



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Contents lists available at ScienceDirect

Diagnostic Microbiology and Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio

Virology

Dynamics of nosocomial parainfluenza virus type 3 and influenza virus infections at a large German University Hospital between 2012 and 2019

David Martin¹, Mario Hönemann^{1,*}, Uwe Gerd Liebert

Institute of Virology, Leipzig University, Johannisallee 30, Leipzig 04103, Germany

ARTICLE INFO

Article history:

Received 20 December 2019
 Revised in revised form 4 October 2020
 Accepted 11 October 2020
 Available online 17 October 2020

Keywords:

Influenza virus
 Parainfluenza virus
 Nosocomial infection
 Hospital acquired infection

ABSTRACT

Nosocomial virus infections cause significant morbidity and mortality. Besides influenza viruses, the disease burden of parainfluenza virus type 3 (PIV-3) is comparatively high among hospitalized patients and severe disease courses can occur. PIV-3 showed the highest rates of nosocomial infections of a panel of respiratory viruses. Therefore, a retrospective observational study was conducted among patients with either PIV-3 or influenza viruses, which served as reference pathogen. The aim was to compare the seasonal dynamics and clinical characteristics of nosocomial infections with these highly transmittable viruses. Nosocomial infection occurred in 15.8% ($n = 177$) of all influenza cases, mainly in the first half of a season. About 24.3% ($n = 104$) of the PIV-3 cases were nosocomial and occurred mainly in the second half of a season. Both nosocomial rates of influenza and nosocomial rates of PIV-3 varied between the seasons. Community acquired and nosocomial cases differed in underlying medical conditions and immunosuppression. Knowledge of the baseline rates of nosocomial infections could contribute to the implementation of appropriate infection control measures.

© 2020 Elsevier Inc. All rights reserved.

1. Introduction

Human parainfluenza virus type 3 (PIV-3) is a common pathogen that may cause severe respiratory symptoms particularly in young children, the elderly, and in immunosuppressed patients (Lee et al., 2011; Maeng et al., 2012; Peck et al., 2007; Shah et al., 2016; Ustun et al., 2012,). It is the most frequently detected type of the 4 human parainfluenza viruses (Villaran et al., 2014; Zhao et al., 2017) and is among the most common pathogens causing acute respiratory infections (ARI) and influenza-like illness (Henrickson, 2003; Reed et al., 1997; Russell and Ison, 2017, Jain et al., 2015a, Jain et al., 2015b). Furthermore PIV-3 is also known to cause nosocomial infection (Chow and Mermel, 2017; Godoy et al., 2016; Lee et al., 2011, Russell and Ison, 2017; Ustun et al., 2012). The disease burden and the magnitude of nosocomial infection rates across consecutive respiratory seasons, however, are poorly understood. A reason might be the underestimation of the clinical impact in comparison to influenza viruses. Influenza is a seasonal disease that is caused by influenza virus A(H3N2), influenza virus A(H1N1)pdm09, and influenza B viruses (Petrova and Russell, 2018). For both PIV-3 and influenza virus, the severity of infections varies and the spectrum of symptoms can range from asymptomatic to severe pneumonia (Henrickson, 2003; Paweczyk and Kowalski, 2017; Russell and Ison, 2017). Besides community-acquired infections, nosocomial influenza is

increasingly deemed an important health risk and recognized as causing significant morbidity and mortality. All influenza types are known to cause nosocomial outbreaks and recent studies found nosocomial rates of 4.3% to 35.5% in hospitals across Germany, Spain, Canada, USA, and Australia (Álvarez-Lerma et al., 2017; Hagel et al., 2016; Heyd et al., 2017; Hönemann et al., 2019; Huzly et al., 2015; Macesic et al., 2013; Ostovar et al., 2012; Taylor et al., 2014,). Most studies, however, focus on a single season, warranting further research on long-term nosocomial infection rates.

The objective of this study was to determine the rate, epidemiological data, clinical characteristics, and outcomes of both nosocomial PIV-3 and influenza virus infections in patients at UKL (Saxony, Germany) during 7 consecutive seasons. The aim was to compare the characteristics of nosocomial and of community-acquired infections between PIV-3 and influenza viruses and in seasons with a different burden of infection. Influenza virus was chosen as reference pathogen for the assessment the clinical impact caused by PIV-3.

2. Methods

2.1. Specimen

A total of 33,854 respiratory samples, including nasal aspirates, nasal and pharyngeal swabs, throat rinsing fluid, tracheal secretions, and broncho-alveolar lavage fluids of 18,722 patients were tested

* Corresponding author. Tel.: +49-34-1971-4350. Fax: +49-34-1971-4309.

E-mail address: Mario.Hoenemann@medizin.uni-leipzig.de (M. Hönemann).

¹ These authors contributed equally to this work.

for respiratory virus infections. Testing was initiated at the discretion of the treating physician.

2.2. Respiratory virus detection

Samples were tested on the commercially available Magpix multiplex platform for respiratory viruses (NxTAG RPP, Luminex corporation; Austin, TX) according to the manufacturer's instructions. The panel included influenza viruses (A(H1N1)pdm09, A(H3N2) and influenza B), respiratory syncytial virus A and B, parainfluenza viruses 1 to 4, endemic coronaviruses (229E, NL63, OC43, and HKU1), metapneumovirus, adenovirus, and bocavirus.

2.3. Study site

UKL is a tertiary care hospital with 1450 beds with 54,000 patients on average per year. All in-patients with a positive test result for PIV-3 or influenza virus (A(H1N1)pdm09, A(H3N2) and influenza B) for 7 consecutive seasons from October 2012 to September 2019 were included in the study. A season was defined as starting on the October 1 of a year and ending September 30 of the next year.

Medical records were reviewed of patients with confirmed PIV-3 or influenza virus infection. If a patient was hospitalized several times independently, each stay was included as a separate case. Patients' medical histories were assessed for co-morbidities. Co-morbidities that were looked for are any history of malignant neoplasia (further divided into blood malignancy and solid cancer), chronic renal failure, chronic heart failure, asthma, chronic obstructive pulmonary disease, obesity, and immunosuppression. Patients with any of the following were considered immunocompromised: receiving active chemotherapy for cancer, severe chronic neutropenia, receiving steroids, or other immunomodulatory medications over a prolonged period, aplasia of the thymus gland, or reported HIV infection.

2.4. Definition of nosocomial infection

An infection was classified as nosocomial when respiratory symptoms were not present on admission and the beginning of ARI symptoms (fever >38 °C or self-reported, new onset of cough, new onset of dyspnoea) occurred at least 72 hours after admission, or readmission with symptoms of ARI within 48 hours after discharge from UKL.

2.5. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp; Armonk, NY). Continuous values were expressed as median (interquartile range) and categorical data as frequencies (percentages). χ^2 test and Mann-Whitney *U* test were performed as appropriate. A *P* level of <0.05 was considered significant.

3. Results

3.1. Respiratory virus detection and rates of nosocomial infections

Absolute numbers of respiratory virus detections and the nosocomial infection rate is presented in Table 1. PIV-3 showed the highest rate for nosocomial infections of all analysed viral pathogens, followed by the 3 influenza types B, A(H3N2), and A(H1N1)pdm09, respectively. Therefore, a further analysis was focused on PIV-3 in relation to influenza virus infections.

3.2. Seasonality of PIV-3 and influenza viruses

During the study period, 428 patients were tested positive for PIV-3 and 1117 for any influenza virus (344 for influenza A(H1N1)pdm09, 445 for influenza A(H3N2), and 333 for influenza B). Influenza virus infections showed a strong seasonality with peak of infections occurring in February or March (Fig. 1). The peak of influenza virus infection for age group 0-4 was observed before the peak of the age group 50+ consistently during all seasons studied. PIV-3 infections did not show a consistent seasonality and were detected throughout the study period (Fig. 2). For season 2012-2013, 2013-2014, and 2017-2018 the maximum of cases occurred in April, whereas it was December for season 2016-2017. Seasons 2014-2015, 2015-2016, and 2018-2019 did not show a marked case maximum.

3.3. Nosocomial PIV-3 and influenza virus infections

One hundred four nosocomial PIV-3 and 177 nosocomial influenza virus infections were identified, translating into a rate of nosocomial infection of 24.3% for PIV-3 and 15.8% for all influenza virus types (11.6% for A(H1N1)pdm09, 19.7% for A(H3N2), and 22.8% for influenza B). For PIV-3, there was no significant difference in the number of infections per season or in the rates of nosocomial infection per season (Table 1). Four small-scale outbreaks were seen in May 2013, September 2014, February 2015, and April 2018. There

Table 1
Rates of nosocomial infection per season.

Pathogen	Season							Total
	2012-2013	2013-2014	2014-2015	2015-2016	2016-2017	2017-2018	2018-2019	
PIV-3	21/72 (29.2)	12/49 (24.5)	13/40 (32.5)	10/55 (18.2)	18/93 (19.4)	20/46 (43.5)	10/73 (13.7)	104/428 (24.3)
Influenza B	4/45 (8.9)	0/1	1/17 (5.9)	3/56 (5.4)	3/10 (30)	65/203 (32.0)	0/1	76/333 (22.8)
A(H3N2)	3/49 (6.1)	0/9	13/74 (17.6)	1/7 (14.3)	37/172 (21.5)	1/13 (7.7)	33/122 (27.0)	88/446 (19.7)
A(H1N1) ^a	9/68 (13.2)	0/5	6/37 (16.2)	8/88 (9.1)	1/4 (25)	4/43 (9.3)	12/99 (12.1)	40/344 (11.6)
RSV	53/228 (23.2)	7/123 (5.7)	19/185 (10.3)	4/158 (2.5)	14/213 (6.6)	18/159 (11.3)	19/161 (11.8)	134/1227 (10.9)
PIV-1	0/8	4/24 (16.7)	1/9 (11.1)	2/15 (13.3)	0/11	4/30 (13.3)	0/4	11/101 (10.9)
PIV-2	0/2	0/3	3/19 (15.8)	1/2 (50.0)	0/14	0/2	2/13 (15.4)	6/55 (10.9)
Coronavirus ^b	7/71 (9.9)	3/40 (7.5)	3/49 (6.1)	7/68 (10.3)	16/109 (14.7)	8/69 (11.6)	10/92 (10.9)	54/498 (10.8)
PIV-4	3/13 (23.1)	0/7	1/14 (7.1)	0/16	2/13 (15.4)	1/12 (8.3)	2/10 (20)	9/85 (10.6)
MPV	5/35 (14.3)	5/67 (7.5)	0/24	10/90 (11.1)	1/42 (2.4)	11/78 (14.1)	2/36 (5.6)	34/372 (9.1)
Bocavirus	1/27 (3.7)	1/39 (2.6)	6/50 (12)	3/68 (4.4)	5/54 (9.3)	2/61 (3.3)	5/62 (8.1)	23/361 (6.4)
Adenovirus	1/59 (1.7)	2/81 (2.5)	4/62 (6.5)	5/97 (5.2)	4/71 (5.6)	6/65 (9.2)	2/43 (4.7)	24/478 (5.0)

PIV = parainfluenza virus; RSV = respiratory syncytial virus A and B; MPV = metapneumovirus.

All rates are given in [n/N (%)] with n/N being the number of nosocomial cases/total cases of that virus in the respective season.

^a A(H1N1) corresponds to A(H1N1)pdm09.

^b Coronavirus includes the endemic coronaviruses 229E, NL63, OC43, and HKU1.

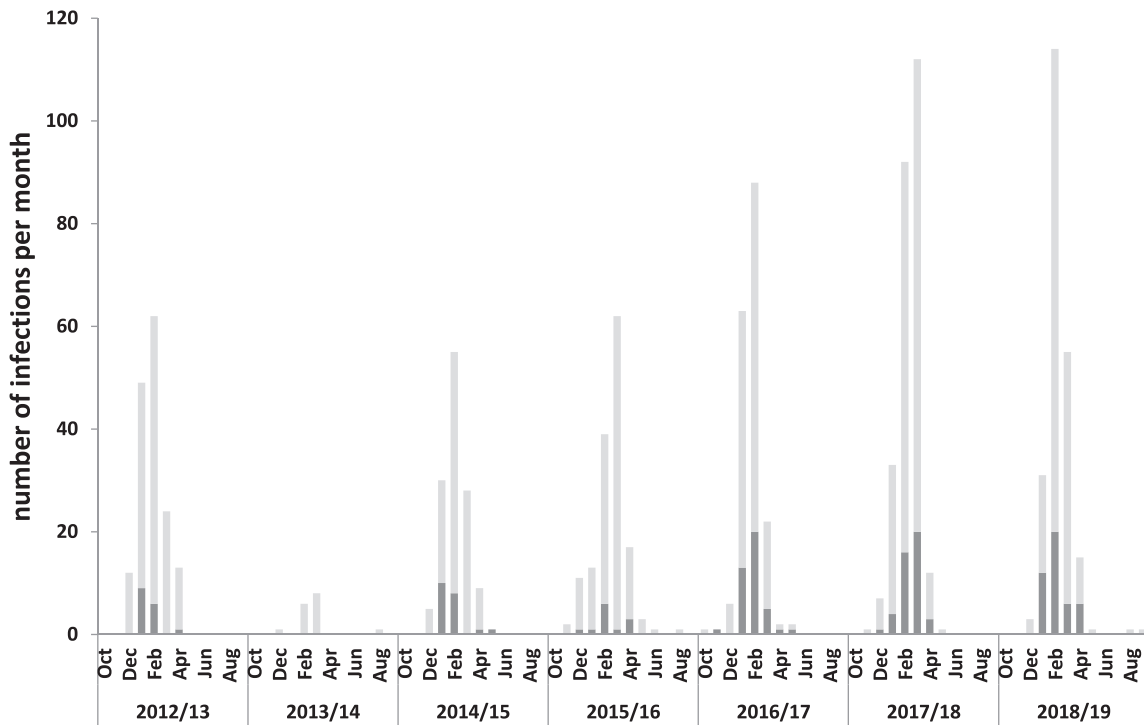


Fig. 1. Number of nosocomial and community-acquired influenza infections per month for the indicated seasons. Community-acquired infections are represented by the light grey part of the bars and nosocomial infections in the dark grey part. Each bar represents 1 calendar month.

was no clear temporal connection between the peaks of nosocomial and community acquired infections. However, the rate and the total number of nosocomial infections tended to be higher in the second half of a predefined season (Table 2). Rates of nosocomial influenza virus infections significantly differed, ranging between 0% and 22.2% per season ($P=0.001$). Most cases of nosocomial infection

occurred during peaks of total infections. In contrast to PIV-3, the rate and the total number of nosocomial infections tended to be higher in the first half of most seasons. Additionally, only for influenza A(H3N2) a positive correlation between the amount of community-acquired and the amount of nosocomial infections could be observed.

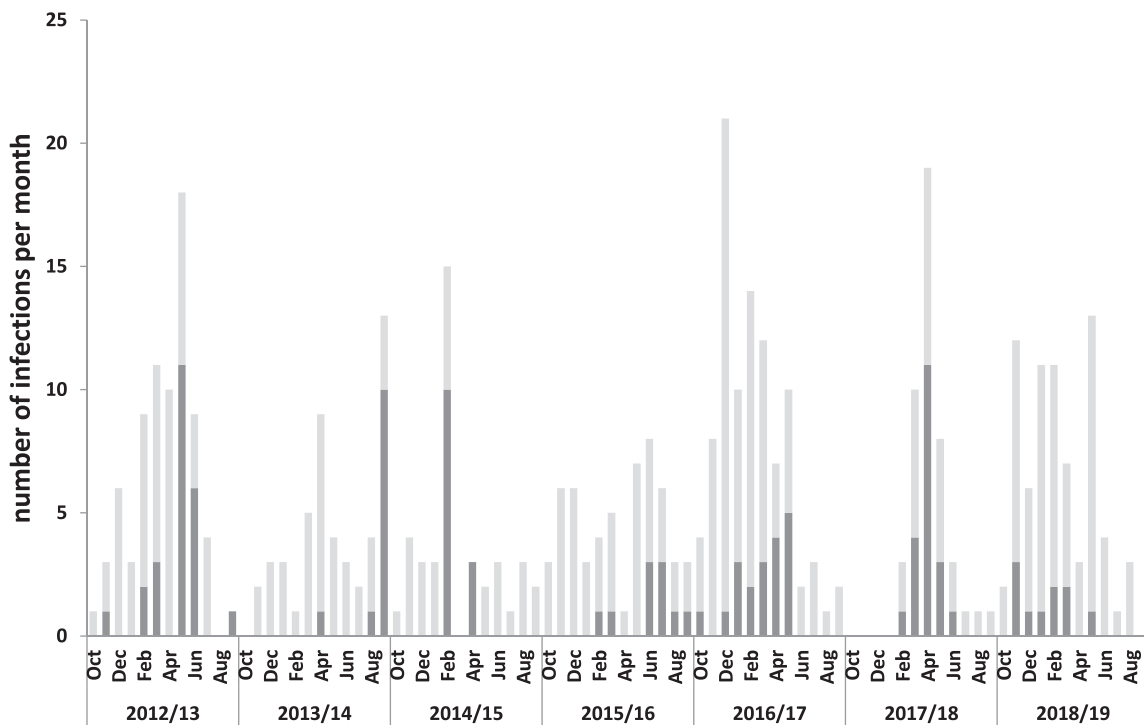


Fig. 2. Number of nosocomial and community-acquired PIV-3 infections per month for the indicated seasons. Community-acquired infections are represented by the light grey part of the bars and nosocomial infections in the dark grey part. Each bar represents 1 calendar month. PIV-3 = parainfluenza virus type 3.

Table 2
Absolute number and rate of nosocomial infection in different periods of a season.

Season	Parainfluenzavirus type 3				Influenza virus (all types)			
	First period ^a		Second period		First period		Second period	
	n/N ^b (%)	rate ^c [%]	n/N (%)	rate [%]	n/N (%)	rate [%]	n/N (%)	rate [%]
2012/13	6/21 (29)	16.7	15/21 (71)	41.7	12/16 (75)	15	4/16 (25)	5
2013/14	1/12 (8)	4.1	11/12 (92)	44.9	0/0	-	0/0	-
2014/15	5/13 (39)	25	9/13 (62)	40	12/20 (60)	18.8	8/20 (40)	12.5
2015/16	2/10 (20)	7.3	8/10 (80)	29.1	9/12 (75)	12.1	3/12 (25)	4
2016/17	5/18 (28)	10.8	13/18 (72)	28	20/41 (49)	21.6	21/41 (51)	22.7
2017/18	11/20 (55)	47.8	9/20 (45)	39.1	20/44 (45)	15.5	24/44 (55)	18.6
2018/19	6/10 (60)	16.7	4/10 (40)	11.1	26/44 (59)	23.6	18/44 (41)	16.3
Total	36/104 (35)	16.8	69/104 (66)	32.2	99/177 (56)	17.7	78/177 (44)	14

^a The first fifty percent of all cases in a season were included into the first period of a season; the second fifty percent were included into the second period of a season.

^b n/N = number of nosocomial cases in the respective period/total number of nosocomial cases of that virus in the respective season.

^c Nosocomial infection rate for the respective period.

3.4. Clinical features

Differences were noted for the symptoms of patients with community-acquired infections. Patients with influenza suffered more frequently from fever while PIV-3 cases presented more often with dyspnoea. Differences between nosocomial and community-acquired infections were mainly identified in the frequency of underlying health conditions (Tables 3A and 3B). Patients with nosocomial infections were older and had higher rates of malignancies, immunosuppression, in the influenza group also higher rates of chronic heart failure, and chronic kidney disease. Reported neuraminidase inhibitor treatment was higher in cases with nosocomial influenza virus infection. Between nosocomial PIV-3 and influenza virus infections, there were no significant differences in severe outcome parameters, i.e., development of acute respiratory distress syndrome, admission the ICU, or death. When compared to nosocomial influenza virus infections, nosocomial PIV-3 cases had a lower median age ($P < 0.001$), a lower rate of chronic obstructive pulmonary disease ($P = 0.042$), chronic heart failure ($P = 0.001$), and chronic kidney disease ($P = 0.001$), longer hospital stays ($P < 0.001$), a higher rate of

haematological malignancies ($P < 0.001$), and a higher rate of immunosuppression ($P < 0.001$).

4. Discussion

Both a high total number of PIV-3 infections - surpassing that of influenza A(H1N1)pdm09 and influenza B - as well as a rate of PIV-3 nosocomial infection higher than that of influenza virus and other respiratory viruses were observed. While the clinical presentations of PIV-3 infections tend to be milder than those with influenza virus, severe infections like pneumonia and bronchiolitis can occur (Henrickson, 2003; Pawełczyk and Kowalski, 2017; Russell and Ison, 2017).

The study period included seasons with high (seasons 2012-2013, 2014-2015, 2016-2017, 2017-2018, and 2018-2019) and low (season 2013-2014) prevalence of viral respiratory infections, according to the data for Germany compiled by the national influenza surveillance network (RKI, 2020). While for PIV-3 the total number of cases as well as the rates of nosocomial infection was equally distributed throughout the entire study period, the analysis of

Table 3A
Comparison of nosocomial and community-acquired PIV-3.

		Hospital-acquired n = 104 (24.3%)	Community-acquired n = 324 (75.7%)	P value
Study population				
Age [years]	[median (IQR)]	58 (29.25-64.75)	3 (1-61)	<0.0005
Female gender	[%(n/total)]	41.3 (43/104)	42.6 (138/324)	0.823
Comorbidities/risk factors				
History of malignant neoplasia	[%(n/total)]	75.0 (78/104)	19.8 (64/324)	<0.0005
Blood malignancy	[%(n/total)]	69.2 (72/104)	14.2 (46/324)	<0.0005
Solid cancer	[%(n/total)]	14.4 (15/104)	7.4 (24/324)	0.031
Immunosuppression	[%(n/total)]	73.1 (76/104)	20.1 (65/324)	<0.0005
Chronic renal failure	[%(n/total)]	22.1 (23/104)	15.4 (50/324)	0.115
Cardiac insufficiency	[%(n/total)]	11.5 (12/104)	14.2 (46/324)	0.491
Asthma	[%(n/total)]	2.9 (3/104)	6.8 (22/324)	0.140
COPD	[%(n/total)]	3.8 (4/104)	14.5 (47/324)	0.004
Obesity (BMI >30 kg/m ²)	[%(n/total)]	19.4 (13/67)	6.2 (14/227)	0.001
Clinical presentation and features				
Leucocytes on admission [exp 9/l]	[median (IQR)]	6.8 (4.2-9.3)	10.3 (6.9-14.3)	<0.0005
Length of hospitalization [days]	[median (IQR)]	36.5 (22-68.75)	7 (4-12.75)	<0.0005
Admission to ICU	[%(n/total)]	27.9 (29/104)	21.9 (71/324)	0.211
Length of stay in ICU [days]	[median (IQR)]	28 (5-70)	5 (3-12.5)	0.001
Acute respiratory distress syndrome	[%(n/total)]	1.0 (1/104)	1.9 (6/324)	0.533
Ventilation	[%(n/total)]	18.4 (19/103)	10.2 (33/324)	0.026
Invasive	[%(n/total)]	15.5 (16/103)	8.3 (27/324)	0.034
Noninvasive	[%(n/total)]	2.9 (3/103)	1.9 (6/324)	0.514
Viral co-infection	[%(n/total)]	23.1 (24/104)	31.2 (101/324)	0.114
Death (<30 days after discharge)	[%(n/total)]	8.7 (9/104)	4.6 (15/324)	0.121

COPD = chronic obstructive pulmonary disease; PIV-3 = parainfluenza virus type 3. Analyzed categories are displayed on the column to the left and either given as frequencies [%] or median and interquartile range [median(IQR)]. (n/total) indicates the respective cases of the total amount of available data. A comparison was done for the whole study period and a P value <0.05 was considered significant (highlighted in bold).

Table 3B
Comparison of nosocomial and community-acquired influenza (all types).

		Hospital-acquired n = 177 (15.8%)	Community-acquired n = 940 (84.2%)	P value
Study population				
Age [years]	[median (IQR)]	65 (54-75)	50.5 (5-71)	<0.0005
Female gender	[%(n/total)]	48.6 (86/177)	41.4 (389/940)	0.075
Comorbidities/risk factors				
History of malignant neoplasia	[%(n/total)]	48.0 (85/177)	16.6 (156/940)	<0.0005
Blood malignancy	[%(n/total)]	26.6 (47/177)	8.5 (80/940)	<0.0005
Solid cancer	[%(n/total)]	23.7 (42/177)	9.0 (85/940)	<0.0005
Immunosuppression	[%(n/total)]	39.0 (69/177)	14.0 (131/939)	<0.0005
Chronic renal failure	[%(n/total)]	42.4 (75/177)	26.2 (246/940)	<0.0005
Cardiac insufficiency	[%(n/total)]	28.2 (50/177)	20.1 (189/940)	0.015
Asthma	[%(n/total)]	4.5 (8/177)	6.9 (65/940)	0.237
COPD	[%(n/total)]	10.7 (19/177)	19.0 (179/940)	0.008
Obesity (BMI >30 kg/m ²)	[%(n/total)]	24.7 (20/81)	13.1 (59/449)	0.007
Clinical presentation and features				
Leucocytes on admission [exp 9/l]	[median (IQR)]	7.9 (5.4-11.3)	8.2 (5.6-12.3)	0.481
Length of hospitalization [days]	[median (IQR)]	22 (11-36)	7 (4-13)	<0.0005
Admission to ICU	[%(n/total)]	35.0 (62/177)	32.6 (306/940)	0.520
Length of stay in ICU [days]	[median (IQR)]	3 (2-11.5)	7 (3-22)	0.111
Acute respiratory distress syndrome	[%(n/total)]	2.8 (5/177)	9.6 (90/940)	0.003
Ventilation	[%(n/total)]	15.8 (28/177)	22.0 (207/940)	0.063
Invasive	[%(n/total)]	14.1 (25/177)	17.4 (164/940)	0.279
Noninvasive	[%(n/total)]	1.7 (3/177)	4.6 (43/940)	0.077
Use of neuraminidase inhibitors	[%(n/total)]	14.7 (26/177)	7.7 (72/939)	0.002
Viral co-infection	[%(n/total)]	14.1 (25/177)	18.4 (173/940)	0.171
Death (<30 days after discharge)	[%(n/total)]	12.4 (22/177)	9.9 (93/940)	0.309

COPD = chronic obstructive pulmonary disease.

Analyzed categories are displayed on the column to the left and either given as frequencies [%] or median and interquartile range [median(IQR)]. (n/total) indicates the respective cases of the total amount of available data. A comparison was done for the whole study period and a P value <0.05 was considered significant (highlighted in bold).

influenza allowed the comparison of the rates of nosocomial infections in seasons with high and low influenza virus prevalence. The findings are consistent with recent studies assessing nosocomial transmission of influenza virus with reported rates from 4.3% to 35.5%. (Álvarez-Lerma et al., 2017; Hagel et al., 2016; Heyd et al., 2017; Hönemann et al., 2019; Huzly et al., 2015; Macesic et al., 2013; Taylor et al., 2014,).

Furthermore, the findings demonstrate that nosocomial infections with both PIV-3 and influenza viruses occur more often in the context of certain pre-existing medical conditions, such as malignancies, immunosuppression, and obesity. For influenza, it was additionally chronic renal insufficiency and heart failure, while this was not observed in the PIV-3 group. The patient population in a hospital thus profoundly impacts the type and the amount of nosocomial infections that are detected. The higher rates of malignancies and immunosuppression are consistent with previous studies highlighting the susceptibility of immunocompromised patients for ARI (Abbas et al., 2017; Chemaly et al., 2012, Chemaly et al., 2014; Shah et al., 2012; Shah et al., 2016), while the higher rates of chronic renal insufficiency and heart failure observed in the group of nosocomial influenza might be due to higher age.

For PIV-3, there are several possible explanations for the differences between nosocomial and community-acquired infections regarding underlying malignancy and immunosuppression. While prolonged hospital stay in the former group might lead to more nosocomial infections due to a higher probability of exposure to the pathogen, this finding could be a result of a testing bias. Besides children, haematological and oncological patients are susceptible to severe disease courses of ARI and PIV-3 infection. A higher awareness of the severe outcomes such as pneumonia and ARDS thus may have led to more liberal testing for viral infections, whereas mild respiratory symptoms were tolerated in other hospitalized patients without further diagnostics. Thus, it is possible that the disease burden of PIV-3 in hospital settings is underestimated and that PIV-3 infection in hospitals is more common, but mainly in the form of an asymptomatic or mild infection. This might also explain the detection of nosocomial infections later

in a season. In contrast, through increasing awareness of flu disease and improved isolation workflows within an ongoing season nosocomial influenza virus infections tend to decrease towards the end of a season

The hospital stay was longer for patients with hospital acquired infection, indicating an increased risk for nosocomial infection or a protracted stay in hospital due to the infection (Beyersmann et al., 2009; Manoukian et al., 2018, Wolkewitz et al., 2017). However, a case control group would be needed to better assess the influence of length of hospital stay on the probability of nosocomial infection.

There were several limitations in this study. The chosen timeframe for nosocomial infection with onset of symptoms >72 hours after admission might be too narrow for PIV-3. Although there is only limited data, the median incubation period is estimated to be 2.6 days (Lessler et al., 2009). Approximately 97.1 % of the nosocomial PIV-3 patients in this study had an onset of symptoms after 5.2 days, more than 2 times the estimated incubation period. This suggests the chosen timeframe to be a robust cut-off for the study of nosocomial PIV-3 virus infections.

Additionally, the clinical outcomes might be biased towards a higher severity in the community-acquired influenza group due to UKL being a reference centre for ARDS. Ninety out of 95 cases of ARDS in influenza are classified as community-acquired. Sixty-six of them were referred from outside hospitals relying on UKL expertise in treating these severely ill patients. Thus, the data set might not be representative in the comparison of outcome parameters between the 2 patient groups. If these transferred patients are excluded, there is no longer a difference in the occurrence of ARDS (2.3% for nosocomial influenza vs. 2.9% for community-acquired influenza).

5. Conclusion

In conclusion, nosocomial infections account for a substantial proportion of infections with PIV-3 and influenza in a hospital setting with immunocompromised or chronically ill patients. Intensified

infection control management that addresses the culture of “working while sick” among health care workers (Danzmann et al., 2013; Huttunen and Syrjänen, 2014; Szymczak et al., 2015,) and increased influenza vaccination rates might be able to lower the rates of nosocomial infections (Ahmed et al., 2014; Bénet et al., 2012; Huttunen and Syrjänen, 2014). For PIV-3 however, neither a vaccination nor specific antiviral agents are available. Due to the various sources of nosocomial infections—visitors, patients, and health care workers—it is not possible to prevent all nosocomial infections. Therefore, the assessment of baseline rates for nosocomial infections facilitates the re-evaluation of hygiene measures should nosocomial infections start to increase.

Declaration of competing interest

The authors report no conflicts of interest relevant to this article.

Authors' contributions

UGL: Study design; DM, MH: Data collection, DM, MH: Data analysis; DM, MH, UGL: Data interpretation; DM, MH, UGL: Writing.

References

- RKI (Arbeitsgemeinschaft Influenza): Saisonberichte. : Robert Koch-Institut; 2020. Available <https://influenza.rki.de/Saisonbericht.aspx>.
- Abbas S, Raybould JE, Sastry S, De la Cruz O. Respiratory viruses in transplant recipients: more than just a cold. Clinical syndromes and infection prevention principles. *Int J Infect Dis* 2017;62:86–93.
- Ahmed F, Lindley MC, Allred N, Weinbaum CM, Grohskopf L. Effect of influenza vaccination of healthcare personnel on morbidity and mortality among patients: systematic review and grading of evidence. *Clin Infect Dis* 2014;58:50–7.
- Álvarez-Lerma F, Marín-Corral J, Vilà C, Masclans JC, Loeches IM, Barbadillo S, et al. Characteristics of patients with hospital-acquired influenza A (H1N1)pdm09 virus admitted to the intensive care unit. *J Hosp Infect* 2017;95:200–6.
- Bénet T, Régis C, Voirin N, Rober O, Lina B, Cronenberg S, et al. Influenza vaccination of healthcare workers in acute-care hospitals: a case-control study of its effect on hospital-acquired influenza among patients. *BMC Infect Dis* 2012;12:30.
- Beyersmann J, Kneib T, Schumacher M, Gastmeier P. Nosocomial infection, length of stay, and time-dependent bias. *Infect Control Hosp Epidemiol* 2009;30(3):273–6.
- Chemaly RF, Hanmod SS, Rathod DB, Ghantaji SS, Jiang Y, Doshi A, et al. The characteristics and outcomes of parainfluenza virus infections in 200 patients with leukemia or recipients of hematopoietic stem cell transplantation. *Blood* 2012;119:2738–45 quiz 2969.
- Chemaly RF, Shah DP, Boeckh MJ. Management of respiratory viral infections in hematopoietic cell transplant recipients and patients with hematologic malignancies. *Clin Infect Dis* 2014;59(Suppl 5):S344–51.
- Chow EJ, Mermel LA. Hospital-acquired respiratory viral infections: incidence, morbidity, and mortality in pediatric and adult patients. *Open Forum Infect Dis* 2017;4:ofx006.
- Danzmann L, Gastmeier P, Schwab F, Vonberg RP. Health care workers causing large nosocomial outbreaks: a systematic review. *BMC Infect Dis* 2013;13:98.
- Godoy C, Peremiquel-Trillas P, Andrés C, Gimferrer L, Uriona S, Codina MG, et al. A molecular epidemiological study of human parainfluenza virus type 3 at a tertiary university hospital during 2013–2015 in Catalonia, Spain. *Diagn Microbiol Infect Dis* 2016;86:153–9.
- Hägel S, Ludewig K, Moeser A, Baier M, Löffler B, Schlenvoigt B, et al. Characteristics and management of patients with influenza in a German hospital during the 2014/2015 influenza season. *Infection* 2016;44:667–72.
- Henrickson KJ. Parainfluenza viruses. *Clin Microbiol Rev* 2003;16:242–64.
- Heyd R, Eis-Hübinger AM, Berger A, Bierbaum S, Pietzonka S, Wenzel JJ, et al. Retrospective analysis of clinical and virological parameters of influenza cases at four university hospitals in Germany, 2015. *Infection* 2017;45:349–54.
- Hönemann M, Martin D, Pietsch C, Maier M, Bergs S, Bieck E, Liebert UG. Influenza B virus infections in Western Saxony, Germany in three consecutive seasons between 2015 and 2018: Analysis of molecular and clinical features. *Vaccine* 2019;37(43):6550–7.
- Huttunen R, Syrjänen J. Healthcare workers as vectors of infectious diseases. *Eur J Clin Microbiol Infect Dis* 2014;33:1477–88.
- Huzly D, Kurz S, Ebner W, Dettenkofer M, Panning M. Characterisation of nosocomial and community-acquired influenza in a large university hospital during two consecutive influenza seasons. *J Clin Virol* 2015;73:47–51.
- Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Bramley AM, et al. Community-acquired pneumonia requiring hospitalization among U.S. adults. *N Engl J Med* 2015a;373:415–27.
- Jain S, Williams DJ, Arnold SR, Ampofo K, Bramley AM, Reed C, et al. Community-acquired pneumonia requiring hospitalization among U.S. children. *N Engl J Med* 2015b;372:835–45.
- Lee AV, Bibby DF, Oakervee H, Rohatiner A, Ishiro-Lumb I, Clark DA, et al. Nosocomial transmission of parainfluenza 3 virus in hematological patients characterized by molecular epidemiology. *Transpl Infect Dis* 2011;13:433–7.
- Lessler J, Reich NG, Brookmeyer R, Perl TM, Nelson KE, Cummings DAT. Incubation periods of acute respiratory viral infections: a systematic review. *Lancet Infect Dis* 2009;9:291–300.
- Macesic N, Kotsimbos TC, Kelly P, Cheng AC. Hospital-acquired influenza in an Australian sentinel surveillance system. *Med J Aust* 2013;198:370–2.
- Maeng SH, Yoo HS, Choi S-H, Yoo KH, Kim Y-J, Sung KW, et al. Impact of parainfluenza virus infection in pediatric cancer patients. *Pediatr Blood Cancer* 2012;59:708–10.
- Manoukian S, Stewart S, Dancer S, Graves N, Mason H, McFarland A, et al. Estimating excess length of stay due to healthcare-associated infections: a systematic review and meta-analysis of statistical methodology. *J Hosp Infect* 2018;100:222–35.
- Ostovar GA, Kohn N, Yu KOA, Nullet S. Nosocomial influenza in a pediatric hospital: comparison of rates of seasonal and pandemic 2009 influenza A/H1N1 infection. *Infect Control Hosp Epidemiol* 2012;33:292–4.
- Pawelczyk M, Kowalski ML. The role of human parainfluenza virus infections in the immunopathology of the respiratory tract. *Curr Allergy Asthma Rep* 2017;17:16.
- Peck AJ, Englund JA, Kuypers J, Guthrie KA, Corey L, Morrow R, et al. Respiratory virus infection among hematopoietic cell transplant recipients: evidence for asymptomatic parainfluenza virus infection. *Blood* 2007;110:1681–8.
- Petrova VN, Russell CA. The evolution of seasonal influenza viruses. *Nat Rev Microbiol* 2018;16:47–60.
- Reed G, Jewett PH, Thompson J, Tollefson S, Wright PF. Epidemiology and clinical impact of parainfluenza virus infections in otherwise healthy infants and young children < 5 years old. *J Infect Dis* 1997;175:807–13.
- Russell E, Ison MG. Parainfluenza virus in the hospitalized adult. *Clin Infect Dis* 2017;65(9):1570–6.
- Shah DP, Ghantaji SS, Mulanovich VE, Ariza-Heredia EJ, Chemaly RF. Management of respiratory viral infections in hematopoietic cell transplant recipients. *Am J Blood Res* 2012;2:203–18.
- Shah DP, Shah PK, Azzi JM, Chemaly RF. Parainfluenza virus infections in hematopoietic cell transplant recipients and hematologic malignancy patients: a systematic review. *Cancer Lett* 2016;370:358–64.
- Szymczak JE, Smathers S, Hoegg C, Klieger S, Coffin SE, Sammons JS. Reasons why physicians and advanced practice clinicians work while sick: a mixed-methods analysis. *JAMA Pediatr* 2015;169:815–21.
- Taylor G, Mitchell R, McGeer A, Frenette C, Suh KN, Wong A, et al. Healthcare-associated influenza in Canadian hospitals from 2006 to 2012. *Infect Control Hosp Epidemiol* 2014;35:169–75.
- Ustun C, Slabý J, Shanley RM, Vydra J, Smith AR, Wagner JE, et al. Human parainfluenza virus infection after hematopoietic stem cell transplantation: risk factors, management, mortality, and changes over time. *Biol Blood Marrow Transplant* 2012;18:1580–8.
- Villaran MV, García J, Gomez J, Arango AE, Gonzales M, Chicaiza W, et al. Human parainfluenza virus in patients with influenza-like illness from Central and South America during 2006–2010. *Influenza Other Respir Viruses* 2014;8:217–27.
- Wolkewitz M, Zortel M, Palomar-Martinez M, Alvarez-Lerma F, Olaechea-Astigarra P, Schumacher M. Landmark prediction of nosocomial infection risk to disentangle short- and long-stay patients. *J Hosp Infect* 2017;96:81–4.
- Zhao H, Harris RJ, Ellis J, Donati M, Pebody RG. Epidemiology of parainfluenza infection in England and Wales, 1998–2013: any evidence of change?. *Epidemiol Infect* 2017;145:1210–20.