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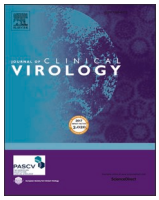

Short Communication

Influenza C virus in U.S. children with acute respiratory infection 2016–2019

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A B S T R A C T

Influenza C virus (ICV) is an orthomyxovirus related to influenza A and B, yet due to few commercial assays, epidemiologic studies may underestimate incidence of ICV infection and disease. We describe the epidemiology and characteristics of ICV within the New Vaccine Surveillance Network (NVSN), a Centers for Disease Control and Prevention (CDC)-led network that conducts population-based surveillance for pediatric acute respiratory illness (ARI). Nasal or/combined throat swabs were collected from emergency department (ED) or inpatient ARI cases, or healthy controls, between 12/05/2016–10/31/2019 and tested by molecular assays for ICV and other respiratory viruses. Parent surveys and chart review were used to analyze demographic and clinical characteristics of ICV+ children. Among 19,321 children tested for ICV, 115/17,668 (0.7 %) ARI cases and 8/1653 (0.5 %) healthy controls tested ICV+. Median age of ICV+ patients was 18 months and 88 (71.5 %) were ≤36 months. Among ICV+ ARI patients, 40 % (46/115) were enrolled in the ED, 60 % (69/115) were inpatients, with 15 admitted to intensive care. Most ICV+ ARI patients had fever (67.8 %), cough (94.8 %), or wheezing (60.9 %). Most (60.9 %) ARI cases had ≥1 co-detected viruses including rhinovirus, RSV, and adenovirus. In summary, ICV detection was rarely associated with ARI in children, and most ICV+ patients were ≤3 years old with co-detected respiratory viruses.

1. Introduction

Influenza C virus (ICV) is an enveloped, negative-sense RNA virus in the *Orthomyxoviridae* family with a 7-segmented genome capable of reassortment that encodes 9 viral proteins. In contrast, influenza A and B viruses have 8-segment genomes encoding 10 major viral proteins [1–4]. ICV encodes a single surface glycoprotein, hemagglutinin-esterase-fusion (HEF), that fulfills the roles of both hemagglutinin and neuraminidase, facilitating host receptor binding, cleavage of sialic acid, and membrane fusion [1,5–7]. HEF is the major target for host neutralizing antibodies; [8,9] however, HEF is only 12 % conserved with influenza A HA [6] and thus there is not thought to be any antibody cross-reactivity. Human CD8+ *T* cells recognize epitopes of ICV internal proteins, some of which are conserved in influenza A and B viruses [10], providing potential for cross-reactive T cell immunity.

ICV is an under-recognized infection with seropositivity increasing with age. ICV seropositivity has been found to be as high as 90 % by 7–10 years of age, suggesting that most people are infected by ICV at least once during childhood [11,12]. Infection also appears to be relatively common among adults. A 5-year longitudinal study of ICV titers in

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Japanese adults found that 17 % had evidence of new seropositivity within the study period [13]. Due to difficulty detecting ICV by cell culture and no readily available commercial molecular or antigen assays, epidemiologic studies of ICV have likely underestimated burden of ICV infection and disease. Recent development of highly sensitive RT-PCR has facilitated epidemiologic studies that provide further insights into the prevalence, seasonality, and characteristics of ICV infection.

ICV is usually associated with mild acute respiratory illness (ARI); however, the virus has been associated with pneumonia, bronchiolitis, and bronchitis [14–17]. Co-detection of other viruses is common among patients with ICV infection, especially in children <2 years of age, and may be associated with increased disease severity [14,17]. In this study, we describe the epidemiology and clinical characteristics of ICV infection and disease detected by molecular methods in a large, population-based pediatric cohort.

2. Methods

The study was conducted within the New Vaccine Surveillance Network (NVSN), a Centers for Disease Control and Prevention (CDC)-led, seven-site network that performs population-based surveillance for ARI in children. For this analysis, only five of the seven sites performed ICV testing routinely on all enrollments (Pittsburgh, PA; Nashville, TN; Rochester, NY; Houston, TX; and Kansas City, MO). For the five sites that did testing, methods used included single-plex real-time RT-PCR assays with CDC primers and probes (Houston, Kansas City) [17] or validated ICV primers and probes [18], or single-plex real-time RT-PCR using Tandem Array Card (TAC) (Rochester) [19]. All sites used automated nucleic extraction methods. Patients were enrolled year-round from emergency department (ED) or inpatient children with ARI, or healthy controls in clinic, between 12/05/2016–10/31/2019. Midturbinate nasal or oropharyngeal flocked swabs were obtained; if both were collected, they were combined and placed together in universal transport medium. Tracheal aspirate was an alternative specimen for patients who were intubated. Specimens were tested at each site by commercial or institution-specific in-house RT-PCR assays. Of 57 ICV+ Pittsburgh samples, 30 were available for HEF sequencing and 18 HEF genes were successfully sequenced. Parent surveys were obtained at time of enrollment and sample collection. Standardized medical chart review was performed for each child to collect data on demographics, clinical findings, and comorbidities. If >30 % of data were missing for demographics or clinical characteristics, this variable was excluded from analysis. Full NVSN enrollment, testing, and data collection methods were previously reported [20]. Medians with interquartile ranges (IQR) are reported for numeric variables and percentages reported for categorical variables. Fisher's exact test was used for comparisons between categorical variables. This study received Institutional Review Board approval from all sites that participated in the present study and the CDC.

3. Results

Among 19,321 children with ARI or healthy controls enrolled and tested for ICV from 2016 to 2019, there were 115/17,668 (0.7 %) ARI cases and 8/1653 (0.5 %) healthy controls that tested positive for ICV. The median age of ICV+ participants was 18 months (IQR 8,44 months) and 88 (71.5 %) were ≤36 months. Seventy-six (61.8 %) were White, 41 (33.3 %) were Black, 22 (17.9 %) were Hispanic, and the remainder were Asian or other race. A total of 111 (90.2 %) of ICV+ children had another child <5 years in the household, and 55 (44.7 %) attended daycare (Table 1).

Most ICV infections were detected in Pittsburgh (46.3 %) and Nashville (26.8 %), with 57 (46.3 %) ICV+ patients in 2016–17, 11 (8.9 %) in 2017–2018, and 55 (44.7 %) in 2018–19 (Table 2). Detections peaked December-February in 2016–2017 and 2018–2019 (Fig. 1).

Table 1
Demographic characteristics of ICV+ children including healthy controls and ARI cases.

	ICV+ children ($N = 123$) N (%)
Median age (months)	18 (IQR 8,44)
Sex (male)	63 (51.2)
Race and Ethnicity [a]	
White	76 (61.8)
Black	41 (33.3)
Hispanic	22 (17.9)
Asian	1 (<1)
Other	3 (2.4)
Insurance status	
Private insurance	72 (58.5)
Public insurance	43 (35.0)
Other or unknown	8 (6.5)
Median number of people 5–17 years in household	1 (IQR 0–2)
Median number of people 0–5 years in household	1 (IQR 1–2)
Child <5 years in the household	111 (90.2)
Daycare attendance	55 (44.7)
Tobacco use in household	29 (23.6)
Location	
Pittsburgh	57 (46.3)
Nashville	33 (26.8)
Rochester	13 (10.6)
Houston	12 (9.8)
Kansas City	8 (6.5)

[a] Data on race and ethnicity are not mutually exclusive, and multiple race and ethnicity categories could be selected.

Among ICV+ ARI patients, 46 (40 %) were enrolled in the ED, while the remainder were inpatients. Median length of stay was 2 days (IQR,1–3) with 15 admitted to the Intensive Care Unit (ICU) and no patients died. Among ICV+ ARI cases, 78 (67.8 %) had fever, 109 (94.8 %) cough, 101 (87.8 %) nasal congestion, and 70 (60.9 %) wheezing (Table 3). Premature birth, congenital heart disease, and asthma were the most frequent comorbidities. Four of 6 cases of congenital heart disease and both children with DiGeorge syndrome were admitted to the ICU.

Seventy of 115 (60.9 %) ICV+ ARI patients had ≥1 co-detected pathogen with rhinovirus (26, 22.6 %), respiratory syncytial virus (RSV) (27, 23.5 %), and adenovirus (14, 12.2 %) most frequently co-detected (Table 4). ARI symptoms including fever, myalgias, chills, and wheezing did not differ significantly between coinfected subjects and those who were only ICV+. Viral co-detection was more frequent among inpatients, including ICU patients, compared to ED ($p = 0.02$). HEF sequences from 18 Pittsburgh samples fell into the two currently circulating Kanagawa and Sao Paulo lineages.

4. Discussion

In this study, ICV detection was infrequent among both ARI cases and healthy controls, with <1 % testing positive in either group. Most children had exposure to other young children at home or in daycare. Most ICV+ children were <3 years of age, consistent with known pattern of increasing seropositivity rates between 1 and 7 years of age, with most children seropositive by 7–10 years of age [14]. The NVSN ARI enrollment protocol during influenza season (December-May) during the years of the study only enrolled children <5 years, which may have led to a lower median age. ICV detection was similar between the ARI cases and healthy controls. This finding supports ICV as a cause of mild respiratory illness that is rarely associated with more severe disease leading to healthcare encounters and is consistent with previous reports [14,17]. The majority of ICV+ children experienced cough and nasal congestion, and no deaths were reported. Four of 6 children with congenital heart disease were admitted to the ICU, consistent with previous reports that children with underlying hemodynamic instability may be susceptible to a more severe clinical course [14,17,21].

Seasonality for ICV is poorly understood; however, there is some

Table 2
Summary of ICV+ patients including healthy controls and ARI cases.

	ICV+ patients per study site per year					
	Site					Total
Year	Nashville n %	Rochester	Houston	Pittsburgh	Kansas City	
2016–2017	12 21.1	8 14.0	5 8.8	27 47.4	5 8.8	57
2017–2018	1 9.1	0	2 18.2	5 45.5	3 27.3	11
2018–2019	20 36.4	5 9.1	5 9.1	25 45.5	0	55
Total	33 26.8	13 10.6	12 9.8	57 46.3	8 6.5	123

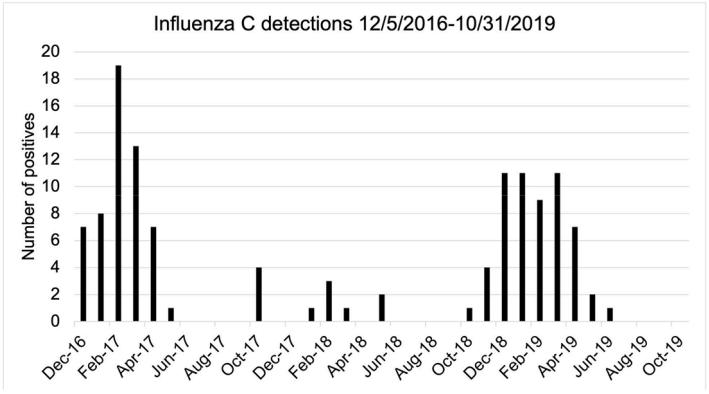

Fig. 1. Epidemiologic curve of influenza C detections including ARI cases and healthy controls.

evidence of biennial epidemics in children [22]. Our results, though limited to just three seasons, support a biennial trend with a peak in cases in 2016–17 then again in 2018–19. However, seasonal patterns of ICV vary greatly between years and by geographic region [23]. Future studies should include more years to support the hypothesis of an ICV biennial pattern.

Co-infection with other respiratory viruses is a common finding among children in whom ICV is detected, particularly younger children, with co-detection reported in 8–50 % of ICV+ cases, most commonly rhinovirus, RSV, or adenovirus [23]. Some evidence suggests that co-infection may be associated with increased severity of disease [17, 23]. In this study, co-detection was more common among inpatients compared to ED patients.

This study has some limitations. We enrolled and tested children for ICV at only five children's hospitals, and these data may not be representative of all pediatric medical centers in the U.S. Moreover, the variability between seasons and geographic regions may have led to underestimation of burden; a 17-year study in Japan found peak years with four-fold higher incidence than other seasons [22]. However, the systematic testing using molecular research assays rather than clinically ordered testing strengthened our ability to detect ICV and co-detected viruses.

In conclusion, ICV was uncommon among children with ARI leading to healthcare encounters. Most children infected with ICV were $\leq$3 years old and had co-detected viral pathogens. Patients admitted to the hospital had a higher frequency of co-detections than those in the ED.

CRediT authorship contribution statement

Bethany K. Sederdahl: Writing – original draft, Formal analysis, Conceptualization. **Geoffrey A. Weinberg:** Writing – review & editing, Investigation. **Angela P. Campbell:** Writing – review & editing, Investigation. **Rangaraj Selvarangan:** Writing – review & editing, Investigation, Data curation. **Jennifer E. Schuster:** Writing – review & editing, Investigation. **Joana Y. Lively:** Writing – review & editing, Project administration, Investigation. **Samantha M. Olson:** Writing – review & editing, Supervision, Project administration, Investigation, Data curation. **Julie A. Boom:** Writing – review & editing, Investigation. **Pedro A. Piedra:** Writing – review & editing, Investigation. **Natasha B. Halasa:** Writing – review & editing, Investigation. **Laura Stewart:** Writing – review & editing, Investigation. **Peter G. Szilagyi:** Writing – review & editing, Investigation. **G.K. Balasubramani:** Writing – review & editing, Formal analysis, Data curation. **Theresa Sax:** Writing – review & editing, Formal analysis, Data curation. **Judith M. Martin:** Writing – review & editing, Supervision, Investigation. **Robert W. Hickey:** Writing – review & editing, Supervision, Investigation. **Marian G. Michaels:** Writing – review & editing, Supervision, Investigation, Conceptualization. **John V. Williams:** Writing – review & editing, Supervision, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Dr Weinberg reported reports honoraria from Merck & Co for writing and revising textbook chapters. Dr Weinberg has served on an Scientific Advisory Board for Inhalon Biopharma. Dr Selvarangan reported receiving grants from Merck & Co, Inc, BioFire, Luminex, Hologic, Abbott, Becton Dickinson, and Cepheid outside the submitted work. Dr Halasa reported receiving grants from Sanofi and Quidel as well as personal fees from Genentech outside the submitted work. Dr Szilagyi reported receiving grants from the University of California, Los Angeles David Geffen School of Medicine BROAD Program during the conduct of the study. Dr Sahni reported receiving grants for her institution from the Centers for Disease Control and Prevention (CDC) outside the submitted work. Dr Martin reported receiving funding from Merck, Sharp and

Table 3
Clinical characteristics of 115 ICV+ ARI patients.

	ED N (%)	Inpatient N (%)	ICU[a] N (%)
Total	46/115 (40)	69/115 (60)	15/115 (13.0)
Median LOS (days)	–	2 (IQR 1–3)	3 (IQR 1.5–7)
Symptoms (parent survey)	**46**	**69**	**15**
Fever	31/46 (67.4)	47/69 (68.1)	10/15 (66.7)
Cough	44/46 (95.7)	65/69 (94.2)	14/15 (93.3)
Wheezing	25/46 (54.3)	45/69 (65.2)	8/15 (53.3)
Nasal congestion	42/46 (91.3)	59/69 (85.5)	10/15 (66.7)
Sore throat	13/46 (28.3)	13/69 (18.8)	2/15 (13.3)
Dyspnea	26/46 (56.5)	60/69 (87.0)	13/15 (86.7)
Myalgias	7/46 (15.2)	5/69 (7.2)	0
Chills	8/46 (17.4)	15/69 (21.7)	2/15 (13.3)
Fatigue	22/46 (47.8)	48/69 (69.6)	11/15 (73.3)
Headache	9/46 (19.6)	8/69 (11.6)	1/15 (6.7)
Vomiting	7/46 (15.2)	18/69 (26.1)	2/15 (13.3)
Diarrhea	12/46 (26.1)	19/69 (27.5)	4/15 (26.7)
Seizure	3/46 (6.5)	3/69 (4.3)	1/15 (6.7)
Clinical findings (chart review)	**46**	**69**	**15**
O2 requirement	0	39/69 (56.5)	15/15 (100)
Mechanical ventilation	0	1/69 (1.4)	1/15 (6.7)
Subcostal retraction	2/46 (4.3)	45/69 (65.2)	11/15 (73.3)
Cyanosis	0	2/69 (2.9)	2/15 (13.3)
Wheezing	10/46 (21.7)	32/69 (46.4)	7/15 (46.7)
Median minimum 0_2 saturation	98 (96.8, 99.2)	94.5 (90–96)	93 (IQR 89–96)
Comorbidities	**46**	**69**	**15**
Prematurity (<35 w gestational age)	3/46 (6.5)	10/69 (14.5)	2/15 (13.3)
Asthma	6/46 (13.0)	9/69 (13.0)	3/15 (20.0)
Sickle cell disease	0	3/69 (4.3)	0
Congenital heart defects	1/46 (2.2)	6/69 (8.7)	4/15 (26.7)
Immunocompromise (DiGeorge Syndrome)	0	2/69 (2.9)	2/15 (13.3)

[a] **Note:** ICU patients are included in Inpatient but listed in a separate column to highlight ICU patients' clinical features.

Table 4
ICV+ patients with co-detected viruses by RT-PCR.

	ED	Inpatient	Total	ICU (15/115)
Total Co-detections	24*	46*	70	12*
Single	20	31	51	8
2+	4	15	19	4
Rhinovirus	13	13	26	1
RSV	9	18	27	6
Adenovirus	7	7	14	1
Parainfluenza viruses	2	3	5	0
Influenza A H1N1	0	2	2	1
Human metapneumovirus	1	8	9	3
Influenza A H3N2	0	1	1	1
Other[a]	0	2	2	2

* Viral co-detection was more frequent among inpatients (66.7 %, $N = 46/69$), including ICU patients, compared to ED (52.2 %, $N = 24/46$) ($P = 0.02$, Chi-squared testing).

[a] Other includes bocavirus and coronavirus NL63.

Dohme outside the submitted work. Dr. Williams reported receiving grants from the NIH outside the submitted work. No other conflicts were reported.

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Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the U.S. Centers for Disease Control and Prevention (CDC).

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