Severe Complications in Influenza-like Illnesses

WHAT'S KNOWN ON THIS SUBJECT: Severe complications, such as respiratory failure, have been described in influenza infection. Clinicians are commonly faced with influenza-like illnesses (ILI), which is the initial nonspecific presentation of many respiratory viruses; the risk of severe complications from ILI are unknown.

WHAT THIS STUDY ADDS: Severe complications occurred in children initially presenting with ILI, irrespective of the virus identified. Risk factors for severe complications did not differ by demographics or respiratory virus, although children with high-risk conditions are at greater risk of severe complications.

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KEY WORDS
viral respiratory infection, pandemic influenza, pneumonia

ABBREVIATIONS
CDC—Centers for Disease Control and Prevention
CI—confidence interval
ED—emergency department
FLU—influenza
ILI—influenza-like infection
non-FLU—noninfluenza infection
PCR—polymerase chain reaction
RSV—respiratory syncytial virus

Dr Mistry participated in all aspects of the study, including conceptualization, design, subject enrollment, and statistical analyses, and drafted and revised the manuscript; Mr Fischer assisted with data collection and data analysis, and reviewed and revised the manuscript; Ms Prasad was primarily responsible for data collection and management, and assisted in data analyses; Drs Coffin and Alpern assisted in conceptualization of the study design and subject enrollment, assisted with design of data collection instruments, and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

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abstract

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OBJECTIVE: Data on complications from upper respiratory infection are limited. We examined development of severe complications in children presenting to the emergency department (ED) for moderate to severe influenza-like illness (ILI).

METHODS: Prospective cohort study of children 0 to 19 years presenting to a tertiary care children's hospital ED during peak respiratory viral seasons from 2008 to 2010. Subjects included had moderate to severe ILI, defined by performance of venipuncture and nasopharyngeal multiplex polymerase chain reaction for respiratory viruses. Severe complications (respiratory failure, encephalopathy, seizures, pneumonia, bacteremia, death) were prospectively determined. Risk factors for severe complications were collected, including demographics, comorbidities, and household exposures.

RESULTS: There were 241 enrolled subjects with median age of 27.4 months (interquartile range 8.9–68.5); 59.3% were boys and 48.5% were black. High-risk conditions were present in 53.5%. Severe complications developed in 35.3% (95% confidence interval [CI] 29.3–41.3), most frequently pneumonia (26.1%). The risk for severe complications was increased in subjects with neurologic or neuromuscular conditions (relative risk 4.0; 95% CI 1.9–8.2). No specific respiratory virus was associated with development of severe complications. Among patients with influenza, severe complications were greater with subtype H1N1 infection (relative risk 1.45, 95% CI 0.99–2.13, $P = .048$), and were at highest risk for pneumonia (relative risk 4.2, 95% CI 1.2–15.9).

CONCLUSION: In children presenting to the ED for moderate to severe ILI, those with neurologic and neuromuscular disease are at increased risk for severe complications. Development of severe complications did not differ by infecting virus; however, risk of severe complications was greater with subtype H1N1 compared with other influenza. *Pediatrics* 2014;134:e684–e690

Children frequently present to the emergency department (ED) for evaluation of acute respiratory tract illnesses. During peak influenza seasons, diagnosis and treatment of these children becomes increasingly complex, as many patients meet criteria for influenza-like illness (ILI), defined as the presence of fever, in addition to cough or sore throat, in the absence of an alternative cause.[1–3] During peak seasons, it is estimated that the incidence of influenza in children with ILI is as high as 40%.[1] Even though most children with ILI have mild illness, clinicians must be cognizant of children at risk for developing more serious illness.[4–8] In the United States, the population-based risk for influenza-related hospitalization is as high as 150 in 100 000, with as many as 125 deaths annually. In the current 2014 season, influenza type A, type B, and pandemic H1N1 are circulating, resulting in hospitalization and severe complications.[9] Consequently, the American Academy of Pediatrics and the Centers for Disease Control and Prevention (CDC) have emphasized empirical antiviral therapy for most children with ILI, as a method for averting severe illness and mortality.[1,10]

Severe complications of influenza include pneumonia, respiratory failure, encephalopathy, and seizures, and may develop from infection with other respiratory viruses.[11–13] Previous studies have examined complications in children with known influenza; however, in the clinical setting, physicians are often faced with a child with ILI. Recognizing the limited availability, turnaround time, and effectiveness of "rapid" or point-of-care influenza testing,[14] clinicians are faced with decisions regarding need for antiviral therapy, hospitalization, and monitoring for severe complications. Interestingly, evaluation of outcomes in children presenting with ILI are limited, and the incidence of severe complications in children with ILI is not previously described in the literature.

The objective of this study was to determine the rates of severe complications among children presenting to the ED with moderate to severe ILI during respiratory viral seasons. Additionally, we sought to determine factors associated with development of severe complications, including infecting virus, patient characteristics, and household-related exposures.

METHODS

Study Subjects and Setting

This was a planned secondary analysis of a prospective cohort study of children 0 to 19 years of age presenting to an urban tertiary care children's hospital ED from 2008 to 2010, during peak respiratory viral season (early winter to late spring). Subjects were eligible if they (1) had a clinical presentation of an ILI by CDC criteria, defined as fever plus cough or sore throat, in the absence of an alternative cause,[1,3] and (2) had moderate to severe presentation, determined by performance of a venipuncture and nasopharyngeal aspirate for multiplex respiratory viral polymerase chain reaction (PCR) in the ED. Children with critical illness or established diagnosis of severe complications were excluded. Venipunctures and respiratory viral testing were obtained per discretion of the ED treatment team, such as for serum diagnostic tests and intravenous hydration. Consent for participation was obtained. The study was approved by the hospital's institutional review board.

Study Variables

The main outcome measure of the study was development of severe complications in children with moderate to severe ILI, subsequent to ED presentation but during hospitalization for the same illness. Severe complications included any of the following: seizures, encephalopathy, pneumonia, bacteremia, bacterial tracheitis, respiratory failure, myocarditis, or death. Encephalopathy was defined by documented alteration in mental status, delirium, or confusion during hospitalization. Pneumonia was defined as presence of focal infiltrate on chest radiograph, reported by an attending radiologist. Bacteremia was determined by isolation of a known pathogen (eg, *Staphylococcus aureus*, pneumococcus) in culture. Bacterial tracheitis was determined by clinical presentation (fever, toxicity stridor, brassy cough) and/or presence of pathogenic bacteria from tracheal aspirate. Respiratory failure was defined as need for mechanical ventilation (continuous positive airway pressure, bilevel positive airway pressure, or endotracheal intubation and ventilation). Data necessary for classification of severe complications were obtained subsequent to the ED visit by using a standard data collection form. After ED disposition, medical records were reviewed from ward, intensive care, and outpatient settings. Severe complications were analyzed individually, and categorized by development of 1 or more complications (any severe complication).

Data on potential risk factors and exposures associated with severe complications included demographics (eg, age, gender, race, and ethnicity) and household exposures. Household exposures included the number of people in the household, day care/school attendance, known ill contacts, presence of smokers in the home, and reported influenza vaccination status. The presence of high-risk conditions, per the CDC Advisory Committee on Immunization Practices, was collected, including asthma or chronic respiratory disease, immunosuppressive condition (eg, sickle cell disease or asplenia), congenital heart disease, and neurologic or neuromuscular disease.[15,16]

Data Collection

Demographic characteristics and high-risk conditions were collected from the patient record while in the ED; household data were collected in the ED via

parental questionnaire. Outcome data were abstracted from medical records. For subjects admitted from the ED to an inpatient ward, outcomes data were obtained after hospital discharge. Record review for the 6 months after ED discharge was performed to ensure subjects did not re-present and develop severe complications. All data were collected onto standardized data collection forms to ensure accuracy consistency.

Virology and Microbiology

Nasopharyngeal aspirates were tested for respiratory viruses using a real-time, multiplex PCR assay developed by our hospital's clinical virology laboratory.[17] Specific viruses identified included influenza A and B, parainfluenza viruses, rhinovirus, human metapneumovirus, adenovirus, and respiratory syncytial virus (RSV). Results of multiplex viral respiratory PCR testing were collected after the ED visit was complete. For the purposes of analysis, subjects were subclassified as having influenza (FLU) if influenza A or B was identified either alone or in combination with other viruses; all other subjects were considered to have non-influenza infection (non-FLU). Among influenza A–infected subjects, subtyping for H1N1 was also performed. Bacterial culture results from sputum, tracheal aspirates, and blood were obtained from the hospital microbiology laboratory.

Analytic Plan and Statistical Considerations

Description of outcomes for subjects with various viruses isolated (influenza, rhinovirus, RSV, human metapneumovirus, adenovirus, parainfluenza virus, multiple viruses, and no virus isolated) was also performed. Specific viruses were recategorized for analysis. Subjects identified with FLU infection were compared with all others (non-FLU); additional subanalyses were performed to evaluate subtype H1N1 infection. Associations with severe complications, and patient characteristics and household exposures were determined. The risk for development of severe complications for FLU and non-FLU groups was determined, as was the risk between H1N1 and non-H1N1 among influenza A–infected subjects.

Data were summarized by using standard descriptive statistics: categorical data were described by using proportions and percentages, and continuous data were summarized by using means and SDs. Statistical comparisons were made using independent-sample t tests for continuous variables, and categorical variables were compared using χ^2 test. Significance was set at the $P < .05$ level. Results were reported with 95% confidence intervals (CIs), where indicated. All statistical analyses were performed by using the Statistical Package for the Social Sciences, version 20 (IBM SPSS Statistics, IBM Corporation, Chicago, IL).

RESULTS

Demographic and Household Exposures

During the period of study enrollment, 125 940 children presented to the emergency department, and a total of 241 subjects were enrolled. Subjects had a median age of 27.4 months (range: 0.3–227.8; 25% to 75% interquartile range 8.9–68.5), and most were boys (n = 147, 59.3%) and African American (n = 117, 48.5%). A total of 129 (53.5%) subjects had at least 1 chronic medical condition, with asthma being the most common; the remaining were otherwise healthy (Table 1). Household exposures were prevalent among the study population, with an average of 4.5 members per household, and more than half of subjects were currently in day care or school. Known ill contacts were reported in 96 (39.8%) subjects.

Viral Epidemiology

Respiratory viruses were identified for most study subjects (Fig 1). A single virus was determined as the cause of infection in 144 (59.8%, 95% CI 53.6–65.9) subjects, whereas 29 (12.0%) had multiple infecting viruses simultaneously. Sixty-eight subjects (28.2%) did not have a virus identified. The most common virus associated with infection was influenza, which was present as the sole virus in 47 (19.5%, 95% CI 14.5–24.5) and in 13 of 29 subjects with >1 virus identified. In total, 60 (24.9%, 95% CI 19.4–30.4) subjects had an influenza virus as a cause of their infection. Evaluation of the 60 subjects with influenza viruses revealed that 49 (81.7%) were influenza A, with 11 (18.3%) influenza B. Subanalysis of subjects with influenza A determined 29 (59.1%, 95% CI 45.4–72.3) of 49 were pandemic subtype H1N1 (Fig 1). Other viruses present as sole causes of respiratory infection included 35 (14.5%) with rhinovirus and 28 (11.6%) RSV, with lesser proportions of human metapneumovirus, adenovirus, and parainfluenza viruses (Fig 1).

Comparison of demographic and household exposures in the subjects with FLU and non-FLU revealed that children with FLU did not demonstrate significant differences (Table 1). Known ill contacts were significantly greater in the FLU group, compared with non-FLU.

Severe Complications

During the study period, severe complications developed in 85 (35.3%, 95% CI 29.3–41.3) subjects: most were pneumonia, which developed in 63 (26.1%, 95% CI 20.7–32.2) subjects, followed by respiratory failure in 12 (7.1%) and seizures in 14 (5.8%) (Table 1). There was 1 patient death, which occurred in a previously healthy 4-week-old infant who developed bacteremia, pneumonia, and respiratory failure; no causative viral infection was identified. The risk for severe complication was significantly increased in subjects with neurologic or neuromuscular conditions (relative risk = 4.0, 95% CI 1.9–8.2). No other specific high-risk conditions were

TABLE 1 Comparison of Subjects with FLU and Non-FLU Infection

	Overall, *n* (%), *n* = 241	FLU, *n* (%), *n* = 60	Non-FLU, *n* (%), *n* = 181	*P* Value
Age, mo, median	27.4	45.0	27.1	.06
Gender, % boys	143 (59.3)	35 (58.3)	108 (59.7)	.86
Race				
White	105 (43.5)	22 (36.7)	83 (46.1)	.21
Black	117 (48.5)	35 (58.3)	82 (45.6)	
Other	19 (7.9)	3 (5.0)	16 (8.3)	
No. in household, mean ± SD	4.51 ± 1.57	4.50 ± 1.49	4.51 ± 1.60	.95
Day care/school attendance	120 (49.8)	30 (50.0)	90 (51.2)	.80
Any high-risk condition[a]	129 (53.5)	39 (65.0)	90 (51.2)	.05
Asthma	58 (24.0)	16 (26.7)	42 (23.2)	.59
Neurologic condition	38 (15.7)	9 (15.0)	29 (16.0)	.85
Chronic respiratory disease	13 (5.4)	1 (1.7)	12 (6.6)	.14
Heart disease	21 (8.7)	5 (8.3)	16 (8.8)	.90
Sickle cell/asplenia	22 (9.1)	9 (15.0)	13 (7.2)	.07
Sick contacts	96 (39.8)	33 (55.0)	63 (34.8)	<.01*
Smokers in household	62 (25.7)	17 (28.8)	45 (26.2)	.69
FLU vaccine	115 (47.7)	31 (57.4)	84 (54.9)	.75
Any severe complication[b]	85 (35.3)	20 (33.3)	65 (35.9)	.72
Pneumonia	63 (26.1)	13 (21.7)	50 (27.6)	.36
Respiratory failure	17 (7.1)	2 (3.3)	15 (8.3)	.19
Seizure	14 (5.8)	3 (5.0)	11 (6.1)	.76
Bacteremia	5 (2.1)	1 (1.7)	4 (2.2)	.80
Encephalopathy	3 (1.2)	2 (3.4)	1 (0.6)	.09
Bacterial tracheitis	2 (0.8)	1 (1.7)	1 (0.6)	.41
Death	1 (0.4)	0 (0.0)	1 (0.6)	.56

*, statistically significant.

[a] Subjects may have had >1 high-risk condition.

[b] Subjects may have developed >1 severe complication.

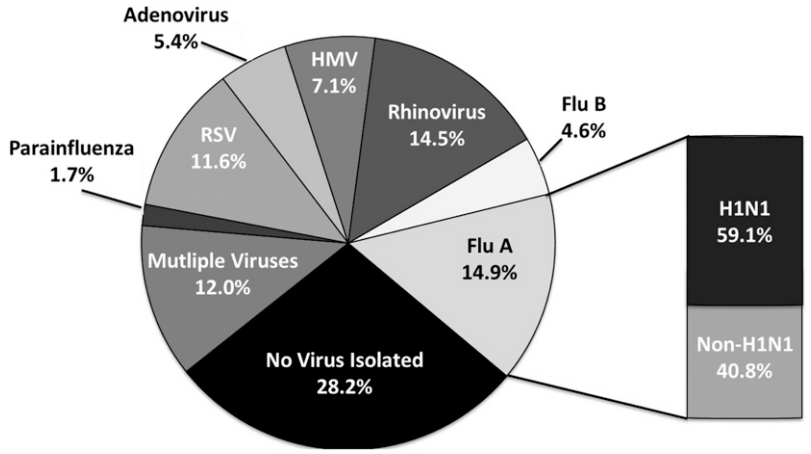

FIGURE 1
Distribution of infecting respiratory viruses identified in study population (*n* =241). *If >1 virus was identified, they are reflected in the "Multiple Viruses" category.

associated with severe complications (Table 2). Analysis of patient characteristics and household factors did not demonstrate any significant association with severe complications (Table 2). Development of severe complications did not differ between FLU and non-FLU groups (Table 1). Subanalyses did not demonstrate that severe complications were significantly more likely when other viral infections were present (eg, RSV, rhinovirus, HMV, adenovirus, parainfluenza viruses), or when multiple virus coinfections were present (Table 3).

Analysis of Subjects With Pandemic H1N1 Influenza Infection

Among subjects with influenza A infection, those infected with subtype H1N1 were compared with all other subtypes (Table 4). Patient characteristics between H1N1 and other subtypes did not differ. Among specific complications, the risk of developing pneumonia was significantly higher in subtype H1N1 (relative risk = 7.6, 95% CI 1.1–54.2). Respiratory failure was less likely to develop in subtype H1N1 (0% vs 15%, *P* = .03). No deaths occurred among any subjects infected with influenza A.

DISCUSSION

In this investigation of children presenting with moderate to severe ILI evaluated in the ED, we determined that 1 in every 3 children will subsequently develop a severe complication, most frequently pneumonia. Notably, children with known neurologic or neuromuscular conditions were at substantially higher risk of complications; however, children with other high-risk conditions did not appear to be at increased risk. Although children with known ill contacts were more likely to have influenza infection, neither ill contacts nor influenza infection were associated with increased risk of severe complications. Our assessment of patient and household factors commonly associated with influenza did not demonstrate any association with risk of severe complications. However, infection with pandemic H1N1 strains of influenza was associated with increased risk of development of pneumonia in children with influenza A, initially presenting with moderate to severe ILI.

We assessed a cohort of children managed in the ED for ILI requiring acute intervention, but before knowledge of the results of viral testing. Clinicians are often faced with such a clinical scenario in the ED, and often manage children with ILI empirically without information

TABLE 2 Comparison of Subjects With and Without Development of a Severe Complication

	Severe Complication, *n* (%), *n* = 85	No Complication, *n* (%), *n* = 156	*P* Value
Age, mo, median	37.7	21.5	.16
Gender, % boys	49 (57.6)	94 (60.3)	.69
Race			
White	39 (46.4)	66 (42.3)	.72
Black	38 (45.2)	79 (50.6)	
Other	7 (8.3)	11 (7.1)	
No. in household, mean ± SD	4.7 ± 1.7	4.4 ± 1.5	.32
Day care/school attendance	43 (51.8)	77 (50.7)	.98
Any high-risk condition[a]	50 (58.8)	79 (50.6)	.28
Asthma	23 (27.1)	35 (22.4)	.42
Neurologic condition	24 (28.2)	14 (9.0)	<.01*
Chronic respiratory disease	5 (5.9)	8 (5.1)	.80
Heart disease	7 (8.2)	14 (9.0)	.85
Sickle cell/asplenia	5 (5.9)	17 (10.9)	.20
Sick contacts	33 (38.8)	66 (42.9)	.59
Smokers in household	19 (23.8)	43 (28.5)	.53
FLU vaccine	38 (54.3)	77 (56.2)	.45

*, statistically significant.

[a] Subjects may have had >1 high-risk condition.

TABLE 3 Comparison of Subjects Developing Severe Complications by Virus Identified

	Severe Complication, *n* (%), *n* = 85	No Complication, *n* (%), *n* = 156	*P* Value
Influenza A	18 (21.2)	31 (19.9)	.81
Influenza B	2 (2.4)	9 (6.0)	.20
RSV	10 (11.8)	26 (16.7)	.31
Rhinovirus	21 (24.7)	35 (23.3)	.81
Adenovirus	4 (4.7)	21 (14.0)	.03*
Human metapneumovirus	10 (11.8)	10 (6.7)	.18
Parainfluenza viruses	1 (1.2)	7 (3.8)	.16
Multiple viruses identified	10 (11.8)	19 (12.2)	.93
No virus identified	30 (35.3)	38 (24.4)	.07

Calculations of individual viruses include if they were identified in isolation or in combination with other viruses.

*, statistically significant.

regarding the infecting virus. In addition, children may present with an ILI and acutely ill; our findings suggest that severe complications, such as pneumonia, respiratory failure, and encephalopathy, occur with equal frequency among this cohort of patients with ILI, irrespective of viral identification. Previous studies of outcomes from ILI have often focused specifically on influenza infection, and have assessed complications, morbidity, and mortality in children.[7,8,18,19] Similar to our study population, respiratory complications, specifically pneumonia, have been suggested as most common in true influenza infection.[7,20] Consistent with previous findings, we noted that children with neurologic and neuromuscular conditions were at higher risk of developing severe complications.[7,21,22] However, we also found that at-risk children develop complications irrespective of the infecting virus. It is equally important to recognize that healthy children of higher ED acuity also developed severe complications. Nonetheless, considering the high prevalence of influenza during peak seasons, and the risk for complications among children presenting with moderate to severe acuity, our findings support prescription of empirical antiviral therapy for both at-risk and previously healthy children. Antiviral therapy has proven to decrease risk of severe complications in children with known influenza[10,15,23] and in those with high-risk conditions.[15,23,24] Although antiviral therapies, such as oseltamivir, are associated with side effects, most notably emesis, the drug is well tolerated in children and the incidence of severe adverse side effects is uncommon. Considering the risk of complications from infection, particularly among children with comorbid conditions, it appears that empirical prescription of antiviral therapy confers greater benefit than risk.

The findings of our subanalysis were consistent with the other investigations of H1N1. Respiratory complications, specifically pneumonia, were significantly higher in children infected with H1N1 infection compared with other influenza.[12,24–26] Reports of pandemic influenza have demonstrated an increased tendency for pneumonia, even among healthy, older children, as determined in our study.[12,24–27] Moreover, we found children with comorbidities represent an at-risk population for these severe complications from H1N1, similar to other forms of influenza.[4,21,22,28] These findings support the need for increased preventive measures in this subgroup of children, including influenza vaccination and early institution of antiviral treatment.[10,29] Our findings remain pertinent, as pandemic H1N1 continues to circulate in the United States, with ongoing infection placing children at risk.[9] As a result, the most recent American Academy of Pediatrics and CDC recommendations suggest influenza vaccination, which includes H1N1 strains,[10] for all high-risk children, such as those identified in our cohort.[10,16,22]

There are limitations to our findings. Foremost, our cohort was composed of children receiving venipuncture and viral PCR testing, which is commonly performed in children with more severe illness in the ED. Therefore, spectrum bias is introduced into our results. However, these children remain at highest risk for severe complications, and permits

TABLE 4 Subanalysis of Children Infected With Pandemic H1N1 Strains, and Non-H1N1 Strains of Influenza A

	H1N1, *n* (%), *n* = 29	Non-H1N1, *n* (%), *n* = 20	*P* Value
Age, mo, median	75.1	53.8	.25
Boys	15 (51.7)	15 (75.0)	.10
Race			
White	12 (41.4)	5 (25.0)	
Black	15 (51.7)	14 (70.0)	.26
Other	2 (6.9)	1 (5.0)	
No. in household, mean ± SD	4.95 ± 1.96	4.41 ± 1.54	.30
Day care/school attendance	16 (55.1)	7 (35.0)	.13
Any high-risk condition[a]	22 (75.9)	10 (50.0)	.06
Asthma	9 (31.0)	4 (20.0)	.39
Neurologic condition	5 (17.2)	3 (15.0)	.84
Chronic respiratory disease	0 (0)	0 (0)	—
Heart disease	2 (6.9)	2 (10.0)	1.0
Sickle cell/asplenia	5 (17.2)	2 (10.0)	.69
Sick contacts	15 (51.7)	11 (55.0)	.82
Smokers in household	6 (21.4)	9 (45.0)	.08
FLU vaccine	14 (48.2)	8 (40.0)	.91
Any severe complication[b]	13 (44.8)	5 (25.0)	.16
Pneumonia	11 (37.9)	1 (5.0)	<.01*
Respiratory failure	0 (0.0)	3 (15.0)	.03*
Seizure	1 (3.4)	0 (0.0)	.40
Bacteremia	1 (3.4)	0 (0.0)	.40
Bacterial tracheitis	1 (3.4)	0 (0.0)	.40
Encephalopathy	0 (0.0)	1 (5.0)	.22
Death	0 (0.0)	0 (0.0)	—

*, statistically significant; —, not applicable.

[a] Subjects may have had >1 high-risk condition.

[b] Subjects may have developed >1 severe complication.

application of our findings into a very common clinical scenario. Moreover, we were unable to address specific provider or ED characteristics that may affect decisions for testing or intravenous placement, such as physician experience or time of presentation. There is also potential for misclassification, as approximately one-quarter of subjects had no virus identified via PCR testing. Lack of identification of a virus may indicate that one was not present in the child, or that a virus not included in the testing group was present. However, it is less likely that a listed tested virus was present and missed, as the PCR testing has >92% sensitivity for each tested virus, except certain adenovirus serotypes.[17] It should be noted that severe complications were not significantly more common among children without virus identified. Additionally, although we were able to perform subanalyses for pandemic H1N1 infection, the analyses were limited because of sample size. For example, respiratory failure is described as a complication from H1N1 in previous literature; however, we did not have a single case of respiratory failure among our subjects with H1N1. We did not collect data regarding administration of oseltamivir in children with ILI; therefore, we are unable to assess the effect of antiviral therapy on development of severe complications in our cohort. Finally, our study was conducted in a large, tertiary-care children's hospital, consequently affecting the generalizability of our findings to other settings.

CONCLUSIONS

Although most children presenting with respiratory illnesses during peak influenza seasons manifest uncomplicated ILI, as many as 1 in 3 children presenting with more acute illness are at high risk for development of severe, complicated illness. Those children with neurologic or neuromuscular comorbid conditions are at greatest risk of developing severe complications of ILI. However, up to 40% of children who developed severe complications did not have any underlying comorbidity, indicating that physicians need a broad concern for children presenting with ILI, and should continue to assess individual patient risk for development to severe complications regardless of known viral testing result. In addition, in light of the persistence of pandemic H1N1 even today, continued surveillance is indicated, as chronically ill and healthy children infected with subtype H1N1 are at increased risk for severe complications.

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