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Characterisation of nosocomial and community-acquired influenza in a large university hospital during two consecutive influenza seasons

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ABSTRACT

Background: Nosocomial influenza is increasingly recognized as an important public health threat causing considerable morbidity and mortality each year. However, data on nosocomial influenza is usually collected during outbreaks only and clinical information of nosocomial influenza is sparsely available.
Objectives: To systematically analyse the distribution of nosocomial and community-acquired influenza and epidemiological characteristics in a tertiary care unit in two consecutive seasons.
Study design: A retrospective observational study was conducted to identify and characterise cases of nosocomial and community-acquired influenza at Freiburg University hospital from 1 January 2013 to 30 April 2014. A validated multiplex RT-PCR to detect influenza virus and other respiratory pathogens was used throughout. Clinical information was retrieved from the hospital-based information system.
Results: Overall, 218 patients with laboratory-confirmed influenza were included (179 in the first, 39 patients in the second season). A rate of 20% of nosocomial influenza was observed throughout. A fatal outcome was recorded for 9% of nosocomial cases, which were mainly associated with influenza virus A(H1N1)pdm09. Nosocomial influenza occurred in all age groups, but fatalities were only observed in patients ≥18 years. Patients with nosocomial influenza were significantly older, underwent therapy for blood malignancies and immunosuppressive regimens more frequently, and received solid organ transplantation more often compared to community-acquired patients.
Conclusions: Despite the different distribution of virus subtypes and epidemiological properties between both influenza seasons, the rate of nosocomial cases remained similar. Systematic detection and targeted prevention measures seem mandatory to minimize nosocomial influenza.

1. Background

Nosocomial influenza is increasingly recognized as an important health threat not only in the acute-care hospital setting [1]. Outbreaks of influenza or influenza-like illness (ILI) in hospitals usually occur during the annual peak of community influenza activity. Of note, hospitalized patients are often vulnerable to infections, e.g. due to underlying medical problems or immunosuppressive therapies. Transmission of influenza within hospitals is facilitated by its short incubation time, transmission via respiratory droplets, and crowded places. The origin of nosocomial infections often remains unknown, but patients, health-care workers (HCW) and visitors are the most common sources of infection.

Knowledge on nosocomial influenza is essential to understand the burden and impact of the disease and to develop strategies for its prevention. However, in most countries there is no systematic surveillance warranting the early detection of nosocomial influenza, and studies are usually triggered by nosocomial outbreaks or the appearance of novel influenza viruses [1]. In addition, data on the clinical characteristics and baseline epidemiological data are only sparsely available for nosocomial influenza. This finding gives rise to the suspicion that a considerable proportion of cases remain undetected. Novel multiplex PCR assays facilitate the rapid detection of various respiratory pathogens including influenza virus.

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2. Objectives

In order to compare the distribution and epidemiological characteristics of nosocomial and community-acquired influenza, we systematically analysed all patients with laboratory-confirmed influenza in a large tertiary care hospital from 2013 to 2014.

3. Study design

3.1. Study population

We conducted a retrospective observational study on all patients with laboratory-confirmed influenza admitted to the Freiburg University Medical Center, from 1 January 2013 to 30 April 2014. A case-patient was defined as a person with influenza-like illness (ILI) and influenza virus detected by real-time PCR (RT-PCR). The criteria for ILI included sudden onset of symptoms, at least one of four systemic symptoms (fever, malaise, headache, myalgia), and at least one respiratory symptom (cough, sore throat, shortness of breath) [2]. Severe influenza was defined by admission of a case-patient to an intensive care unit (ICU) or in-hospital death. Influenza-associated death was defined as death due to influenza as primary or contributing cause. Nosocomial influenza was defined as a case-patient with symptom onset ≥72 h after admission to hospital and admission not related to respiratory symptoms. Testing of patients for influenza was performed upon request of the treating physician. We extracted the positive influenza results from our laboratory information system and clinical information was retrieved from the hospital-based information system. Influenza vaccination history was collected by the local public health authorities or obtained from the patient's general practitioner. Routine conventional bacteriology was not uniformly performed for all patients and is not reported in this study. Informed consent was obtained and documented by contract between patients and Freiburg University Medical Center.

3.2. Laboratory methods

Pharyngeal swabs or broncho-alveolar lavage fluids were collected from patients and processed immediately. Total nucleic acid was extracted from samples using the QIAmp MinElute Virus kit (Qiagen, Hilden, Germany) on an automated QIAcube (Qiagen) according to the recommendations of the manufacturer. Detection of respiratory pathogens was done using the FTD respiratory pathogens 21 kit (Fast track diagnostics, Junglingster, Luxemburg). The assay is able to detect influenza A and B viruses, and also enables detection on a subtype level for A(H1N1) pdm09. In addition, the assay is capable to detect coronaviruses 229E, NL63, OC43, HKU1, enterovirus/parechovirus, parainfluenza viruses 1–4, human metapneumovirus A/B, human bocavirus, rhinovirus, respiratory syncytial virus A/B, and adenovirus. Of note, all samples positive in the general influenza A assay were classified as A(H3N2) without further typing. This was based on the finding that only influenza virus A(H1N1) pdm09 and A(H3N2) had circulated in Germany from 2010 on according to national surveillance data [3]. Thermal cycling was done using an ABI 7500 machine (Applied Biosystems, Wiesbaden, Germany) as recommended. The FTD respiratory pathogens 21 kit was supplemented with three in-house real-time PCR assays for the detection of *Bordetella pertussis*, *Legionella pneumophila*, and *Chlamydia pneumonia* as described elsewhere [4].

3.3. Statistical analysis

Continuous variables (age) were analysed using Student's *t*-test and categorical variables using Fisher's exact test. Frequencies of patient characteristics, case severity, and virus subtypes were compared between the first and the second influenza season and between nosocomial and non-nosocomial influenza cases. *P*-values ≤0.05 were considered as statistically significant. Data analysis was carried our using IBM SPSS Statistics 22 software.

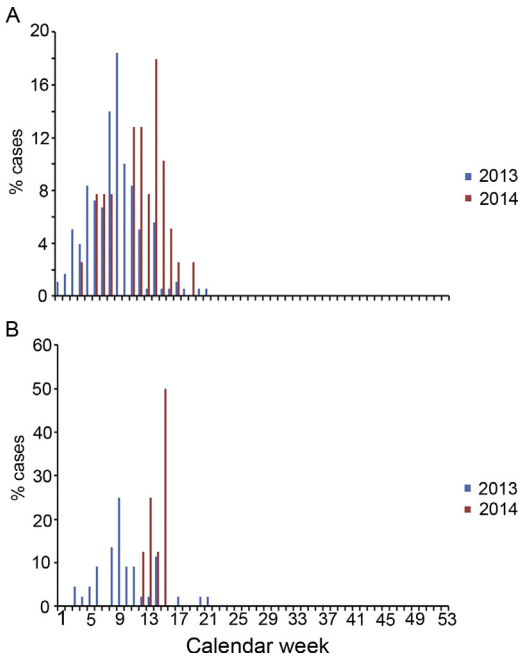

Fig. 1. Distribution of influenza cases (A) and nosocomial influenza cases (B) from January 2013 until April 2014.

4. Results

4.1. Patient characteristics

A total of 218 case-patients with laboratory-confirmed influenza were included, 179 in the influenza season 2012/13, and only 39 patients in 2013/14 (Table 1). The clinical characteristics are shown in Table 1. A total of 8/88 (9%) immunosuppressed patients were vaccinated, compared to only 3/116 (2.6%) of immunocompetent individuals (vaccination data was missing for 14 patients).

4.2. Descriptive epidemiology

In the 2012/13 season, the overall detection of influenza among admitted patients gradually increased from January 2013 on and peaked around week 9 with a steady decline (Fig. 1). In the 2013/14 season, two peaks were observed around week 9 and 14 of 2014, respectively (Fig. 1). The distribution of influenza virus subtypes in each season is shown in Table 1 and Supplemental Fig. 1. In 2013, A(H1N1) pdm09 was most frequently detected across all age groups, whereas in 2014 A(H3N2) dominated (Fig. 2).

In addition to influenza virus, another respiratory virus (i.e. the co-detection of influenza virus and another non-influenza virus in the same sample) was identified in 11/179 (6%) of patients in 2012/13 and 2/39 (5%) in 2013/14, respectively. Co-detection of non-influenza virus occurred with RSV ($n=5$), coronavirus ($n=5$), bocavirus ($n=1$), rhinovirus ($n=1$), and parainfluenza virus ($n=1$). None of the atypical bacteria included in the multiplex assays were detected among the 218 patients.

Table 1
Overview of patient characteristics (total number of patients, $n = 218$) and outcome as described in this study.

Characteristics	No. (%) patients			No. (%) patients		
	2012–2013	2013–2014	*p* Value	Nosocomial	Non-nosocomial	*p* Value
Total no. admitted patients	179	39		52	166	
Males sex	100 (55)	23 (58)	0.85	27 (52)	96 (58)	0.52
Age (y), mean	47.8	52.7	0.30	55.2	46.6	0.042[b]
ICU admission	48 (26)	8 (20)	0.54	9 (17)	47 (28)	0.14
Nosocomial influenza	44 (24)	8 (20)	0.68	na[a]	na[a]	
Died	21 (11)	2 (5)	0.38	5 (9)	18 (10)	1.0
Pneumonia	94 (52)	25 (64)	0.21	29 (55)	89 (53)	0.87
Mechanical ventilation	42 (23)	8 (20)	0.83	9 (17)	41 (24)	0.34
Immunosuppression	77 (43)	18 (46)	0.72	41 (78)	54 (32)	<0.0001
Cancer	9 (5)	2 (5)	1	2 (3)	9 (5)	1.0
Blood malignancy	31 (17)	11 (28)	0.12	23 (44)	19 (11)	<0.0001
Solid organ transplantation	31 (17)	10 (25)	0.25	21 (40)	20 (12)	<0.0001
HIV	2 (1)	0	1	1 (1)	1 (0.6)	0.42
Pregnancy	3 (1)	0	1	0 (0)	3 (1)	1.0
Diabetes	22 (12)	6 (15)	0.6	7 (13)	21 (12)	0.81
Renal impairment	41 (22)	6 (15)	0.39	15 (28)	32 (19)	0.17
Cardiovascular disease	42 (23)	13 (33)	0.22	13 (25)	42 (25)	1.0
Chronic lung disease	48 (26)	11 (28)	0.84	13 (25)	46 (27)	0.85
Influenza virus A	41 (22)	26 (66)	<0.0001	17 (32)	50 (30)	0.73
Influenza virus A(H1N1) pdm09	89 (49)	11 (28)	0.0204	22 (42)	78 (46)	0.63
Influenza virus B	49 (27)	2 (5)	0.0016	13 (25)	38 (22)	0.85
Non-severe influenza	130 (74)	31 (79)	0.43	42 (81)	121 (73)	0.27
Severe influenza	49 (26)	8 (20)	0.43	10 (19)	45 (27)	0.27

Bold numbers indicate statistically significance using Fisher's exact test unless otherwise specified.
[a] na: not applicable.
[b] Student's *t*-test.

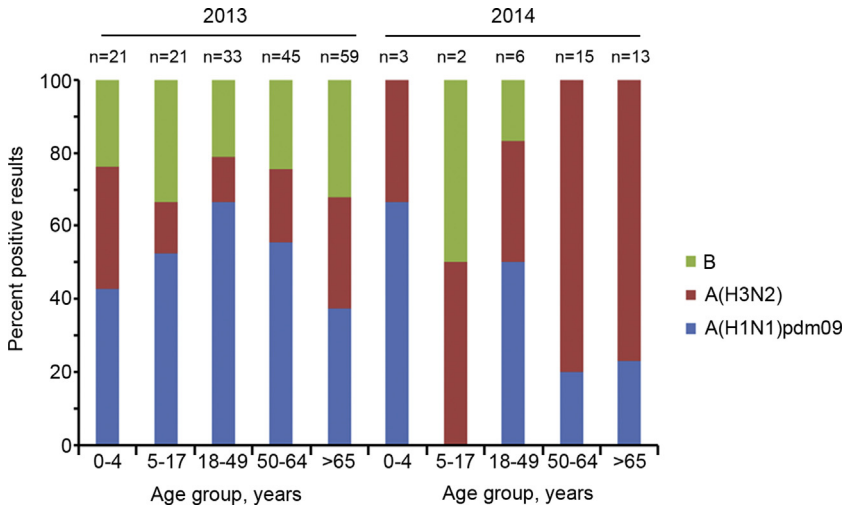

Fig. 2. Distribution of influenza subtypes across all age groups included in this study. Numbers above each column indicate number of patients.

4.3. Case severity

No difference between both seasons was observed in the severity of influenza, occurrence of pneumonia, admission to intensive care unit (ICU), or need for mechanical ventilation (Table 1).

Overall, 23/218 (11%) patients died during the study period. Influenza-associated deaths were observed only in patients ≥18 years (Fig. 3). In the first season, a total of 21 patients died and the median age of these patients was 56 years (range 24–88 years). Only one of the 21 patients who died in the first season, a 75-year-old woman, had previously received influenza vaccination. Of note, 10/21 (48%) patients received immune-suppressive therapies. The majority [20/21 (95%) cases] were admitted to the ICU and all fatal cases presented with pneumonia. None of the two patients who died in 2013/14 (60 and 65 years of age), had been vaccinated against influenza, and none received immunosuppressive regimens. Clinically, both patients presented

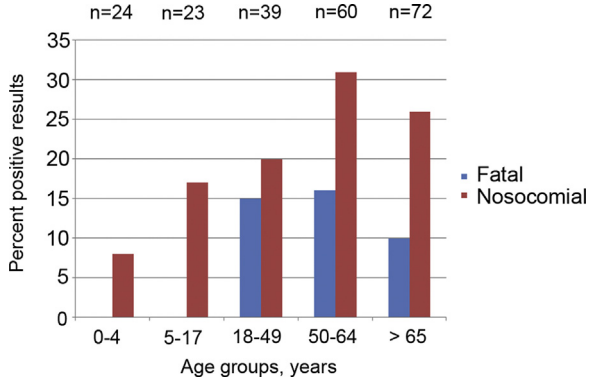

Fig. 3. Rate of fatal and nosocomial cases across all age groups included in this study. Numbers above each column indicate number of patients.

with pneumonia and were admitted to ICU due to mechanical ventilation.

The majority of fatalities were associated with influenza virus A(H1N1) pdm09 [13/23 (57%) in 2012/13 and 2/23 (9%) in 2013/14]. A total of 4/23 (17%) deaths each were associated with influenza viruses A(H3N2) and B, respectively. The distribution of subtypes in fatalities across age groups is shown in Supplemental Fig. 2.

None of the patients with co-detection of another respiratory virus died. Half of the patients with a viral co-detection were on immunosuppressive therapy [6/13 (46%)]. A total of 6/13 (46%) patients developed pneumonia and 1/13 (8%) was admitted to ICU and required mechanical ventilation. Of note, in 4/13 (31%) cases with a co-detection (three coronaviruses, one parainfluenza virus) nosocomial influenza was recorded.

4.4. Nosocomial influenza

A total of 52 nosocomial influenza cases were detected. The rate of nosocomial influenza remained stable with 24% in 2012/13 and 20% in 2013/14 (Table 1). Nosocomial cases were observed across all age groups and the rate was highest among those aged 50–64 years (Fig. 3). The distribution of influenza virus subtypes in nosocomial and non-nosocomial cases is shown in Table 1 and Supplemental Figs. 1 and 2. During the whole study period, only one cluster with 3 nosocomial cases infected with influenza virus A(H1N1) pdm09 on a single ward was observed in week 9, 2013. All other nosocomial cases were randomly scattered across different wards of the university hospital.

Patients with nosocomial influenza were older than patients with community-acquired influenza ($p = 0.042$). Frequent underlying medical problems in these patients were immunosuppressive therapies, blood malignancies, or solid organ transplantation (Fisher's exact test, $p < 0.001$) (Table 1). Severity of ILI was not different between nosocomial and community-acquired cases, and a comparable proportion of patients were admitted to ICU. Of note, a total of 5/52 (9%) patients with nosocomial influenza died. Median age of fatal cases was 64 years (range 31–75 years) and not significantly different from non-fatal cases with nosocomial influenza (median 59 years, range 0–88 years). A total of 4/5 fatal cases were under immunosuppression due to underlying haematological diseases. Influenza A(H1N1) pdm09 was detected in 4/5 and influenza virus A(H3N2) in 1/5 fatal cases. Influenza vaccination rates were comparably low in both cohorts [3/48 (6%) of nosocomial cases and 8/156 (5%) of community-acquired cases]. For only 1/5 fatal cases with nosocomial influenza, vaccination was documented; for another case, vaccination history remained unknown.

5. Discussion

In our study, we could show that, despite major differences in in the distribution of influenza subtypes and morbidity, the rate of nosocomial influenza did not change in a tertiary care hospital over two subsequent influenza seasons. The season-to-season variability of influenza is well described but only a few studies analysed nosocomial influenza over two or more seasons. Mitchell and colleagues reported a mean rate of 23% of nosocomial influenza, which is comparable to the rate found in our study [5]. In another study by the same group 17.3% of hospitalized cases were considered as hospital-acquired influenza [6]. Of note, the authors used a conservative estimate of the incubation time of ≥96 h. In the lack of a standardized definition of healthcare-associated influenza we used a shorter incubation time of ≥72 h to classify cases as hospital-acquired based on a median incubation time of 1.4 days for influenza A [7].

In Germany, the influenza season 2012/13 was rather severe according to national surveillance data, which is also reflected by the higher numbers of admitted patients. Although weekly updates on influenza are available in Germany, apparently, this had little impact on increased awareness and infection control measures. Interestingly, the only cluster of nosocomial cases, which was retrospectively identified, occurred at the peak of influenza cases in the 2012/13 season. All other nosocomial cases were scattered throughout the hospital supporting the notion of a random and irregular introduction of influenza into the hospital. In contrast, the following season was comparably less severe according to national surveillance data. However, the rate of nosocomial infections was similar and highlights the importance of strict adherence to year-round infection control guidelines irrespective of the annual influenza activity [1]. Of note, besides routine infection control measures, no additional infection control initiatives were conducted during the study period which might have confounded the results.

It should be noted that respiratory viruses other than influenza are transmitted in a similar fashion and may cause nosocomial infections. Nosocomial outbreaks of RSV are well described and associated with considerable morbidity and mortality [8]. However, viral nosocomial infections are less likely to be diagnosed and receive less attention compared to bacterial infections.

We could demonstrate co-detections in 6% of all study patients. This rate is comparable to that found in another study [4]. Importantly, this rate was also observed in the cohort of nosocomial cases. Interestingly, we did not detect the three atypical bacteria included in the multiplex PCR in our cohort. However, other bacterial co-infections, which have been commonly detected in fatal A(H1N1) pdm09 cases were not systematically analysed in our cohort [9].

From a technical point of view, it should be noted that the wide variety of laboratory methods used for the detection of influenza in the hospital setting make prior studies hardly comparable. We used the same method throughout, which was thoroughly validated [4]. Further studies are needed to determine if multiplex PCR assays are cost effective and can help minimize nosocomial outbreaks by rapid and sensitive case detection.

Overall, the number of influenza-associated deaths was highest for influenza A(H1N1) pdm09, followed by A(H3N2) and B, respectively. The high number of fatalities associated with influenza A(H1N1) pdm09 has already been described in the first post-pandemic seasons [9]. It might be speculated that immunosuppressive therapies constitute an independent risk factor for fatal outcome. Inter alia influenza vaccination is recommended in Germany for persons older than 60 years of age, for HCW, for those with underlying disease, and for those who are immunosuppressed. Vaccine failure (i.e. influenza despite previous vaccination) was observed more often in immunosuppressed patients compared to immunocompetent individuals. It must be recognized, however, that vaccine effectiveness can be lower in immunocompromised individuals compared to the healthy ones [10,11]. It is evident, that there is an overall need to improve vaccination rates in those at highest risk, and vaccination campaigns including those targeting HCW should be decidedly promoted. Critically, influenza vaccines might prove less effective due to antigenic drift as seen in the influenza season 2014/15 [12]. Thus, for the future a concept of a "universal" influenza vaccine is highly desirable [13].

Routes of infection could not be retrieved in this retrospective study. Recently, Giannella et al. demonstrated that influenza virus could be detected in a considerable proportion of patients from intensive care units in whom influenza was not suspected clinically and nosocomial influenza was reported in 66% of those patients [14]. This supports the notion that underreporting of nosocomial cases in our study seems likely since multiplex testing was initiated upon request of the physician only. Ideally, during influenza

epidemics screening of all patients irrespective of ILI would allow early case detection and proper patient management including isolation or cohorting. However, data on overall benefit for the patients and overall costs of such an approach are lacking so far. We have now implemented an online-database in cooperation between the Institute of Virology and the Department of Environmental Health Sciences to detect nosocomial cases prospectively. Results from routine multiplex testing for respiratory pathogens are submitted on a daily basis and cases with a positive multiplex PCR result are now actively investigated. Preliminary analysis of our database showed a rate of 17% of nosocomial infections in 2014/15.

Infected HCW have been shown not to refrain from work despite showing symptoms suggestive of influenza [1,15]. Intriguingly, a recent study demonstrated that afebrile and vaccinated HCW can introduce influenza into the hospital [16]. On the other hand, it is well documented that vaccination rates among HCW are insufficient to minimize the risk of nosocomial influenza in most acute care hospitals and mandatory vaccination against influenza is discussed [17]. In our study, it remains open to which extent infected health care workers or visitors were the source for nosocomial cases. However, it is well known that, during influenza epidemics, HCW serve as an important virus reservoir and can initiate nosocomial influenza outbreaks [1,18]. Unfortunately, we could not determine the vaccination status of HCW at our university hospital. Among other important issues e.g. increasing vaccination rates, it should be discussed if active surveillance including rapid detection and notification can be initiated on wards caring for patients at increased risk for nosocomial influenza. Prospective studies may elucidate the feasibility and possible benefit of this approach and are needed to confirm the findings of our and previous studies on nosocomial influenza.

6. Conclusions

To summarize, despite year-to-year variability, the rate of nosocomial influenza remained stable over two consecutive seasons in our hospital. Promotion of testing by sensitive methods not restricted to influenza seems mandatory for rapid case detection and the anticipation of epidemiological trends. Education of patients, visitors, and HCW as well as promotion of influenza vaccination may further decrease the risk of nosocomial infections.

Conflict of interest

None declared.

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Ethical approval

Informed consent was obtained and documented by contract between each patient and Freiburg University Medical Center.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jcv.2015.10.016.

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