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Major Article

Incidence of hospital-acquired influenza in adults: A prospective surveillance study from 2004 to 2017 in a French tertiary care hospital

Clotilde El Guerche-Séblain MSc [a,b,*], Sélilah Amour MSc [c], Thomas Bénet MD, PhD [c], Laetitia Hénaff BSc [d], Vanessa Escuret PD, PhD [d,e], François Schellevis MD, PhD [f,g], Philippe Vanhems MD, PhD [c,h]

[a] *Global Vaccine Epidemiology and Modeling Department (VEM), Sanofi Pasteur, Singapore*
[b] *University Claude Bernard Lyon 1, Lyon, France*
[c] *Service d'Hygiène, Épidémiologie et Prévention, Hôpital Édouard Herriot, Hospices Civils de Lyon, Lyon*
[d] *CIRI, Centre International de Recherche en Infectiologie, (Epidemiology and International Health Team, Emergent Pathogens Laboratory), Univ Lyon, Inserm, U1111, Université Claude Bernard Lyon 1, CNRS, UMR5308, ENS de Lyon, F-69007, Lyon, France*
[e] *Hospices Civils de Lyon, Centre National de Référence des virus des infections respiratoires, Laboratoire de Virologie, Institut des Agents Infectieux, Groupement Hospitalier Nord, F-69317, Lyon Cedex 04, France*
[f] *Netherlands Institute for Health Services Research, Utrecht, The Netherlands*
[g] *Department of General Practice, Amsterdam Public Health Research Institute, Amsterdam University Medical Centres, Amsterdam, The Netherlands*
[h] *Epidemiology and International Health Team, Emergent Pathogens Laboratory, Fondation Mérieux, International Center for Research in Infectiology, National Institute of Health and Medical Research, U1111, National Center of Scientific Research, Mixed Scientific Unit 5308, École Nationale Supérieure de Lyon, Université Claude Bernard Lyon 1, Lyon, I-REIVAC, France*

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Background: Hospital-acquired influenza potentially leads to significant morbidity and mortality in already vulnerable patients, but its overall burden is not fully understood. We undertook this study to estimate the incidence and trends of hospital-acquired laboratory-confirmed influenza among adults, and to compare clinical characteristics between hospital-acquired and community-acquired influenza cases.

Methods: This was a prospective surveillance study over 11 years of adults with influenza-like-illness (ILI) hospitalized in surgery, medicine and geriatric wards in a tertiary acute-care hospital in Lyon, France. Nasal swabs were systematically collected from those with ILI and tested for influenza by reverse transcriptase-polymerase chain reaction at the national influenza reference laboratory (Lyon, France).

Results: Influenza was laboratory confirmed at a rate of 1 in 13 patients who developed ILI during their hospitalization. Having an underlying disease was an important characteristic of hospital-acquired ILI cases. Cardiovascular disease was the most frequent underlying condition in both influenza-positive and influenza-negative patients. Complications were more frequent for influenza-positive than influenza-negative patients. The influenza incidence rate was highest in the geriatric ward and increased over the study period.

Conclusions: Hospital-acquired influenza poses a significant risk to already vulnerable patients. Longitudinal surveillance data are essential to support better recognition and monitoring of viral infections in hospitals.

* Address correspondence to Clotilde El Guerche-Séblain, MSc, Global Vaccine Epidemiology and Modeling Department (VEM), Franchise Epidemiologist, Sanofi Pasteur, 38 Beach Road #18-11, South Beach Tower, 189767 Singapore.

E-mail address: clotilde.elguercheseblain@sanofi.com (C. El Guerche-Séblain).

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Conflicts of interest: CEG is an employee of Sanofi Pasteur, which is developing vaccines against Influenza. SA, TB, LH, VE, FS have no competing interest to declare. PV received grants from French Ministry of Health (2008-2010), grants from Sanofi (2004-2008), during the conduct of the study.

Author contributions: Authors have made substantial contributions as follows: (1) the conception and design of the study (CEG, SA, TB, FS, PV) or acquisition of data, (SA, LH, VE, PV) or analysis (CEG, SA, TB) and interpretation of data (all authors), (2) drafting the article (CEG, SA) or revising it critically for important intellectual content (all authors), (3) final approval of the version to be submitted (all authors).

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BACKGROUND

Globally, hospital-acquired infections are the most frequent adverse event in health care delivery. Hundreds of millions of patients are affected annually by healthcare-acquired infections worldwide, leading to significant morbidity and mortality, and financial burden on health care systems.[1] Of every 100 hospitalized patients at any given time, 7 and 10 in developed and developing countries, respectively, will acquire at least 1 hospital-acquired infection. In France, the estimated risk of hospital-acquired infection is 5%-7% of hospitalizations. This represents approximately 750,000 cases annually.[2-4] Although several cross-sectional studies have investigated the burden of hospital-acquired infections, most report bacterial infections and classify viral infections as "other organisms" without further distinction or specification.[5-7] However, a few studies have reported that hospital-acquired respiratory viral infections are frequent and can result in morbidity and mortality in hospitalized patients.[8-10]

Influenza is a viral infection that is globally responsible for 3-5 million severe cases leading to 290,000-650,000 deaths annually.[11,12] Hospitalized patients exposed to other potentially infectious patients or health care workers with influenza-like illness (ILI) are at risk of acquiring ILI.[13] The burden of ILI infections aquired in hospitals mostly impacts older adults in short-stay units[14] and immunocompromised individuals.[10] In addition, hospitalized patients are at greater risk of acquiring ILI than those in the community setting.[15] These studies have helped identify priorities regarding preventive measures for respiratory infections.

The contribution of seasonal influenza and in particular hospital-acquired influenza (HAI) to the overall burden of hospital-acquired infections is not fully understood, but likely underestimated nonetheless.[13] Only a few studies have described the incidence of HAI with laboratory confirmation, but additional studies are needed to better inform strategies for the prevention of seasonal influenza in hospitals and guide hospital surveillance.

Here, we report the findings from an 11-year prospective surveillance study assessing the incidence and clinical characteristics of seasonal HAI in a French tertiary care hospital. The main objective of the study was to estimate the incidence and trends of HAI among adult patients. The secondary objectives were to compare patients with confirmed influenza to other patients with ILI, and to describe the characteristics of HAI cases compared to community-acquired influenza cases.

METHODS

Study design

This was a prospective hospital-based, surveillance study of ILI (study reference: NCT03413228), which started in 2004 and planned to continue up to 2022. Details of the surveillance protocol have been described elsewhere[14] and the questionnaire used is available in the Supplementary Materials. We used surveillance data collected during the months from October to April only (during the period 2004-2017) at Édouard Herriot Hospital (Lyon, France), a tertiary, acute-care university hospital with approximately 1,000 beds. The study was approved by the Édouard Herriot Hospital Institutional Review Board. All participants provided written informed consent.

Surveillance conduct and data collection

The study setting included surgery, medicine, and geriatric wards of the hospital. Participation of wards was on a voluntary basis, as decided by the medical staff, and varied between seasons. The surveillance conduct and procedures have been previously described,[10,14,16] and were only initiated when the Ministry of Health and Santé Publique France declared the start of influenza season, the duration of which varied between seasons from October to April (with the end of the season also declared by the Ministry of Health). Briefly, during the influenza season, the medical staff at the participating wards were contacted daily for identification of patients with ILI.

ILI was defined as a rectal or axillary temperature of ≥37.8°C in the absence of antipyretic drug therapy, with cough or sore throat.[17,18] All patients with ILI were included regardless of the timing of ILI onset (before or during hospitalization). On ILI diagnosis, a questionnaire (Supplementary Material) was used to collect information from the patient and their medical records. The following data were collected: dates of admission and discharge or death, underlying diseases based on medical record, start and end dates of ILI symptoms, whether there was a severe event (eg, complications or death during the hospital stay), seasonal influenza vaccination status and date of vaccination as declared by the patient. Nasopharyngeal swabs were systematically collected from all participating patients at onset of ILI symptoms by the physician and tested for influenza A and B viruses by reverse transcriptase-polymerase chain reaction (RT-PCR) at the influenza national reference laboratory (Hospices Civils de Lyon, Lyon, France). HAI was defined as an RT-PCR-confirmed influenza with symptom onset ≥72 hours after hospital admission.[16] Community-acquired influenza was defined as an RT-PCR-confirmed influenza case with symptom onset <72 hours after hospital admission. No surveillance data were collected during the 2009-2010 season because the H1N1 pandemic started earlier than the surveillance study period. Surveillance data could neither be collected during the 2012-2013 season due to lack of funding.

Analyses

For each participating ward the cumulative number of hospitalized patients during the surveillance period in each season was calculated. The incidence rate of HAI was calculated as the number of HAI cases divided by the number of patient-days for all hospitalized patients in the participating wards for each season during the surveillance period. Five different time periods were defined to calculate the incidence rates (season 2004-2005 to season 2006-2007; season 2007-2008 to season 2008-2009; season 2010-2011 to season 2011-2012; season 2013-2014 to season 2014-2015; and season 2015-2016 to season 2016-2017). Because of the small numbers of patients included in the medicine and surgery wards, the data from both wards were combined for incidence calculation.

Population characteristics were described by numbers and percentages for categorical variables and by medians and interquartile ranges (IQR) for continuous variables, and compared between those from the geriatric ward *versus* those from the medicine and surgery wards. Chi-squared tests were used to compare population characteristics between the ward groups and the characteristics of patients with HAI versus community-acquired influenza. P values ≤.05 were considered statistically significant. The incidence rates of HAI were estimated with their 95% confidence intervals (95% CI). Univariate Poisson regression was used to quantify HAI incidence rates between time periods, as described above. The event was HAI and the denominator cumulative number of patient-days. Statistical analyses were performed using SPSS version 19 (IBM, Chicago, IL).

RESULTS

Patient characteristics

Overall, 756 adult patients with ILI symptoms while hospitalized were included between 2004-2005 and 2016-2017 (Table 1). During

Table 1
Characteristics of patients with influenza like illness at Édouard Herriot University Hospital, Lyon (2004–2017)

Characteristics	Value (N = 756)	Geriatric ward (N = 573)	Other wards* (N = 183)	*P* value
Median age (IQR)	85.0 (13)	88 (8)	59 (32)	<.001
Sex, *n* (%)				
Male	287 (38.0)	197 (34.4)	90 (49.2)	<.001
Female	469 (62.0)	376 (65.6)	93 (50.8)	
Median length of stay, days (IQR)	10.0 (15)	10 (16)	10 (16.3)	.079
Hospitalization ward, *n* (%)				
Medicine	164 (21.7)			
Surgery	19 (2.5)			
Geriatric	573 (75.8)			
Vaccinated against influenza, *n* (%)	364† (58.5)	305 (68.4)	59 (33.5)	<.001
Underlying disease, *n* (%)				
Cardiovascular	556 (73.5)	477 (83.2)	79 (43.2)	<.001
Respiratory	225 (29.8)	180 (31.4)	45 (24.6)	.094
Neurological	276 (36.5)	253 (44.2)	23(12.6)	<.001
Endocrine	238 (31.5)	184 (32.1)	54 (29.5)	.524
Immunodeficiency	27 (3.6)	4 (0.7)	23 (12.6)	<.001
Digestive	224 (29.6)	178 (31.1)	46 (25.1)	.137
Oncologic	139 (18.4)	106 (18.5)	33 (18.0)	1.000
Infectious	104 (13.8)	70 (12.2)	34 (18.6)	.036
Rheumatologic	297 (39.3)	243 (42.4)	54 (29.5)	.002
At least 1 underlying disease	719 (95.1)	560 (97.7)	159 (86.9)	<.001
Laboratory confirmed influenza, *n* (%)				
Positive	160 (21.2)	101 (17.6)	59 (32.2)	<.001
Negative	596 (78.8)	472 (82.4)	124 (67.8)	
Influenza virus subtype (*n*, %)				
Influenza A	125 (78.1)			
Influenza B	35 (21.9)			

Abbreviation: IQR, interquartile range.
*Medicine and surgery wards.
†N = 622.

all consecutive surveillance study periods, 46,071 patients were hospitalized in the participating wards, accounting for a cumulative number of 244,944 patient-days of hospitalization.

The majority of patients were hospitalized in a geriatric ward (75.8%). The remainder were hospitalized in medicine (21.7%) and surgery wards (2.5%). Consistent with this, the median of age was 85.0 ± 13 years (range, 19 to 111 years). Hospitalized patients were significantly older in the geriatric ward group than in other wards (median of age (IQR) was 88 (8) years *versus* 59 (32) years, respectively). Median length of stay (IQR) was 10 (15) days and similar between ward groups. More than half of patients (62.0%; $n = 469$) were female, and most (95.1%; $n = 719$) had at least 1 underlying disease. The most common underlying disease was cardiovascular disease (73.5%; $n = 556$) in both groups. Overall, 58.5% ($n = 364$) of patients had received influenza vaccination for the corresponding influenza season, a proportion which was significantly lower in the surgery and medicine wards (33.5%) compared to geriatric ward (68.4%) (Table 1).

Influenza was laboratory confirmed in 160 (21.2%) patients. Influenza virus type A was responsible for most of the infections (78.1%; $n = 125$). Among the influenza-positive cases, 39.4% ($n = 63$) had been previously vaccinated with similar proportions of positive cases vaccinated over time.

When differences between influenza-positive and -negative cases were explored, influenza-positive patients were more likely to have had headaches and chills as presenting symptoms than influenza-negative patients (Supplementary Table 1). Complications were more frequent for influenza-positive patients than for influenza-negative patients (13.1% vs 6.4%; $P = .007$), especially respiratory complications. There was no difference in the median length of hospital stay between influenza-positive and influenza-negative cases (9 days vs 10 days; $P = .646$). Antibiotics were used in 81.9% ($n = 118$) of influenza-positive and 75.8% ($n = 369$) of influenza-negative patients ($P = .038$).

HAI incidence rates

Of the 160 influenza cases, 57 (35.6%) were hospital-acquired (Table 2). The HAI crude attack rate was 13 per 10,000 (95% CI: 9.90-16.9) hospitalized patients. The crude incidence of HAI was 0.25 (95% CI: 0.19-0.32) per 1,000 patient-days for the entire study period.

Overall, the incidence of HAI per 1,000 patient-days increased from 0.07 (95% CI: 0.03-0.13) in 2004-2007 to 1.46 (95% CI: 0.84-2.38) in 2015-2017 ($P < .001$) (Table 2 and Fig 1). Incidence rates also increased in the different wards over time and were higher in the geriatric ward (from 0.40 [95% CI: 0.08-1.18] per 1,000 patient-days in years 2004-2007 to 2.05 [95% CI: 1.12-3.44] per 1,000 patient-days in years 2015-2017) than in the other wards (from 0.05 [95% CI: 0.02-0.10] to 0.49 [95% CI: 0.06-1.77] per 1,000 patient-days).

Comparison between hospital-acquired and community-acquired influenza cases

HAI and community-acquired influenza cases had a similar median age ($P = .55$) and sex ratio ($P = .16$) (Table 3). In both groups, most patients (71.9% and 62.1%, respectively) with an underlying disease had a cardiovascular disease, as well as a rheumatic disease and a neurological disorder, with no significant differences between the groups. The occurrence of severe events (complications and deaths) not necessarily due to influenza infections was also similar between groups, as well as the crude mortality rate (5.2 % and 4.8% for HAI and community-acquired cases, respectively; $P = 1.00$). Only the length of hospital stay differed between the 2 populations, 24 days and 6 days, respectively ($P < .001$).

DISCUSSION

This study, based on a prospective surveillance, estimated the crude incidence of HAI as 2.5 (95% CI; 1.9-3.2) per 10,000 patient-days, or 1

Table 2
Incidence estimates of hospital-acquired influenza (HAI) by ward and by time period

Ward	Time period	HAI cases	Patient-days	Estimated incidence per 1,000 patient-days (95% CI)	Crude incidence rate ratio (95% CI)
All wards	2004–05 to 2006–07	10	146,940	0.07 (0.03–0.13)	1.0 (ref.)
	2007–08 to 2008–09	0	21,062	0	NC
	2010–11 to 2011–12	9	25,213	0.36 (0.16–0.68)	5.2 (1.9–14.4)
	2013–14 to 2014–15	22	26,727	0.82 (0.52–1.25)	12.1 (5.5–28.6)
	2015–16 to 2016–17	16	10931	1.46 (0.84–2.38)	21.5 (9.2–53.0)
Geriatric ward	2004–05 to 2006–07	3	7,433	0.40 (0.08–1.18)	1.0 (ref.)
	2007–08 to 2008–09	0	3,533	0	NC
	2010–11 to 2011–12	8	6,608	1.21 (0.52–2.39)	3 (0.7–17.6)
	2013–14 to 2014–15	8	6,843	1.17 (0.50–2.30)	2.9 (0.7–17.0)
	2015–16 to 2016–17	14	6,838	2.05 (1.12–3.44)	5.1 (1.4–27.5)
Other wards*	2004–05 to 2006–07	7	139,507	0.05 (0.02–0.10)	1.0 (ref.)
	2007–08 to 2008–09	0	17,529	0	NC
	2010–11 to 2011–12	1	18,605	0.05 (0.01–0.30)	1.1 (0.02–8.3)
	2013–14 to 2014–15	14	19,884	0.70 (0.38–1.18)	14.0 (5.3–41.1)
	2015–16 to 2016–17	2	4,093	0.49 (0.06–1.77)	9.7 (1.1–51.2)
Total	2004–05 to 2016–17	57	230,871	0.25 (0.19–0.32)	–

Abbreviation: CI, confidence interval; NC, not calculable
*Medicine and surgery wards.

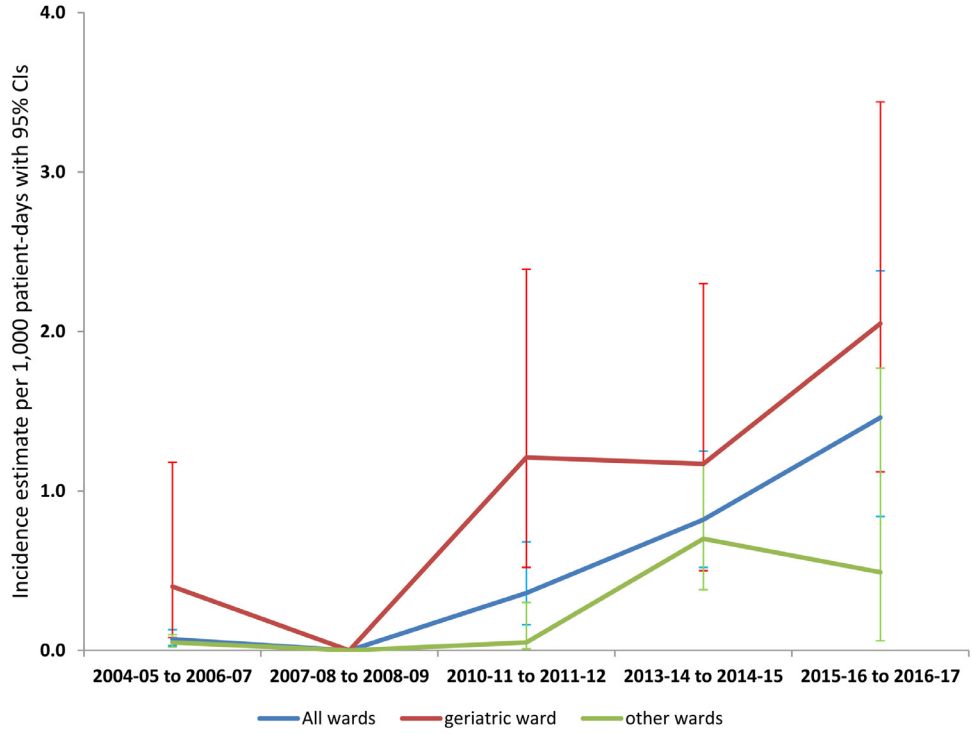

Fig 1. Evolution of hospital-acquired influenza incidence estimates by ward over time. Abbreviations: CI, confidence interval. Note: Because of the small numbers of patients included in the medicine and surgery wards, the data from both wards were combined for incidence calculation.

in 13 hospitalized patients with ILI. Having at least 1 underlying disease was an important characteristic of hospitalized patients with ILI, with cardiovascular disease the most frequent underlying condition irrespective of the hospitalization ward, and in both influenza-positive and -negative patients. The incidence of HAI was the highest in the geriatric ward and increased over the study period. This increase over time may be explained, in part, by improved capacity in geriatric wards to implement the surveillance protocol and report ILI cases in a timely manner in the most recent years. In addition, beds from the medicine wards were moved to other hospitals during the study period, which may have disrupted the continuity of the surveillance and reduced the capacity to detect ILI cases in that ward. The denominator in the incidence calculation varied during the period as it relied on the definition of influenza epidemics declared by Santé Publique France. The timing of influenza epidemics have been reported to vary in the last decades occurring progressively later in Western Europe[19] with seasonal epidemic size decreasing over time as notably reported in France.[20]

Hospital stay was significantly longer in patients with HAI than those with community-acquired influenza. This suggests that HAI lengthens hospital stay, or that patients had an increased risk of acquiring influenza because of a longer hospital stay. Some symptoms such as headaches and chills, were significantly more common in influenza-positive than in influenza-negative cases whereas dyspnea was more common in influenza-negative patients. Clinicians should take these symptoms into account when patients develop ILI.

Table 3
Comparison of hospital-acquired and community-acquired influenza cases

Characteristic	Hospital-acquired influenza (N = 57)	Community-acquired influenza (N = 103)	*P* value
Age (years), median (IQR)	85 (17.5)	85 (13)	.55
Sex ratio, males/females	27/30	37/66	.16
Length of stay (days), median (IQR)	24 (46.5)	6 (7)	<.001*
Number of patients by ward, *n*(%)			
Medicine and surgery wards	25 (43.9)	33 (32.0)	.14
Geriatric ward	32 (56.1)	70 (68.0)	
Underlying disease, n (%)			
Cardiovascular disease	41 (71.9)	64 (62.1)	.21
Neurological disorder	24 (42.1)	30 (29.1)	.10
Rheumatologic disease	23 (40.4)	35 (34.0)	.21
Gastrointestinal disease	18 (31.6)	21 (20.4)	.11
Endocrine disease	17 (29.8)	36 (35.0)	.51
Influenza subtype, *n* (%)			
Influenza A	47 (82.5)	78 (75.7)	.32
Influenza B	10 (17.5)	25 (24.3)	
Severe outcome, *n* (%)			
Complications	6 (10.5)	15 (14.6)	.47
Deaths	3 (5.2)	5 (4.8)	1.00
Vaccinated against influenza	21* (41.2)	42† (50.0)	.32
Antibiotics	39‡ (79.6)	79§ (83.2)	.40

Abbreviation: IQR, interquartile range
*N = 51;
†N = 84;
‡N = 49;
§N = 95.

Morbidity and mortality associated with HAI are not generally reported and most prevalence studies focus mainly on bacterial infections acquired from care, surgery rooms, and intensive care units.[5-7,21] In addition, in such studies, the study period is often chosen arbitrarily during the year and does not necessarily include the window of influenza epidemics, which thus precludes determination of the influenza burden. For instance, April was chosen by Kallel et al.[5] and May by Vincent et al.[7] for their studies of hospital-acquired infections, outside the influenza season in most of the countries assessed.

Our study provides incidence estimates of laboratory-confirmed influenza, complementing previous analyses of hospital surveillance of ILI as well as providing a longitudinal perspective with 11 years of patient and virological data. Previous analyses estimated the risk of ILI focusing on 3 consecutive seasons (2004-2007)[10] and the burden of ILI and influenza in geriatric units from 2004 to 2009.[15]

Of the influenza cases in our study, 35.6% were hospital-acquired. This differs from a similar surveillance study of hospitalized adults undertaken in Australia which reported 4.3% of influenza cases as hospital-acquired during the 2010-2011 season,[22] but is consistent with a Canadian surveillance study of hospitalized adults that reported 39.5% cases were hospital-acquired in an acute-care setting between 2006 and 2012.[9] The HAI crude rate estimate of 2.5 per 10,000 patient-days in our study approximates that for hospital-acquired *Clostridium difficile* infection rates of 3.7 (95% CI; 0.6-18.5) per 10,000 patient-days reported following surveillance of a network of 37 hospitals in 2013 in Europe,[23] with the latter being a more generally accepted hospital-acquired infection of concern.

To our knowledge, there are no incidence estimates of HAI for consecutive seasons based on an enhanced surveillance. This lack of evidence has been identified in a review by Voirin et al.[24] who recommended the development of active surveillance in combination with improved data collection and quantitative studies to determine incidence rates.

Vaccination uptake in our study was almost 60%, which is above the estimated coverage in adults aged over 65 years in France in 2016-2017, but below vaccination coverage target of 75% recommended by the World Health Organization.[12] With a larger sample size and a longer period of surveillance, it would be interesting to measure potential effects of vaccination of both patients and health care workers on the incidence of HAI infections.

The definition for HAI is an important parameter and is heterogeneous between studies. The delay from admission to first ILI symptoms has been reported to range from 48 to 196 hours, with a median of 72 hours, and most studies (36 out of 50) define HAI cases as onset of symptoms after 48 hours since admission.[16] The incidence estimates in our study may change if a different definition is used instead of ≥72 hours after hospital admission. Small differences in the definition used can translate into under- or overestimating the burden of HAI. Analysis of the surveillance database in Édouard Herriot Hospital has recently reported a median of 12 days between admission to hospital and symptoms' onset among reported HAI cases. In addition, the proportion of patients reporting ILI within the first 48 hours was 9.8%. These results emphasize the importance of a standardized definition to identify and manage HAI cases.[25]

The incidence estimates in our study may have been affected by missing surveillance data in the 2009-2010 season, due to the pandemic A/H1N1 (which started much earlier and required dedicated surveillance resources outside the scope of the current study), and the missing surveillance data in the 2012-2013 season because of a lack of funding support. Furthermore, participating hospital wards were defined based on a voluntary basis (not all wards participated in all years), which may have biased population profile recruitment to the study and subsequent incidences estimates. Besides age and underlying diseases, the overrepresentation of geriatric patients represents another possible bias in our estimates.

Influenza A virus subtypes and influenza B virus lineages were not determined, which limits the possibility of interpreting the evolution of incidence estimates with changes in virus circulation. Only crude incidence rate ratios could be calculated because we did not have information from other patients hospitalized at the same period of time, making it impossible to adjust our results (eg, by age, sex, and underlying disease) with respect to the overall hospitalized patient population.

Laboratory confirmation of infections caused by other respiratory virus was not always documented in our study, preventing comparison between our results on influenza and other respiratory viruses, notably respiratory syncytial virus. The role of different respiratory viruses in hospital-acquired infections has been described by Choi et al.[26], who found the most common were human coronavirus (30.2%), parainfluenza virus (29.8%), and influenza virus (28.1%) infections.

The main strengths of our study are the prospective longitudinal study design over a long period of time and laboratory confirmation of influenza cases. Furthermore, we collected detailed individual data to gain insight into HAI in at-risk populations within a large tertiary hospital of more than 1,000 beds.

Influenza spreads easily within hospitals and poses a significant risk to patients, visitors, and health care workers. More data are needed to recognize the true burden of viral infections in hospitals and in particular influenza, a vaccine-preventable disease. Improved surveillance of influenza, together with better recognition of the multifactorial determinants of transmission from the community at the individual level, would help health care professionals and public health authorities better implement prevention practices at hospital.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.ajic.2020.12.003.

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