Fever in the Toddler-Aged Child: Old Concerns Replaced With New Ones

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The widespread use of highly effective and safe vaccines against Haemophilus influenzae type b and Streptococcus pneumoniae has impacted the epidemiology of serious bacterial illness in the febrile child. Because of the resultant decline in the incidence of invasive pneumococcal disease, one needs to reconsider the evaluation and management of the febrile child. In particular, for well-appearing febrile children who are vaccinated, routine screening for occult bacterial infections with or without empiric treatment can no longer recommended. At the same time, early evidence suggests that infections due to nonvaccine serotypes are increasing along with selected invasive diseases such as complicated pneumonia. Therefore, although likely to evolve, the optimal management strategy for the well-appearing, immunized, febrile child may be screening for urinary tract infections and observation with adequate follow-up. Continued surveillance of disease due to nonvaccine serotypes is essential.

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Fever is one of the most important reasons for childhood visits to the emergency department (ED) and accounts for approximately 5.4 million ED visits annually in the United States [1]. Although most febrile children have an apparent source of infection or self-limited viral infections, approximately 6% to 14% will have fever without an apparent source (FWS) [2,3]. Most children with FWS have a nonbacterial cause of fever and are clinically indistinguishable from the small proportion of those with serious bacterial infections (SBIs) (occult bacteremia [OB], meningitis, lobar pneumonia, and urinary tract infections [UTIs]) when they first present to the ED. Because there is no single reliable clinical or laboratory (or a combination thereof) predictor of SBIs in otherwise well-appearing febrile children, practitioners frequently depend on a variety of guidelines in the evaluation of FWS [2]. This area continues to be debated, and substantial practice pattern variation has been documented in the evaluation of a child with FWS. In addition, the widespread use of highly effective and safe vaccines against Haemophilus influenzae type b (Hib) and Streptococcus pneumoniae (conjugate pneumococcal vaccine PCV7) has impacted the epidemiology of SBIs, prompting experts to reconsider the evaluation and management of the febrile child [4]. However, despite effectiveness against vaccine serotypes, there is evidence that invasive disease due to nonvaccine serotypes of S pneumoniae is increasing since the introduction of PCV7 [5]. The disease caused by these serotypes is troubling because of its severity and resistance to antibiotics [6-8].

This article will focus on FWS in young children (3-36 months old). We will discuss the changing epidemiology, diagnosis, and management of OB, meningitis, pneumonia, and UTIs in the era of widespread Hib and PCV7 immunization.
**The Epidemiology of OB in the Pre-PCV7 Era**

*Occult bacteremia* is defined as the presence of bacteria in the blood of a child who does not appear to be clinically septic or toxic. The epidemiology of OB has evolved substantially since the 1970s [9]. Before the introduction of Hib conjugate vaccine in 1990, the prevalence of OB was 2.4% to 11.6% in all children with FWS [10,11]. *S pneumoniae* OB was responsible for 50% to 90% of cases, 3% to 25% were due to *H influenzae*, and the rest of the cases were due to *Salmonella* species and *Neisseria meningitidis*. Since the introduction of the Hib vaccine, the incidence of invasive *H influenzae* (all types) infections among children younger than 5 years has decreased by 96%; and importantly, invasive disease due to Hib has decreased by 99% (34 cases per 100 000 in 1989 to 0.4 case in 1995) [12]. Two large studies of febrile children in the post-Hib era demonstrated a significant drop in the OB rate. In a prospective study of 9465 febrile children (3-36 months of age), Lee et al [13] found an OB prevalence of 1.57% (95% confidence interval [CI], 1.32%-1.83%). In a retrospective cohort of 5901 febrile children aged 2 to 24 months, Alpern et al [14] found an OB prevalence of 1.9% (95% CI, 1.5%-2.3%). *S pneumoniae* was responsible for 92% and 82.9% of all bacteremia pathogens, respectively.

**Streptococcus pneumoniae**

*S pneumoniae* continues to remain a serious pathogen in the developing and developed world. Its only known reservoir is the human nasopharynx, and there are 90 known immunologically distinct serotypes. This organism is responsible for 1.2 million deaths in children younger than 2 years and causes more deaths than any other vaccine-preventable organism [15]. In the United States, in the absence of vaccination, *S pneumoniae* caused approximately 17 000 cases per year of invasive disease among children younger than 5 years, 13 000 of which were of OB, 700 cases of meningitis, and 200 deaths [16]. Although most cases of pneumococcal bacteremia resolve spontaneously, it was estimated that 10% to 25% of infected children develop focal complications including cellulitis, pneumonia, meningitis, and sepsis [17]. Empiric treatment with antibiotics at the time of initial evaluation has been shown to reduce the rate of focal complications (from 10% to 4%), bacteremia (from 17% to 1%), fever (from 73% to 24%), and the need for hospitalization (from 50% to 12%) [18]. The above estimates were derived on data in the pre-PCV7 era, and more recent data suggest that the risk of developing meningitis is closer to 0.04% (1 in 2500) [19,20]. In the study of Alpern et al [14], 96% of pneumococcal OB resolved spontaneously and only 0.03% developed sepsis or meningitis. Yet despite its low case fatality rate, the morbidity and mortality associated with *S pneumoniae* meningitis are higher than those caused by *N meningitidis*, *Streptococcus* group B, *Listeria monocytogenes*, or Hib.

**Prevention of Pneumococcal Invasive Disease**

Prevention of invasive pneumococcal disease (IPD) by the use of vaccines is the most effective approach to reduce the burden of illness and its sequelae. The 23-valent polysaccharide pneumococcal vaccine that was licensed in 1983 is ineffective in children younger than 2 years. Covalent coupling of weakly immunogenic polysaccharides with a carrier protein, called conjugate vaccine, elicits strong antibody production and a booster response [15]. Based on the experience acquired with the highly effective Hib conjugate vaccine, a similar conjugate vaccine against *S pneumoniae* was developed. This vaccine, PCV7, has 7 serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) that are responsible for 80% to 95% of invasive diseases; and these same serotypes are also the most likely to be resistant to antimicrobials. Prelicensure studies [21] showed a 94% (95% CI, 80%-99%) decline in IPD in children who received PCV7, prompting the American Academy of Pediatrics and the Advisory Committee for Immunization Practices to recommend routine immunization for all children at 2, 4, 6, and 12 to 15 months of age in 2000 [16]. Postlicensure surveillance data published in 2003 by Black et al [22] revealed no cases of vaccine serotype disease in children younger than 1 year, with similar disease reductions seen in children younger than 5 years. The most recent report by the Active Bacterial Core Surveillance Group of the Centers for Disease Control and Prevention continues to demonstrate the impact of PCV7, with the largest percentage decline (82%) and the largest absolute rate reduction in overall IPD (175.8 cases per 100 000) observed among children aged 1 year, the age group with the highest baseline disease rate [5].

**The Epidemiology of OB in the Post–Pneumococcal Vaccine Era**

There are few ED-based studies in the post-PCV7 era that have specifically looked at the incidence of OB. A retrospective study conducted by Stoll and Rubin [23] demonstrated that the incidence of *S pneumoniae* OB was less than 1% (0.91%; 95% CI, 0%-1.9%) in febrile children (n = 329) 2 to 36 months of age. Herz et al (2006) [24] examined 41 948 blood cultures obtained from febrile children 3 to 36 months of age over a 5-year period (1998-2003) in the EDs and outpatient clinic. They compared the epidemiology of OB before and after the implementation of PCV7 vaccination in the Kaiser Permanente Clinics of Northern California. There was an 84% reduction in *S pneumoniae* bacteremia (1.3%-0.2%) and a 67% reduction in overall bacteremia (1.6%-0.7%).
over the 5 years. In another ED-based study by Sard et al [25], the overall rate of OB was 0.7% in a community hospital ED among well-appearing febrile children 1 to 36 months of age. Sixty-one percent of the cases of OB were due to *S. pneumoniae*. Finally, Carstairs et al [26] conducted a prospective observational study on febrile children (38°C, <36 months) and compared the prevalence of OB between those who had received PCV7 (n = 833) vs those who had not (n = 550). The overall rate of bacteremia was 4.2% (including contaminants), with 2.4% of nonimmunized children having OB compared with 0% of those who were immunized with any dose of PCV7 [26]. The authors were able to verify the immunization status of each enrolled child.

Although pneumococcus is the most common cause of OB, other causes of bacteremia can present with FWS. Data on other pathogens in the post-PCV7 era are lacking. The largest outpatient surveillance study in the post-PCV7 era offers some updated perspective on the relative frequency of infecting organisms [24]. This 5-year data set from Northern California revealed that bacteremia is now caused by *Escherichia coli*, nonvaccine serotypes of *S. pneumoniae*, *Staphylococcus aureus*, *N meningitidis*, *Salmonella* spp., and *Streptococcus pyogenes*. *Escherichia coli* was the second most common organism grown from the blood culture reflecting bacteremia in patients with UTI, which is the most common SBI in children with FWS. Experts suggest that without the availability of effective vaccines, the incidence of invasive disease caused by *Salmonella* and *Staphylococcus aureus* is likely to remain constant [27].

In summary, the overall prevalence of *S. pneumoniae* OB after PCV7 is less than 1%, much lower than the previous estimate of 1.5% to 1.9%. Nonpneumococcal organisms account for a higher proportion of OB in the post-PCV7 era.

### Occult Pneumonia

The decision to obtain a chest radiograph in the evaluation of a child with FWS is controversial and not evidence based. Accurate diagnosis of bacterial pneumonia is difficult because (a) even if *S. pneumoniae* is the most common bacterial cause of lobar pneumonia in children, most lower respiratory tract infections will be viral in nature; (b) chest radiograph results are often negative in the early stages of pneumonia; (c) it is often difficult to ascribe etiology, that is, bacterial or non-bacterial, on “positive” chest radiograph findings; and finally, (d) there is substantial variation in interpretation of chest radiographs even among trained radiologists [28]. Although the presence of pulmonary symptoms (cough) and signs (tachypnea, rales, respiratory distress, etc) increases the likelihood of a positive finding on chest radiograph, Bachur et al [29] showed that occult pneumonia was present in 26% of children younger than 5 years with fevers of more than 39°C and white blood cell (WBC) counts of at least 20 000 cells per microliter. Most research on occult pneumonia was conducted during the pre-PCV7 era. Zhou et al [30] have shown that the routine use of PCV7 has markedly reduced the rates of all causes of pneumonia including pneumococcal pneumonia in children younger than 2 years. The only published study addressing occult pneumonia in the post-PCV7 era was done by Murphy et al [31]. They reviewed the records of all febrile children younger than 10 years who had a chest radiograph for pneumonia. Among patients categorized as having no signs of pneumonia (n = 1084), 5.3% (95% CI, 4%-6.8%) had occult pneumonia. The likelihood of occult pneumonia increased with increasing duration of fever (likelihood ratio (LR+) 1.62 for fever greater than 3 days and LR+ 2.24 for fever greater than 5 days), presence of cough (LR+ 1.24), prolonged cough (greater than 10 days, LR+ 2.25), and a WBC count greater than 20 000 cells per microliter (LR+ 2.17). The authors concluded that there is limited utility in obtaining chest radiographs in febrile children without cough [31].

In summary, the impact of the PCV7 and the available data on occult pneumonia, it seems reasonable to obtain a chest radiograph in well-appearing children with FWS who have cough, fever longer than 3 days, and leucocytosis greater than 15 000/μL (if done).

### Meningitis

The most recent epidemiology of bacterial meningitis in children in the post-PCV7 era is provided by Tsai et al [32] based on an extensive review of the Nationwide Inpatient Sample (1994-2004). They found a 66% decrease in the average annualized rate of pneumococcal meningitis in children younger than 2 years and a 51.1% decrease in mortality. An estimated 1822 cases of meningitis in children younger than 5 years were prevented because of PCV7. In addition, there was a 43% decrease in overall rates of meningitis in children younger than 2 years. They also documented a 17.5%, 54%, and 50% decrease in meningitis due to group B streptococcal meningitis, meningococcal meningitis, and Hib meningitis.

Thus, PCV7, along with the use of peripartum antibiotics and use of meningococcal vaccine, has substantially reduced the incidence of bacterial meningitis. In well-appearing children with FWS, routine evaluation of meningitis by a lumbar puncture cannot be recommended.

### Occult UTI

Urinary tract infection is the most common cause of SBI in children with FWS, and the prevalence of UTI has not changed because of PCV7 vaccine. This topic is further discussed elsewhere in this journal, and a recent
comprehensive evidence-based review on the evaluation and management of febrile UTI was published by Shaikh et al [33].

**Guidelines for the Management of FWS**

The earliest version of management guidelines published simultaneously in 1993 in Pediatrics and Annals of Emergency Medicine were based on consensus opinions of an expert panel and on the available evidence [2]. These guidelines were revised by Baraff [34] in 2000. In these guidelines, screening urine analysis was recommended (based on age and sex) for all children with a fever greater than 39°C. For children who had not received PCV7 and had a temperature of 39.5°C, the recommendations were to obtain a complete blood count. Empirical treatment with ceftriaxone was recommended if the WBC count was at least 15 000 cells per microliter (absolute neutrophil count ≥10 000). A chest radiograph was recommended in children with a WBC count greater than 20 000 cells per microliter, an oxygen saturation of less than 95%, or clinical evidence of respiratory disease. In 2003, the American College of Emergency Physicians Clinical Policy Committee revised the guidelines based on a comprehensive review of literature and graded recommendations based on the strength of evidence [28]. They recommend empiric antibiotic therapy for all febrile non–toxic-appearing children with a WBC count of at least 15 000 cells per microliter. Interestingly, the temperature cutoff in the American College of Emergency Physicians guideline is lower at 39°C; and there is no mention of the immunization status of the child, although the preceding discussion does comment on the substantial impact of PCV7 vaccine. Apart from the fact that there is variation among practitioners [35], there are several guidelines that reflect local consensus opinion and practitioner comfort in the evaluation of a child with FWS. Children’s Hospital of Boston’s guideline [36] recommends obtaining urine studies (analysis and cultures) if the febrile well-appearing child is older than 6 months and has received 3 doses of both Hib and PCV7 vaccine. They recommend obtaining blood (complete blood counts, blood cultures) and urine (analysis and urine cultures) only if the temperature is at least 39°C and if the infant’s immunizations are incomplete or if the patient’s age is younger than 6 months. Empiric antibiotics are recommended for WBC counts of at least 15 000 cells per microliter, and chest radiographs are recommended if the WBC counts are at least 20 000 cells per microliter. The algorithm suggested in the evidence-based clinical practice guidelines for FWS in children 2 to 36 months old at Children’s Hospital Medical Center in Cincinnati is even less conservative [37]. The guidelines recommend screening for OB if the child has an incomplete PCV7 series for age (the child does not have to have all 3 doses of PCV7), is ill appearing, has fever of at least 40°C, or has meningococcal contacts.

In summary, there are several available management guidelines that reflect varying concerns about the prevalence and likelihood of identifying SBI in the evaluation of the well-appearing child with FWS.

**FWS—Old Concerns Replaced With New**

Conjugate vaccines provide serotype-specific protection. They also reduce carriage of vaccine-related serotypes that are often antibiotic resistant in the vaccinated individual, as well as in the population at large through herd immunity. However, by reducing the carriage of vaccine-related serotypes, an ecologic niche is left open that could be filled by nonvaccine serotypes [7]. The first report documenting a rise in IPD by nonvaccine serotypes was in a multicenter study of children requiring hospitalization for IPD by the United States Pediatric Multicenter Pneumococcal Surveillance Group. Kaplan et al [38] noted a rise in disease caused by nonvaccine serotypes (types 15 and 33) in children younger than 2 years (the nonvaccine serotypes accounted for 37.6% of isolates in 2002 compared with 6% of isolates in the pre-PCV7 era). In a population-based study describing the temporal trends of IPD in Utah, Byington et al [6] documented a significant increase in the proportion of severe IPD and empyema cases due to non-PCV7 serogroups. Singleton et al [39] demonstrated an 82% increase in IPD in a highly vaccinated cohort of Alaskan children younger than 2 years. Importantly, there was a 140% rise in IPD in the post-PCV7 era by nonvaccine serotypes, with serotype 19A accounting for 28.3% of all invasive disease [39]. Others have shown a rise in IPD due to serogroups 15 and 33 [40]. The Centers for Disease Control and Prevention surveillance data released in 2008 showed that the largest absolute rate increase in non-PCV7 serotype IPD was observed among children younger than 1 year (10.8 cases per 100 000). Among children younger than 5 years, the incidence of serotype 19A IPD increased from 2.6 cases in 1998-1999 to 9.3 cases per 100 000 in 2005, the largest increase for any 1 serotype. In addition, in 2005, 40% of IPD among children younger than 5 years was caused by serotype 19A. Although PCV7 serotype incidence rates continued to decline through 2005 for all children younger than 5 years, overall IPD rates plateaued during 2002-2005 [23].

The recent documented increase in antibiotic resistance among nonvaccine strains may be occurring because of “serotype switching”—an ability of the pneumococcus to incorporate parts of capsules of other serotypes [41]. Thus, the potential exists for a vaccine serotype clone that is resistant to an antibiotic to switch its capsule to a nonvaccine serotype and evade the protective effects of PCV7 [7]. In particular, 19A variants have emerged as a major driver of nonvaccine serotype multiresistant IPD.
Complicated Pneumonia

The most common complications of pneumonia in children include necrosis, empyema, parapneumonic effusion, and lung abscess. Until the introduction of the pneumococcal conjugate vaccine, \( S \) \( pneumoniae \) was the most frequently isolated bacteria in children with complicated pneumonia; but \( S \) \( aureus \) has become the most frequently isolated bacteria since 2000 [42]. A multicenter, retrospective study involving 8 children's hospitals in the United States examined 368 hospitalized children with pneumococcal pneumonia before the widespread use of the pneumococcal vaccine. Of these, 133 were complicated cases and required thoracostomy drainage. The frequency of complicated cases increased during the study period from 23% in 1994 to 53% in 1999. Ninety-eight percent of all patients recovered completely from the pneumonia [43]. A retrospective study published in 2005 looked at 230 cases of pediatric complicated community-acquired pneumonia pre- and post-universal pneumococcal vaccination in the United States (1999-2000 vs 2001-2002) and found that (1) the number of patients admitted with empyema (per 10 000 admissions) had decreased from 23 to 12.6; (2) the prevalence of \( S \) \( pneumoniae \) had decreased from 66% (29 of 44) to 27% (4 of 15); and (3) \( S \) \( aureus \) had become the most common pathogen isolated (18% vs 60%), with 78% of those being methicillin resistant [42].

Issues Surrounding the Evaluation and Management of FWS in the Post-PCV7 Era

Screening tests lack sufficient sensitivity and specificity in detecting OB. Although appearance of the child, height of fever, and young age increase the likelihood of SBI, they are by themselves insufficient for diagnosis. Screening tests such as a peripheral WBC count cutoff of 15 000/\( \mu \)L have been traditionally used as predictors of SBI, but recent literature continues to indicate that the WBC is neither sensitive nor specific (sensitivities have ranged from 45% to 80% and specificities from 67% to 79% in different studies) [44]. It is also important to recognize that traditionally accepted WBC cutoffs may no longer be relevant as the epidemiology of OB shifts away from \( S \) \( pneumoniae \). Twelve percent to 16% of all children with meningococcal disease have an unsuspected infection, and Kuppermann et al [19] suggest that routine screening of febrile children for meningococcal bacteremia with complete blood counts is not useful. Zaidi et al [45] retrospectively reviewed non-\( typhi \) \( Salmonella \) bacteremia and showed that 54% had a median WBC count of 10 000/\( \mu \)L. The addition of biomarkers such as \( C \)-reactive protein, procalcitonin, and interleukins to routine screening tests for detecting SBIs has been unsuccessful in improving the clinician's ability to evaluate well-appearing febrile infants for SBI [44].

There is lack of agreement between published guidelines, and substantial practice pattern variation exists in the evaluation of the febrile child. A survey conducted among 7500 pediatricians and 7500 ED physicians in 2004 regarding management of 2 hypothetical cases of well-appearing febrile children (ages 7 and 20 months) with and without pneumococcal vaccine documented general reduction in the need for tests and empiric antibiotics attributed to the perceived impact of the vaccine [35]. This study also documented that there was a significant practice pattern variation in the evaluation and management of the febrile child based on the clinical setting, office vs ED.

The diagnosis of bacterial infections in young febrile children is largely dependent on culture of the microbial pathogen in the appropriate clinical specimens (cerebrospinal fluid, blood, urine, or respiratory secretions). However, many pathogens grow slowly or require complex media [46]. A significant number of clinically important microbial pathogens remain unrecognized because they are resistant to cultivation in the laboratory [47]. Furthermore, 90% of all blood cultures do not grow any organism; and of the approximately 10% that do grow organisms, only half represent true bacteremia (ie, true positives) and half represent contaminants (ie, false positives). The issue of false positives (contaminants) cannot be overemphasized because they lead to further testing, use of antibiotics, hospitalization, and iatrogenic complications [48]. All 4 studies in the post-PCV7 era had a higher false-positive blood culture rate than true positives. In fact, the analysis of Herz et al [24] revealed that more than 70% of all blood cultures were contaminants in the post-PCV7 population and the rate increased with decreasing age. The 8-year study of Sard et al [25] revealed an 80% false-positive rate; and they identified a low WBC count, lower presenting temperature, and a longer time to culture positivity as predictors for contaminants. They estimated that the cost of reevaluating a febrile child with a false-positive blood culture would be $12 340 for every true-positive blood culture given that the rate of false-positive blood cultures has increased from 4 times to 7.2 times compared with true-positive cultures [25].

Given the declining rate of OB, it may be no longer cost effective to perform routine screening and treat young children with FWS with empiric antibiotics. Lee et al [3] conducted a cost-effectiveness analysis and concluded that if the rate of OB falls below 0.5% with widespread use of the PCV7, then strategies that use empiric testing and treatment should be eliminated. Yamamoto [49] conducted a decision analysis for febrile children at risk for OB in the post-PCV7 population and concluded that observing these children without routine blood tests or antibiotics may be the superior management strategy.
Because most children with FWS are likely to have viral etiologies for fever, advances in rapid viral detection technologies have led to increasing use of these assays for evaluation of young febrile infants; and their use is changing management strategies [50-52]. Sharma et al [50] and Bonner et al [51] in their respective studies on febrile children noted that the practitioner’s awareness of influenza positivity affected ancillary testing as well as antibiotic use. Febrile children with documented viral infections had a lower prevalence of SBI, and the authors recommend that blood cultures may not be necessary in their evaluation [52].

Summary
The epidemiology of SBI (mainly OB) continues to evolve; and the impact of the 2 conjugate vaccines, Hib and PCV7, has been substantial. The overall prevalence of OB is likely well below 1%; and routine screening with blood tests should no longer be recommended because (a) they are not cost effective, (b) there is an unacceptably high rate of false-positive blood cultures, (c) screening tests lack test characteristics that would make them sufficiently discriminative, (d) there is significant practice pattern variation based on age of the child and setting of the practitioner, and (e) advances in rapid viral testing and widespread use of PCV7 are already altering physician behavior. Studies on SBI conducted in the past have used different inclusion criteria (especially age and temperature), have been retrospective in nature, have used screening tests inconsistently, and have often been conducted in single or small numbers of academic centers. It is highly unlikely in this age of effective Hib and PCV7 vaccination that a prospective multicenter study that enrolls and consistently evaluates (to eliminate selection and verification bias) febrile children with a battery of comprehensive screening tests will be undertaken. It is our opinion that, as of yet, no single published algorithm in the evaluation of FWS can be recommended. Present evidence suggests that screening for urinary tract infection must be done in well-appearing febrile children (based on age, sex, and circumcision status). Given the prior discussion, the best management strategy for well-appearing children with FWS may be observation without screening tests as long as appropriate follow-up can be ensured. Age-appropriate immunization status should be an important consideration in the decision to obtain screening blood tests. The impact of nonvaccine serotypes causing invasive disease is still unclear, but continued surveillance is important. In conclusion, we suggest that a multidisciplinary panel of experts in pediatrics, pediatric emergency medicine, and infectious diseases be formed to develop a consensus guideline that takes the impact of conjugate vaccine, physician and parent preferences, and evolving epidemiology of SBI into account and provide recommendations for the evaluation of the well-appearing child with FWS.

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References
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[52] Smitherman HF, Caviness AC, Macias CG. Retrospective review of serious bacterial infections in infants who are 0 to 36 months and have influenza A infection. Pediatrics 2005;115:710-8.