



Association of Bacteremia with Vaccination Status in Children Aged 2 to 36 Months

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Objective To determine the association between bacteremia and vaccination status in children aged 2-36 months presenting to a pediatric emergency department.

Study design Retrospective cohort study of children aged 2-36 months with blood cultures obtained in the pediatric emergency department between January 2013 and December 2017. The exposure of interest was immunization status, defined as number of *Haemophilus influenzae* type B (Hib) and *Streptococcus pneumoniae* vaccinations, and the main outcome positive blood culture. Subjects with high-risk medical conditions were excluded.

Results Of 5534 encounters, 4742 met inclusion criteria. The incidence of bacteremia was 1.5%. The incidence of contaminated blood culture was 5.0%. The relative risk of bacteremia was 0.79 (95% CI 0.39-1.59) for unvaccinated and 1.20 (95% CI 0.52-2.75) for undervaccinated children relative to those who had received age-appropriate vaccines. Five children were found to have *S pneumoniae* bacteremia and 1 child had Hib bacteremia; all of these subjects had at least 3 sets of vaccinations. No vaccine preventable pathogens were isolated from blood cultures of unvaccinated children. We found no *S pneumoniae* or Hib in children 2-6 months of age who were not fully vaccinated due to age (95% CI 0-0.13%) and the contamination rate in this group was high compared with children 7-36 months (6.6% vs 3.7%).

Conclusions Bacteremia in young children is an uncommon event. Contaminated blood cultures were more common than pathogens. Bacteremia from *S pneumoniae* or Hib is uncommon and, in this cohort, was independent of vaccine status. (*J Pediatr* 2021;232:207-13).

Before the introduction of the *Haemophilus influenzae* type B (Hib) and pneumococcal conjugate vaccines (PCVs), the incidence of occult bacteremia in children aged 3-36 months was 3%-11%.¹⁻³ Historically, Hib was responsible for 10% of pathogens isolated from the blood, and *Streptococcus pneumoniae* was the source in 85% of cases.⁴ The rates of bacteremia are affected by vaccines.⁵⁻⁸ The Hib vaccine, introduced in the late 1980s, was associated with a drop in cases of Hib-related disease in the US from 200 000 per year to 40 per year.⁹ Several studies have demonstrated vaccine effectiveness in both nasal carriage and overall disease rates.¹⁰⁻¹² By the year 2000, after widespread routine vaccination against Hib, the incidence of bacteremia in febrile children aged 3-36 months fell to 1.6%-4.3%^{5,6,13}; >90% of cases of bacteremia were caused by *S pneumoniae*.¹³ Significant decreases in rates of bacteremia also were noted after introductions of the 7-valent PCV (PCV7) in the year 2000^{6,14,15} and 13-valent PCV (PCV13) in 2010.^{5,6,16} As of 2017, the estimated rate of pneumococcal bacteremia in 3- to 36-month-old children was as low as 0.02%.⁵

The increase in parental preference for alternate vaccine schedules and undervaccination^{17,18} has resulted in concern for resurgence of vaccine-preventable bacteremia.¹⁸⁻²⁰ International studies of bacteremia in populations with partial vaccine coverage mirror results in the US, noting a decline in invasive pneumococcal disease.^{5,6,21} This suggests the presence of herd immunity within these populations.²²

Vaccination has led to a marked change in diagnostic practices for febrile infants and toddlers.^{6,23-25} The only serious bacterial illness of concern in a vaccinated child aged 3-36 months is a urinary tract infection.¹ Further, blood cultures obtained in emergency departments (EDs) are more likely to grow contaminant bacteria than pathogens.²⁶ These data have led to decreases in the need for obtaining blood cultures in otherwise well-appearing and vaccinated children.^{25,27-30}

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ED	Emergency department
Hib	<i>Haemophilus influenzae</i> type B
PVC	Pneumococcal conjugate vaccine
WBC	White blood cell

We sought to determine the association of bacteremia and vaccination status in children aged 2-36 months presenting to a pediatric ED. We also set out to estimate the rate of bacteremia and vaccine-preventable bacteremia in unvaccinated children aged 2-36 months compared with age-matched vaccinated children.

Methods

A retrospective cohort study of all children aged 2-36 months with blood cultures obtained in a single pediatric ED from January 1, 2013, through December 31, 2017, was performed after local institutional review board approval. This study took place in a 312-bed quaternary care pediatric referral hospital in the Northeastern US. The institution includes a 45-bed ED where 90 000 patients are seen annually by pediatric emergency medicine attendings and fellows, general pediatricians, advanced practice providers, and residents.

Selection of Participants

Children aged 2-36 months with blood cultures obtained in the ED were eligible for inclusion. We chose 2 months as the lower age limit due to an institutional febrile neonate guideline addressing the care of infants up to 60 days of life and 36 months as our upper age limit to maintain consistency with previous fever without source studies.^{5,27,31-33} Children with comorbidities at the time of visit that increased their risk of bacteremia were excluded. Feudtner criteria were reviewed in the setting of bacteremia, and expert consensus identified these conditions: presence of central catheters or peripherally inserted central catheters, active chemotherapy, short gut syndrome, organ transplantation, chronic steroid use, and congenital immunodeficiency syndromes.³⁴ In rare instances in which chart abstractors felt that an additional comorbidity should be considered for exclusion, senior authors discussed and adjudicated. Finally, patients were excluded if their vaccination status was unable to be determined.

Measurements

A total of 5534 blood cultures was obtained during the study period. A random sample of 1000 encounters was selected to estimate vaccination status, patient characteristics, presence of comorbidities, and bacteremia for the entire population. The complete dataset was sorted by year, with each encounter assigned a random number in Excel (Microsoft); 200 records from each of the 5 years were included in the random sample. Due to the rarity of the outcome, all encounters with positive blood cultures during the study period were reviewed to accurately determine their vaccination status. All data points were reviewed and reported for these subjects; therefore, extrapolation was not performed for subjects with positive blood cultures. These extrapolation methods have been used previously to describe populations where review of all subjects would be impractical.³⁵ Two abstractors performed manual chart review and data extraction via the electronic health record (Cerner) into Research Electronic Data

Capture (REDCap) (Vanderbilt University) database. REDCap is a secure, Web-based software platform designed to support data capture for research studies. The abstractors were blinded to the organism and pathogenicity of each blood culture. Data collection included date and time of visit, patient age, medical history, vaccination status, complete blood count results, appearance on initial examination, duration of fever, and blood culture results. Ten percent of charts were reviewed for congruency in data transfer and discrepancies were resolved by consensus. PCV13 and Hib vaccination status was ascertained by accessing the state vaccine registry through the electronic health record. If vaccination records were incomplete or inconsistent with physician documentation for the encounter, the patient's pediatrician was contacted by 1 of the authors for complete vaccination records. Ill appearance was defined as documentation of "ill-appearing," "toxic-appearing," poor perfusion including capillary refill time >3 seconds, or respiratory distress. Missing variables were excluded from the analysis. Unvaccinated and undervaccinated subjects were analyzed as mutually exclusive groups. Subjects were assigned a vaccination status based on the lowest number of Hib or PCV doses. Unvaccinated was defined as not receiving any Hib or PCV vaccines. Undervaccinated was defined as subjects receiving only 1 set of vaccines before 5 months and 1 or 2 sets of vaccines before 7 months. Children older than 7 months of age were considered undervaccinated if they had received fewer than 3 sets of vaccines. An infectious disease specialist, blinded to subject information, reviewed the organisms present to determine pathogens and contaminants.^{36,37} In the case of multiple organism growth, cultures were cataloged based on the most pathogenic organism. After completion of data collection, culture results were reviewed by 2 authors to confirm the pathogenicity of each organism in the clinical context. Contaminants were subsequently analyzed as negative blood cultures.

Outcomes

The primary outcome was rate of bacteremia from pathogenic organisms. The exposure of interest was vaccination status. Patients were grouped according to the number of PCV and Hib vaccinations received. Secondary outcomes included organisms responsible for bacteremia, rate of bacterial contamination of blood cultures, and historical and laboratory characteristics of children with bacteremia.

Statistical Analyses

Visit-level analysis was performed, allowing for inclusion of repeat visits by the same child. Descriptive statistics are presented as means and SDs for continuous variables and number and percentages for discrete variables. Bootstrapping performed with 1000 repetitions was used to estimate bias for rate of bacteremia and positive blood culture rate and 95% CIs (Matlab R2020b; The Mathworks Inc). Demographics and clinical characteristics were compared between groups using χ^2 testing for categorical variables and Kruskal-Wallis analysis of variance for continuous variables. Bivariate

logistic regression analysis was performed between the outcome and the variables listed in [Table I](#) (available at www.jpeds.com) and no collinearity was established. Subsequently, a multivariable logistic regression model was developed to estimate the association between pathogenic blood culture and vaccination status, age, fever duration, clinical appearance, white blood cells (WBC), platelets, neutrophils, and bands. Relative risk for pathogenic growth on blood culture was calculated using on-schedule vaccinated children as a reference group. Significance was set a priori at $P \leq .05$ for all statistical comparisons (Prism 8.0.1; GraphPad).

Results

During the study period, a total of 5534 blood cultures were obtained from children aged 2-36 months who presented to a single pediatric ED. After applying exclusion criteria to the 1000 encounter random sample, 857 encounters met inclusion criteria ([Figure 1](#)). In the excluded population, 2 subjects had blood cultures positive for *S pneumoniae*. One subject was excluded for oncologic disease and the other

was excluded for chronic steroid use; both were fully vaccinated for age. By applying our extrapolation factor, 4742 encounters served as the denominator for eligible patients ([Table II](#)). Of the 651 encounters with positive blood cultures during this time period, 313 met inclusion criteria ([Figure 2](#) and [Table II](#)). Unvaccinated subjects comprised 15.16% (719/4742) of the cohort, and 6.64% (315/4742) were undervaccinated for age. [Table II](#) displays the characteristics of the study sample.

Vaccination status was not significantly associated with bacteremia. The relative risk of bacteremia was 0.79 (95% CI 0.39-1.59) for unvaccinated and 1.20 (95% CI 0.52-2.75) for undervaccinated children relative to those who had received age-appropriate vaccines. In all vaccination groups, the rate of bacteremia was less than 2% ($n = 73$, [Table III](#)). When considering vaccine-preventable bacteremia, the rate in 2- to 6-month-old unvaccinated and undervaccinated children was 0% (95% CI 0-0.53%). Of older unvaccinated and undervaccinated children, the rate of vaccine-preventable bacteremia was 0% (95% CI 0-1.43%) in 7- to 12-month-old children and 0% (95% CI 0-1.15%) in 13 to 36-month-old children.

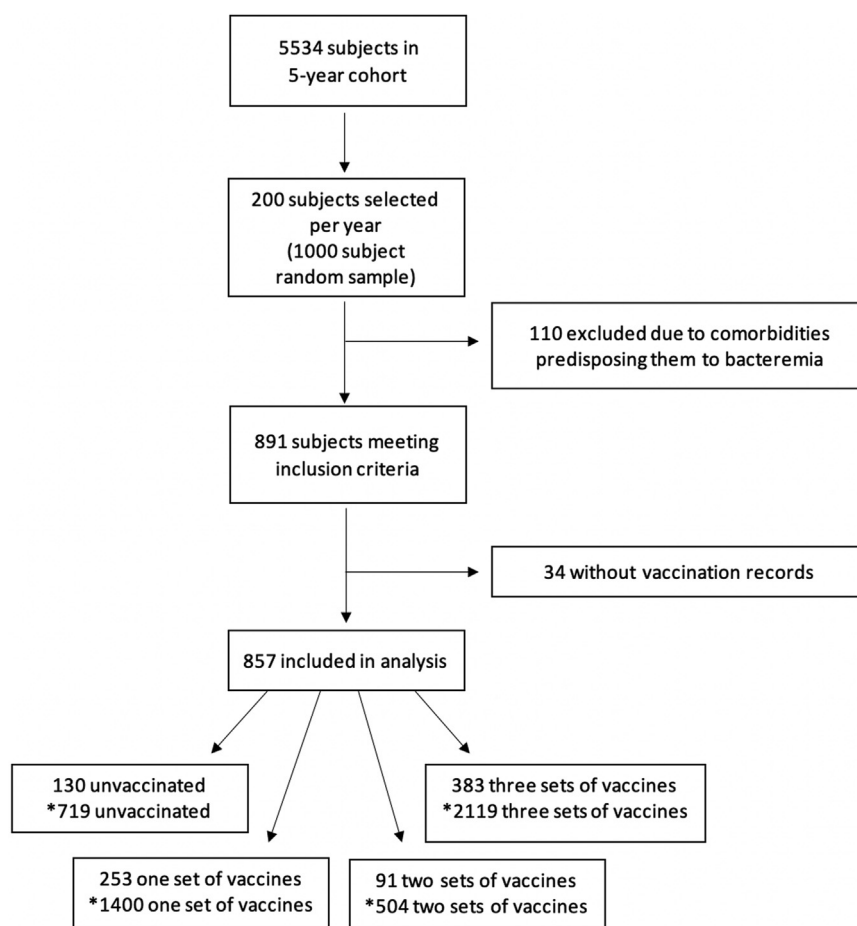


Figure 1. Flowsheet of encounters in random sample, including both positive and negative blood cultures. *Extrapolation factor of 5.534 applied, resulting in final cohort.

Table II. Characteristics of children meeting inclusion criteria in the extrapolated cohort (n = 4742)

Characteristics	Number of <i>S pneumoniae</i> and Hib vaccines				P value
	0	1	2	3	
Blood cultures, n	719	1400	504	2119	
Age, mo, median (range)	2 (2-36)	3 (2-31)	5 (2-26)	16 (6-36)	<.001
Female, n (%)	332 (46.2)	647 (46.2)	227 (45.0)	986 (46.5)	.95
Race, n (%)					
White	493 (68.5)	847 (60.5)	304 (60.3)	1515 (71.5)	
Black	149 (20.7)	404 (28.8)	138 (27.4)	448 (21.1)	
Asian	17 (2.4)	61 (4.4)	28 (5.6)	17 (0.8)	
Other	60 (8.5)	88 (6.3)	34 (6.7)	139 (6.6)	

The overall incidence of positive blood cultures in this study sample was 6.6%. However, after we removed cultures growing only contaminants, only 73 encounters were found to have blood cultures with pathogenic organisms. Thus, the rate of bacteremia was 1.5%. After bootstrapping was performed to determine the potential bias of the sample population compared with the overall population, the rate of positive blood cultures was 6.8% (95% CI 6.8%-5.9%, bias 0.12%) and the rate of bacteremia was 1.5% (95% CI 1.5%-1.6%, bias +0.0056%).

The most commonly isolated pathogens were *Staphylococcus aureus* (n = 19, 24%), *Escherichia coli* (n = 13, 16.5%), *Streptococcus pyogenes* (n = 6, 7.6%), and *S pneumoniae* (n = 5, 6.3%) (Table II and Table IV [available at www.jpeds.com]). No vaccine-preventable pathogens were

isolated from blood cultures of unvaccinated children. Unvaccinated children had the lowest rate of bacteremia (1.25%). Five children were found to have *S pneumoniae* bacteremia and 1 child had Hib bacteremia; all of these subjects had at least 3 sets of vaccinations (Table V; available at www.jpeds.com). Serotype information was available on 4 of the subjects with *S pneumoniae*, and all isolates were nonvaccine serotypes.

In the multivariable regression model, patient factors significantly associated with bacteremia included older age (aOR 1.05, 95% CI 1.0-1.09), increased WBC (aOR 1.09, 95% CI 1.04-1.14), increased absolute band count (aOR 1.05, 95% CI 1.01-1.10), and ill-appearance (aOR 6.01, 95% CI 3.09-11.67) (Table I and Table VI [available at www.jpeds.com]).

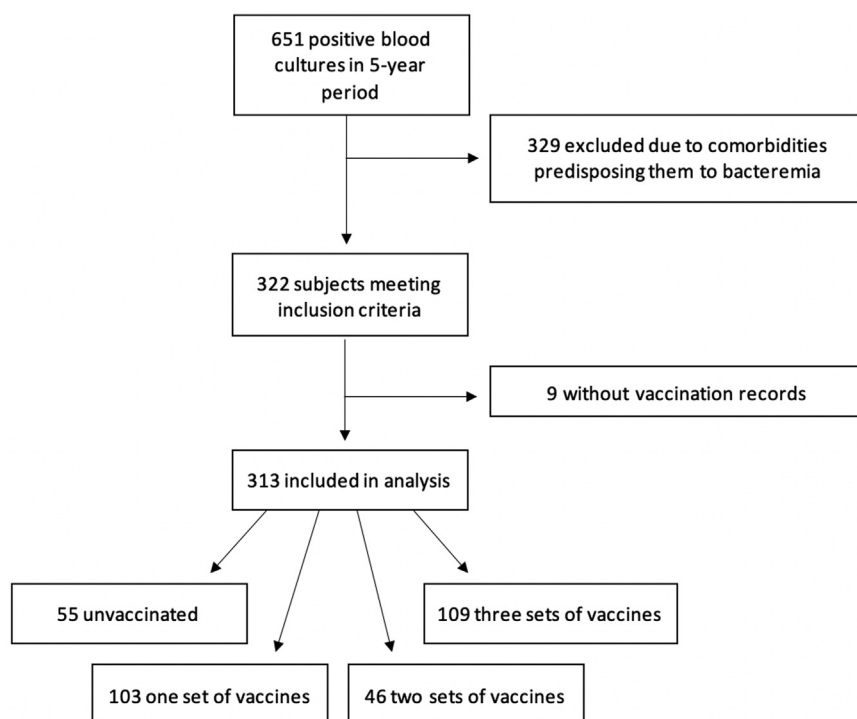
**Figure 2.** Flowsheet of encounters with positive blood cultures.

Table III. Distribution of pathogenic and contaminant BCx by vaccination status

Blood culture results	Number of <i>S pneumoniae</i> and Hib vaccines				P value
	0	1	2	3	
Blood cultures, n	719	1400	504	2119	
Positive BCx, n (%)	55 (7.7)	103 (7.4)	46 (9.1)	120 (5.1)	.02
Pathogens, n (%)	9 (1.3)	22 (1.6)	10 (2.0)	32 (1.5)	.64
Pathogen relative risk (95% CI)	0.83 (0.40-1.73)	1.04 (0.61-1.78)	1.31 (0.65-2.66)	1 [reference]	
Pathogenic organism, n					
<i>S aureus</i>	2	6	5	4	
<i>S pneumoniae</i>	0	0	0	5	
<i>S pyogenes</i>	1	2	0	3	
<i>E coli</i>	4	5	1	3	
Hib	0	0	0	1	
Other	2	9	4	16	
Contaminant, n (%)	46 (6.4)	81 (5.8)	36 (7.1)	77 (3.6)	<.01
Contaminant relative risk (95% CI)	1.76 (1.23-2.51)	1.59 (1.17-2.16)	1.89 (1.34-2.89)	1 [reference]	

BCx, blood cultures.

Blood culture data also were analyzed by the age of the subjects, regardless of vaccination status (Table VII; available at www.jpeds.com). The rate of bacteremia was not significantly different between age groups. Blood cultures were obtained most commonly in 2- to 6-month-old children but did not demonstrate a greater rate of bacteremia (1.6%).

Overall, 5.0% (n = 238) of blood cultures were found to have contaminant growth. The rate of contaminated blood cultures was greater than pathogenic blood cultures in all vaccination groups.

Discussion

In this retrospective cohort study of 4742 blood cultures obtained from children in the pediatric ED, we found that vaccination status was not associated with bacteremia. The overall incidence of bacteremia in this cohort was 1.5%. The rate of bacteremia in unvaccinated children was 1.3%, whereas the rate of contaminant blood cultures was 6.4%. Well-appearing children were significantly less likely to have pathogens isolated from their blood cultures than children who were deemed ill-appearing.

Almost as many blood cultures were obtained in children 2-6 months of age (n = 2225) than in the remaining age groups combined (n = 2517). This is likely driven by concern that these children are not fully vaccinated against *S pneumoniae* or Hib. However, we found no cases of either pathogen in children aged 2-6 months (95% CI 0-0.13%). We suspect this is related to the presence of maternal antibodies protecting these young infants,^{38,39} as this age group was at the lowest risk for *S pneumoniae* and Hib before the development of these vaccines, and herd immunity secondary to successful vaccination campaigns.^{7,8} We found that children aged 2-6 months are unlikely to be at greater risk of *S pneumoniae* and Hib merely because of their age and vaccination status.

Studies completed after the establishment PCV13 and Hib vaccine programs have demonstrated a rate of bacteremia at or below 1%,^{5,6,14,25,29} lower than the overall rate of bacteremia in our study of 1.5%. Our cohort is composed of children cared for at a pediatric quaternary care facility. It is

possible that the acuity of patients presenting to our institution is greater than other studies in which subjects were included from outpatient offices and urgent care centers, thus leading to a greater rate of serious illness. Further, as more literature is produced on the declining rates of bacteremia,^{5,6,10,11,14,15} it is possible that the institutional norm of ordering laboratory analyses has changed such that blood cultures are not routinely obtained for children presenting with fever without a source but rather reserved for those instances when bacteremia is strongly considered. Still, there remains an overall lack of guidance on when to obtain blood cultures, leaving this clinical decision at the discretion of the provider and an area for future research. Future prospective studies are necessary to confirm these findings on a larger scale to guide targeted institutional and regional approaches to obtaining blood cultures in this lower risk population. Our results support revisiting the need for routine blood cultures based on age, as nonvaccine preventable pathogens were more prominent findings, indicating that children may have had a source for their bacteremia.

The rates of *S pneumoniae* and Hib bacteremia in our study mirrored previous publications at 0.11% for *S pneumoniae* and 0.02% for Hib. Hernandez-Bou et al identified the rate of *S pneumoniae* to be 0.5%²⁵ and Wilkinson et al reported isolating *S pneumoniae* in only 0.17% of blood cultures.²⁹ All of the cases of *S pneumoniae* and Hib bacteremia in this study were isolated from subjects who were fully vaccinated. In cases in which serotype data were available, all *S pneumoniae* isolates represented nonvaccine serotypes. According to school records, 96.3% of children enrolled in schools in the county of our institution received the recommended vaccines.⁴⁰ The extremely low rate of vaccine-preventable diseases found in this study is contingent on maintaining vaccine coverage that achieves herd immunity. The percentage of persons needing vaccinations to achieve herd immunity is dependent on numerous factors, such that there is not a universally defined threshold.²² A population-based study in Australia demonstrated a disease rate reduction from 1.74 per 100 000 to 0.08 per 100 000 after 90% vaccination coverage in children.⁴¹ Similarly, a study in England and Wales showed near eradication of

Hib with 89% vaccine coverage.⁴² However, in areas in which this coverage is not achieved or if vaccination rates decline, our results may not be generalizable.

Contaminant rates vary in the literature, with many studies of pediatric subjects reporting rates from 1.9% to 4%.^{5,25,29,43-45} In this study, 5.0% of blood cultures were contaminated and younger infants were significantly more likely to have contaminant growth, likely owing to the greater number of overall cultures obtained. In a systematic review of children presenting with fever without a source, the rate of contaminant growth exceeded that of pathogenic growth in all subjects.⁴⁶ This results in hundreds of thousands of dollars in healthcare costs.^{43,46} Mullan et al reported that the added healthcare cost of each contaminated blood culture was >\$3000 and others estimate \$6200.^{43,46} In addition to cost, patients with contaminated blood cultures are subject to additional unnecessary testing, antibiotics, and hospitalizations. Institutional guidelines limiting unnecessary blood culture ordering have been shown to significantly reduce the rate of contaminated cultures.⁴³

Considering the overall decline in vaccine-preventable diseases, specifically invasive pneumococcal disease and Hib, it is not surprising that experts have begun to suggest outpatient management rather than laboratory analysis, antibiotics, and hospitalization for otherwise-healthy and well-appearing febrile children.^{6,25} Well-appearance was the strongest predictor against bacteremia in our multivariable analysis. Subjective appearance has previously been shown to correlate to serious illness, with well-appearing children having a substantially lower risk than those who are felt to be ill- or toxic-appearing.³⁰ Although age, WBC, and absolute band count were found to be statistically associated with bacteremia, the absolute magnitudes make these factors unlikely to be clinically significant. Further studies are necessary to confirm these predictors in a larger study population.

Our study has several limitations, including biases inherent to a retrospective single-center study design. We were unable to determine the provider's reason for ordering blood cultures in all cases. It is possible that children with bacteremia were excluded due to lack of vaccination records. We attempted to mitigate this risk by contacting pediatricians when vaccination records were missing or incomplete. In addition, we reviewed the culture information for all excluded patients. Of the encounters excluded for missing vaccination data, no subjects had blood cultures positive for *S pneumoniae* or Hib. Only 2 subjects excluded for comorbidities had growth of *S pneumoniae* on blood culture. These subjects had received age-appropriate vaccinations at the time of the visits. No excluded encounters had Hib bacteremia.

Our results are based on an extrapolated cohort of patients. If this subcohort differs significantly from the entire population, the analysis may not be representative. However, we deemed the sample size of 1000 records an adequate representation of the overall study population based on historical rates of bacteremia. The bias in overall rates of bacteremia

was <0.01% as determined by bootstrapping, which provides additional validation of the sample population vs the study population. As all positive blood cultures were reviewed and all data points reported, the results of these encounters are unchanged by the extrapolation. Further, the proportion of positive blood cultures in the sample is the same as that in the cohort.

It is important to note that the county of our institution has a vaccination rate of 96.3% in children attending public, private, and parochial schools.⁴⁰ Herd immunity likely impacted the low number of children with blood cultures positive for vaccine-preventable organisms in our cohort. The rates of vaccination and/or bacteremia at our site may not be generalizable to other locales with variable vaccination rates.

Vaccination against *S pneumoniae* and *H influenza* has virtually eliminated these pathogens in children aged 2-36 months. Obtaining blood cultures based on vaccination status may not be routinely indicated unless these specific pathogens are of high clinical suspicion or in populations that may lack herd immunity due to low rates of vaccination. Young infants, between the ages of 2 and 6 months, are at especially low risk of vaccine-preventable bacteremia, regardless of their vaccination status. In the age of routine vaccinations against *S pneumoniae* and Hib, clinicians require further guidance on specifically when blood cultures are indicated in pediatric patients younger than the age of 3 years. ■

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References

1. Cioffredi L-A, Jhaveri R. Evaluation and management of febrile children: a review. *JAMA Pediatr* 2016;170:794-800.
2. Baraff LJ, Oslund SA, Schriger DL, Stephen ML. Probability of bacterial infections in febrile infants less than three months of age: a meta-analysis. *Pediatr Infect Dis J* 1992;11:257-64.
3. Dagan R, Powell KR, Hall CB, Menegus MA. Identification of infants unlikely to have serious bacterial infection although hospitalized for suspected sepsis. *J Pediatr* 1985;107:855-60.
4. Baraff LJ, Bass JW, Fleisher GR, Klein JO, McCracken GH, Powell KR, et al. Practice guideline for the management of infants and children 0 to 36 months of age with fever without source. *Pediatrics* 1993;92:1-12.
5. Greenhow TL, Hung Y-Y, Herz A. Bacteremia in children 3 to 36 months old after introduction of conjugated pneumococcal vaccines. *Pediatrics* 2017;139:e20162098.
6. Herz AM, Greenhow TL, Alcantara J, Hansen J, Baxter RP, Black SB, et al. Changing epidemiology of outpatient bacteremia in 3- to 36-month-old children after the introduction of the heptavalent-conjugated pneumococcal vaccine. *Pediatr Infect Dis J* 2006;25:293-300.
7. Alpern ER, Alessandrini EA, Bell LM, Shaw KN, McGowan KL. Occult bacteremia from a pediatric emergency department: current prevalence, time to detection, and outcome. *Pediatrics* 2000;106:505-11.
8. Morris SK, Moss WJ, Halsey N. Haemophilus influenzae type b conjugate vaccine use and effectiveness. *Lancet Infect Dis* 2008;8:435-43.

9. Childhood Hib Vaccines [Internet]. NIH Office of Science Policy. p. 1–3. Accessed July 10, 2020. <https://www.nih.gov/sites/default/files/about-nih/impact/childhood-hib-vaccines-case-study.pdf>
10. Mohle-Boetani JC, Ajello G, Breneman E, Deaver KA, Harvey C, Plikaytis BD, et al. Carriage of *Haemophilus influenzae* type b in children after widespread vaccination with conjugate *Haemophilus influenzae* type b vaccines. *Pediatr Infect Dis J* 1993;12:589–93.
11. Barbour ML, Mayon-White RT, Coles C, Crook DW, Moxon ER. The impact of conjugate vaccine on carriage of *Haemophilus influenzae* type b. *J Infect Dis* 1995;171:93–8.
12. WHO Position Paper on *Haemophilus influenzae* type b conjugate vaccines [Internet]. *Weekly Epidemiological Record*. 2006. p. 445–452. Accessed May 7, 2020. <https://www.who.int/wer/2006/wer8147.pdf?%20>
13. Kuppermann N. Occult bacteremia in young febrile children. *Pediatr Clin North Am* 1999;46:1073–109.
14. Sard B, Bailey MC, Vinci R. An analysis of pediatric blood cultures in the postpneumococcal conjugate vaccine era in a community hospital emergency department. *Pediatr Emerg Care* 2006;22:295–300.
15. Toltzis P, Jacobs MR. The epidemiology of childhood pneumococcal disease in the United States in the era of conjugate vaccine use. *Infect Dis Clin North Am* 2005;19:629–45.
16. Galanis I, Lindstrand A, Darenberg J, Browall S, Nannapaneni P, Sjöström K, et al. Effects of PCV7 and PCV13 on invasive pneumococcal disease and carriage in Stockholm, Sweden. *Eur Respir J* 2016;47:1208–18.
17. Omer SB, Richards JL, Ward M, Bednarczyk RA. Vaccination policies and rates of exemption from immunization, 2005–2011. *N Engl J Med* 2012;367:1170–1.
18. Siddiqui M, Salmon DA, Omer SB. Epidemiology of vaccine hesitancy in the United States. *Hum Vaccin Immunother* 2013;9:2643–8.
19. Feikin DR, Lezotte DC, Hamman RF, Salmon DA, Chen RT, Hoffman RE. Individual and community risks of measles and pertussis associated with personal exemptions to immunization. *JAMA* 2000;284:3145–50.
20. Glanz JM, McClure DL, O’Leary ST, Narwaney KJ, Magid DJ, Daley MF, et al. Parental decline of pneumococcal vaccination and risk of pneumococcal related disease in children. *Vaccine* 2011;29:994–9.
21. Ciruela P, Izquierdo C, Broner S, Muñoz-Almagro C, Hernández S, Ardanuy C, et al. The changing epidemiology of invasive pneumococcal disease after PCV13 vaccination in a country with intermediate vaccination coverage. *Vaccine* 2018;36:7744–52.
22. Rashid H, Khandaker G, Booy R. Vaccination and herd immunity: what more do we know? *Curr Opin Infect Dis* 2012;25:243–9.
23. Mekitarian Filho E, Carvalho WB de. Current management of occult bacteremia in infants. *J Pediatr (Rio J)* 2015;91:S61–6.
24. Zeretzke CM, McIntosh MS, Kalynych CJ, Wylie T, Lott M, Wood D. Reduced use of occult bacteremia blood screens by emergency medicine physicians using immunization registry for children presenting with fever without a source. *Pediatr Emerg Care* 2012;28:640–5.
25. Hernandez-Bou S, Trenchs V, Batlle A, Gene A, Luaces C. Occult bacteraemia is uncommon in febrile infants who appear well, and close clinical follow-up is more appropriate than blood tests. *Acta Paediatr* 2015;104:e76–81.
26. Hernández-Bou S, Trenchs Sainz de la Maza V, Esquivel Ojeda JN, Gené Giralt A, Luaces Cubells C. Predictive factors of contamination in a blood culture with bacterial growth in an emergency department. *An Pediatr (Barc)* 2015;82:426–32 [in Spanish].
27. Simon AE, Lukacs SL, Mendola P. Emergency department laboratory evaluations of fever without source in children aged 3 to 36 months. *Pediatrics* 2011;128:e1368–75.
28. Aronoff SC. How useful are laboratory tests in diagnosing serious infections in febrile children? *BMJ* 2011;342:d2782.
29. Wilkinson M, Bulloch B, Smith M. Prevalence of occult bacteremia in children aged 3 to 36 months presenting to the emergency department with fever in the postpneumococcal conjugate vaccine era. *Acad Emerg Med* 2009;16:220–5.
30. Ishimine P. The evolving approach to the young child who has fever and no obvious source. *Emerg Med Clin North Am* 2007;25:1087–115. vii.
31. American College of Emergency Physicians Clinical Policies Committee, American College of Emergency Physicians Clinical Policies Subcommittee on Pediatric Fever. Clinical policy for children younger than three years presenting to the emergency department with fever. *Ann Emerg Med* 2003;42:530–45.
32. Baraff LJ. Management of fever without source in infants and children. *Ann Emerg Med* 2000;36:602–14.
33. Baraff LJ. Management of infants and young children with fever without source. *Pediatr Ann* 2008;37:673–9.
34. Feudtner C, Feinstein JA, Zhong W, Hall M, Dai D. Pediatric complex chronic conditions classification system version 2: updated for ICD-10 and complex medical technology dependence and transplantation. *BMC Pediatr* 2014;14:199.
35. Perry MC, Yaeger SK, Toto RL, Suresh S, Hickey RW. A modern epidemic: increasing pediatric emergency department visits and admissions for headache. *Pediatr Neurol* 2018;89:19–25.
36. Tran P, Dowell E, Hamilton S, Dolan SA, Messacar K, Dominguez SR, et al. Two blood cultures with age-appropriate volume enhance suspected sepsis decision-making. *Open Forum Infect Dis* 2020;7:ofaa028.
37. Laupland KB, Leal JR. Defining microbial invasion of the bloodstream: a structured review. *Infect Dis (Lond)* 2020;52:391–5.
38. Niewiesk S. Maternal antibodies: clinical significance, mechanism of interference with immune responses, and possible vaccination strategies. *Front Immunol* 2014;5:446.
39. Voysey M, Pollard AJ, Sadarangani M, Fanshawe TR. Prevalence and decay of maternal pneumococcal and meningococcal antibodies: a meta-analysis of type-specific decay rates. *Vaccine* 2017;35:5850–7.
40. Forest S, Mertz K. Allegheny County School Immunization Report School Year 2017–2018 [Internet]. 2018. Accessed March 2, 2020. https://www.alleghenycounty.us/uploadedFiles/Allegheny_Home/Health_h_Department/Health_Services/Immunization_Clinic/2017-18-Allegheny-County-School-Immunization-Report-FINAL.pdf
41. Wang H, Deeks S, Glasswell A, McIntyre P. Trends in invasive *Haemophilus influenzae* type B disease in Australia, 1995–2005. *Commun Dis Intell Q Rep* 2008;32:316–25.
42. Collins S, Litt D, Almond R, Findlow J, Linley E, Ramsay M, et al. *Haemophilus influenzae* type b (Hib) seroprevalence and current epidemiology in England and Wales. *J Infect* 2018;76:335–41.
43. Mullan PC, Scott S, Chamberlain JM, Pettinichi J, Palacios K, Weber A, et al. Decreasing blood culture contaminants in a pediatric emergency department: an interrupted time series analysis. *Pediatr Qual Saf* 2018;3:e104.
44. Hall RT, Domenico HJ, Self WH, Hain PD. Reducing the blood culture contamination rate in a pediatric emergency department and subsequent cost savings. *Pediatrics* 2013;131:e292–7.
45. Murni IK, Duke T, Daley AJ, Kinney S, Soenarto Y. True pathogen or contamination: validation of blood cultures for the diagnosis of nosocomial infections in a developing country. *J Trop Pediatr* 2018;64:389–94.
46. Rappaport DI, Cooperberg D, Fliegel J. Should blood cultures be obtained in all infants 3 to 36 months presenting with significant fever? *Hosp Pediatr* 2011;1:46–50.

Table I. Multivariable logistic regression analysis results with bacteremia as the dependent variable

Risk factors	Regression coefficient (β)	SE	P value	OR	95% CI	
					Lower	Upper
Age, mo	0.045	0.022	.041	1.046	1.001	1.092
Fever duration, d	−0.012	0.046	.787	0.987	0.885	1.062
Appearance (well vs ill)	−1.793	0.336	<.001	0.167	0.086	0.323
Vaccines received, no.	−0.103	0.184	.576	0.903	0.635	1.310
WBC, cells/mL	0.083	0.022	<.001	1.086	1.041	1.137
Platelets, cells/ μ L	−0.001	0.002	.615	0.999	0.996	1.002
Neutrophils, %	0.010	0.012	.390	1.010	0.988	1.034
Bands, %	0.052	0.020	.008	1.054	1.006	1.096

Table IV. Pathogens isolated from blood cultures (n)

Gram-positive cocci
<i>Staphylococcus aureus</i> (17)
<i>Streptococcus pneumoniae</i> (5)
<i>Streptococcus pyogenes</i> (6)
<i>Enterococcus faecalis</i> (5)
<i>Streptococcus agalactiae</i> (4)
<i>Enterococcus faecium</i> (1)
<i>Viridans streptococci</i> (1)
<i>Peptostreptococcus</i> species (1)
<i>Granulicatella</i> species (1)
Gram-positive bacilli
<i>Actinomyces species</i> (1)
<i>Actinomyces israelii</i> (1)
Gram-negative bacilli (aerobes)
<i>Escherichia coli</i> (13)
<i>Enterobacter cloacae</i> (2)
<i>Haemophilus influenzae</i> (3)
<i>Moraxella catarrhalis</i> (3)
<i>Klebsiella oxytoca</i> (1)
<i>Serratia marcescens</i> (1)
<i>Salmonella typhi</i> (2)
<i>Haemophilus</i> species (1)
<i>Pseudomonas aeruginosa</i> (1)
Gram-negative bacilli (anaerobes)
<i>Fusobacterium necrophorum</i> (1)
<i>Fusobacterium</i> species (1)

Table V. Characteristics of children found to have vaccine-preventable bacteremia

Ages, mo	Number of vaccines	Pathogen	Serotype	Site of infection	Medical history	Disposition
7	3	<i>S pneumoniae</i>	15B	Blood	None	Discharged
8	3	<i>H influenzae</i>	Type B	Blood	33-wk prematurity	Discharged
10	3	<i>S pneumoniae</i>	15B	Blood	None	Discharged
13	3	<i>S pneumoniae</i>	Undetermined	Blood	None	Discharged
15	3	<i>S pneumoniae</i>	15A	Blood	Poor weight gain	Discharged
16	3	<i>S pneumoniae</i>	15C	CSF, blood	None	Deceased

CSF, cerebrospinal fluid.

Table VI. Patient characteristics on presentation to the ED in children with and without bacteremia

Characteristics	Number of <i>S pneumoniae</i> and Hib vaccines			
	0	1	2	3
Bacteremia, n (%)	9 (1.3)	22 (1.6)	10 (2.0)	32 (1.5)
CBC, median (range)				
WBC	17.6 (1.4-65.4)	16.4 (7.4-34.3)	17.7 (9.1-41)	13.1 (5.2-32)
Neutrophils (%)	52 (11-86)	55.5 (19-82)	56 (30-80)	57.5 (6-89)
Bands	4 (1-24)	6 (1-12)	5 (5-5)	3 (1-17)
Platelets	277 (114-667)	436.5 (233-632)	336 (153-584)	309 (74-810)
Ill-appearing, n (%)	3 (33.3)	3 (13.7)	4 (40.0)	11 (34.4)
Fever duration, d, median (range)	0 (0-3)	1 (0-4)	1 (0-4)	2 (0-12)
No bacteremia, n* (%)	710 (98.7)	1378 (98.4)	494 (98.0)	2087 (98.5)
CBC, median (range)				
WBC	10.7 (2.5-36.1)	12.1 (3.2-36.1)	12.5 (3.5-39.6)	11.6 (2.5-53.4)
Neutrophils (%)	41 (11-81)	40 (6-87)	49 (2-81)	54 (5-90)
Bands	0 (0-32)	0 (0-22)	0 (0-89)	0 (0-26)
Platelets	383 (120-832)	414 (149-905)	349.5 (123-787)	294 (15-1093)
Ill-appearing, n* (%)	72 (10.1)	144 (10.4)	89 (18.0)	332 (15.9)
Fever duration, d, median (range)	0 (0-14)	0 (0-21)	1 (0-8)	2 (0-60)

CBC, complete blood count.

*Represents extrapolated n from the cohort of 1000 patients reviewed.

Table VII. Distribution of pathogenic and contaminant BCx by age of child

Characteristics	Age, mo		
	2-6	7-12	13-36
Blood cultures, n	2225	841	1676
Unvaccinated,* n (%)	498 (22.4)	72 (8.6)	150 (8.9)
Undervaccinated,† n (%)	66 (3.0)	138 (16.4)	111 (6.6)
Positive BCx, n (%)	182 (8.2)	48 (5.7)	83 (4.9)
Pathogens, n (%)	35 (1.6)	15 (1.8)	23 (1.4)
Contaminants, n (%)	147 (6.6)	33 (3.9)	60 (3.6)

BCx, blood cultures.

*Unvaccinated: 0 Hib or PCV vaccines.

†Undervaccinated: 1 set of vaccines before 5 months, 1 or 2 sets of vaccines before 7 months, or less than 3 sets of vaccines after 7 months.