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1 **Incidence and characteristics of nosocomial influenza in a country with low**  
2 **vaccine coverage**

3

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20

21 **Running title:** Nosocomial influenza

## 22 **Summary**

23 **Background:** Influenza vaccination coverage is low in France, in at-risk patients and in  
24 health-care workers.

25 **Aim:** We aimed to estimate the incidence of nosocomial influenza, its characteristics and  
26 outcome.

27 **Methods:** During one influenza season, we retrospectively evaluated all cases of documented  
28 influenza. Inpatients with symptoms onset  $\geq 48$  hours after admission were enrolled. Data  
29 were collected on a standardized questionnaire.

30 **Results:** From November 2017 to April 2018, 860 patients tested positive for influenza by  
31 PCR on a respiratory sample. Among them, 204 (23.7%) were diagnosed  $\geq 48$  hours after  
32 admission, of whom 57 (6.6% of all influenza cases) fulfilled inclusion criteria for  
33 nosocomial influenza: 26 women and 31 men, median age 82 years [interquartile range, 72.2-  
34 86.9]. Twenty patients (38.6%) had recently ( $< 6$  months) received the seasonal influenza  
35 vaccine. Median time between admission and symptoms onset, and between symptoms onset  
36 and diagnosis were, respectively, 11 days [7-19.5] and 29 hours [15.5-48]. Influenza was  
37 mostly acquired in a double-bed room (n=39, 68.4%), with documented exposure in 14 cases.  
38 Influenza B virus was more common in nosocomial (46/57, 80.7%), than in community-  
39 acquired cases (359/803, 44.6%),  $P < 0.001$ . Mortality rate at three months was 15.8% (n=9).  
40 Incidence of nosocomial influenza was estimated at 0.22 per 1000 hospital-days during the  
41 study period.

42 **Conclusion:** Nosocomial influenza is not rare in elderly inpatients, and may have severe  
43 consequences. Influenza B virus was over-represented, which suggests higher transmissibility  
44 and/or transmission clusters.

45 **Keywords** Nosocomial influenza, vaccine, outcome, incidence, elderly, influenza B virus

## 46 **Introduction**

47 Influenza is a common cause of hospital admission during the influenza season, but it remains  
48 often undiagnosed. Failure to identify influenza cases, and to implement infection control  
49 measures, put contact patients and health care workers at risk of nosocomial influenza,  
50 especially in settings with low vaccination coverage, as in France [1][2]. Limited data are  
51 currently available on the burden of nosocomial influenza, although it may be life-threatening  
52 in patients with comorbidities, in pregnant women, or in elderly patients. In addition, its  
53 impact on health care workers absenteeism may be devastating, as workload is particularly  
54 high during influenza seasons in most hospitals.

55

56 Previous studies on nosocomial influenza contributed to estimate the burden and the  
57 characteristics of nosocomial influenza, in different settings [3][4]. These studies used various  
58 time thresholds, spanning from 48 to 96 hours between hospital admission and symptoms  
59 onset, to define nosocomial influenza [5]. The proportion of influenza classified as  
60 nosocomial in these hospital-based studies varied from 4 to 23%. The level of influenza  
61 vaccine coverage in health care workers may be a strong determinant of nosocomial influenza  
62 risk, for patients as well as for health care workers [6][7]. In France, immunization coverage  
63 against influenza in at-risk patients [2] and health care workers [8], has been dramatically low  
64 over recent years, due to vaccine hesitancy, fuelled by dissemination of fake news through  
65 various communication channels. We aimed to evaluate the incidence of nosocomial  
66 influenza in a tertiary care centre, its characteristics, and consequences.

67

## 68 **Methods**

### 69 *Study population*

70 Rennes University Hospital is a 1,500 bed-tertiary care hospital, which serves as a referral  
71 centre in Western France (population catchment area, one million inhabitants). We performed  
72 a retrospective study of all cases of nosocomial influenza documented during the 2017-2018  
73 influenza season. Inpatients with influenza documented by PCR on respiratory samples were  
74 identified from the virology lab computerized database. Two different techniques of PCR  
75 were used during the study period: Seegene Allplex<sup>®</sup> respiratory panel 1 (Eurobio, Les Ulis,  
76 France), and GeneXpert<sup>®</sup> flu (Cepheid, Sunnyvale, CA, USA).

77

78 We reviewed the medical files of all patients who were tested positive  $\geq 48$  hours after  
79 hospital admission. Only patients who had no symptoms suggestive of influenza during the  
80 first 48 hours after admission (i.e. cough, fever, myalgia, rhinitis, pharyngitis, or headache)  
81 were finally included in this study. Data were collected with a standardized questionnaire,  
82 including demographics, comorbidities, recent (<6 months) influenza vaccination, symptoms  
83 reported by the time of influenza diagnosis, medical ward, type of room (single versus  
84 double), and 90-day outcome. When the latter data was not available from medical charts, the  
85 general practitioner was contacted by phone.

86

### 87 *Statistical analysis*

88 We compared nosocomial cases, and community-acquired cases, for the variables available in  
89 both categories (i.e. age, sex, influenza virus type, and date of diagnosis). Categorical  
90 variables were compared using Fisher's exact test. Continuous variables were compared using

91 Student's t-test. P-values <0.05 were considered as significant. To estimate incidence, we  
92 divided the number of patients with nosocomial influenza as defined above, by the total  
93 number of hospital-days for all patients admitted during the study period, extracted from our  
94 hospital administrative system (Saphir). Statistical analyses were carried out using R-Studio  
95 2015, Integrated Development for R (R-Studio, Boston, MA, USA).

96

### 97 *Ethics*

98 The study was approved by the Ethics Committee of Rennes University Hospital (approval  
99 number: 20.17).

100

101

## 102 **Results**

103 During the study period, 860 inpatients had influenza documented on respiratory samples, by  
104 Seegene Allplex<sup>®</sup> (n=504), or GeneXpert<sup>®</sup> (n=356). Of these, 204 were diagnosed on a  
105 respiratory sample obtained  $\geq 48$  hours after admission. Systematic review of the medical files  
106 of these 204 cases identified 57 cases who fulfilled our definition criteria for nosocomial  
107 influenza (Figure 1). Hence, the proportion of nosocomial cases among inpatients with  
108 documented influenza was 6.6% (57/860) during the study period. Characteristics of patients  
109 with nosocomial influenza are summarized in Table 1: They were 26 women and 31 men,  
110 with a median age of 82 years [interquartile range, 72-86.8]. Major comorbidities included  
111 diabetes (n=12, 21.1%), cardiopathy (n=11, 19.3%), and chronic respiratory disease (n=9,  
112 15.8%). Twenty patients (35.1%) had received the seasonal influenza vaccine within the last  
113 six months. More than half of nosocomial influenza were acquired in the geriatric department  
114 (30/57), especially in middle- or long-term care facilities (28/57). Influenza was mostly  
115 acquired in a double-bed room (n=39, 68.4%), with documented exposure in 14 cases. The  
116 median time between admission and symptoms onset was 11 days [7-19.5], and the median  
117 time between symptoms onset and diagnosis was 29 hours [15.5-48]. The proportion of  
118 nosocomial influenza remained stable during the whole influenza season (Figure 3). The  
119 management and outcome of the 57 patients with nosocomial influenza are summarized in  
120 Table 2. Briefly, although most patients were treated with oseltamivir (42/57, 73.6%), and/or  
121 antibacterial agents (13/57, 22.8%), four patients were transferred to the intensive care unit,  
122 and nine patients (15.8%) died.

123

124 As compared to patients with community-acquired influenza admitted to the hospital during  
125 the study period, patients with nosocomial influenza were older (median, 82 vs. 47 years;

126  $P < 0.00001$ ), and more likely to be infected by influenza virus type B: 46/57 (80.8%) vs.  
127 359/803 (44.7%),  $P < 0.00001$  (Table I). Of note, patients with nosocomial influenza B were  
128 more likely to be vaccinated (19/46, 41.3%), than patients with nosocomial influenza A (1/11,  
129 9.1%),  $P < 0.001$ . During the study period, the total number of hospital-days in our institution  
130 was 262,190. Hence, the incidence of nosocomial influenza in inpatients was estimated at  
131 0.22 per 1000 hospital-days.

132

## 133 **Discussion**

134 In this retrospective single-centre study, we found that nosocomial transmission of influenza  
135 is responsible for 6.6% of influenza cases managed in a tertiary care centre, that it  
136 disproportionately affects elderly patients, with 90-day mortality of 15.8%. Most cases of  
137 nosocomial influenza were caused by type B influenza virus: 46/57 (80.8%), as compared to  
138 359/803 (44.7%) in community-acquired influenza,  $P < 0.00001$ . These findings are in line  
139 with previous series of nosocomial influenza cases, except that i) influenza A virus was the  
140 main cause of nosocomial influenza in all published studies to date [3][9][10]; ii) in-hospital  
141 mortality was usually lower (3.8-9%), despite higher proportion of immunocompromised  
142 patients (50-72%, but with heterogeneous definition) [9][4].

143

144 To our knowledge, this study is the first to identify an association between influenza B virus  
145 and nosocomial influenza. Of note, the 2017-2018 influenza season (i.e., the study period)  
146 was remarkable for an unusually high proportion of influenza B virus, in outpatients as well  
147 as in inpatients, in a context of mismatch between the influenza B virus included in the  
148 recommended trivalent vaccine, and the main circulating strain in France that year: Indeed,  
149 the B/Yamagata strain was not included in the vaccine although it was responsible for 94% of  
150 all influenza B [11]. This sub-optimal vaccine effectiveness was particularly obvious in the  
151 population most affected by nosocomial influenza, the elderly [12][11]. However, these  
152 particularities are unlikely to explain why influenza B virus was disproportionately involved  
153 in nosocomial influenza that season, as it would similarly affect community-acquired  
154 influenza. Other hypotheses include higher transmissibility of influenza B virus in the  
155 nosocomial context, and/or cluster(s) of transmission. However, the latter would most likely  
156 be associated with heterogeneity over time, in the proportion of influenza B among

157 nosocomial cases during the study period, which we did not observe (Figure 3). In-depth  
158 epidemiological investigations assisted by phylogenetic analysis would contribute to decipher  
159 the mechanisms of influenza transmission in healthcare settings, but this could not be  
160 performed in our study, as isolates were not available for thorough molecular characterization  
161 [13].

162

163 Our estimates of the burden of nosocomial influenza must be interpreted with caution, given  
164 the very low vaccine coverage against influenza in France during the study period, i.e. 35.1%  
165 in at-risk patients targeted by official recommendations for yearly influenza vaccination, and  
166 20-30% in health care workers [14]. In addition, around two thirds of nosocomial cases  
167 affected patients who were admitted in a double-bed room, although the proportion of double-  
168 bed rooms is gradually decreasing in France. Admission in a double-bed room is a risk factor  
169 for nosocomial influenza [15]. We found that nosocomial influenza disproportionately affects  
170 elderly patients in our hospital, as previously reported [9]. Only one paediatric case was  
171 identified, although Dionne et al. found that one third of nosocomial influenza occurs in  
172 children [10]. These discrepancies may be related to differences in case-mix, under-diagnosis  
173 of influenza in our paediatric units, or clusters of active transmission between children in  
174 Dionne et al's study.

175

176 The median time between symptoms onset and diagnosis was rather short in our study, around  
177 29 hours [interquartile range, 15.5-48]. Others have found that time-to-diagnosis is reduced  
178 for nosocomial, as compared to community-acquired influenza [3]. This may be related to  
179 systematic monitoring of temperature and symptoms in inpatients. In addition, our institution  
180 has implemented extended working hours with rapid molecular testing assays and turn-

181 around-time <3 hours during the influenza season, which reduces the diagnosis delay [16] and  
182 allows earlier implementation of infection control measures, including patient isolation, use of  
183 masks for health care workers, and oseltamivir as curative and/or preventive treatment.

184

185 Of the 860 patients with documented influenza during the study period, 147 (17.1%) were  
186 retrospectively classified as community-acquired, as they presented ILI symptoms on  
187 admission, but they were tested more than 48 hours after admission. Delayed diagnosis of  
188 influenza is not uncommon due to the low specificity of ILI symptoms. This may contribute  
189 to the burden of nosocomial influenza, through delayed implementation of infection control  
190 measures. We found that droplet measures were implemented in most, but not all cases  
191 (82.5%), and that oseltamivir was prescribed for three quarters of patients. Systematic use of  
192 surgical masks was associated with a two-fold decline in the incidence of health care-  
193 associated influenza [17]. However, mandatory mask policy is difficult to maintain  
194 throughout the influenza seasons, and is considered as a motivation to promote influenza  
195 vaccine in health care workers, when imposed as the only alternative to vaccination [18].

196

197 One study found that the risk of nosocomial transmission is higher in case of contacts with  
198 contagious patients (relative risk, 17.96, 95%CI 10.1-32.0), as compared to health-care  
199 workers (relative risk 5.48, 95%CI 2.1-14.4) [19], although this was not confirmed by others  
200 [20]. In our study, 14 of 57 nosocomial influenza cases could be linked to contacts with  
201 another patient with influenza in a double-bed room, but the source remained unknown in  
202 43/57 (75.4%) of cases. Health care workers may be involved in a substantial proportion of  
203 these nosocomial influenza with unknown source, given the dramatically low influenza  
204 vaccine coverage in health care workers in France during the study period, although we

205 cannot rule out transmission from other patients with undiagnosed influenza, or from relatives  
206 during hospital visits. High vaccination coverage decreases the risk of nosocomial influenza  
207 [21][22]. Different actions to promote influenza vaccine in health care workers have been  
208 implemented, including educational programs, and mandatory policy [7]. In our institution,  
209 education and communication efforts have been associated with a 50% increase in health care  
210 workers vaccination coverage, from 30% in 2018-2019 to 45% in 2019-2020 (manuscript in  
211 preparation). Timely electronic notifications of nosocomial influenza cases may also  
212 contribute to decreased in-hospital transmission [23]. Nosocomial influenza control is  
213 complex and may rely on a comprehensive package of prevention tools: influenza vaccine for  
214 patients and health care workers, barrier control measures, antiviral prophylaxis in selected  
215 cases, control of visits, and early exclusion of health care workers with ILI [24]. Antiviral  
216 prophylaxis with oseltamivir has been recommended as soon as two cases of documented  
217 influenza are identified within 72 hours in residents or patients of the same ward [25][26][27].

218

219 This study has limitations. Firstly, as a single-centre study, our findings may not apply to  
220 other settings, especially given the low influenza vaccine coverage in France during the study  
221 period, for health care workers and for at-risk patients. The proportion of nosocomial cases  
222 among inpatients with influenza, and the incidence of nosocomial influenza, may be much  
223 lower in countries with better influenza vaccine coverage. Secondly, cases were identified  
224 through passive surveillance, when suspected by physicians in charge and documented.  
225 Hence, we probably underestimated the burden of nosocomial influenza in our institution, as  
226 the proportion of pauci-symptomatic influenza may be high [28]. In line with this hypothesis,  
227 only two cases of nosocomial influenza were documented in surgery departments during the  
228 study period, which may reflect lower awareness by surgical teams. Thirdly, cases classified  
229 as nosocomial may in fact be delayed diagnosis of community-acquired influenza, if early

230 symptoms of influenza have not been reported on admission. Finally, we defined nosocomial  
231 influenza as cases with no influenza symptoms during the first 48 hours after admission, in  
232 line with previous studies, and the natural course of influenza [5][29], although other used a  
233 larger time window (72-96 h). We performed a sensitivity analysis, extending the threshold to  
234 define nosocomial influenza at 72 hours, and 96 hours, between admission and symptom(s)  
235 onset. With a delay of 72, and 96 hours, the number of nosocomial influenza cases would be  
236 55, and 52 respectively, as compared to 57 with the 48 hours threshold. The 5 patients that  
237 would not be enrolled with the longest threshold (96 hours) had no complication (i.e. ICU  
238 admission, pneumonia, or death).

239

## 240 **Conclusions**

241 The burden of nosocomial influenza may be substantial in a country with low influenza  
242 vaccination coverage, accounting for 6.6% of all influenza cases managed in a tertiary care  
243 centre, with an estimated incidence of 0.22 per 1000 hospital-days and 90-day mortality of  
244 15.8%. Influenza B virus was more common in nosocomial (46/57, 80.7%), than in  
245 community-acquired cases (359/803, 44.6%,  $P < 0.001$ ) in the absence of any identified cluster  
246 of transmission. This study advocates for increased influenza vaccine coverage for high-risk  
247 patients as well as for health care workers.

248

249 **Conflict of interest statement**

250 None

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256

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363 **Table I.** Baseline characteristics of inpatients with influenza

	<b>Nosocomial cases (n=57)</b>	<b>Community- acquired cases (n=803)</b>	<b><i>P</i> value</b>
Age, years	82 [72-86.8]	47 [4.7-76.4]	<0.001
Male	31 (54.4)	392 (48.9)	0.64
Influenza virus type			<0.001
Influenza A	11 (19.2)	444 (55.3)	
Influenza B	46 (80.8)	359 (44.7)	
Comorbidities			
Diabetes	12 (21.1)		
Cardiopathy	11 (19.3)		
Chronic respiratory disease	7 (12.3)		
Ward			
Medical, acute care	21 (36.7)		
Surgery	2 (3.5)		
Middle-term care facility	18 (31.6)		
Long-term care facility	10 (17.6)		
Other	6 (10.5)		
Geriatric department	30 (52.6)		
Time from admission to symptoms onset, days	12 [7-19.5]		
Time from symptoms onset to diagnosis, hours	29 [15.5-48]		
Influenza vaccine status			
Vaccinated	20 (35.1)		
Not vaccinated	16 (28.1)		
Unknown	21 (36.8)		
Type of room			
Double bed-room	39 (68.4)		
Single bed-room	10 (17.5)		
Unknown	8 (14.0)		

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367 **Table II.** Management and outcome of patients with nosocomial influenza (n=57)

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<b>Management of nosocomial influenza</b>	<b>n (%)</b>
Oseltamivir	42 (73.6)
Antibacterial treatment for pneumonia	13 (22.8)
Droplet precaution	47 (82.5)
<b>Outcome</b>	
30-day mortality	7 (12.3)
90-day mortality	9 (15.8)
Intensive care unit admission	4 (7.0)

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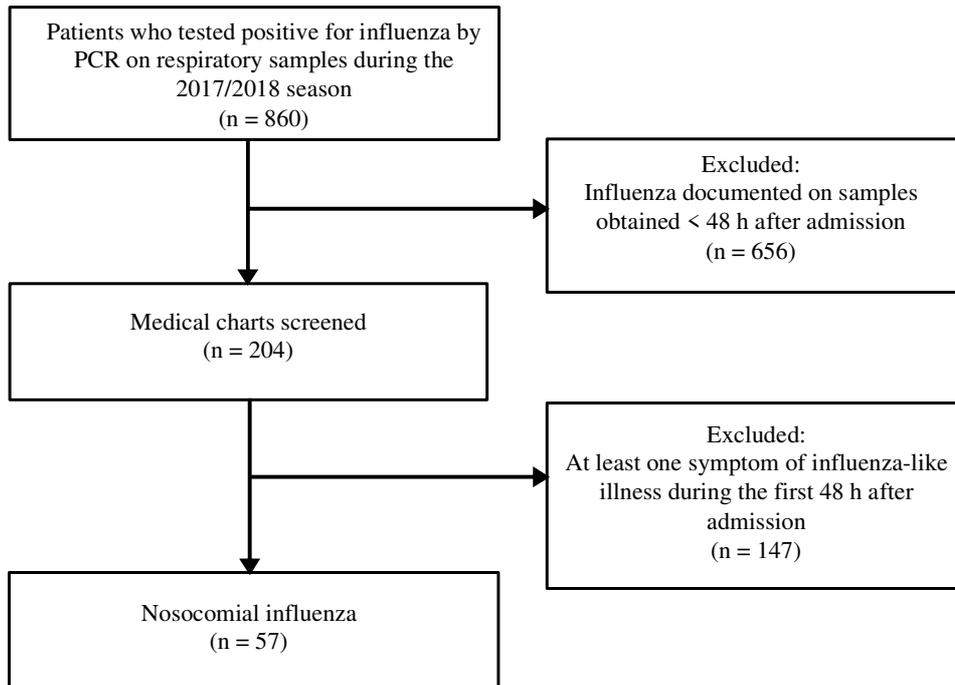
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372 **Figure 1.** Flowchart of the study

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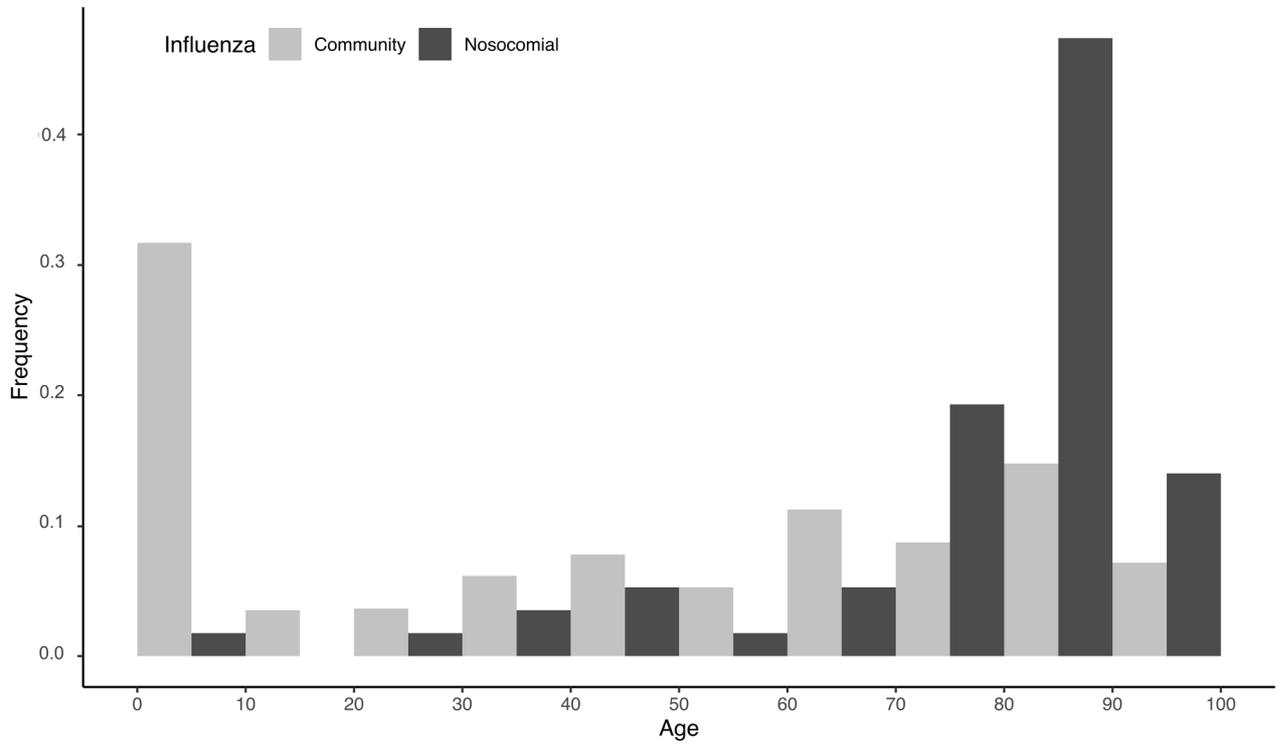
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376 **Figure 2.** Age of patients with nosocomial and community-acquired influenza.

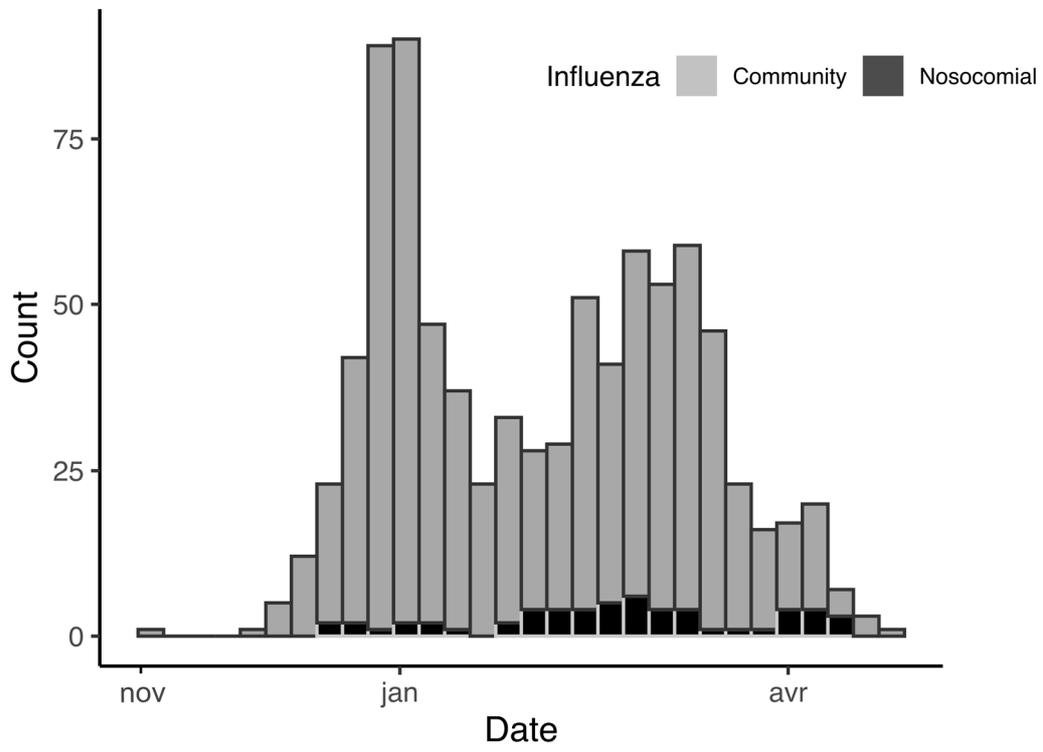
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380 **Figure 3.** Nosocomial and community-acquired influenza, date of diagnosis



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