

# Clinical and Virological Characteristics of Acute Sinusitis in Children

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**Background.** Acute bacterial sinusitis is a frequent complication of viral upper respiratory infection (URI). We describe the clinical and virologic features of URIs that remain uncomplicated and those that precede an episode of sinusitis. We hypothesize that certain viruses are more likely to lead to acute sinusitis, and we compare viruses identified at the time of diagnosis of sinusitis with those identified early in the URI.

**Methods.** Children aged 48–96 months were followed longitudinally for 1 year. Nasal samples were obtained at surveillance visits, on Day 3–4 of the URI, and on Day 10, when sinusitis was diagnosed. Molecular diagnostic testing was performed on nasal washes for common respiratory viruses and pathogenic bacteria. A standardized score was used to quantify symptom severity.

**Results.** We evaluated 519 URIs, and 37 illnesses in 31 patients met the criteria for sinusitis. Respiratory syncytial virus was detected more frequently in URI visits that led to sinusitis, compared to in uncomplicated URIs (10.8% vs 3.4%;  $P = .05$ ). New viruses were detected in 29% of sinusitis episodes, and their pattern was different than those patterns observed at surveillance. The median number of URIs per subject per year was 1 (range 0–9) in uncomplicated URI subjects and 3 (range 1–9) in sinusitis subjects ( $P < .001$ ).

**Conclusions.** Children who developed sinusitis experienced more frequent URIs, compared to children whose URIs remained uncomplicated. When nasal samples were obtained on the day of diagnosis of acute sinusitis, nearly 30% of children had a new virus identified, suggesting that some children deemed to have sinusitis were experiencing sequential viral infections.

**Keywords.** sinusitis; sinus; virus; upper respiratory infection; children.

Acute bacterial sinusitis is usually preceded by a viral respiratory infection. A viral upper respiratory infection (URI) causes mucosal inflammation within the nose and nasopharynx that promotes the obstruction of the sinus ostia [1]. The virus-induced proliferation of pathogenic bacteria in the nasopharynx can set the stage for the development of complications, such as acute sinusitis and acute otitis media [2, 3]. The diagnosis of acute sinusitis is made on clinical criteria alone and is based on the presence and pattern of symptoms that differentiate acute sinusitis from an uncomplicated viral URI [4, 5]. Our previous investigations described virus identification and bacterial colonization in asymptomatic children and in those with uncomplicated URIs [2, 3, 6]. Here, we focus on the subpopulation of children with acute bacterial sinusitis and compare the clinical and virologic features of viral URIs that remain uncomplicated to those that precede an episode of sinusitis in an expanded cohort of children. This study was designed to test the hypothesis

that infections with certain respiratory viruses are more likely to predispose children to acute sinusitis than other viruses. In addition, in a post hoc analysis, we questioned whether some episodes of presumed acute sinusitis actually represent sequential infections with unique viruses. We conducted a prospective study of young children, which included monitoring clinical respiratory symptoms and the repeated collection of samples of nasal mucus and analysis with viral molecular diagnostics.

## METHODS

### Enrollment and Inclusion Criteria

Healthy children aged 48–96 months were recruited throughout the study period (2012–2016) from 2 pediatric practices in Madison, Wisconsin, and were followed for 1 year, as previously described and as detailed in the [Supplementary Methods](#) [2, 3].

### Procedures

Nasal samples were obtained at entry and during 4 surveillance visits when children were asymptomatic, as verified by the study nurses. Nasal samples were also obtained on Day 3–4 of acute URIs and on Day 10, if and when acute sinusitis was diagnosed. A final “recovery” sample was retrieved from those children with uncomplicated URIs when their symptoms were completely resolved, at approximately Day 15. Parents were instructed to call the study nurses at the first signs of an upper

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respiratory illness; a symptom survey was filled out on Day 3–4 and was subsequently administered by telephone on Days 7, 10, and 15, as previously described in detail and as described in the [Supplementary Methods](#) [7].

### Classification of Respiratory Episodes

Each respiratory episode was classified as either an uncomplicated viral URI or sinusitis. The diagnosis of sinusitis was based on 1 of the following clinical criteria: (1) persistent symptoms—nasal discharge, cough, or both—that lasted more than 10 days without improvement, or (2) worsening symptoms, as evidenced by the sudden renewal of respiratory symptoms (nasal discharge or cough) or fever after an apparent improvement, usually beyond the sixth day of illness [5]. Radiographs were not performed to diagnose sinusitis, in accordance with national guidelines [5].

### Collection of Samples

Samples of nasal mucus were obtained using an established nose-blowing technique [8–10]. Saline nasal solution was sprayed into each of the child's nostrils. The study nurse then held a plastic "baggie" to the nose and occluded 1 of the nostrils, taking care to not touch the inside of the baggie. If a child was unable to blow their nose, a sufficient sample was obtained by allowing the sprayed saline to drip into the plastic baggie.

### Virus Identification

Diagnostic virology was performed on nasal samples by multiplex polymerase chain reaction (PCR), as previously described [2, 3]. Nasal specimens were also analyzed by partial sequencing, to determine which rhinovirus types were present and differentiate closely related enterovirus from rhinovirus [11].

### Bacterial Polymerase Chain Reaction

Nasal samples were also analyzed for *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* using quantitative real-time PCR. DNA was extracted with the BiOstic Bacteremia DNA Isolation Kit (Mo Bio laboratories, Carlsbad, CA) as previously described [2]. Each assay included a standard curve, derived from bacteria of known concentrations, and results are reported as colony-forming unit equivalents/mL (cfue/mL).

### Statistical Analysis

Statistical methods are provided in detail in the [Supplementary Materials](#).

## RESULTS

### Study Population

During the 5-year study period, 4516 letters of invitation were sent to families with eligible children; 1878 children were excluded due to an underlying condition, 323 patients were enrolled, and 237 completed 1 year of follow-up ([Supplementary](#)

[Figure 1](#)). Subjects who developed sinusitis had similar demographic characteristics as those with uncomplicated URIs, except were slightly more likely to report their race as American Indian or Alaska Native ([Table 1](#)). There were 519 reported URIs in all subjects during the study period; 37 illnesses in 31 distinct patients met the diagnostic criteria for acute sinusitis. The rate of sinusitis-complicating URIs was 7.1% (95% confidence interval [CI] 5.2–9.7%).

### Viruses Detected in Acute Upper Respiratory Infections and at Diagnosis of Acute Sinusitis

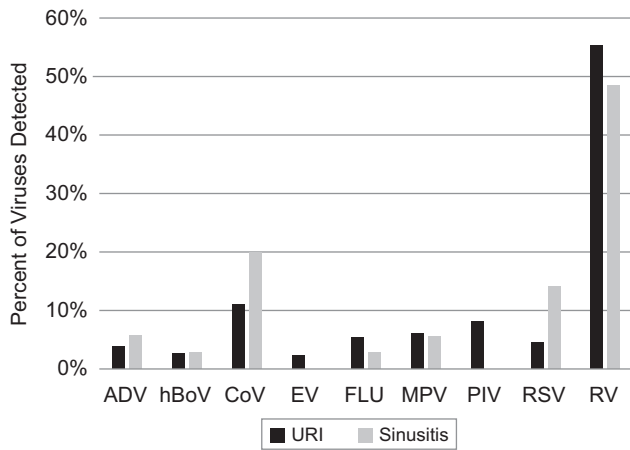
A virus was detected on Day 3 in the nasal washes of 81% and 76% of uncomplicated URIs and sinusitis episodes, respectively ([Figure 1](#)). Respiratory syncytial virus (RSV) was detected significantly more often in URI visits that led to sinusitis (10.8% vs 3.4%;  $P = .05$ ); the distribution of the remaining viruses was similar between uncomplicated URI and sinusitis events. No viruses were detected in 19.3% and 24.3% of uncomplicated URIs and sinusitis visits, respectively ( $P = .5$ ).

To determine whether the clinical characteristics that defined an episode of acute sinusitis might, in some cases, be caused by sequential viral infections, we compared the viral PCRs performed on the nasal washes obtained at Days 3 and 10 after the onset of an illness. Of the 37 episodes of sinusitis, 6 did not have a second nasal wash on the tenth day of illness, leaving 31 of the 37 sinusitis events available for analysis. There were 18 cases of sinusitis diagnosed based on persistent symptoms

**Table 1. Subject Demographics**

	URI Subjects (n = 292)	Sinusitis Subjects (n = 31)	PValue
Age, in years			
Mean	5.2	5.1	NS
Range	4–8.0	4–8.0	NS
Gender, % female	46.9	48	NS
Race, %			
American Indian or Alaska Native	0	3	0.02
Asian	5.5	0	NS
African-American	6.8	6.4	NS
Other	6.5	0	NS
Unknown or not reported	0.3	0	NS
Caucasian	80.5	90.3	NS
Ethnicity			
Hispanic, %	7.3	6.4	NS
Attends day care, %	84	83	NS
Tobacco exposure, %	3.8	0	NS
Maternal education level, %			
Graduate/professional	39.8	25.8	NS
College degree	35.6	45.1	NS
Some college	12.1	22.6	NS
Vocational/tech	5.5	0	NS
High School	6.6	5.5	NS
No or public insurance (%)	17	19	NS

Abbreviations: NS, not significant; URI, upper respiratory infection.



**Figure 1.** Viruses detected in Day 3 nasal washes for URIs that remained uncomplicated and those that progressed to sinusitis. Abbreviations: ADV, adenovirus; CoV, coronavirus; EV, enterovirus; FLU, influenza virus; hBoV, human bocavirus; MPV, metapneumovirus; PIV, parainfluenza virus; RSV, respiratory syncytial virus; RV, rhinovirus; URI, upper respiratory infection.

and 13 based on worsening symptoms (Table 2). Compared to the results of their Day 3 sample, 78% of children with persistent symptoms and 62% of children with worsening symptoms had a Day 10 nasal sample that was negative for a virus or had the same virus as at Day 3. A new virus was detected in 22% of children with persistent and 38% with worsening symptoms, respectively. When taken together, a new virus was detected in the Day 10 nasal sample in 29% of all 31 episodes. There was no difference in the type of respiratory viruses between children with worsening vs persistent symptoms. On Day 10, 55% of subjects with sinusitis had a virus detected in their nasal wash samples. This compares to 31% of recovery nasal washes taken within the same time frame from children with uncomplicated URIs and 34% taken during surveillance visits ( $P < .01$ ; Table 3). When nasal wash samples from subjects with sinusitis were compared with those obtained at surveillance visits, the new viruses detected on Day 10 were more likely to be adenovirus, influenza, or respiratory syncytial virus and were less likely to be rhinovirus. In comparison, those sinusitis subjects with the

**Table 2. Virus Identification at Day 10 Nasal Sample Compared to Day 3 Sample, According to Clinical Presentation**

Presentation	Clinical		
	Persistent, N (%)	Worsening, N (%)	All cases, N (%)
Virus Identification on Day 10			
Negative or same as Day 3	14 (78)	8 (62)	22 (71)
New virus	4 <sup>a</sup> (22)	5 <sup>b</sup> (38)	9 (29)
Total	18 (58)	13 (42)	31 (100)

<sup>a</sup>In 1 subject, the same virus (metapneumovirus) was detected in addition to a new virus (influenza virus).

<sup>b</sup>In 1 subject, the same virus (respiratory syncytial virus) was detected in addition to a new virus (adenovirus).

same virus detected on Day 10 as on Day 3 showed a similar virus distribution as observed at surveillance visits (Table 4).

#### Bacterial Colonization in Patients With Acute Sinusitis

As shown in Supplementary Tables 1 and 2, nasal bacterial colonization rates and bacterial densities on Day 3 during URI visits were similar to the sinusitis visits for *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* (Supplementary Tables 1 and 2). We next compared the detection rates of bacterial pathogens in subjects diagnosed with sinusitis, according to the virus identified in the 10-day sample (ie, new virus vs negative or same virus). The absence of *M. catarrhalis* on Day 3 ( $P < .02$ ) and Day 10 ( $P = .11$ ) appeared to be a risk factor for the acquisition of a new virus on Day 10 (Table 5). There were no differences between those subjects with a new virus and those with negative or the same virus samples for the density or presence of *S. pneumoniae* or *H. influenzae* in either the 3- or 10-day samples.

#### Frequency and Severity of Upper Respiratory Infections in Patients With Sinusitis

The rate of URIs in the 209 subjects who had only uncomplicated URIs was compared to the rate in the 31 subjects who had sinusitis. The median number of URIs per subject per year was 1 (range 0–9) in the uncomplicated URI subjects and 3 (range 1–9) in the sinusitis subjects ( $P < .001$ ; Figure 2).

To test the hypothesis that URIs leading to sinusitis would be associated with more severe clinical symptoms than URIs which remained uncomplicated, symptom scores were compared on Days 3, 7, 10, and 15 of illness (Figure 3). Symptom scores were indeed higher on Day 3 ( $P = .03$ ) and Day 7 ( $P = .005$ ) for URIs leading to sinusitis compared to uncomplicated URIs (Supplementary Table 3). As expected, the symptom scores were also significantly higher on Days 10 and 15, by definition.

To determine which individual symptoms were increased during the acute URIs that led to sinusitis, we compared the area under the curve from Days 0 to 15 for each symptom (Supplementary Table 3). Congestion, cough, and nasal discharge showed the greatest differences between the uncomplicated URIs, compared to the URIs complicated by sinusitis. Impaired appetite, sleep, and activity were also significantly higher at visits for URI that were complicated by sinusitis. Reports of facial pain or swelling, fever, and headache were not different between URI events. When considering Day 7 as the single time point with the greatest differences, the mean (95% CI) scores for the symptoms of congestion, discharge, and cough were 1.4 (95% CI 1.2–1.8), 1.3 (95% CI 1.1–1.6), and 1.2 (95% CI 0.9–1.5), respectively, at URI visits that became complicated with sinusitis and 1.0 (95% CI 0.9–1.1), 1.0 (95% CI 0.9–1.0), and 0.8 (95% CI 0.7–0.9), respectively, at URI visits that remained uncomplicated. These scores were significantly different between the 2 visit types ( $P < .01$  for all 3 symptoms), but were not different for the other symptoms (data not shown).

**Table 3. Virus Detection in Nasal Samples Performed on Day 3 and Day 10 in 31 Patients With Sinusitis Compared With Uncomplicated URI and Asymptomatic Surveillance Visits**

Virus	Sinusitis	Sinusitis	URI	URI	Surveillance
	Day 3 Sample (n = 31)	Day 10 Sample (n = 31)	Day 3 Sample (n = 352)	Recovery (n = 274)	
ADV	0%	3%	0%	1%	0%
hBoV	0%	0%	1%	1%	1%
CoV	13%	6%	6%	4%	3%
EV	3%	3%	2%	0%	0%
FLU	0%	6%	3%	0% <sup>a</sup>	0% <sup>a</sup>
MPV	3%	0%	3%	0%	1%
PIV	0%	0%	6%	1%	1%
RSV	10%	3%	3%	1%	0%
RV	35%	19%	45%	19%	24%
Mixed	23%	13%	11%	3% <sup>a</sup>	2% <sup>a</sup>
Negative	13%	45%	19%	69% <sup>a</sup>	66% <sup>a</sup>

Abbreviations: ADV, adenovirus; CoV, coronavirus; EV, enterovirus; FLU, influenza virus; hBoV, human bocavirus; MPV, metapneumovirus; PIV, parainfluenza virus; RSV, respiratory syncytial virus; RV, rhinovirus; URI, upper respiratory infection.

<sup>a</sup>P < .01 for comparison with Sinusitis Day 10 Sample.

## DISCUSSION

This is the first study to describe the clinical and virologic features of episodes of acute sinusitis, compared with URIs, in a population of children followed longitudinally over a 1-year time period. Children who developed an episode of sinusitis as a complication of URI experienced more frequent URIs and had higher symptom scores early in their illnesses, compared to children whose URIs remained uncomplicated. Most importantly, when nasal samples were obtained on the day of diagnosis of acute sinusitis, nearly 30% of children had a new virus identified, with a different pattern than that observed during surveillance or recovery, strongly suggesting that some children deemed to have sinusitis were actually experiencing sequential viral URIs.

### Sinusitis as a Complication of Upper Respiratory Infections

The rate of complications of URIs with sinusitis, of 7.1%, is slightly lower than the 8.8% figure that we reported in an interim analysis of this study population [3], but remains similar to that reported by Marom et al [12]. This decrease may reflect our efforts in the last 24 months of the study to enhance our reporting of URIs. As we have now demonstrated that the rate of sinusitis is related to the severity of the initial URI, increased reporting of milder URIs would be expected to result in a decreased rate of complications. In this study, RSV was detected more frequently at URI events that became complicated by sinusitis, compared to uncomplicated URI visits, suggesting a more prominent pathogenic role for this virus. Although no other studies correlating

**Table 4. Comparison of Virus Detection Rates on Day 10 of Sinusitis Visits Versus Surveillance Visits**

Virus	Sinusitis	Sinusitis	Surveillance	PValue <sup>a</sup>	PValue <sup>b</sup>
	New Virus Day 10 (n = 13)	Same Virus Day 10 (n = 7)			
ADV	2 (15.4)	0 (0.0)	7(2.2)	.04	NS
BoV	1 (7.7)	0 (0.0)	20 (6.4)	NS	NS
CoV	1 (7.7)	1 (14.3)	33 (10.5)	NS	NS
EV	0 (0.0)	0 (0.0)	5 (1.6)	NS	NS
FLU	2 (15.4)	1 (14.3)	6 (1.9)	.03	NS
MPV	1 (7.7)	0 (0.0)	9 (2.9)	NS	NS
PIV	0 (0.0)	0 (0.0)	9 (2.9)	NS	NS
RSV	3 (23.1)	0 (0.0)	5 (1.6)	<.01	NS
RV	3 (23.1)	5 (71.4)	220 (70.1)	<.01	NS

Abbreviations: ADV, adenovirus; BoV, bocavirus; CoV, coronavirus; EV, enterovirus; FLU, influenza virus; MPV, metapneumovirus; PIV, parainfluenza virus; RSV, respiratory syncytial virus; RV, rhinovirus.

<sup>a</sup>P value for comparison rates between New Virus Day 10 vs Surveillance.

<sup>b</sup>P value for comparison rates between Same Virus Day 10 vs Surveillance.

**Table 5. Detection Rates of Bacterial Pathogens at Sinusitis Visits**

		Sinusitis Subjects With New Virus on Day 10	Sinusitis Subjects With Negative or Same Virus on Day 10	
		(n = 9)	(n = 22)	
		N (%)	N (%)	P Value <sup>a</sup>
<i>Streptococcus pneumoniae</i>	Day 3	5 (55.6)	14 (63.6)	.70
	Day 10	5 (55.6)	16 (72.7)	.41
<i>Haemophilus influenzae</i>	Day 3	2 (22.2)	7 (31.8)	.68
	Day 10	2 (22.2)	5 (22.7)	.99
<i>Moraxella catarrhalis</i>	Day 3	2 (22.2)	16 (72.7)	.02
	Day 10	3 (33.3)	15 (68.2)	.11
No bacteria	Day 3	3 (33.3)	2 (9.1)	.13
	Day 10	3 (33.3)	2 (9.1)	.13

<sup>a</sup>Comparison of sinusitis subjects with new virus on Day 10 vs sinusitis subjects with negative or same virus on Day 10.

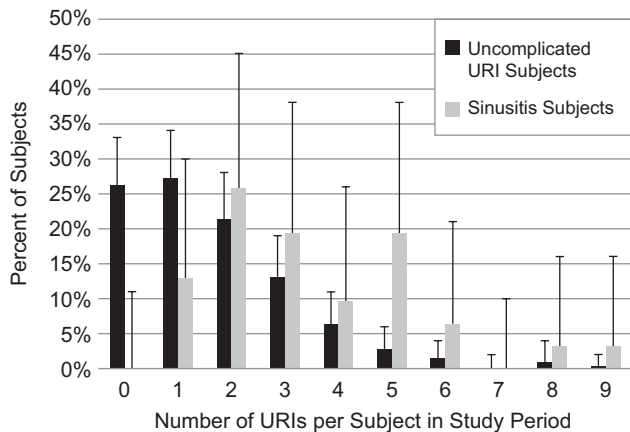
sinusitis with virology have been reported, similar studies have been done for acute otitis media. Chonmaitree et al [13] followed 362 infants from birth to 12 months of age and performed viral PCRs on nasopharyngeal swabs. The development of acute otitis media was associated with increasing age and with infection with RSV, rhinovirus, enterovirus, or bocavirus. Although we did not find an association with the other viruses, it is pertinent that RSV was associated with complications in both studies. RSV is known to elicit a robust immune response in the nose and lower respiratory tract [14]. It is probable that this virus produces more local inflammation in the nasal mucosa, thereby affecting the sinus ostia.

**Viruses Detected at Diagnosis of Sinusitis**

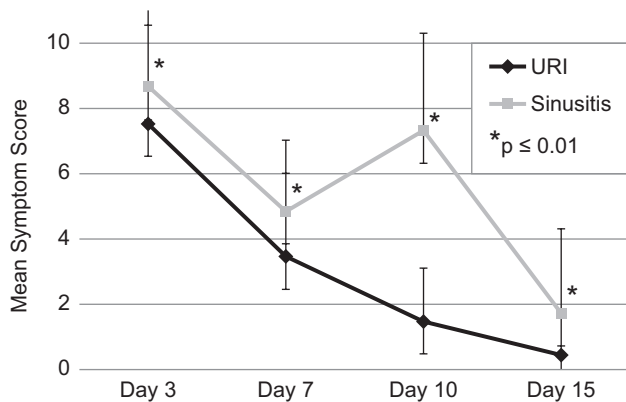
National guidelines for the diagnosis of acute sinusitis have relied on clinical criteria to conclude that a child is experiencing an episode of sinusitis: the persistence of respiratory symptoms for 10 or more days without improvement or the worsening of symptoms after a period of improvement [4, 5]. An important

problem related to the clinical diagnosis of sinusitis is that persistent or worsening upper respiratory symptoms may result from the development of a classic, secondary bacterial infection or a second viral infection that is closely spaced to the first. We found that, when using the criteria of persistent or worsening symptoms, 71% of patients had the same or no virus detected on the 10-day nasal sample, supporting the diagnosis of bacterial sinusitis in these patients. However, nearly 30% had a new virus identified, suggesting that sequential viral infections may explain the symptoms. This observation is supported by data from several clinical trials, demonstrating that about one-third of children clinically diagnosed to have sinusitis lack evidence of a bacterial infection [7, 15, 16]. In addition, in a randomized, double-blind, controlled trial of placebo vs amoxicillin/clavulanic acid in children with clinically diagnosed sinusitis, the non-response rate to the antibacterial was 36%, while the spontaneous cure rate in recipients of the placebo was 32%; each of these correspond closely to the percentage of patients in our study who had sequential viral infections [7]. This is also close to the number of children (20%) who have normal radiographs despite meeting the diagnostic criteria for acute sinusitis [17].

When surveillance samples of nasal wash are examined in asymptomatic children, about 30% will show the presence of a virus [3]. Accordingly, although it is likely, there is no certainty that the virus identified at Day 10 (at the time of diagnosis of acute sinusitis) is the cause of the respiratory symptoms, since asymptomatic detection is common. Furthermore, the identification of a new virus does not preclude the possibility of a dual infection caused by both a virus and bacteria. However, the compelling data show that when a new virus was detected in subjects with sinusitis on Day 10, it was statistically more likely to be adenovirus, influenza, or RSV (rather than rhinovirus), as compared to the viruses identified during surveillance. Furthermore, a virus was identified in 55% of the 31 patients with sinusitis on Day 10, a frequency of detection significantly different than the identification of viruses during surveillance or recovery.



**Figure 2.** Frequency of URIs in subjects with uncomplicated URIs and subjects with sinusitis (error bars indicate 95% confidence intervals). Abbreviation: URI, upper respiratory infection.



**Figure 3.** Mean symptom score by day of illness. Error bars indicate 95% confidence intervals.

### Bacterial Detection During Sinusitis

To assess the relative role of the bacteria and virus at the 10-day visit, we compared bacterial densities in the nasal washes of children with the same or no virus with those in whom a new virus was identified, using washes from Day 3 and Day 10 for each category and between categories. We found no significant differences in either the bacterial presence or density. Of note, the absence of *M. catarrhalis* was associated with the acquisition of a new virus. In contrast, Xu et al [18] showed higher rates of colonization with bacterial pathogens in the nasopharynx in otitis media-prone children, compared with those with uncomplicated URIs. However, otitis-prone children may not be comparable to previously healthy children with an episode of sinusitis, with regard to the intensity of their previous respiratory infections.

Overall, these data support the supposition that patients diagnosed with sinusitis using current guidelines who have a new virus detected on the tenth day of illness actually have sequential viral infections. An alternative supposition is that subjects diagnosed with sinusitis with a new virus on Day 10 have both a new viral infection and bacterial sinusitis. Further studies that assess responses to antimicrobials are necessary to fully explore these hypotheses.

### Clinical Characteristics of Upper Respiratory Infections Preceding Sinusitis

Children who developed sinusitis as a complication of URI at least once during the 1-year study had more than 3 times the annual rate of URIs than those children who had only uncomplicated URIs. This may be explained by the observation that complete histologic recovery of the mucosa after a viral URI is much slower than clinical recovery [19]. Therefore, even a mild infection could become symptomatic when imposed on a recently damaged respiratory mucosa.

We demonstrated that symptom scores during the early phase of the URI were higher for episodes complicated by sinusitis vs uncomplicated URIs. However, the overlap of scores

was substantial, and this finding alone cannot distinguish those patients with URIs who will go on to develop sinusitis.

The strengths of this study include a large sample size, multiple respiratory seasons, and a longitudinal, observational cohort design with extensive, prospective monitoring of both symptoms and microbiology during periods of wellness, URIs, and sinusitis. Limitations of this study include a narrow age range (4–7 years). However, this is the peak age group for children with acute sinusitis and avoids infants and toddlers, who experience a much higher rate of acute otitis media. Children with acute otitis media are likely to receive antibiotics earlier in a URI, which could blunt the appearance of sinusitis. Samples were obtained using nasal washes, which may not represent the microbial conditions in the nasopharynx but are more tolerable in longitudinal studies than repeated nasopharyngeal swabs [20]. Our rate of detection of viruses is similar to other studies, suggesting that—at least for viruses—this method was reliable [8, 21–23]. Finally, despite the substantial sample size, the number of children who developed sinusitis was relatively small. The low prevalence of sinusitis limits the power of the study to detect specific risk factors.

The clinical implication of this study is that sinusitis may be overdiagnosed using current guidelines. While viral PCR on nasal samples is not feasible or sufficient to exclude bacterial sinusitis at the time of a clinical diagnosis, the measurement of nasal cytokines (adaptable to a point-of-care assay) may reflect a host response ascribable to a viral infection [24–28].

## CONCLUSIONS

Acute bacterial sinusitis is a common complication of upper respiratory tract infections in children. This study supports the use of published clinical criteria for the diagnosis of acute sinusitis in children and in distinguishing uncomplicated URIs from sinusitis. However, the data presented provide preliminary evidence suggesting that some children deemed to have sinusitis are, instead, experiencing sequential viral infections.

### Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

### Notes

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Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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