

Incidence of Asymptomatic and Symptomatic Influenza Among Healthcare Workers: A Multicenter Prospective Cohort Study

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Background. Influenza is an important cause of viral hospital-acquired infection involving patients, healthcare workers (HCW), and visitors. The frequency of asymptomatic influenza among HCW with possible subsequent transmission is poorly described. The objective is to determine the cumulative incidence of asymptomatic, paucisymptomatic, and symptomatic influenza among HCW.

Method. A multicenter prospective cohort study was done in 5 French university hospitals, including 289 HCW during the 2016–2017 influenza season. HCW had 3 physical examinations (time [T] 0, before epidemic onset; T.1, before epidemic peak; T.2, T.3, after epidemic peak). A blood sample was taken each time for influenza serology and a nasal swab was collected at T1 and T2 for influenza detection by polymerase chain reaction (PCR). Positive influenza was defined as either a positive influenza PCR, and/or virus-specific seroconversion against influenza A, the only circulating virus, with no vaccination record during follow-up. Symptoms were self-reported daily between T1 and T2. Cumulative incidence of influenza was stratified by clinical presentation per 100 HCW.

Results. Of the 289 HCW included, 278 (96%) completed the entire follow-up. Overall, 62 HCW had evidence of influenza of whom 46.8% were asymptomatic, 41.9% were paucisymptomatic, and 11.3% were symptomatic. Cumulative influenza incidence was 22.3% (95% confidence interval [CI]: 17.4%–27.2%). Cumulative incidence of asymptomatic influenza was 5.8% (95% CI: 3.3%–9.2%), 13.7% (95% CI: 9.9%–18.2%) for paucisymptomatic influenza, and 2.9% (95% CI: 1.3%–5.5%) for symptomatic influenza.

Conclusions. Asymptomatic and paucisymptomatic influenza were frequent among HCW, representing 47% and 42% of the influenza burden, respectively. These findings highlight the importance of systematic implementation of infection control measures among HCW regardless of respiratory symptoms from preventing nosocomial transmission of influenza.

Clinical Trials Registration. NCT02868658.

Keywords. asymptomatic influenza; healthcare workers; prospective cohort; incidence; nosocomial.

Influenza is a highly contagious viral disease that constitutes a major concern in hospital settings owing to its high incidence among patients and healthcare workers (HCW), the epidemic risk, and the related mortality among patients [1]. Influenza is known to increase hospital costs and is a substantial cause of

absenteeism among HCW [2]. In France, 2–7 million people are symptomatically infected each year [3] and in the United States, 9–36 million individuals present influenza each season [4]. On average, 18% (95% confidence interval [CI]: 16–22%) of unvaccinated individuals are infected each winter season [5]. Hospital-acquired influenza epidemics are suspected when influenza-like illness (ILI) cases are observed in a healthcare facility during the influenza season [6, 7]. The prevention and control of hospital-acquired influenza is based on vaccination of HCW and patients, completed by control measures combining hand hygiene, mask wearing, patient isolation, antiviral treatments, and prophylaxis [8].

Influenza transmission is mainly by droplets during close contact, with possible transmission by air or direct contact [9]. Clinical influenza, as described in text books, combines fever associated

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with other respiratory symptoms such as cough, sore throat, and general symptoms such as headache or myalgia [10]. However, a recent study has reported that clinical presentation can be more self-limited or even asymptomatic in a significant number of influenza-documented cases in the community [5], but data are lacking for HCW. In hospital settings, exposure to symptomatic and influenza-infected patients and/or HCW increases the risk of influenza in patients [11] and infected HCW are frequently sources of nosocomial influenza [1, 12, 13]. We hypothesize that asymptomatic HCW could be responsible for transmission of influenza to patients [14–16] and colleagues and probably play a significant role in the transmission/spread of the infection [17].

The identification of asymptomatic HCW is therefore fundamental for the prevention and control of hospital-acquired influenza. For this purpose, a prospective cohort study with systematic sampling of HCW was implemented during the 2016–2017 influenza season to assess the incidence and the proportion of asymptomatic, paucisymptomatic, and symptomatic influenza among HCW in short-stay wards in 5 university hospitals in France.

METHODS

Settings, Population

A prospective multicenter cohort study was carried out in 5 French University hospitals between 1 September 2016 and 30 March 2017. Volunteer HCW from Lyon (Edouard Herriot and Lyon Est hospitals), Grenoble, Saint-Etienne, and Dijon University Hospitals were included. The identification and inclusion of HCW was carried out in each center by the occupational medicine department, the infection control unit, or the clinical research center. Information about the study was also given at the institutional level. Inclusion criteria were: (1) age ≥ 18 years, (2) voluntary participation, and (3) working in a short-stay healthcare unit. Exclusion criteria were: (1) presence of an ILI on the day of the first consultation, (2) programmed absence during the follow-up period, whatever the reason, or (3) a professional activity without patient contact (eg, secretary, administrative officer).

The inclusion period started on 4 October 2016 and ended on 5 December 2016. Time 0 (T.0), that is, the inclusion consultation, consisted of presentation of the study, signature of consent, face-to-face interviewer-administrated questionnaire with collection of demographic and professional information, and vaccination status. A blood sample (T.0 serology) was also collected on dry tube. The second consultation (consultation T.1) was scheduled from 2 to 18 January 2017 during the peak epidemic period. The latter was determined based on the French National Influenza Surveillance System [18]. The third consultation (consultation T.2) was scheduled 3-weeks (± 7 days) after the T.1 consultation. T.1 and T.2 consultations consisted of face-to-face interviewer-administrated questionnaires to collect information

on the existence of any recent ILI, blood sample collection (T.1, T.2 serologies), and nasopharyngeal swab on virocult (T.1 and T.2 polymerase chain reaction [PCR]). Between T.1 and T.2, a logbook with daily self-collection of clinical signs and symptoms, current treatment, and sick leave periods was completed prospectively by the enrolled HCW. Weekly contact by phone was performed to check that the logbook was completed and to ask for the presence of symptoms, which were also reported to the investigator. In case of clinical signs or symptoms, an additional consultation (T.s) was planned and included another nasopharyngeal swab for additional PCR viral research. The last consultation (T.2 + 30) was scheduled 30 days (± 7 days) after the T.2 consultation and consisted of a phone questionnaire to identify the occurrence of an ILI since the T.2 consultation.

Virologic Investigations

Nasopharyngeal specimens were taken using Virocult swab (Sigma Virocult® Purflock® 2ml, Elitech). Each center performed aliquots of nasal swabs and sera according to a standardized protocol. All clinical samples were analyzed by the Influenza National Reference Center (CNG) of Southern France located in Lyon, except for the potential T.s test that was analyzed locally by PCR. Influenza diagnosis was performed by duplex A/B reverse transcription polymerase chain reaction (RT-PCR) (in-house PCR), and the result was positive or negative according to the detection for influenza A or B. The samples detected positive by RT-PCR for influenza were further subtyped by PCR. Serology was done by hemagglutination inhibition assay for the specific investigation of anti-A(H3N2) A/Hong Kong/4801/2014 and B-Victoria Lineage B/Brisbane/60/2008. The presence of antibodies against influenza was tested by a hemagglutination inhibition test (IHA). The sera were tested against influenza A (H3N2) and B virus strains circulating in the 2016–2017 winter season. All sera from a patient were tested with the same IHA test. Analyses of the respiratory samples and the sera received at the 3 consultations (T.0, T.1, and T.2) were centralized.

Outcomes, Endpoints

The main outcome was laboratory-confirmed influenza defined by the presence of at least 1 of the following criteria with the absence of seroconversion or significant increase in the level of anti-B/Brisbane/60/2008 antibodies (no circulation of influenza virus B during the season):

- Positive influenza PCR at T.1, T.2, and/or T.s.;
- Influenza seroconversion defined by a negative anti-A antibody titer in Hong-Kong/4801/2014 (< 10 units) at T.0 or T.1 and positive anti-A antibody titer in Hong-Kong/4801/2014 (≥ 40) at the next time (T.1 or T.2);
- A significant increase in the anti-A antibody titer in Hong-Kong/4801/2014 defined as an antibody titer between 10 and 40 at T.0 or T.1 and antibody titer multiplied by ≥ 2 in the following consultation (T.1 or T.2).

As for signs and symptoms, influenza was defined for each period (T.0–T.1, T.1–T.2) among confirmed cases as the following:

- Asymptomatic influenza, defined by the absence of any signs or symptoms and temperature $<37.8^{\circ}\text{C}$;
- Paucisymptomatic influenza, defined by the presence of ≥ 1 sign(s) or symptom(s) for >1 day, with temperature $<37.8^{\circ}\text{C}$, or absence of cough and pharyngeal pain;
- Symptomatic influenza defined by the presence of fever $\geq 37.8^{\circ}\text{C}$ with presence of cough or pharyngeal pain, which corresponded to a widely accepted definition of ILI [19].

Statistical Analysis

The primary endpoint was quantified by the cumulative incidence of asymptomatic, paucisymptomatic, and symptomatic influenza per 100 HCW. It was also evaluated by the proportion of HCW presenting asymptomatic/paucisymptomatic/symptomatic influenza among all HCW with laboratory-confirmed influenza during the entire influenza season. Sample size calculation was based on a 75% asymptomatic or paucisymptomatic proportion of confirmed influenza cases and an incidence of 20/100 HCW per year [5]. Inclusion of 196 HCW would make it possible to describe an incidence of 15% asymptomatic influenza and 5% symptomatic influenza with a precision of $\pm 5\%$. Due to possible loss of follow-up, the initial objective was to include 50 HCW in each center (ie, 250 HCW in all).

The ILI date was defined as the day of first ILI presentation. The date of symptomatic presentation was defined as the date of first signs or symptoms. For influenza cases, the most plausible date of infection was established individually. Categorical variables were described as number (%)

and compared by χ^2 test or Fischer exact test. Continuous variables were described as median (interquartile range [IQR]) and compared by Mann-Whitney *U*-test or Wilcoxon test. Factors associated with asymptomatic influenza or paucisymptomatic/symptomatic influenza assessed by univariate and multivariate multinomial logistic regression were absence of influenza and were the reference category. Tested variables were: age category (<30 years, 30–39 years, ≤ 40 years), sex, number of adults in the household (1, 2, ≥ 3), number of children in the household (0, 1, ≥ 2), profession (medical doctor, nurse, nursing auxiliary, other), and type of unit (medicine, surgery, pediatrics/gynecology-obstetrics, intensive care unit and emergency, other). After univariate analysis, variables with *P*-value $< .10$ in univariate analysis were entered in multivariate logistic regression analysis. A backward stepwise model was then fitted until all *P*-values were $< .05$. $P < .05$ was considered significant. All of the tests were 2-tailed. EpiData Entry was used for data entry, and Stata 13-0 (StataCorp. LP) was used for data analysis. The synthesis is reported according to the Strobe checklist (Supplementary Table 1) [20].

Ethics

The study was approved by the Regional Ethics Committee (31 August 2016, *Comité de protection des Personnes Sud-Est II*), the French National Agency for Medicine and Health Product Safety (12 August 2016, *Agence Nationale des Produits de Santé*) and conformed to the reference methodology MR-001 of the French Data Protection Authority (*Commission Nationale de l'Informatique et des Libertés*).

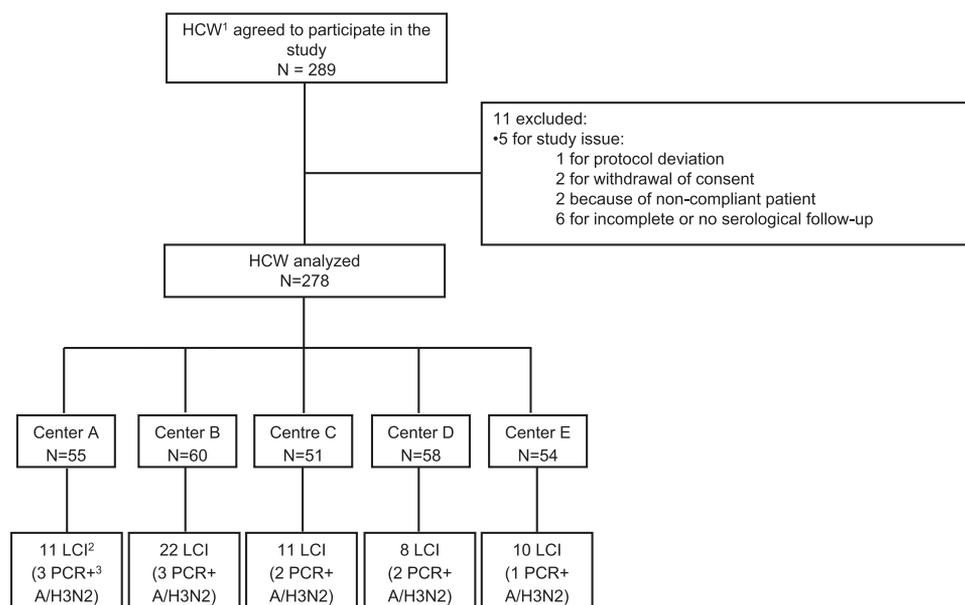


Figure 1. Flow-chart of study enrollment in the Asymptomatic Flu Project (AFP) cohort. Abbreviations: HCW, healthcare workers; LCI, laboratory confirmed influenza; PCR+, polymerase chain reaction positive.

RESULTS

Overall Population

Overall, 289 volunteer HCW were included. Six were excluded because at least 1 consultation was missed and 5 for other study issues (Figure 1). The final analysis included 278 HCW, accounting for 30 415 person-days of follow-up. The female/male ratio was 5.3 (234/278, 84.2% female), and the median age was 36 years (IQR: 29–47 years, Table 1). Characteristics differed by study center for sex, age, and professional activity ($P < .001$, $P = .002$, $P < .001$, respectively, Supplementary Table 2). Influenza vaccination coverage in 2016–2017 was 49.6%, was higher in men than in women (70.5% vs 45.7%, respectively, $P = .003$) and varied by profession (90.3%, 38.1%, and 37.8%, respectively, among medical doctors, nurses, and other professions, $P < .001$).

Virologic Findings

Sixty-two (22.3%, 95% CI: 17.4%–27.2%) HCW had evidence of influenza A based on the case definition during follow-up. No influenza B was detected by PCR in the study population.

Table 1. Characteristics of Healthcare Workers at Enrollment, the Asymptomatic Flu Project (AFP) Cohort, N = 278

Characteristics, No. / No. With Data (%) ^a	Overall Population
Hospital	
A	55/278 (19.8)
B	60/278 (21.6)
C	51/278 (18.4)
D	58/278 (20.9)
E	54/278 (19.4)
Age, y, median (IQR)	36 (29–47)
Sex	
Female	234/278 (84.2)
Male	44/278 (15.8)
Family home	
Number of children, median (IQR)	0 (0–2)
Number of adults, median (IQR)	2 (1–2)
Number of individuals, median (IQR)	3 (2–4)
Profession	
Medical doctor	62/278 (22.3)
Nurse	134/278 (48.2)
Nursing auxiliary, other	82/278 (29.5)
Type of unit	
Medicine	146 (52.5)
Surgery	30 (10.8)
Pediatrics, gynecology-obstetrics	33 (11.9)
Intensive care unit	40 (14.4)
Emergency, other	29 (10.4)
Vaccinated against influenza virus	
2013–2014	106 / 270 (39.3)
2014–2015	114 / 276 (41.3)
2015–2016	117 / 277 (42.2)
2016–2017	138 / 278 (49.6)

Abbreviation: IQR, interquartile range.

^aOtherwise specified.

On a national level, >99% influenza strains were influenza A during the 2016–2017 season [18]. Among the 62 confirmed influenza, 7 (11.3%) were diagnosed according to PCR, 51 (82.3%) according to serology, and 4 (6.7%) according to PCR and serology. Anti-A antibodies increased between periods in asymptomatic HCW ($P < 10^{-3}$) as well as paucisymptomatic or symptomatic HCW ($P < 10^{-3}$) with confirmed influenza, as shown in Figure 2. We detailed virological findings in Supplementary Table 3. Some heterogeneity was found between sites (Supplementary Table 2).

Incidence of Asymptomatic and Symptomatic Influenza

Among HCW with influenza, 46.8% (95% CI: 34.2%–59.4%, $n = 29$) presented with asymptomatic influenza, 41.9% (95% CI: 29.5%–54.4%, $n = 26$) had paucisymptomatic influenza, and 11.3% (95% CI: 3.3%–19.3%, $n = 7$) presented with symptomatic influenza. Most (80.6%) influenza infections occurred before the T.1 consultation. Among HCW with positive influenza PCR, 8 (72.7%) were detected at T.1, 2 (18.2%) at T.s, and 3 (27.3%) at T.2. The cumulative incidence of laboratory-confirmed influenza (LCI) did not differ between vaccinated and unvaccinated HCW (20.3% vs 24.3%, respectively, $P = .38$, Table 2).

Table 3 details the proportions of HCW presenting influenza and cumulative incidences according to the main characteristics of HCW. Global cumulative influenza incidence was 22.3% (95% CI: 17.7%–27.5%). Cumulative incidence of asymptomatic influenza was 10.4% (95% CI: 6.9%–14.0%), 9.4% (95% CI: 5.9%–12.8%) for paucisymptomatic influenza, and 2.5% (95% CI: .7%–4.4%) for symptomatic influenza. Some heterogeneity was found depending on patient characteristics (Supplementary Figures 1, 2).

Characteristics Associated With the Clinical Presentation of Influenza

The most frequent symptoms among HCW with paucisymptomatic or symptomatic influenza were rhinorrhea, cough, and sneeze during the T.0–T.1 period (68%, 64%, and 56%, respectively) and rhinorrhea, cough, and headache during the T.1–T.2 period (55%, 45%, and 36%, respectively). Fever was present in <10% of all influenza cases. After univariate multinomial logistic regression, compared to the noninfluenza HCWs, the risk of asymptomatic influenza and the risk of paucisymptomatic/symptomatic influenza was not associated with sex, age category, number of children in family, or vaccinal status in 2016–2017 ($P > .10$ for all). Working in an intensive care unit (crude odds ratio [cOR] = 3.5, 95% CI: 1.3–9.4) and the presence ≥ 3 adults in a family (cOR = 3.7, 95% CI: 1.1–12.7) were associated with an increased risk of asymptomatic influenza but not with paucisymptomatic/symptomatic influenza. The professions of nurse (cOR = 5.0, 95% CI: 1.1–22.2), auxiliary nursing or other (cOR = 5.5, 95% CI: 1.2–25.7) were associated with an increased risk of paucisymptomatic/symptomatic

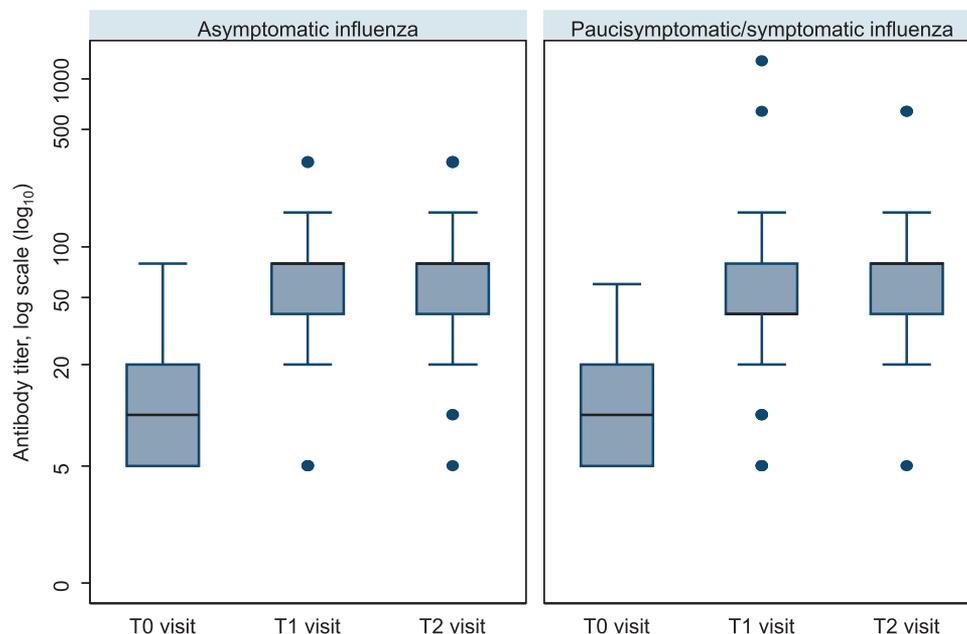


Figure 2. Influenza antibody titer by consultation in HCW with asymptomatic and paucisymptomatic/symptomatic influenza, by consultation (T.0, T.1, T.2), the Asymptomatic Flu Project (AFP) cohort, N = 278. Overall median anti-A antibody level was 1.6 log₁₀ (IQR: 1–1.9, minimum: 0.7, maximum: 3.7), it was 1.3 log₁₀ (IQR: 0.7–1.9) at the T.0 consultation, 1.6 log₁₀ (IQR: 1.0–2.2) at the T.1 consultation, and 1.6 log₁₀ (IQR: 1–2.1) at the T.2 consultation. Anti-A antibodies increased between periods in asymptomatic HCW ($P < 10^{-3}$) as well as paucisymptomatic or symptomatic HCW ($P < 10^{-3}$) with confirmed influenza. Abbreviations: HCW, healthcare worker; IQR, interquartile range.

influenza, whereas previous influenza vaccination in 2015–2016 (cOR = 0.4, 95% CI: .2–.93) was protective.

In multivariate multinomial logistic regression including adjustment on centers, working in an intensive care unit (adjusted [a]OR = 5.2, 95% CI: 1.8–15.2), and the presence of ≥ 3 adults in a family (aOR = 2.6, 95% CI: 1.1–6.6) were independently associated with an increased risk of asymptomatic influenza. The professions of nurse (aOR = 5.1, 95% CI: 1.1–24.2), auxiliary nursing or other (aOR = 6.6, 95% CI: 1.3–33.3) and working in an emergency unit or another unit (aOR = 3.1, 95% CI: 1.0–9.3) were independently associated with an increased risk of paucisymptomatic/symptomatic influenza, whereas the presence of ≥ 2 children in a family was independently associated with decreased risk (aOR = 0.3, 95% CI: .1–.9).

DISCUSSION

The main objective of this multicenter prospective study was to determine the incidence of asymptomatic, paucisymptomatic, and symptomatic influenza among HCW in short-stay

hospital wards. We found that influenza was frequent in this population because 22.3% (95% CI: 17.4%–27.2%) of HCW had a documented influenza infection during a single winter season. Most influenza infections were either asymptomatic (46.8%, 95% CI: 34.2%–59.4%) or paucisymptomatic (41.9%, 95% CI: 29.5%–54.4%). Similar to what was reported in the community during the 2016–2017 influenza epidemic, all of the influenza cases that were identified were influenza A (H3N2) [18].

These results confirm the importance of atypical clinical presentation of influenza, as previously suggested [21]. For example, in a retrospective study of 518 HCW initially included in a serological surveillance following vaccination against hepatitis, 120 subjects had recent influenza seroconversion. Among them, 71 (59%) had no memory of influenza, and 32 (28%) subjects found no notion of any respiratory infection in the previous months. The higher proportion of asymptomatic and paucisymptomatic influenza identified in our study could be explained in part by a lower rate

Table 2. Characteristics of Healthcare Workers With Confirmed Influenza, the Asymptomatic Flu Project (AFP) Cohort, N = 62

Clinical Presentation	Overall	Vaccinated HCWs	Unvaccinated HCWs
Number of HCWs with influenza	N = 62	N = 28	N = 34
Asymptomatic influenza, N (%)	29/62 (46.8)	17/28 (60.7)	12/34 (35.3)
Paucisymptomatic influenza	26/62 (41.9)	10/28 (35.7)	16/34 (47.1)
Symptomatic influenza	7/62 (11.3)	1/28 (3.6)	6/34 (17.6)

Abbreviation: HCW, healthcare worker.

Table 3. Proportion of Healthcare Workers (HCW) Presenting Influenza and Cumulative Incidence of Influenza, the Asymptomatic Flu Project (AFP) Cohort, N = 278

Characteristics	No. Influenza Cases / No. HCW (%)	Relative Distribution, per 100 HCW Presenting Influenza			Cumulative Incidence of Influenza, per 100 HCW		
		Asymptomatic	Paucisymptomatic	Symptomatic	Asymptomatic	Paucisymptomatic	Symptomatic
Overall	62/278 (22)	46.8%	41.9%	11.3%	10.4%	9.4%	2.5%
Age category							
<30 y	15/80 (19)	40.0%	46.7%	13.3%	7.5%	8.8%	2.5%
30–39 y	18/90 (20)	44.4%	33.3%	22.2%	8.9%	6.7%	4.4%
≥40 y	29/108 (27)	51.7%	44.8%	3.5%	13.9%	12.0%	0.9%
Sex							
Male	11/44 (25)	72.7%	0%	27.3%	18.2%	0%	6.8%
Female	51/234 (22)	41.2%	51.0%	7.8%	9.0%	11.1%	1.7%
No. of other adults in the household							
1	12/70 (17)	33.3%	41.7%	25.0%	5.7%	7.1%	4.3%
2	33/152 (22)	45.5%	42.4%	12.1%	9.9%	9.2%	2.6%
≥3	16/55 (29)	62.5%	37.5%	0%	18.2%	10.9%	0%
No. of children in the household							
0	37/155 (24)	43.2%	46.0%	10.8%	10.3%	11.0%	2.6%
1	11/47 (23)	45.4%	36.4%	18.2%	10.6%	8.5%	4.3%
≥2	13/75 (17)	61.5%	30.8%	7.7%	10.7%	5.3%	1.3%
Profession							
Medical doctor	8/62 (13)	75.0%	0%	25.0%	9.7%	0%	3.2%
Nurse	31/134 (23)	38.7%	54.8%	6.5%	9.0%	12.7%	1.5%
Nursing auxiliary, other	23/82 (28)	47.8%	39.1%	13.0%	13.4%	11.0%	3.7%
Type of unit							
Medicine	29/146 (20)	37.9%	44.8%	17.2%	7.5%	8.9%	3.4%
Surgery	8/30 (27)	50.0%	50.0%	0%	13.3%	13.3%	0%
Pediatrics, gynecology-obstetrics	4/33 (12)	100.0%	0%	...	12.1%	0%	...
Intensive care unit	13/40 (33)	69.2%	15.4%	15.4%	22.5%	5.0%	5.0%
Emergency, other	8/29 (28)	12.5%	87.5%	0%	3.5%	24.1%	0%
Vaccinated against influenza, 2015–2016							
No	43/160 (27)	41.9%	46.5%	11.6%	11.3%	12.5%	3.1%
Yes	19/117 (16)	57.9%	31.6%	10.5%	9.4%	5.1%	1.7%
Vaccinated against influenza, 2016–2017							
No	34/140 (24)	35.3%	47.1%	17.7%	8.6%	11.4%	4.3%
Yes	28/138 (20)	60.7%	35.7%	3.6%	12.3%	7.3%	0.7%

of classification bias owing to the prospective collection of symptoms [21]. A systematic review of 11 outbreak or epidemic investigations based on LCI found a pooled mean of asymptomatic cases of 16% (95% CI: 13%–19%) with low heterogeneity ($I^2 = 0\%$) [22]. In a community-based cohort study, the proportion of asymptomatic cases was 11%, with 32% influenza A (H3N2) [23]. The authors also found that the mean levels of influenza viral RNA shedding were similar between asymptomatic and symptomatic influenza A (H3N2) cases. These findings and ours suggest the potential risk of transmission through asymptomatic influenza cases.

In the present study, <10% of HCW with LCI had fever. In current practice, fever is often a criteria for sick leave among HCW with influenza symptoms [17], but it can be too restrictive. The

most frequent symptoms among HCW with paucisymptomatic or symptomatic confirmed influenza are rhinorrhea or cough. These clinical signs may suggest a common cold interpreted by HCW as a mild infection that does not require sick leave. Moreover, if the proportion of asymptomatic patients depends on the proportion of the immunized population, it can also be skewed by taking antipyretics or other drugs that may mask the classic influenza V on the temperature curve—sometimes the only clinical sign of infection [14]. The consequence of asymptomatic influenza presentation is a risk of cross-transmission between HCW and hospitalized patients [12] or between HCW themselves. Indeed, an asymptomatic HCW would be able to transmit the virus to both patients and colleagues. He or she can expose hospitalized patients to severe forms, which may in turn

generate secondary infections. If the HCW index case is asymptomatic, the first chain of transmission would not be identified. The first step should therefore focus on accurate diagnosis and infection control measures when an HCW presents atypical symptoms for which influenza could be the etiological agent.

The main strength of our study includes the multicenter design that increases the external validity of the results, prospective collection of clinical samples, epidemiological data, and the active follow-up implemented in each center with weekly contact of volunteers by telephone. Potential classification bias was limited by the prospective design and virological testing performed at the national reference center for influenza.

Some limitations should also be noted. First, because of the precocity of the influenza outbreak, the majority of cases were detected by serological test and only 11 by PCR. In practice, virological diagnosis is performed on a respiratory sample such as nasopharyngeal swab and not by serology testing. Another limitation is that the study was performed during a single influenza season. There may be a variation in circulating strains according to the outbreak but also to the geographical location.

CONCLUSIONS

In conclusion, asymptomatic influenza is frequent among HCW. They can be a potential source of transmission to hospitalized patients, especially frail patients and to other colleagues. Paucisymptomatic influenza represents the main burden of influenza among HCW. The classic definition of nosocomial influenza should therefore be reassessed because it does not consider atypical forms of influenza [24]. Future studies could evaluate the role of HCW or even patients with asymptomatic and paucisymptomatic influenza in the transmission/spread of influenza in healthcare settings and the efficiency of additional infection control measures to limit influenza transmission from asymptomatic HCW.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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References

- Vanhems P, Bénét T, Munier-Marion E. Nosocomial influenza: encouraging insights and future challenges. *Curr Opin Infect Dis* 2016; 29:366–72.
- Gianino MM, Politano G, Scarmozzino A, et al. Estimation of sickness absenteeism among Italian healthcare workers during seasonal influenza epidemics. *PLoS One* 2017; 12:e0182510.
- Belchior E, Bonmarin I, Bousquet V, et al. Surveillance Épidémiologique et Virologique de La Grippe En France Métropolitaine, Saison 2013–2014. 2014. Available at: http://opac.invs.sante.fr/index.php?lvl=notice_display&id=12232.
- Rolfes MA, Foppa IM, Garg S, et al. Annual estimates of the burden of seasonal influenza in the United States: a tool for strengthening influenza surveillance and preparedness. *Influenza Other Respir Viruses* 2018; 12:132–7.
- Hayward AC, Fragaszy EB, Bermingham A, et al; Flu Watch Group. Comparative community burden and severity of seasonal and pandemic influenza: results of the Flu Watch cohort study. *Lancet Respir Med* 2014; 2:445–54.
- Stott DJ, Kerr G, Carman WF. Nosocomial transmission of influenza. *Occup Med* 2002; 52:249–53.
- Barlow G, Nathwani D. Nosocomial influenza infection. *Lancet* 2000; 355:1187.
- Gerdil C. The annual production cycle for influenza vaccine. *Vaccine* 2003; 21:1776–9.
- Brankston G, Gitterman L, Hirji Z, Lemieux C, Gardam M. Transmission of influenza A in human beings. *Lancet Infect Dis* 2007; 7:257–65.
- Paules C, Subbarao K. Influenza. *Lancet* 2017; 390:697–708.
- Vanhems P, Voirin N, Roche S, et al. Risk of influenza-like illness in an acute health care setting during community influenza epidemics in 2004–2005, 2005–2006, and 2006–2007: a prospective study. *Arch Intern Med* 2011; 171:151–7.
- Eibach D, Casalegno JS, Bouscambert M, et al. Routes of transmission during a nosocomial influenza A(H3N2) outbreak among geriatric patients and healthcare workers. *J Hosp Infect* 2014; 86:188–93.
- Voirin N, Barret B, Metzger MH, Vanhems P. Hospital-acquired influenza: a synthesis using the Outbreak Reports and Intervention Studies of Nosocomial Infection (ORION) statement. *J Hosp Infect* 2009; 71:1–14.
- Evans AS, Kaslow RA. Viral infection of human. *Epidemiology and Control*. 4th ed. Plenum Publishing Corporation, 1997.
- Monto AS, Hornbuckle K, Ohmit SE. Influenza vaccine effectiveness among elderly nursing home residents: a cohort study. *Am J Epidemiol* 2001; 154:155–60.

16. Bridges CB, Kuehnert MJ, Hall CB. Transmission of influenza: implications for control in health care settings. *Clin Infect Dis* **2003**; 37:1094–101.
17. Ridgway JP, Bartlett AH, Garcia-Houchins S, et al. Influenza among afebrile and vaccinated healthcare workers. *Clin Infect Dis* **2015**; 60:1591–5.
18. Équipes de surveillance de la grippe. Surveillance de la grippe en France, saison 2016–2017. *Bull Épidémiol Hebd* **2017**; 466–75. Available at: http://beh.santepubliquefrance.fr/beh/2017/22/2017_22_1.html.
19. Penttinen P, Pebody R. Influenza case definitions - optimising sensitivity and specificity. *Euro Surveill* **2015**; 20:21148.
20. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* **2007**; 147:573–7.
21. Elder AG, O'Donnell B, McCrudden EA, Symington IS, Carman WF. Incidence and recall of influenza in a cohort of Glasgow healthcare workers during the 1993–4 epidemic: results of serum testing and questionnaire. *BMJ* **1996**; 313:1241–2.
22. Leung NH, Xu C, Ip DK, Cowling BJ. Review article: the fraction of influenza virus infections that are asymptomatic: a systematic review and meta-analysis. *Epidemiology* **2015**; 26:862–72.
23. Ip DK, Lau LL, Leung NH, et al. Viral shedding and transmission potential of asymptomatic and paucisymptomatic influenza virus infections in the community. *Clin Infect Dis* **2017**; 64:736–42.
24. Vanhems P, Landelle C, Bénet T. Toward a standardized definition of healthcare-associated influenza? *Infect Control Hosp Epidemiol* **2014**; 35:1074–5.