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► To cite this version:

Fabiana Cazzorla, Othmane Azzam, Emeline Buet, Meghann Gallouche, Sylvie Larrat, et al.. Is it possible to hospitalize patients in multiple-bed room without increasing the risk of hospital-acquired influenza? Description of a pragmatic preventive strategy in a French university hospital. American Journal of Infection Control, 2022, 50 (2), pp.155-158. 10.1016/j.ajic.2021.09.016 . hal-04762168

HAL Id: hal-04762168

<https://hal.science/hal-04762168v1>

Submitted on 13 Nov 2024

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Is it possible to hospitalize patients in multiple-bed room without increasing the risk of hospital-acquired influenza? Description of a pragmatic preventive strategy in a French university hospital

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1 **Is it possible to hospitalize patients in multiple-bed room without increasing the risk of hospital-**
2 **acquired influenza? Description of a pragmatic preventive strategy in a French university hospital**

3
4 **RUNNING TITLE:** Hospitalization in multiple-bed room and hospital-acquired influenza

5
6 **ABSTRACT**

7 **Purpose**

8 Large inrush of patients through Emergency Department during influenza season can be dramatic.

9 The purpose of this study was to evaluate the impact of an emergency preventive strategy, namely admission
10 of patients with influenza in multiple-bed room with patients free from influenza, on the occurrence of
11 hospital-acquired influenza (HAI).

12 **Methods**

13 When a patient with an influenza RT-PCR diagnosis was hospitalized in a multiple-bed room, the
14 emergency preventive strategy was applied: selection of non-immunocompromised neighbor,
15 implementation of physical barriers (rigid screen pulled between beds, surgical mask for healthcare workers
16 and visitors), preemptive Oseltamivir therapy for the neighbor.

17 **Results**

18 From 29/11/2017 to 10/05/2018 a total of 464 hospitalized influenza patients were included; 318 were
19 placed in multiple-bed room and 141 in single room. Emergency preventive strategy was correctly applied
20 for 75.1% of patients in multiple-bed room. A total of 8 exposed neighbors matched HAI definition despite
21 strategy. Seven were already exposed to the case before the set-up of the strategy. Only one case of
22 documented transmission of influenza occurred after application of an incorrect emergency preventive
23 strategy: preventive posology of Oseltamivir was not correct.

24 **Conclusion**

25 These preliminary results suggest that the occurrence of HAI in multiple-bed rooms can be limited by the
26 implementation of maximum precautions and urge us to promote further evaluation of the strategy. A
27 detection bias should be considered without a systematic neighbors monitoring.

28

29 **KEYWORDS:** multiple-bed room, hospital-acquired influenza, Oseltamivir, prevention, transmission.

30

31

32 INTRODUCTION

33 Seasonal influenza outbreak is a major public health concern. Every year it occurs worldwide, with a global
34 attack rate estimated at 5–10% in adults and around 290,000-650,000 respiratory associated deaths¹.

35 The more, influenza is responsible for an annual economic burden on USA healthcare system of
36 \$11.2 billion².

37 Influenza outbreak in 2017-2018 was particularly long and intense all over the world with a majority of
38 influenza B virus and an excess mortality reported for 21 European countries in people aged 65 years or
39 older³.

40 In France, the outbreak trend was similar but characterized by a first wave of influenza A and a second wave
41 where type B was more represented⁴. The excess all-cause mortality was estimated at 12,982 deaths⁴. An
42 insufficient vaccination coverage of the French target population (elderly people of 65 y.o. and over,
43 pregnant women and people with comorbidity; 45.6%) and a sub-optimal efficacy of vaccine around 36% on
44 general population were registered^{4,5}.

45 The burden of additional inrush through Emergency Department (ED) during epidemic season, leading to an
46 overload of the capacity of care and consequently a need for new emergency strategies, has already been
47 described in literature⁶.

48 In this context, Grenoble Alpes University Hospital decided to set up an emergency preventive strategy to
49 face the upsurge of hospitalized patients.

50 The aim of this study was to evaluate the impact of an emergency preventive strategy, namely admission of
51 patients with influenza in multiple-bed room with patients free from influenza, on the occurrence of
52 hospital-acquired influenza (HAI).

54 PATIENTS AND METHODS

55 A prospective pragmatic study was performed on a cohort of adult patients hospitalized during the influenza
56 outbreak between 29th November 2017 and 10th May 2018 in Grenoble Alpes University Hospital
57 (GAUH). GAUH is the reference hospital of Isère department, it has 2,133 beds and serves a population of

58 675 000 inhabitants. The epidemic period was defined as more than 10 new cases per week in our hospital.
59 All patients hospitalized in our institution with a laboratory-confirmed influenza by Real Time-Polymerase
60 Chain Reaction (RT-PCR) were included. The criteria for testing for ILI included fever or feverishness and
61 at least one of the following symptoms: sore throat, cough, myalgia, or headache. Testing of patients for
62 influenza was performed upon request of the treating physician. Nasopharyngeal swabs in viral transport
63 media (Σ -Virocult®, MWE) or bronchoalveolar lavages were used to perform the diagnosis by RT-PCR
64 assays (Xpert® Flu, Cepheid; R-DiaFlu, Diagenode Diagnostic; RespiFinder 2SMART PathoFinder).
65 Paediatric cases, cases occurring outside epidemic period and non-hospitalized patients were excluded.
66 Moreover, if the origin of infection (community-acquired or hospital-acquired) was undetermined (existence
67 of a previous hospitalization, onset of symptoms difficult to determine), cases were excluded.
68 Centers for Disease Control and Prevention recommends droplet precautions for patients with influenza, i.e.
69 single room and use of surgical mask for Healthcare Workers (HCW)⁷. Due to a lack of single rooms (33%
70 of the total of rooms) in our institution, and the large inrush of patients through the ED during the winter
71 period, medical teams were not always able to respect the principle of single room, so an epidemic
72 emergency strategy was set up.
73 The strategy consisted of installing an influenza patient in a multiple-bed room while respecting 3
74 principles: selection of an immunocompetent neighbor free from influenza, physical barrier methods, an
75 influenza prophylaxis for the neighbor. Two physical barrier methods were deployed: a rigid screen pulled
76 between the two beds and use of surgical mask for HCW and visitors upon entry into the room. The
77 prophylaxis administered to the neighbor was Oseltamivir 75mg, two times per day for five days, or at a
78 dose adapted to the renal function. Information about the strategy was diffused within the hospital wards at
79 the beginning of the epidemic season by written recommendation, meeting and mailing. Staff members were
80 aware of the emergency strategy protocol and the need to screen the neighbor in case of flu suspicion. Other
81 measures included promotion of HCW flu vaccination, epidemiologic surveillance of influenza cases, and
82 communication campaigns in the whole institution.

83 A daily data extraction was conducted from the virology laboratory database to collect positive RT-PCR
84 results. Two residents of the Infection Control Unit investigated each positive result to ensure the correct
85 collection of data. Clinical and hospitalization characteristics were retrieved from patients' charts, namely:
86 required hospitalisation in intensive care unit (ICU), vital status at the end of hospitalisation, influenza
87 vaccine status, room placement. Electronic patients' records were systematically checked in search of the
88 hospital or community-acquired origin of infection, the presence of roommate, the droplet precautions
89 prescription and correct administration of Oseltamivir for both patient and neighbor. Patients that were
90 moved from single room to double room at least one day during contagious period (1 day before the onset of
91 symptom to 5 days after, or 7 if immunocompromised) were categorized as double room stays. If the record
92 was incomplete, the resident or doctor in charge of the patient was contacted to check information and verify
93 the implementation of adequate precautions. Medico-administrative databases were used to collect
94 information on Charlson score.

95 HAI was defined by a positive influenza RT-PCR and an onset of symptoms ≥ 3 days after patient's
96 admission⁸. Community-acquired infection was defined by a positive influenza RT-PCR and symptoms at
97 admission or an onset less than 2 days after admission. Investigation of hospital-acquired cases included a
98 systematic research for the presence of a neighbor within the three days before the onset of symptoms. A
99 case of transmission was defined by the occurrence of a HAI for a patient in a multiple-bed room despite the
100 emergency preventive strategy. A maximal exposition period for the neighbor of one day before the onset of
101 symptom of index case and 13 days after (5 days of index case contagion + 8 days of neighbor incubation
102 period/onset of symptoms/test result) was considered. Considering the proportion of patients that were not
103 tested because they were discharged before the end of the maximum exposition period, a detection bias was
104 estimated.

105 Categorical variables were summarized as numbers and percentages, continuous variables as medians and
106 interquartile ranges (IQR). Groups were compared by the Mann–Whitney U test, Pearson chi-square test, or
107 Fisher's exact test as appropriate for continuous and categorical variables. All statistical tests were two-
108 tailed, and a P value ≤ 0.05 was considered statistically significant. Data were analyzed with the "R studio"

109 software (version 1.4.1103). Study ethics approval was obtained on 03/03/2021 (CECIC Rhône-Alpes-
110 Auvergne, Clermond-Ferrand, IRB 5891).

111

112 **RESULTS**

113 From November 2017 to May 2018, 729 cases of influenza were diagnosed in our hospital; 298 cases came
114 through the adult ED and 58 from paediatric ED. Type B virus (69.6%) dominated the influenza epidemic in
115 our hospital. Two peaks were reached: the first during week 02-2018 was characterized by both A and B
116 types, the second at week 08-2018 and mostly represented by B type.

117 A total of 466 adult patients were hospitalized and 464 were included in the study (Table 1); two patients
118 were excluded due to a lack of information on the origin of infection.

119 The median age of included patients was 78 years (IQR: 64-87) for men and 81 years (IQR: 64-89) for
120 women with a male/female ratio of 0.89. A total of 72.5% of patients had a Charlson score ≥ 3 . Most
121 common co-morbidities were congestive heart failure and chronic pulmonary disease. A total of 39.7% of
122 patients were vaccinated against influenza, of note, for 23.7% the information wasn't available. During
123 hospitalization, 42 patients had severe manifestation of influenza that required admission in ICU. At the end
124 of the influenza outbreak, we registered 33 (7%) deaths. HAI was diagnosed in 84 patients (18.1%). The
125 proportion of HAI in multiple-bed room was higher in short term hospitalization compared to long term
126 hospitalization (69.2% vs 21.1%, $p < 0.001$).

Variables	N= 464
Age in years, median (IQR)	78 (64-87)
Male	76 (64-85)
Female	81 (64-89)
Sex	
Male, n (%)	218 (47)
Charlson score	N= 437

Median (IQR)	5 (3-6)
Charlson score \geq 3, n (%)	317 (72.5)
Congestive heart failure, n (%)	100 (22.9)
Chronic pulmonary disease, n (%)	86 (19.7)
Diabetes without chronic complication, n (%)	84 (19.2)
Neoplastic disease, n (%)	80 (18.3)
Peripheral vascular disease, n (%)	67 (15.3)
Renal disease, n (%)	35 (8.0)
Dementia, n (%)	29 (6.6)
Hemiplegia or paraplegia, n (%)	25 (5.7)
Diabetes with chronic complication, n (%)	24 (5.5)
Cerebrovascular disease, n (%)	12 (2.7)
Metastatic cancer, n (%)	10 (2.0)
Myocardial infarction, n (%)	10 (2.0)
Mild liver disease, n (%)	8 (1.8)
Moderate or severe liver disease, n (%)	4 (0.9)
Rheumatic disease, n (%)	3 (0.7)
AIDS/HIV, n (%)	1 (0.2)
Peptic ulcer disease, n (%)	0
Influenza type, n (%)	
A	141 (30.4)
B	323 (69.6)
Influenza vaccination, n (%)	
Yes	170 (39.7)
No	184 (36.6)

Unknown	110 (23.7)
Room setting, n (%)	N= 459
Single room	141 (30.7)
Multiple-bed room	318 (69.3)
Influenza acquisition, n (%)	
Community-acquired	380 (81.9)
Hospital-acquired	84 (18.1)
Prescription of preventive measures*, n (%)	N= 462
Yes	343 (74.2)
No	119 (25.8)
ICU stay, n (%)	42 (9)
Deaths, n (%)	33 (7)

127 * Preventive measures were: mask for visitors and HCW when in contact with the patient, pulled screen
128 between beds if multiple-bed room, preemptive Oseltamivir therapy for the neighbor.

Abbreviations: IQR- interquartile range; ICU- Intensive Care Unit.

Table 1: Characteristics of adult patients with a RT-PCR diagnosis of influenza and hospitalized at Grenoble Alpes University Hospital.

129

130

131 Placement of patients in single or multiple-bed room was dictated by the inrush on ED and tension on
132 available hospital beds. About two thirds of patients (318/464) were placed in multiple-bed room (316 in
133 double-bed room and 2 in hall beds) and 141 in single room; type of room was unknown for 5 patients.
134 Therefore, 261 neighbors were exposed to infectious influenza-positive patient. Among them, 50 were tested
135 for ILI symptoms and only 12 were positive (24%). Three were community acquired and one had an
136 uncertain PCR result (two different techniques were used, one with a positive result and the other with a
137 negative result). A total of 8 cases matched HAI definition despite strategy but 5 of them were already

138 exposed to the case before the set-up of the strategy and 2 were neighbors with a same day of onset of
139 symptom. Eventually only one case was exposed after the set-up of the strategy. In this last case, droplet
140 precautions were set-up at the entrance of the index case and Oseltamivir pre-emptive therapy for the
141 neighbor began at 30 mg once a day, which was not conforming to the procedure (30 mg twice a day
142 according to his renal function, GFR: 35 mL/min); the neighbor, 87 years old, had been hospitalized already
143 for 16 days because of cardiac failure on atrial fibrillation, he had multiple comorbidities and he wasn't
144 vaccinated against seasonal influenza. One day after the contact with the index case, he developed ILI
145 symptoms and died two days after for respiratory distress.

146 A total of 160 patients were not tested and were discharged before the end of the maximum exposition
147 period, resulting in a detection bias of 61.3% (160/261 neighbors).

148 Concerning prescription of preventive measures, they were correctly set up for a total of 343 patients
149 (73.9%): droplet precautions were correctly applied for 99 patients (71.2%) placed in single room and the
150 emergency preventive strategy was correctly applied for 239 patients (75.1%) placed in multiple-bed room
151 ($p=0.38$). The compliance to the strategy was slightly higher for patients in multiple-bed rooms but not
152 statistically significant ($p=0.38$). Median time between the onset of symptoms and the introduction of the
153 strategy was 4 days (IQR: 2-6), but no statistical difference was found according to room setting ($p= 0.84$).

154 Preemptive Oseltamivir therapy was prescribed with droplet precautions (± 1 day) for 108 out of 261
155 neighbors. During epidemic flu season, investigation and surveillance of flu cases and roommates required a
156 consistent amount of time. At the peak period, for approximately 10 cases per day, it took around two hours
157 daily to investigate cases, to contact HCW and to ensure droplet precautions implementation.

158

159 **DISCUSSION**

160 During influenza outbreak in 2017-2018, a total of 318 patients with influenza were placed in multiple-bed
161 room in Grenoble Alpes University Hospital. The emergency preventive strategy was applied: selection of
162 non-immunocompromised neighbor, implementation of physical barriers (a rigid screen pulled between the
163 two beds, use of surgical mask for HCW and visitors upon entry into the room), preemptive Oseltamivir

164 therapy for the neighbor, and verification of the strict compliance with previous recommendations. A total of
165 261 neighbors were exposed, only 50 were tested for ILI symptoms and 12 were positive. Eight cases of
166 HAI occurred in patients who benefited of our preventive strategy, but only in one case the exposition
167 occurred after setting up the strategy. The neighbor started having symptoms just one day after the contact,
168 the minimum delay of incubation. So, the nosocomial transmission could be previous to the contact with the
169 index case.

170 The others 7 cases of HAI, showed that the emergency preventive strategy cannot be efficient if the
171 exposition already occurred.

172 In general, HAI in double room was more frequent in short term hospitalization, probably due to the higher
173 turnover of patients and the chance to have more than one neighbor. On the other hand, the frequency of
174 HAI in single room in long term hospitalization can be explained with the profile of patients (wandering
175 patients and group activities)⁹.

176 Every year influenza outbreak brings tension on hospitalization beds and increases the inrush at the ED. The
177 aim of our strategy was to help reducing bed tension without increasing infectious risk in our patients.
178 Previous studies showed the importance of adopting single room policy, showing an increased HAI risk of
179 ILI in double occupancy room compared to single room (RR= 2.67) in addition to better global patient care
180 regarding privacy and comfort¹⁰⁻¹³. Despite this scientific evidence, single room policy isn't always
181 possible. During this epidemic season, at GAUH, HCW vaccination rate stood at 29.1% with differences
182 among categories: students are the most vaccinated, followed by midwife and physicians. Low rate of
183 vaccination can represent a risk for HAI.

184 In our study, the adherence to preventive measures (droplet precautions prescription and Oseltamivir
185 prescription) was high (74%), with a comparable adherence between single room and multiple-bed room.
186 We observed in a previous study that lower application of droplet precautions could lead to an increase of
187 nosocomial transmission¹³. The time between symptoms onset and prescription of preventive measures was
188 around 4 days. It did not vary between single and multiple-bed rooms, but should be shorter to follow the
189 recommendation to introduce Oseltamivir treatment within 48 hours after symptoms onset or after

190 exposition with an influenza patient. In a meta-analysis, Oseltamivir was consistently associated with a 0.5-1
191 day decrease in symptoms duration¹⁴. Moreover, a review found that Oseltamivir (in comparison to the
192 absence of prophylaxis) was consistently associated with a decrease in the odds/risk of symptomatic
193 secondary transmission¹⁵. On the other hand Oseltamivir resistance is known in literature but it doesn't
194 seem to be associated with higher risk of complication in immunocompetent host¹⁶.

195 Use of surgical mask for HCW and visitors has already demonstrated his efficacy in prevention of the
196 transmission of respiratory pathogens^{17,18}. There are more uncertainties about the interest of rigid screen
197 pulled between the two beds. No literature is available on the use of these physical barriers, but this measure
198 seemed to be logical. A great work has been done to improve HCW awareness and to let them understand
199 the importance of physical barriers, not just for privacy and comfort but also as a real protection against
200 transmission through droplets. Finally, the careful selection of the immunocompetent neighbor is paramount;
201 the difficulty to adapt the dosage of Oseltamivir in case of renal failure must be taken into account.

202 Furthermore, the possible selection of influenza vaccinated neighbor needs to be investigated. The only
203 patient that was contaminated after the set-up of the strategy was not vaccinated. Of note, he didn't receive
204 the correct Oseltamivir dose. Our strategy was time consuming but it showed encouraging results: large
205 information of HCW, implementation of a multimodal preventive protocol and verification of the strict
206 compliance with recommendations can be useful to reduce influenza transmission in inrush situations.

207 Although it was a prospective study, the first limit of the study is the detection bias estimated at 61.3%, it
208 probably drives a possible underestimation of HAI cases due to a lack of follow-up of neighbors. Though,
209 seeing the characteristics of our population, including median age and comorbidities, we can suppose that
210 other possible HAI cases would have generated a new hospitalization. Furthermore, systematic screening of
211 the roommate searching for asymptomatic influenza was not performed. We recently demonstrated that
212 asymptomatic and pauci-symptomatic influenza were frequent among HCW, representing 47% and 42% of
213 the influenza burden respectively¹⁹. We cannot extrapolate these data to patients because the 2 populations
214 present major differences in terms of age and comorbidities, but we can reasonably suppose that there is also
215 a part of asymptomatic or pauci-symptomatic influenza also among hospital patients. Secondly, use of

216 physical barriers (a rigid screen pulled between the two beds, use of surgical mask for healthcare workers
217 and visitors at the entrance of the room) was not evaluated, and the design of this observational study did not
218 allow to ascertain that transmission occurred from the patient's roommate. Nevertheless, prior publications
219 described the role of sick HCW and infected patients in the occurrence of HAI: contact with sick HCW can
220 increase the relative risk of HAI of 5.48 while contact with sick patient increase the relative risk of 17.96²⁰.
221 Third, determining which individual components of our multimodal strategy led to its success was not
222 possible. Fourthly, our study was performed in a single center. Whether the implementation of our program
223 or data collection procedures can be generalized to other institutions remains to be determined. Finally, this
224 strategy cannot be extrapolated to all respiratory viruses for which there is no available vaccine nor viral
225 therapy.

226

227 CONCLUSION

228 In conclusion, this study shows a first encouraging result regarding an emergency preventive strategy that
229 should be further evaluated with a randomized controlled trial (RCT). A RCT, though, pose some ethical
230 issues as it would require to expose patients to infective neighbor without maximum of protection. An
231 alternative solution can be a rigorous follow-up of neighbors after hospitalization to assess an evaluation of
232 the relative risk of HAI. These preliminary results urge us to promote a novel evaluation of the strategy and
233 comfort us to maximize precautions to ensure patient safety in inrush situation.

234

235

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ACKNOWLEDGMENT

289 Thank to Claire Dinh for her crucial help in the investigation.

290

291 **CONFLICT OF INTEREST:** None

292

293 **FUNDING SOURCES:** This research did not receive any specific grant from funding agencies in the
294 public, commercial, or not-for-profit sectors.

295

296 **LIST OF SPECIAL CHARACTERS:**

297 Σ

298 $\text{\textcircled{R}}$