Clinical Infectious Diseases

BRIEF REPORT

Sensitive Diagnostics Confirm That Influenza C is an Uncommon Cause of Medically Attended Respiratory Illness in Adults

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Among 4200 adults who presented with acute respiratory symptoms at a variety of medical practice settings (November 2006 through May 2012), only 13 (0.3%) nasal/throat swabs were positive for influenza C. Influenza C was rarely associated with medical care visits in adults.

Keywords. Influenza C; RT-PCR; adults.

Influenza C, originally called the "1233 aberrant strain," was first recognized in 1947 [1]. This virus had distinct antigenic properties but was difficult to isolate by culture. Serologic studies noted humoral responses to influenza C in early life and continued presence of antibody levels throughout adulthood [2], suggesting that influenza C was a human pathogen.

With the advent of improved influenza diagnostic techniques such as reverse transcription polymerase chain reaction (RT-PCR), the epidemiology of influenza C as a pathogen has been reevaluated. This virus has been associated with acute respiratory illnesses in children, especially those less than 2 years of age and in a variety of clinical circumstances (inpatient and outpatient) [3–5], and its geographic distribution is diverse, with disease occurring in studies from a number of countries including Nigeria, Cuba, Japan, France, Scotland and the United States [6–11]. However, data on disease presentation and burden associated with influenza C in adults are limited, especially in older adults. Hence, we evaluated a prospective cohort of adults that had previously been used to describe influenza A & B, respiratory syncytial virus, and human metapneumovirus [12–19] for the prevalence of influenza C associated with medical care visits and hospitalizations for acute respiratory illness.

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METHODS

Adults who presented with respiratory symptoms at a variety of medical practice settings in Davidson County, Tennessee (1 acute outpatient clinic, 1 academic emergency department (ED), and 4 acute care hospitals) during 6 influenza seasons (November 2006 through May 2012) were eligible for enrollment [15–17, 20].

Criteria for inclusion included 1or more of the following symptoms or admissions diagnoses. Presenting symptoms included cough, non-localizing fever, shortness of breath, sore throat, nasal congestion, or coryza. Admission diagnoses (*International Classification of Diseases, 9th Revision* Number) included pneumonia (480–486), upper respiratory infection (465), bronchitis (466), influenza (487), chronic obstructive pulmonary disease (490 to 492; 496), asthma (493), viral illness (079.9), dyspnea (786), acute respiratory failure (518.81), pneumonitis due to solids/liquids (507), or fever (780.6) without localizing symptoms.

For each participant, both a mid-turbinate nose and a throat swab sample were obtained for RT-PCR testing. Specimens were placed into viral transport media and placed into coolers until delivered to the laboratory where they were stored at 4°C until processing. Patient questionnaires were used to capture symptoms and influenza vaccination history. Additionally, chart abstraction was performed to collect demographic data, past medical history, results of microbiologic and radiographic tests, hospital course (if hospitalized), outcome at discharge, and verification of influenza vaccination status from the named source of vaccination and/or the patient's primary care provider.

RNA was extracted from each nose/throat sample on the MagMAX-96 Express instrument using the MagMAX-96 Viral RNA Isolation Kit (Thermo Fisher). RNA was tested for influenza C using a real-time RT-PCR assay designed and optimized by our laboratory targeting the nucleoprotein (NP) gene with the following sequences: forward primer CCGYTCAAGAATTGTTCAAA, reverse primer CTTGCTGCRTTTCTTCCTCT and dual-labeled probe TCGGCTTCTCWGCACTCTTYGCTTC. The assay was specific and did not react with coronavirus, influenza A or B, human metapneumovirus, parainfluenzavirus, respiratory syncytial virus, or rhinovirus. The real-time RT-PCR assay was validated against a panel of influenza C clinical isolates and was capable of detecting <50 RNA copies (unpublished data). Samples were previously tested for influenza A and B, respiratory syncytial virus, and human metapneumovirus as previously described [15, 18, 21].

We performed descriptive analyses of influenza C clinical manifestations by medical care setting (outpatient, [ED], inpatient), age group (18–49, 50–64, ≥65 years), and demographic

characteristics including age, sex, race, and insurance status. The clinical manifestations included symptoms (cough, coryza, fever, etc.), duration of symptoms, comorbid illness, length of hospitalization, intubation, intensive care unit (ICU) stay, and death. Fisher exact and Wilcoxon rank-sum tests were performed to identify any statistically significant associations.

RESULTS

During the 6 study years, 4272 patients were enrolled. Of these, 4200 (98.3%) had samples available for testing, and 13 (0.3%) were positive for influenza C. The 13 influenza C positive patients were 61% women (n = 8), 54% white (n = 7), 38% black (n = 5), and 8% other race (n = 1) (Table 1). Influenza C was identified in 7 (54%) patients 18–49 years, 1 (8%) in those 50–64 years, and 5 (38%) in adults ≥65 years. The most common underlying conditions present in influenza C infected patients were cardiovascular and chronic pulmonary disease. None of these patients had immunocompromising conditions including transplant, human immunodeficiency virus (HIV), or recent chemotherapy. Two of the 13 samples had another virus codetected along with influenza C; 1 patient was coinfected with influenza A and another was coinfected with respiratory syncytial virus. No codetection with human metapneumovirus was found.

Influenza C had a low prevalence in all medical care settings including 0.55% (5/909) outpatient, 0.49% (3/610) ED, and 0.19% (5/2681) inpatient. Although 391 patients in this cohort required ICU level care, only 1 patient with influenza C required ICU level care. No influenza C positive patients required ventilator support, and there were no in-hospital deaths in the 5 hospitalized patients.

Primary visit and discharge diagnoses included acute sinusitis (ICD9 code: 461.8; 7.7%), acute bronchitis and bronchiolitis (466; 7.7%), pneumonia (486; 15.4%), obstructive chronic bronchitis with acute exacerbation (491.21; 15.4%), other disease of lung (518.89; 7.7%), malaise and fatigue (780.79; 15.4%), throat pain (784.1; 7.7%), and cough (786.2; 23%).

Influenza C was not detected in 2 of the 6 seasons (2007–2008 and 2011–2012), whereas 5 of the 13 cases occurred in 2010–11.

DISCUSSION

Viruses such as influenza A, respiratory syncytial virus, and human metapneumovirus cause severe disease in the extremes of age. With the recently reported outbreaks of influenza C in children, we evaluated a cohort of adults to determine if influenza C was significantly associated with heath care utilization, especially hospitalization, in older adults. Despite the reported disease burden in children, little medically-attended disease due to influenza C was appreciated in adults including older adults. Of the 2681 hospitalizations for acute respiratory illness over a 6-year period, only 5 (0.19%) were associated with influenza C.

Table 1. Characteristics of Patients by Detection of Influenza C

	Influenza C Negative	Influenza C Positive
Age, years		
18–49	1647	7
50–64	1241	1
65+	1299	5
Sex		
Female	2541	8
Male	1646	5
Race		
White	2938	7
Black	1045	5
Asian/Pacific Islander	44	0
Other	93	1
Don't know	67	0
Medical care setting		
Outpatient	904	5
Inpatient	2676	5
ED	607	3
Hospitalization (n = 2676)		
LOS, mean (range), days	4.26 (0–92)	2.6 (1–4)
ICU (patients requiring ICU stay)	336	1
Ventilated (intubated patients tested for Flu C)	125	0 (0%)
Oxygen during hospitalization	1867	4
Symptoms		
Myalgias	2456	6
Change in mental status	1435	6
Chills	2312	10
Cough	3416	12
Ear pain[a]	1107	8
Fatigue	3455	12
Fever/feverish[a]	2486	11
Headache	2522	12
Nasal congestion or rhinorrhea	2871	11
Decrease appetite	2532	9
Dyspnea	3338	13
Sore throat	1981	10
Wheezing	2620	10
Nausea/vomiting/diarrhea	1958	5
Study year (influenza season)		
2006–2007	189	1
2007–2008	101	0
2008–2009	391	4
2009–2010	2147	1
2010–2011	662	5
2011–2012	195	0
Comorbid conditions		
Diabetes mellitus	941	1
Cardiovascular disease	248	4
Kidney disease	317	1
Chronic pulmonary disease	1698	5
Cancer	355	0
Splenectomy	13	0
History of transplant	96	0
Liver disease	97	0
Immunocompromised	276	0

Abbreviations: ED, emergency department; ICU, intensive care unit; LOS, length of stay.
[a]$P < .05$

Our cohort included a substantial number of immunocompromised patients (96 transplant patients, 355 cancer patients, 13 asplenic patients). We hypothesized that influenza C might be more common in the immunocompromised adult population. However, in these populations, no adults were found to have influenza C. The most common underlying disorders in patients with influenza C were asthma or COPD (5 patients, 38%). Patients with detectable influenza C presented to the ED, hospitals, and an outpatient clinic, but the proportion of those with influenza C detected were higher in the outpatient setting (0.55%).

Influenza C was detected in 7 (0.42%) patients ages 18 to 49 years of age. A previous study performed in military recruits in Finland detected 38 cases of influenza C by RT-PCR and serology in 720 episodes of acute infection [22]. This suggests a potential population that may experience high rates of influenza C may be those living in close quarters such as military recruits or residents of long-term care facilities.

This study was limited by seasonal surveillance (November thru April) except for the 2009–2010 pandemic season, which included surveillance of the preceding summer. This study may have underestimated the true number of influenza C cases by missing cases that occurred outside of the typical influenza A and B seasons that were not captured.

Influenza C was an uncommon cause of either outpatient visits or hospitalizations in adults. Although the frequency of detection varied by year, there were no epidemics of Influenza C over the 6 years of the study.

Notes

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