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Influenza Virus Infection and the Risk of Serious Bacterial Infections in Young Febrile Infants



WHAT'S KNOWN ON THIS SUBJECT: Influenza virus is a leading cause of infection in febrile children. Previous studies have demonstrated a substantial reduction in SBI in infants with easily recognizable viral infections. However, an association between influenza virus infections and secondary bacterial infections has long been established.



WHAT THIS STUDY ADDS: Young febrile infants with influenza infections are at a significantly lower risk of SBI. However, the rate of UTI remains appreciable in febrile, influenza-positive infants.

abstract

OBJECTIVE: We aimed to determine the risk of SBIs in febrile infants with influenza virus infections and compare this risk with that of febrile infants without influenza infections.

PATIENTS AND METHODS: We conducted a multicenter, prospective, cross-sectional study during 3 consecutive influenza seasons. All febrile infants ≤ 60 days of age evaluated at any of 5 participating pediatric EDs between October and March of 1998 through 2001 were eligible. We determined influenza virus status by rapid antigen detection. We evaluated infants with blood, urine, cerebrospinal fluid, and stool cultures. Urinary tract infection (UTI) was defined by single-pathogen growth of either $\geq 5 \times 10^4$ colony-forming units per mL or $\geq 10^4$ colony-forming units per mL in association with a positive urinalysis. Bacteremia, bacterial meningitis, and bacterial enteritis were defined by growth of a known bacterial pathogen. SBI was defined as any of the 4 above-mentioned bacterial infections.

RESULTS: During the 3-year study period, 1091 infants were enrolled. A total of 844 (77.4%) infants were tested for the influenza virus, of whom 123 (14.3%) tested positive. SBI status was determined in 809 (95.9%) of the 844 infants. Overall, 95 (11.7%) of the 809 infants tested for influenza virus had an SBI. Infants with influenza infections had a significantly lower prevalence of SBI (2.5%) and UTI (2.4%) when compared with infants who tested negative for the influenza virus. Although there were no cases of bacteremia, meningitis, or enteritis in the influenza-positive group, the differences between the 2 groups for these individual infections were not statistically significant.

CONCLUSIONS: Febrile infants ≤ 60 days of age with influenza infections are at significantly lower risk of SBIs than febrile infants who are influenza-negative. Nevertheless, the rate of UTI remains appreciable in febrile, influenza-positive infants. *Pediatrics* 2009;124:30–39

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KEY WORDS

fever, infants, influenza virus, serious bacterial infection, bacteremia, urinary tract infection, RSV, bronchiolitis

ABBREVIATIONS

SBI—serious bacterial infection
UTI—urinary tract infection
RSV—respiratory syncytial virus
ED—emergency department
CSF—cerebrospinal fluid
CXR—chest radiograph
WBC—white blood cell
RIA—rapid immunoassay
YOS—Yale Observation Scale
CI—confidence interval
RR—relative risk
CFU—colony-forming unit

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Fever is often the only presenting symptom or sign of serious bacterial infection (SBI) in infants ≤ 60 days of age. Approximately 6% to 12% of febrile infants in this age group will have either a urinary tract infection (UTI), bacteremia, or bacterial meningitis.^{1–6} When no bacterial source for the fever is found, however, a virus is the likely etiology.^{7,8} Although previous research has demonstrated a considerably lower rate of SBI among febrile infants with specific viral infections compared to those without these infections, the rates of SBIs, most notably UTIs, remain appreciable.^{1,7,9–11}

Influenza viruses are orthomyxoviruses that are classified as types A, B, and C. Seasonal epidemics are caused by influenza A and B.^{12,13} Efficient transmission by respiratory droplets or by contact with contaminated surfaces has made the influenza virus one of the most commonly acquired infections by children during the fall and winter months, infecting 15% to 42% of children annually.^{14,15} Infants infected with influenza virus may present with fever, rhinitis, cough, vomiting, diarrhea, and occasionally a sepsis-like appearance.¹⁶ Influenza-related illnesses account for many pediatric hospitalizations, with the highest rates seen among children ≤ 1 year of age.^{15,17}

The diagnosis of influenza virus infection on physical examination is difficult, because clinical signs and symptoms can be indistinguishable from other infections. There are currently several commercially available rapid diagnostic assays that allow for the accurate diagnosis of influenza virus types A and B in both the hospital and office settings.^{12,18,19} Rapid diagnosis of influenza virus has led to decreases in the number of ancillary tests and the amount and duration of antimicrobial therapy in infants and toddlers who test positive.^{20–24} However, there have been few studies evaluating the risk of

SBI in young febrile infants who test positive for influenza virus, which could have important implications for clinical care. Of particular note, there have also been investigations that have demonstrated an increased risk of bacterial infections in individuals with influenza virus infections.^{25–28}

The objective of our study was to determine the risk of SBI in young febrile infants with influenza virus infections and compare this risk with that of young febrile infants without influenza infections. We hypothesized that young febrile infants infected with influenza virus would have a significantly lower risk of SBI than those not infected.

PATIENTS AND METHODS

Patient Selection

We performed a secondary analysis of a previously conducted study designed to assess the risk of SBI in infants infected with respiratory syncytial virus (RSV) versus febrile infants not infected with RSV. That study was a prospective, cross-sectional study conducted at 8 pediatric emergency departments (EDs) from 1998 through 2001.¹ Details of this study have been previously published.¹ For the current study, we analyzed the data from the 5 centers in which standard diagnostic evaluation of fever included testing for influenza virus. All infants ≤ 60 days of age with a history or presentation to the ED of a rectal temperature $\geq 38^\circ\text{C}$ were eligible for participation. Enrollment occurred between the months of October through March. Patients were excluded if they had received antibiotics within 48 hours of presentation to the ED or if their legal guardian refused consent for participation. We included in the current analysis all infants who were tested by nasopharyngeal sampling for influenza virus and for whom at least 1 bacterial culture was obtained (culture of the urine, blood, cerebrospinal fluid [CSF],

and/or stool). We defined patients to have “failed protocol” if no bacterial cultures were obtained or viral testing was not performed, and these patients were excluded from the current analysis. Patients who met enrollment criteria but who were not prospectively enrolled were defined as “missed” patients.

Clinical Evaluation

Physicians evaluating the patients in the ED obtained a detailed history and performed a complete physical examination on all enrolled patients. A Yale Observation Scale (YOS) score was determined by the examining physician before the laboratory evaluation,²⁹ followed by a standardized laboratory evaluation.³⁰ This included collection of blood for complete blood count and differential, as well as blood culture, urine for urinalysis and urine culture, and CSF for analysis and culture. Urine was obtained either by bladder catheterization or suprapubic aspiration. We considered a YOS score of ≤ 10 to represent well-appearance.²⁹ Chest radiographs (CXRs) and stool cultures were obtained at the discretion of the attending physician in the ED. All CXRs performed were reviewed by the study pediatric radiologist, blinded to the patients’ clinical information.

Management and hospitalization decisions were made at the discretion of the attending physician. We performed telephone follow-up on patients discharged from the ED within 4 to 7 days, to assess for missed SBI. Patients were considered to have an SBI if any of the cultures obtained in the ED were positive for a bacterial pathogen (see the following definitions), or if the patient was found at telephone follow-up to have been diagnosed with an SBI at a subsequent medical visit.

We determined influenza status by rapid antigen detection in nasopharyngeal aspirates or washes. All 5 study

centers performed the Directigen Flu Test (Becton Dickinson, Sparks, MD), a rapid immunoassay (RIA) membrane test designed to detect influenza viral nucleoprotein by using monoclonal antibodies. Three of the centers tested for both influenza type A and B, and the 2 remaining centers tested for influenza type A alone. The Directigen™ flu test has a sensitivity and specificity for influenza A of 95.7% (95% confidence interval [CI]: 85.2%–99.5%) and 91.4% (95% CI: 87.6%–94.3%), respectively, and a sensitivity and specificity for influenza B of 87.5% (95% CI: 71.0%–96.5%) and 98.1% (95% CI: 95.9%–99.3%), respectively.⁵¹ Per protocol of the original study, all patients were tested for RSV with rapid antigen testing.

Definitions and Outcome Measures

We analyzed infants according to their influenza status, either test positive or negative. Upper respiratory infection was defined as a history or presence of cough and/or rhinorrhea. Bronchiolitis was defined as the presence of wheezing and/or retractions in association with an upper respiratory infection and the absence of radiologic evidence of pneumonia. Pneumonia was defined as a focal consolidation on the CXR, as determined by the study pediatric radiologist.

The primary outcome measure was the presence or absence of an SBI. We defined an SBI as the presence of a UTI, bacteremia, bacterial meningitis, or bacterial enteritis. We defined a UTI as the growth of a single known pathogen meeting any of the following 3 criteria: (1) ≥ 1000 colony-forming units (CFU)/mL from a suprapubic aspiration; (2) $\geq 50\,000$ cfu/mL from a catheterized specimen; or (3) $\geq 10\,000$ cfu/mL from a catheterized specimen in association with a positive urinalysis.³² The urinalysis was considered positive if there was leukocyte ester-

ase and/or nitrites or ≥ 5 white blood cells (WBCs) per high-power field in a spun urine specimen.³³ These criteria were devised to minimize the risk of miscategorizing infants with asymptomatic bacteruria from those with true UTIs.^{33,34} Urine cultures were considered contaminated if >1 bacterial organism was isolated. Bacteremia, bacterial meningitis, and bacterial enteritis were defined as the growth of a single known bacterial pathogen in their respective specimen cultures. Patients who did not have lumbar punctures performed and did not receive antibiotics after their ED evaluation, and who were well at the telephone follow-up, were categorized as not having bacterial meningitis.^{1,35} We did not consider radiographic pneumonia as an SBI for purposes of analysis, because of the difficulty in differentiating between bacterial and viral pneumonia by CXR.^{36,37}

We considered overall SBI status as unknown, and therefore excluded from analysis, if urine, blood, or CSF culture results were missing and the remaining cultures obtained were negative. If any culture, including stool culture, was positive, the patient was considered to have an SBI. In separate analyses, we compared the rate of culture positivity for each type of fluid cultured by influenza virus status. In subanaly-

ses, we investigated the rates of SBI according to age category (≤ 28 or 29–60 days of age), as well as compared infants with influenza infections to infants with RSV infections. Finally, we evaluated infants who were eligible for the study but were missed to assess whether missed patients differed from those enrolled in regard to influenza status and rate of SBIs.

Statistical Analysis

We categorized and analyzed the data according to the patients' influenza RIA results: positive or negative. We performed descriptive and bivariable analyses using Fisher's exact test for categorical data, Student's *t* test for continuous variables, and the Wilcoxon rank-sum test for ordinal data. All tests of significance were 2-sided with an α value of .05. Statistical analysis was performed by using SPSS 13 (SPSS Inc, Chicago, IL) and Stata 8.2 (Stata Corp, College Station, TX) statistical software.

RESULTS

Patient Population

During the 3-year original study period, 1574 patients were eligible for the study, of whom 1091 (69.3%) were enrolled (Fig 1). Of the 1091 patients enrolled, 844 (77.4%) were tested for in-

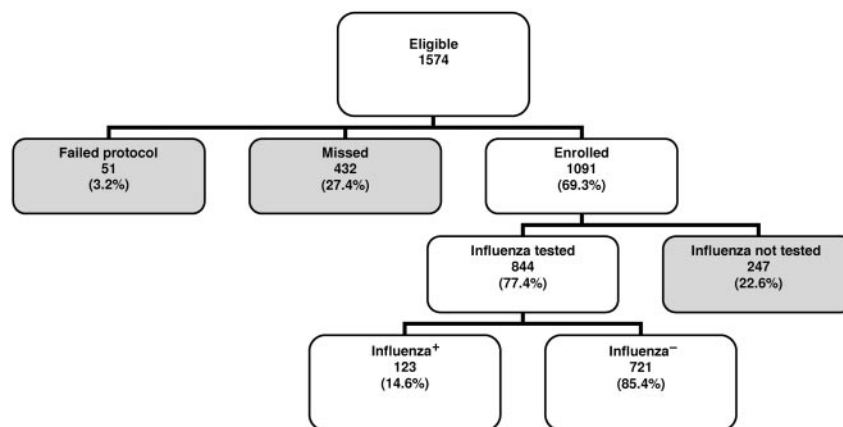


FIGURE 1 Patient eligibility and enrollment.

influenza virus and constitute the current analytic data set. One hundred twenty-three (14.6%) infants tested positive for influenza virus. Of the 844 patients enrolled and tested for the influenza virus, 712 (84.6%) were admitted to the hospital, 88 (12.4%) of whom were influenza-positive. Telephone follow-up was successfully completed on 103 (78.0%) of the 132 infants who were discharged from the ED.

Patient Demographics and Clinical Presentation of Patients Tested for Influenza Virus

The mean age of the 844 patients tested for the influenza virus was 35.2 days (SD: ± 14.1 days) and 33.4% were <29 days of age. A total of 458 (54.3%) of the 844 patients were boys, and the mean maximum rectal temperature recorded was 38.6°C (SD: ± 0.52). At presentation, most patients (94.2%) appeared clinically well by the YOS score.

Influenza-positive patients and influenza-negative patients were similar in age, gender, clinical appearance (YOS score), and maximum temperature recorded (Table 1). However, the influenza-negative group had a significantly greater rate of wheezing, clinical bronchiolitis, and significantly more elevated WBC counts, absolute neutrophil counts, and absolute band counts. When infants with RSV infection were removed from the influenza-negative group, however, the difference in the

rate of wheezing ($P = .8$) and bronchiolitis ($P = .99$) was no longer significantly different between groups.

SBI and Influenza Status

Of the 844 infants tested for influenza virus, 835 (99%) had urine cultures, 838 (99%) had blood cultures, and 810 (96%) had CSF cultures obtained. An additional 7 (1%) patients without CSF cultures were determined not to have bacterial meningitis by telephone follow-up. CXRs were obtained and interpretable on 262 (31%) infants, and stool cultures were obtained on 63 (7%) infants. Complete SBI status could be determined from a total of 809 (95.9%) infants. Overall, 95 of the 809 (11.7% [95% CI: 9.6–14.2]) infants with determinable SBI outcomes had SBIs. Of the evaluable enrolled patients, 80 of 835 (9.6%) had UTIs, 16 of 838 (1.9%) had bacteremia, 6 of 817 (0.7%) had bacterial meningitis, and 1 of 63 (1.6%) had bacterial enteritis. Five (0.6%) of the infants with UTIs had bacteremia, and 3 (0.4%) infants had meningitis and bacteremia.

Influenza-positive infants had a significantly lower prevalence of SBI compared with influenza-negative patients (Table 2). All 3 patients with SBIs in the influenza-positive group had UTIs. However, patients who were influenza-positive were significantly less likely to have UTIs than those who were influenza-negative (2.4% vs 10.8%, respectively). There were 16 (2.2%) cases of

bacteremia and 6 (0.9%) cases of meningitis among the influenza-negative group. Although there were no cases of bacteremia, meningitis, or bacterial enteritis in the influenza-positive group, when compared with the influenza-negative group, the differences were not statistically significant. There were no statistically significant changes in the comparison of the 2 groups when RSV-positive patients were removed from the influenza-negative group.

The 3 patients in the influenza-positive group with SBIs (UTIs) had $\geq 50\,000$ cfu/mL of *Escherichia coli* isolated from their urine cultures. All 3 patients were boys and did not appear clinically ill. One patient had a peripheral blood WBC count of 20 100/ μ L and a negative urinalysis. The 2 remaining patients had positive urinalyses and normal blood WBC counts.

Pneumonia and Influenza Status

Lobar pneumonia was diagnosed in 19 (7.3%) of 262 infants in whom CXRs were obtained and were interpretable. Lobar pneumonia was found in 1 of 36 (2.8% [95% CI: 0.5%–14.2%]) infants with influenza infection in whom CXRs were obtained compared with 18 of 226 (8.0% [95% CI: 5.1%–12.2%]) infants who were influenza-negative (difference: -5.2% [95% CI: -11.2% to 1.2%]). The influenza-positive infant with pneumonia was a 50-day-old girl who appeared clinically well, with a YOS score of 10. Her WBC count was 13 700/ μ L, with 27% bands, and she was hospitalized and treated with parenteral antibiotics.

Subanalysis of Patients According to Age

The overall rate of SBI in infants aged ≤ 28 days was 13.1% (35 of 268 [95% CI: 9.5%–17.6%]). None of the 36 (0% [95% CI: 0%–8.0%]) patients with influenza infection versus 36 of 232 (15.5% [95% CI: 11.1%–20.8%]) patients who were

TABLE 1 Patient Demographics According to Influenza Status

Variable	Influenza-Positive (n = 123)	Influenza-Negative (n = 721)	Mean Risk Difference (95% CI)	P
Mean age, d	36.6	34.9	1.7 (–1.1 to 4.3)	.2
Male gender, n/N (%)	68/123 (55)	390/721 (54)	1.1 (–8.3 to 10.7)	.8
Mean temperature, °C	38.7	38.6	0.03 (–0.06 to 0.12)	.5
Median YOS score (IQR)	6 (6–6)	6 (6–8)		.2
Wheezing, n/N (%)	2/123 (1.6)	48/719 (6.7)	–5.1% (–7.9% to –2.2%)	.02 ^a
Bronchiolitis, n/N (%)	8/123 (6.5)	101/719 (14.0)	–7.5% (–12.6% to –2.5%)	.02 ^a
Mean WBC, $\times 10^3/\mu$ L	9.4	12.1	–2.7 (–3.4 to –1.9)	$<.001$
Mean ANC, $\times 10^3/\mu$ L	3.6	5.1	–1.5 (–1.9 to –1.0)	$<.001$
Mean ABC, $\times 10^3/\mu$ L	0.4	0.9	–0.5 (–0.6 to –0.3)	$<.001$

^a $P > .05$ when RSV-infected patients were removed from the influenza-negative group. IQR indicates interquartile range; ANC, absolute neutrophil count; ABC, absolute band count.

TABLE 2 SBI According to Influenza Status

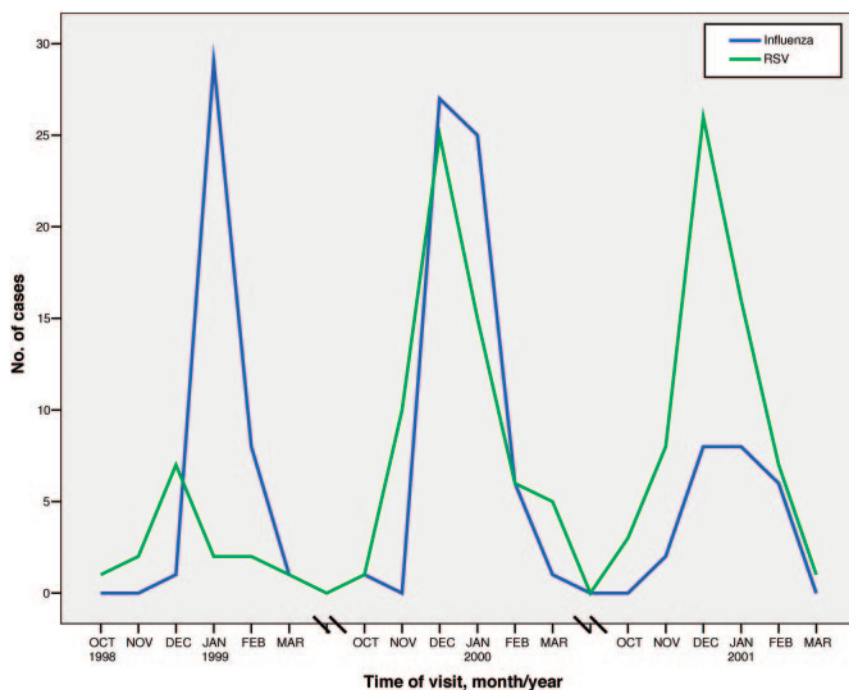
Variable	Influenza-Positive (N = 123)		Influenza-Negative (N = 721)		Relative Risk (95% CI)	P
	n/N	% (95% CI)	n/N	% (95% CI)		
SBI	3/119	2.5% (0.5%–7.2%)	92/690	13.3% (10.9%–16.1%)	0.19 (0.06–0.59)	<.001
UTI	3/123	2.4% (0.5%–6.9%)	77/712	10.8% (8.6%–13.3%)	0.23 (0.07–0.70)	.002
Bacteremia	0/123	0% (0%–2.4%)	16/715	2.2% (1.3%–3.6%)	0.00	.15
Meningitis	0/119	0% (0%–2.5%)	6/698	0.9% (0.3%–1.9%)	0.00	.6
Enteritis	0/3	0% (0%–56.2%)	1/60	1.7% (0.3%–8.9%)	0.00	.99

TABLE 3 Patient Demographics: Comparison by Influenza and RSV Status

Variable	Influenza-Positive (N = 114) ^a	RSV-Positive (N = 129) ^a	Mean Risk Difference (95% CI)	P
Mean age, d	36.1	36.2	−0.1 (−3.6 to 3.4)	.96
Male gender, n/N (%)	64/114 (56)	67/129 (52)	4.2 (−8.3 to 16.5)	.5
Mean temperature, °C	38.7	38.5	0.1 (0.02 to 0.2)	.03
Median YOS score (IQR)	6 (6–6)	6 (6–8)		.08
Wheezing, n/N (%)	2/114 (1.8)	31/129 (24.0)	−22.2 (−30.0 to −14.5)	<.001
Bronchiolitis, n/N (%)	8/114 (7.0)	57/129 (44.2)	−37.2 (−46.9 to −27.4)	<.001
Mean WBC, ×10 ³ /μL	9.5	12.8	−3.3 (−4.3 to −2.3)	<.001
Mean ANC, ×10 ³ /μL	3.6	4.9	−1.3 (−2.1 to −0.6)	<.001
Mean ABC, ×10 ³ /μL	0.4	1.2	−0.8 (−1.1 to −0.5)	<.001
SBI, n/N (%)	3/110 (2.7)	8/121 (6.6) ^b	−3.9 (−9.3 to 1.5)	.2

^a Excludes 9 infants who tested positive for both RSV and influenza.

^b Seven infants had UTIs and 1 infant had bacteremia; 2 of the infants with UTIs and the infant with bacteremia were <29 days of age.

**FIGURE 2**

Number of cases of influenza and RSV infections according to time of visit.

influenza-negative in the 0 to 28 age group had an SBI ($P = .007$).

In the 29 to 60 days age group, the overall rate of SBI was 11.1% (60 of 541 [95% CI: 8.7%–14.0%]). An SBI (UTI) was

present in 3 of 83 (3.6% [95% CI: 1.2%–10.1%]) patients with influenza infections versus 57 of 458 (12.5% [95% CI: 9.7%–15.8%]) patients who were influenza-negative ($P = .02$).

Comparison of Infants With Influenza Infections With Those With RSV Infections (Table 3)

Every infant tested for influenza virus was concomitantly tested for RSV. Of the 844 infants tested for both RSV and influenza virus, 129 (15.2%) were RSV-positive and 114 (13.5%) were influenza-positive. An additional 9 (1.1%) infants were positive for both RSV and influenza virus and were excluded from this comparative analysis. In 3 consecutive seasons, both influenza virus and RSV had peak activity in our study populations during the months of December and January (Fig 2). Analysis of the 243 patients who were either RSV-positive or influenza-positive in this analysis revealed similar mean age, gender, and clinical appearance (YOS score) between groups. Infants with RSV infections were also significantly more likely than infants with influenza infections to present to the ED with wheezing and bronchiolitis. RSV-positive infants also had significantly higher WBC counts, absolute neutrophil counts, and absolute band counts than influenza-positive infants (Table 3). The rate of SBI was greater in the RSV-positive infants when compared with the influenza-positive infants, although this comparison did not achieve statistical significance. Please refer to the original study for greater details on risk of SBI with RSV infections.¹

Evaluation of Missed Eligible Patients With Influenza Infections

Of the 432 infants who met eligibility criteria, but were not enrolled, 205

(47.5%) were tested for influenza virus, and 37 of the 205 (18.0% [95% CI: 13.4%–23.9%]) tested positive for influenza infection. The overall SBI status could be determined in 159 (77.6%) of the 205 infants tested for influenza. Overall, missed infants had a significantly lower rate of SBI (3.1% vs 11.7%; $P = .001$) and were less likely to be hospitalized (72.6% vs 84.6%; $P < .001$) than infants who were enrolled. These missed infants with influenza infections were similar in mean age, mean temperature, and percent male gender compared with enrolled infants with influenza infections (data not shown). None of the missed patients with influenza virus infections had an SBI.

DISCUSSION

This prospective, multicenter study demonstrates that febrile infants ≤ 60 days of age with influenza virus infections are at significantly lower risk of SBI than febrile infants without influenza virus infections. However, the rate of UTI among the influenza-positive patients remained nontrivial at a prevalence of 2.4%. We also demonstrated that influenza virus is not commonly associated with lower respiratory tract infections in young febrile infants. Finally, this study also demonstrates that influenza virus infections are one of the leading identifiable causes of fever and hospitalizations in infants ≤ 60 days of age during the winter months.

There have been several previous investigations that have demonstrated that the risk of SBI is significantly reduced in the presence of viral infections, such as bronchiolitis, croup, and stomatitis.^{1,9,38} In febrile infants with RSV infections, the prevalence of bacteremia has been reported to range from 0% to 1.1% and UTIs from 1.1% to 5.4%, both significantly lower prevalences than in RSV-negative infants.^{1,39–41}

In addition, febrile infants with enterovirus infections have been reported to have a concurrent rate of SBI of 6.6%, with the majority being UTIs.¹⁰

There has been limited study, however, about the risk of SBI in febrile infants with documented influenza infections. In a retrospective investigation of 705 febrile infants ≤ 36 months of age, of whom 163 (23%) had influenza virus infections, bacteremia was present in 0.6% and UTI in 1.8% of infants with influenza virus infections, which was significantly lower than the 4.2% rate of bacteremia and 9.9% rate of UTI in the infants who tested negative for influenza virus.¹¹ There were no cases of meningitis in the influenza-positive group. That study, however, included only 58 infants < 90 days of age with influenza virus infections, none of whom had a diagnosed SBI. Furthermore, the retrospective nature of the study precluded the assessment of clinical appearance. A prospective study evaluated the risk of SBI in febrile infants ≤ 90 days of age who were diagnosed with a variety of viral infections, including influenza virus.⁷ Infants who tested negative for viral infections were nearly 3 times more likely to have SBIs compared to infants with diagnosed viral infections (12.3% vs 4.2%; $P < .001$). There were no cases of SBI diagnosed in the 80 infants who were influenza-positive.

An association between influenza virus infections and bacterial infections has long been established.⁴² Typically, however, these are secondary infections rather than concurrent infections.^{28,43} Bacterial pneumonia is a leading cause of morbidity and mortality attributed to influenza virus infections.^{12,44,45} Proposed mechanisms include virus destruction of respiratory epithelium, virus-induced immunosuppression, upregulation of the expression of bacterial receptors, and increased bacterial adherence, which

allow for secondary bacterial invasion.^{26,27} This association is further evidenced by the significant reduction of bacterial infections, such as otitis media and pneumonia, in patients after receiving the influenza vaccination.^{46–49}

This study differs methodologically from previous studies in several important ways. Our study was conducted in a prospective fashion, therefore, we were able to incorporate historical and clinical data, including clinical appearance, from the time of presentation in the ED. This greatly avoids potential reporting bias that is often found in retrospective studies. The study sample size of the current study was large, in great part because of its multicenter involvement, which allowed for a powerful analysis. By including 5 separate pediatric EDs from wide geographical areas and serving diverse populations, the results are also likely to be widely generalizable. Finally, we limited enrollment to febrile infants ≤ 60 days of age, a group for which current ED practice guidelines strongly recommend a complete evaluation for sepsis, including lumbar puncture.^{6,50,50}

There have been several strategies proposed over the last decade to identify young febrile infants at very low risk for SBI on the basis of a constellation of clinical and laboratory evaluation.^{4–6,50} The emphasis of these strategies has been on their negative predictive values for SBI. It should be noted that using influenza status alone as a screening test for infants with SBI, with a positive influenza test being indicative of low risk for SBI, would result in a negative predictive value of 97.5% (95% CI: 93.0%–99.2%) for all infants in this study. Although other novel diagnostic technologies have been investigated, such as procalcitonin, C-reactive protein, interleukins, polymerase chain reaction, and gene expression patterns,^{10,51–57} larger mul-

ticenter studies need to be performed to better understand their role in the identification of SBIs in young febrile infants. The rapid detection of influenza infection by RIA may have important implications in the management of young febrile infants. Most notably, RIA is a relatively noninvasive test that may identify those infants at very low risk for SBI during influenza season, and reduce some laboratory testing and antibiotic treatment of young febrile infants >1 month of age.

Our study has some potential limitations. Although, to our knowledge, our investigation of young febrile infants with influenza infection is the largest prospective study of this type reported to date, we did not have sufficient power to find statistical differences in rates of bacteremia and meningitis between infants with and without influenza virus infections. In addition, the upper boundary of the 95% CI for both bacteremia and meningitis in infants with influenza infections was ~2.5%, and therefore, we cannot definitively exclude the possibility of a clinically relevant prevalence of concomitant SBIs in these infants. This is particularly true for the <29-day age group, in which we did not have a large number of patients. Another potential limitation is that not all centers tested for influenza B. On the basis of the prevalence of influenza B during the 3 winter seasons of patient recruitment (3.3%, 0.09%, and 4.9%),⁵⁸ we estimate that 20 to 25 infants may have been misclassified as influenza-negative. However, this does not impact the assessment of risk of SBI in patients with documented

influenza infections. In addition, enrolled patients were somewhat more ill compared with missed patients as assessed retrospectively by a lower rate of SBI and hospitalization in the latter group. However, none of the influenza-positive patients in either the enrolled or missed eligible group had bacteremia or meningitis, thereby strengthening our conclusions.

Finally, we selected RIA as our reference standard test, although viral cell culture remains the reference standard in the diagnosis of influenza virus infections.¹² The diagnosis of influenza virus by culture can take up to 10 days^{59,60} and, therefore, has no impact on acute clinical management of patients in the ED. However, viral cell culture, unlike RIA, is not dependent on antigen load, which may have resulted in false-negative results among some infants in our study population. Noteworthy is that the performance of influenza RIA is better in infants ≤90 days of age compared with older children, perhaps because of a higher viral load in the younger population.⁶¹

CONCLUSIONS

In our large, multicenter, prospective study, we found that febrile infants ≤60 days of age with influenza virus infections are at a significantly lower risk of SBI than those without influenza virus infections, although larger studies are needed to evaluate with greater confidence the risk of bacteremia and meningitis in infants infected with influenza virus. This has potential implications for the laboratory evaluation of young febrile infants >1 month of age with influenza virus infections.

Point-of-care testing for the influenza virus may aide the clinician in the evaluation of these infants and, therefore, should be considered. Finally, young febrile infants with influenza virus infections still have a clinically important prevalence of UTIs.

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Influenza Virus Infection and the Risk of Serious Bacterial Infections in Young Febrile Infants

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