



HAL
open science

Characteristics of human metapneumovirus infection in adults hospitalized for community-acquired influenza-like illness in France, 2012-2018: a retrospective observational study

Paul Loubet, Pauline Mathieu, Nezha Lenzi, Florence Galtier, Fabrice Lainé, Zineb Lesieur, Philippe Vanhems, Xavier Duval, Deborah Postil, Sélilah Amour, et al.

► To cite this version:

Paul Loubet, Pauline Mathieu, Nezha Lenzi, Florence Galtier, Fabrice Lainé, et al.. Characteristics of human metapneumovirus infection in adults hospitalized for community-acquired influenza-like illness in France, 2012-2018: a retrospective observational study. *Clinical Microbiology and Infection*, 2021, 27 (1), pp.127.e1-127.e6. 10.1016/j.cmi.2020.04.005 . hal-02563359

HAL Id: hal-02563359

<https://hal-univ-rennes1.archives-ouvertes.fr/hal-02563359>

Submitted on 19 May 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

1 **Characteristics of Human Metapneumovirus Infection in Adults**
 2 **Hospitalized for Community-acquired Influenza-Like Illness in**
 3 **France, 2012-2018: a retrospective observational study**

4
 5 **Paul Loubet^{1,2‡*}, Pauline Mathieu^{3‡}, Nezha Lenzi², Florence Galtier^{2,4}, Fabrice**
 6 **Lainé^{2,5}, Zineb Lesieur², Philippe Vanhems^{2,6}, Xavier Duval^{2,7}, Deborah Postil⁸,**
 7 **Sélilah Amour⁶, Sylvie Rogez⁹, Gisèle Lagathu¹⁰, Anne-Sophie L'Honneur¹¹,**
 8 **Vincent Foulongne¹², Nadhira Houhou¹³, Bruno Lina¹⁴, Fabrice Carrat¹⁵, Odile**
 9 **Launay^{2,3} for the Fluvac study group**

- 10
 11 1. VBMI, INSERM U1047, Department of Infectious and Tropical Disease , CHU
 12 Nîmes, Univ Montpellier, Nîmes, France
 13 2. Inserm, F-CRIN, Réseau Innovative Clinical Research in Vaccinology (I-REIVAC),
 14 Paris, France
 15 3. Université Paris Descartes, Sorbonne Paris Cité ; Inserm, CIC Cochin Pasteur,
 16 Assistance Publique Hôpitaux de Paris, Hôpital Cochin, Paris, France
 17 4. CIC1411, CHU Montpellier, Hôpital Saint Eloi, Montpellier, F-34295, France
 18 5. Centre d'Investigations Cliniques, INSERM UMR CIC 1414, Hôpital Pontchaillou,
 19 Rennes, France
 20 6. Service d'Hygiène, Epidémiologie et Prévention, Hospices Civils de Lyon, F-
 21 69437 Lyon, France
 22 7. CIC1125, Hôpital Bichat Claude Bernard, Paris, France
 23 8. CHU Dupuytren, CIC 1435, Limoge Cedex, France
 24 9. CHU Dupuytren, Service Bactériologie, Virologie, Hygiène, Limoges Cedex,
 25 France
 26 10. Université Rennes-I, Virologie, Hôpital Pontchaillou, Rennes, France
 27 11. AHU, Service de Virologie, Hôpital Cochin, Paris, France
 28 12. Service de Virologie, CHU Montpellier, Hôpital Saint Eloi, Montpellier, F-34295,
 29 France
 30 13. Laboratoire de Virologie, Hôpital Bichat Claude Bernard, Paris, France
 31 14. Hospices Civils de Lyon, Laboratoire de Virologie, Institut des Agents Infectieux
 32 (IAI), Centre National de Référence des virus Respiratoires France Sud, Hôpital
 33 de la Croix-Rousse, 69317 Lyon Cedex04, France
 34 15. Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé
 35 Publique IPLESP, AP-HP, Hôpital Saint Antoine, F75013 Paris, France

36
 37 ‡ These authors contributed equally to this work

38 *Corresponding author:

39
 40 Dr Paul Loubet, Service des Maladies infectieuses et tropicales, CHU Nîmes, Nîmes,
 41 France

42 Tel: +33466684149

43 Email: paul.loubet@chu-nimes.fr

44 **Abstract**

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

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

56 **Results.** Among the 3148 patients included (1449 (46%) women, 1988 (63%) aged 65 and
57 over; 2508 (80%) with chronic disease), at least one respiratory virus was detected in 1604
58 (51%, 95%CI [49-53]), including 100 cases of hMPV (100/3148, 3% 95%CI [3-4]), of which
59 10 (10%) were viral co-infection. In the hMPV+ patients, mean length of stay was 7 days,
60 62% (56/90) developed a complication, 21% (14/68) were admitted to intensive care unit and
61 4% (4/90) died during hospitalization. In comparison with influenza+ patients, hMPV+
62 patients were more frequently > 65 years old (aOR=3.3, 95%CI[1.9-6.3]) and presented more
63 acute heart failure during hospitalization (aOR=1.8, 95%CI[1.0-2.9]). Compared to RSV+
64 patients, hMPV+ patients had less cancer (aOR=0.4, 95%CI[0.2-0.9]) and were less likely to
65 smoke (aOR=0.5, 95%CI[0.2-0.9]) but had similar outcomes especially high rate of
66 respiratory and cardiovascular complications.

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

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

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

72

Journal Pre-proof

73 **Introduction**

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

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

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

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

94

95 **Methods**

96 **Study design**

97 We performed a post-hoc, retrospective analysis of the FLUVAC study. FLUVAC is a French
98 prospective case-test negative design study evaluating influenza vaccine effectiveness on
99 influenza-associated hospitalization conducted in five (2012/13, 2015/16 to 2017/18) or six
100 (2013/14 to 2014/15) teaching hospitals. All adults hospitalized for at least 24 h for ILI during
101 influenza circulation period, with symptom onset <7 days before screening, were included in
102 FLUVAC. ILI was defined according to the European Centre for Disease Prevention and
103 Control (ECDC) definition [13] as a combination of the following: (a) at least one of the
104 following systemic symptoms: fever or feverishness, headache, myalgia or malaise, and (b)
105 at least one of the following respiratory symptoms: cough, sore throat or dyspnea. Patient
106 with contra-indication for influenza immunization, those who had previously tested positive
107 for influenza virus in the same season and those without French social security affiliation
108 were excluded. Each participant was interviewed, and nasopharyngeal samples were
109 obtained at enrolment to screen for influenza and other respiratory viruses.

110 In the present study, we included all the patients from the first six FLUVAC seasons
111 (2012/13, 2013/14, 2014/15, 2015/16, 2016/17, 2017/18) for whom virologic results on
112 respiratory viruses were available (Figure 1).

113

114 **Outcomes**

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

119

120

121

122

123

124

125 Microbiological data

126 Respiratory viruses were identified using multiplex RT-PCR performed on nasopharyngeal
127 swabs. Clinical bronchoalveolar lavage fluid samples and tracheal aspirates were also
128 tested. Samples were first tested in the virology laboratory of each participating hospital
129 using real-time (RT) influenza A and B PCR after manual nucleic acid extraction. All samples
130 were then sent to the French National Influenza Reference Centre (CNR-Lyon) for influenza
131 confirmation and screening for other respiratory viruses (adenoviruses, bocaviruses, hMPV,
132 picornavirus, RSV, coronaviruses, parainfluenza viruses (since 2013)) by RT-PCR using the
133 Respiratory Multiwell System r-gene® on an ABI 7300 analyzer between 2012/13 and
134 2014/15. Since 2015/16, all the virology laboratories of the five sites used the same Eurobio
135 kit and only B lineage was provided by the CNR-Lyon.

136

137 Statistical analysis

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

143 Patients with multiple viral infections were excluded from the analyses. Univariate analysis
144 was used to assess risk factors for the detection of hMPV infection, influenza infection, RSV
145 infection and acute heart failure. We performed two multivariate analyses using a backward
146 stepwise logistic regression model using hMPV test result (positive/negative) and acute heart
147 failure (yes/no) as the dependent variable in the first and second model respectively.

148 Covariates with a p-value <0.2 in univariate analysis were tested in the multivariate model.

149 Results from regression models are expressed as crude odds ratios (OR) and adjusted ORs
150 (aOR) with 95% CI. A p-value of <0.05 was considered statistically significant. Analyses were
151 performed using R software (Version 1.1.463).

152 Ethics

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

157 Results**158 Comparison of hMPV+ and hMPV- patients**

Journal Pre-proof

159 Of the 3148 patients included in the FLUVAC study, 1604 (51%, 95%CI [49-53]) tested
160 positive for at least one respiratory virus. Most had influenza (1123/1604, 70%, 95%CI [68-
161 72]), while 167 had picornavirus (10%, 95%CI [9-12]), 145 had RSV (9%, 95%CI [8-10]), 100
162 had hMPV (6%, 95%CI [5-7]), 38 had adenovirus (2%, 95%CI [2-3]) and 23 had bocavirus
163 (1%, 95%CI [1-2]) (Figure 1 and Table S1). Ten of the 100 hMPV infections (10%) were co-
164 infection cases with at least one other virus: 3 with influenza A virus, 1 with coronavirus, 1
165 with both influenza A virus and coronavirus, 2 with picornavirus, 1 with parainfluenza virus, 1
166 with adenovirus and 1 with RSV.

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

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

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

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

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

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

192 **Comparison of hMPV and influenza+ patients**

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

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

201

202 **Comparison of hMPV+ and RSV+ patients**

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

206 In the final multivariate model, in comparison with RSV+ patients, hMPV+ patients had less
207 cancer (aOR=0.4 [0.2-0.9], $p=0.02$) and were less likely to smoke (aOR=0.5 [0.2-0.9],
208 $p=0.04$). Clinical presentation and outcomes were similar between the two groups (**Table 2**).

209

210 Discussion

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

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

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

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

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

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

252

253 **Transparency declaration**

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

258 **Authors' Contributions**

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

262 **Acknowledgments**

263 We thank Sarah Kabani for her editing assistance.

264 **Funding**

265 The current work received no funding. However, the study sites received funding from Sanofi
266 Pasteur, Sanofi Pasteur MSD and Janssen for the FLUVAC study. Vaccine producers had no
267 role in the study design, data analysis, decision to publish or preparation of the manuscript.

268
269

References

- 270
271
272 1. Ieven M, Coenen S, Loens K, Lammens C, Coenjaerts F, Vanderstraeten A, et al.
273 Aetiology of lower respiratory tract infection in adults in primary care: a prospective study in
274 11 European countries. *Clin. Microbiol. Infect.* 2018;24:1158-63.
- 275 2. Souty C, Masse S, Valette M, Behillil S, Bonmarin I, Pino C, et al. Baseline
276 characteristics and clinical symptoms related to respiratory viruses identified among patients
277 presenting with influenza-like illness in primary care. *Clin. Microbiol. Infect.* [Internet] 2019
278 [cité 2019 févr 18]; Available from:
279 <https://linkinghub.elsevier.com/retrieve/pii/S1198743X19300369>
- 280 3. Uyeki TM, Bernstein HH, Bradley JS, Englund JA, File TM, Fry AM, et al. Clinical
281 Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on
282 Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of
283 Seasonal Influenza. *Clin. Infect. Dis.* 2019;68:e1-47.
- 284 4. Stockton J, Stephenson I, Fleming D, Zambon M. Human Metapneumovirus as a
285 Cause of Community-Acquired Respiratory Illness. *Emerg. Infect. Dis.* 2002;8:5.
- 286 5. Falsey AR, Erdman D, Anderson LJ, Walsh EE. Human Metapneumovirus Infections
287 in Young and Elderly Adults. *J. Infect. Dis.* 2003;187:785-90.
- 288 6. Panda S, Mohakud NK, Pena L, Kumar S. Human metapneumovirus: review of an
289 important respiratory pathogen. *Int. J. Infect. Dis.* 2014;25:45-52.
- 290 7. Li Y, Reeves RM, Wang X, Bassat Q, Brooks WA, Cohen C, et al. Global patterns in
291 monthly activity of influenza virus, respiratory syncytial virus, parainfluenza virus, and
292 metapneumovirus: a systematic analysis. *Lancet Glob. Health* 2019;7:e1031-45.
- 293 8. Principi N, Esposito S. Paediatric human metapneumovirus infection: Epidemiology,
294 prevention and therapy. *J. Clin. Virol.* 2014;59:141-7.
- 295 9. Boivin G, Abed Y, Pelletier G, Ruel L, Moisan D, Côté S, et al. Virological Features
296 and Clinical Manifestations Associated with Human Metapneumovirus: A New
297 Paramyxovirus Responsible for Acute Respiratory-Tract Infections in All Age Groups. *J.*
298 *Infect. Dis.* 2002;186:1330-4.
- 299 10. Walsh EE, Peterson DR, Falsey AR. Human Metapneumovirus Infections in Adults:
300 Another Piece of the Puzzle. *Arch. Intern. Med.* 2008;168:2489.
- 301 11. Vidaur L, Totorika I, Montes M, Vicente D, Rello J, Cilla G. Human
302 metapneumovirus as cause of severe community-acquired pneumonia in adults: insights from
303 a ten-year molecular and epidemiological analysis. *Ann. Intensive Care* [Internet] 2019 [cité
304 2019 déc 31];9. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6656825/>
- 305 12. van den Hoogen BG. Respiratory Tract Infection Due to Human Metapneumovirus
306 among Elderly Patients. *Clin. Infect. Dis.* 2007;44:1159-60.

- 307 13. European Centre for Disease Prevention and Control (ECDC). Influenza case
308 definition [Internet]. Available from: [https://ecdc.europa.eu/en/surveillance-and-disease-
data/eu-case-definitions](https://ecdc.europa.eu/en/surveillance-and-disease-
309 data/eu-case-definitions)
- 310 14. Van den Hoogen BG, Osterhaus AD, Fouchier RA. Clinical impact and diagnosis of
311 human metapneumovirus infection. *Pediatr Infect J* 2004;
- 312 15. Sentilhes A-C, Choumlivong K, Celhay O, Sisouk T, Phonekeo D, Vongphrachanh P,
313 et al. Respiratory virus infections in hospitalized children and adults in Lao PDR. *Influenza
314 Other Respir. Viruses* 2013;7:1070-8.
- 315 16. Lim YK, Kweon OJ, Kim HR, Kim T-H, Lee M-K. Clinical Features, Epidemiology,
316 and Climatic Impact of Genotype-specific Human Metapneumovirus Infections: Long-term
317 Surveillance of Hospitalized Patients in South Korea. *Clin. Infect. Dis.* [Internet] [cité 2019
318 déc 31]; Available from: [https://academic-oup-com.proxy.insermbiblio.inist.fr/cid/advance-
article/doi/10.1093/cid/ciz697/5540161](https://academic-oup-com.proxy.insermbiblio.inist.fr/cid/advance-
319 article/doi/10.1093/cid/ciz697/5540161)
- 320 17. Lefebvre A, Manoha C, Bour J-B, Abbas R, Fournel I, Tiv M, et al. Human
321 metapneumovirus in patients hospitalized with acute respiratory infections: A meta-analysis.
322 *J. Clin. Virol.* 2016;81:68-77.
- 323 18. Haas LEM, de Rijk NX, Thijsen SFT. Human metapneumovirus infections on the
324 ICU: a report of three cases. *Ann. Intensive Care* 2012;2:30.
- 325 19. Hamelin ME, Cotu S, Laforge J, Lampron N, Bourbeau J, Weiss K, et al. Human
326 Metapneumovirus Infection in Adults with Community-Acquired Pneumonia and
327 Exacerbation of Chronic Obstructive Pulmonary Disease. *Clin. Infect. Dis.* 2005;41:498-502.
- 328 20. Hasvold J, Sjoding M, Pohl K, Cooke CR, Hyzy RC. The role of human
329 metapneumovirus in the critically ill adult patient. *J. Crit. Care* 2016;31:233-7.
- 330 21. Patel NJ, Nalluri N, Deshmukh A, Pant S, Shah N, Badheka AO, et al. Seasonal trends
331 of heart failure hospitalizations in the United States: A national perspective from 2000 to
332 2011. *Int. J. Cardiol.* 2014;173:562-3.
- 333 22. Ivey KS, Edwards KM, Talbot HK. Respiratory Syncytial Virus and Associations
334 With Cardiovascular Disease in Adults. *J. Am. Coll. Cardiol.* 2018;71:1574-83.
- 335 23. Lee N, Lui GCY, Wong KT, Li TCM, Tse ECM, Chan JYC, et al. High Morbidity and
336 Mortality in Adults Hospitalized for Respiratory Syncytial Virus Infections. *Clin. Infect. Dis.*
337 2013;57:1069-77.
- 338 24. Falsey AR, Walsh EE. Respiratory Syncytial Virus Infection in Adults. *CLIN
339 MICROBIOL REV* 2000;13:14.
- 340 25. Loubet P, Lenzi N, Valette M, Foulongne V, Krivine A, Houhou N, et al. Clinical
341 characteristics and outcome of respiratory syncytial virus infection among adults hospitalized
342 with influenza-like illness in France. *Clin. Microbiol. Infect.* 2017;23:253-9.

343 26. Falsey A, Criddle M, Walsh E. Detection of respiratory syncytial virus and human
344 metapneumovirus by reverse transcription polymerase chain reaction in adults with and
345 without respiratory illness. *J. Clin. Virol.* 2006;35:46-50.

346

Journal Pre-proof

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	Crude OR		Multivariate analysis 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]
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 (%)								
Chronic respiratory disease, n (%)	2428/3048 (80%)	73/90 (81%)	0.74					
Chronic heart disease, n (%)	1361/3048 (45%)	40/90 (44%)	0.96					
Diabetes, n (%)	1267/3048 (42%)	45/90 (50%)	0.12	1.1	[0.7;1.8]	0.57		
Chronic renal failure, n (%)	714/3048 (23%)	18/90 (20%)	0.52					
Cancer, n (%)	468/3048 (15%)	9/90 (10%)	0.17	0.5	[0.2;1.0]	0.08		
Cirrhosis, n (%)	515/3048 (17%)	13/90 (14%)	0.45					
Immunosuppressive treatment, n (%)	109/3035 (4%)	4/90 (4%)	0.55					
Pregnancy, n (% of women of childbearing age)	514/3043 (17%)	15/90 (17%)	0.85					
Influenza vaccination, n (%)	28/339 (8%)	0	1					
Hospitalization in the previous 12 months, n (%)	1418/3011 (47%)	52/90 (58%)	0.03	1.1	[0.7;1.7]	0.69		
Presence of child/children <5 in the household, n (%)	1405/3031 (46%)	37/90 (41%)	0.33					
	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]
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 (%)					
Chronic respiratory disease, n (%)	73/90 (81%)	678/908 (75%)	0.18	117/129 (91%)	0.04
Chronic heart disease, n (%)	40/90 (44%)	344/908 (38%)	0.22	70/129 (54%)	0.15
Diabetes, 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

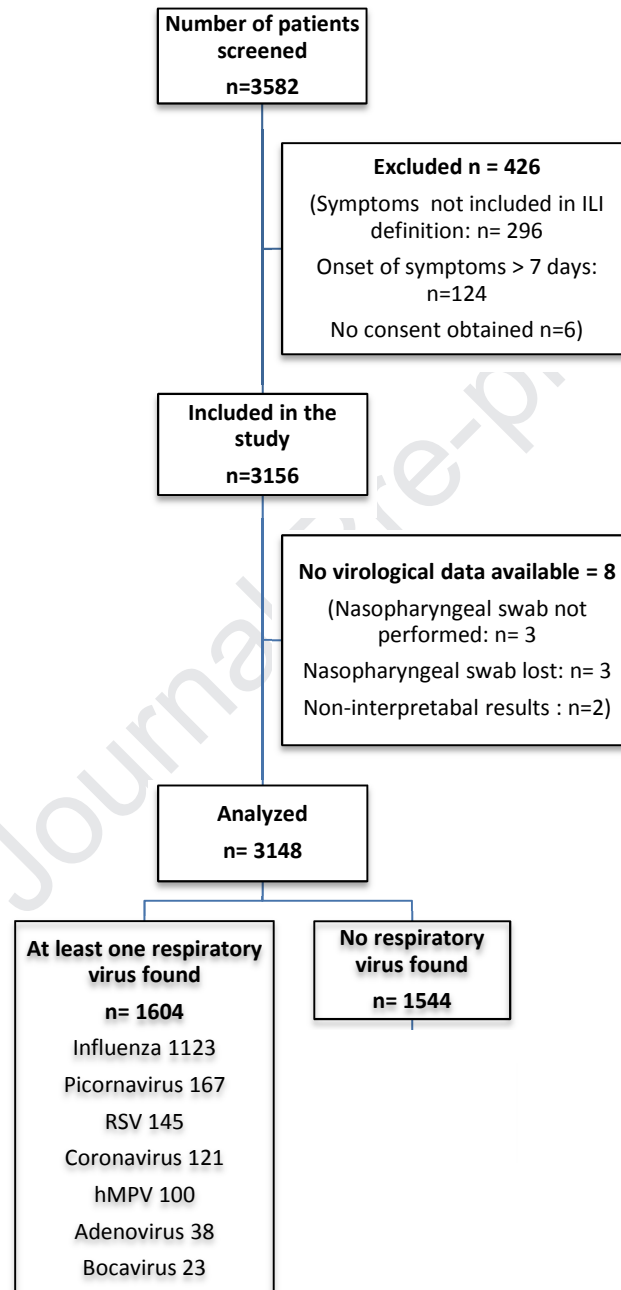
Acute heart failure, n (%)	22/89 (25%)	114/903 (13%)	0.002	21/128 (16%)	0.13
Acute respiratory distress syndrome, n (%)	8/89 (9%)	83/904 (9%)	0.95	15/128 (12%)	0.52
Median length of stay, days (IQR)	7 (4-13)	6 (3-10)	0.06	7 (5-14)	0.50
ICU admission after hospitalization in acute care, n (%)	15/90 (17%)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

Journal Pre-proof

FIGURE

Figure 1. Flowchart.



ILI: Influenza-like Illness

RSV: Respiratory Syncytial Virus

hMPV: human Metapneumovirus

Journal Pre-proof