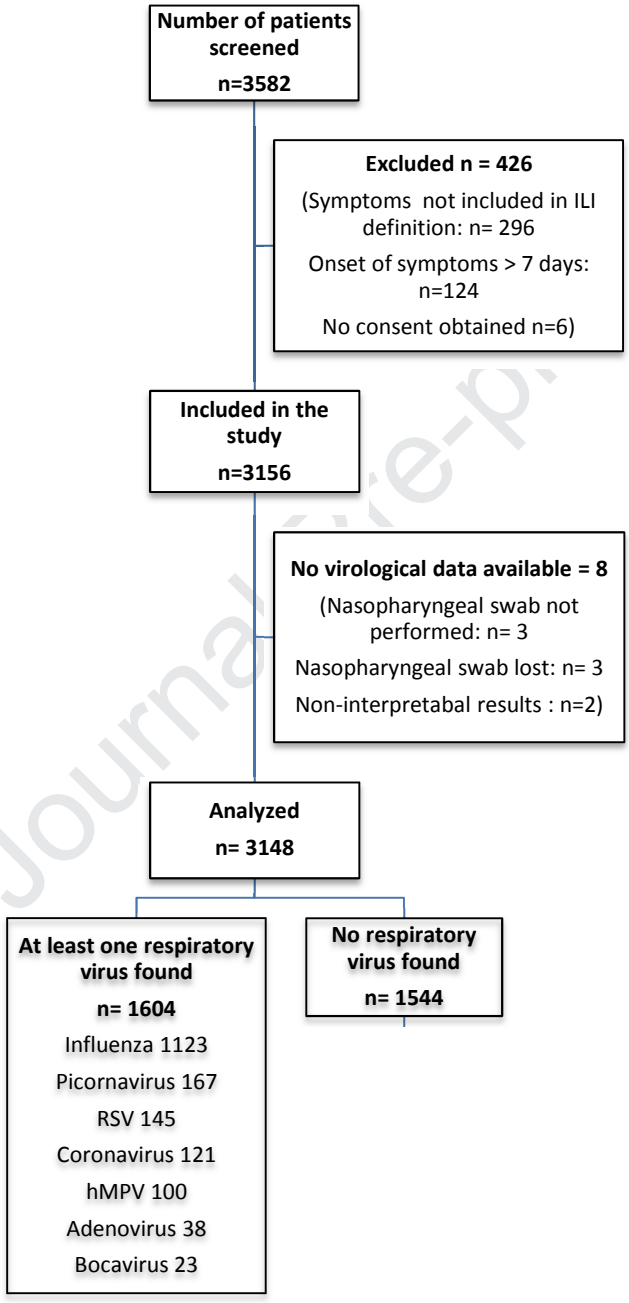
	hMPV+ (n=90)	Influenza+ (n=908)	p-value	RSV+ (n=129)	p-value
Baseline characteristics					
Gender					
Women, n (%)	50/90 (56%)	430/908 (47%)	0.14	67/129 (52%)	0.60
Men, n (%)	40/90 (44%)	478/908 (53%)		62/129 (48%)	
Age					
Median age, years (IQR)	78 (70-86)	69 (54 - 82)	<0.001	74 (64-84)	0.06
Age > 65, n (%)	76/90 (84%)	538/908 (59%)	<0.001	95/129 (74%)	0.06
Median BMI, kg/m2 (IQR)	24.8 (21.5 -28.5)	25.1 (22.1 - 28.4)	0.85	24.6 (21.6-28.8)	0.91
Smoking status					
Smoker, n (%)	12/87(14%)	178/874 (21%)	0.12	31/126 (25%)	0.05
Ex-smoker, n (%)	28/87 (32%)	260/874 (30%)	0.72	44/126 (35%)	0.70
Non-smoker, n (%)	47/87 (54%)	420/874 (49%)	0.37	51/126 (40%)	0.05
Chronic diseases (at least one), n (%)	73/90 (81%)	678/908 (75%)	0.18	117/129 (91%)	0.04
Chronic respiratory disease, n (%)	40/90 (44%)	344/908 (38%)	0.22	70/129 (54%)	0.15
Chronic heart disease, n (%)	45/90 (50%)	362/908 (40%)	0.06	64/129 (50%)	0.96
Diabetes, n (%)	18/90 (20%)	204/908 (22%)	0.59	30/129 (23%)	0.57
Chronic renal failure, n (%)	9/90 (10%)	116/908 (13%)	0.45	26/129 (20%)	0.04
Cancer, n (%)	13/90 (14%)	131/908 (14%)	0.99	33/129 (26%)	0.05
Cirrhosis, n (%)	4/90 (4%)	28/922 (3%)	0.52	4/129 (3%)	0.60
Immunosuppressive treatment, n (%)	15/90 (17%)	151/904 (17%)	0.99	26/128 (20%)	0.50
Pregnancy, n (% of women of childbearing age)	0	13/123 (11%)	1.00	0	1.00
Influenza vaccination, n (%)	52/90 (58%)	351/919 (39%)	<0.001	70/126 (56%)	0.68
Hospitalization in the previous 12 months, n (%)	37/90 (41%)	360/908 (40%)	0.79	64/129 (50%)	0.21
Presence of child/children <5 in the household, n (%)	5/90 (6%)	69/915 (8%)	0.67	8/129 (6%)	0.84
Clinical presentation					
Median time from symptom onset to hospitalization, days (IQR)	2 (1-3)	2 (1-4)	0.23	2 (1-3)	0.7
Symptoms					
Fever or feverishness, n (%)	79/90 (88%)	811/907 (89%)	0.63	109/128 (85%)	0.58
Cough, n (%)	75/90 (83%)	784/908 (86%)	0.43	106/128 (83%)	0.92
Dyspnea, n (%)	76/90 (84%)	650/908 (71%)	0.05	112/128 (88%)	0.42
Weakness/malaise, n (%)	13/90 (14%)	244/904 (27%)	0.01	29/128 (23%)	0.13
Headache, n (%)	16/90 (18%)	277/902 (31%)	0.01	30/128 (23%)	0.31
Myalgia, n (%)	19/90 (21%)	260/897 (29%)	0.11	19/128 (15%)	0.23
Sore throat, n (%)	8/90 (9%)	184/901 (20%)	0.008	22/126 (17%)	0.07
Outcome					
At least one complication during the hospital stay, n (%)	56/90 (62%)	473/908 (52%)	0.07	85/129 (66%)	0.58
Pneumonia, n (%)	32/89 (36%)	257/904 (28%)	0.14	50/128 (39%)	0.64
Respiratory failure, n (%)	32/89 (36%)	254/904 (28%)	0.12	47/128 (37%)	0.91

Acute heart failure, n (%)	22/89 (25%)	114/903 (13%)	0.002	21/128 (16%)	0.13
Acute respiratory distress syndrome, n (%)	8/89 (9%)	83/904 (9%)	0.95	15/128 (12%)	0.52
Median length of stay, days (IQR)	7 (4-13)	6 (3-10)	0.06	7 (5-14)	0.50
ICU admission after hospitalization in acute care, n (%)	15/90 (17%)	155/908 (17%)	0.88	33/128 (26%)	0.20
Death, n (%)	4/90 (4%)	36/906 (4%)	0.78	9/129 (7%)	0.44

hMPV: human Metapneumovirus, RSV : Respiratory Syncytial Virus, BMI : body mass index, IQR : inter quartile range

FIGURE

Figure 1. Flowchart.



ILI: Influenza-like Illness
RSV: Respiratory Syncytial Virus
hMPV: human Metapneumovirus