# Bacteremia in Children 3 to 36 Months Old After Introduction of Conjugated Pneumococcal Vaccines

Tara L. Greenhow, MD,[a] Yun-Yi Hung, PhD,[b] Arnd Herz, MD[c]

abstract

**BACKGROUND AND OBJECTIVES:** In June 2010, Kaiser Permanente Northern California replaced all 7-valent pneumococcal conjugate vaccine (PCV7) vaccines with the 13-valent pneumococcal conjugate vaccine (PCV13). Our objectives were to compare the incidence of bacteremia in children 3 to 36 months old by 3 time periods: pre-PCV7, post-PCV7/pre-PCV13, and post-PCV13.

**METHODS:** We designed a retrospective review of the electronic medical records of all blood cultures collected on children 3 to 36 months old at Kaiser Permanente Northern California from September 1, 1998 to August 31, 2014 in outpatient clinics, in emergency departments, and in the first 24 hours of hospitalization.

**RESULTS:** During the study period, 57 733 blood cultures were collected in the population of children 3 to 36 months old. Implementation of routine immunization with the pneumococcal conjugate vaccine resulted in a 95.3% reduction of *Streptococcus pneumoniae* bacteremia, decreasing from 74.5 to 10 to 3.5 per 100 000 children per year by the post-PCV13 period. As pneumococcal rates decreased, *Escherichia coli*, *Salmonella* spp, and *Staphylococcus aureus* caused 77% of bacteremia. Seventy-six percent of all bacteremia in the post-PCV13 period occurred with a source.

**CONCLUSIONS:** In the United States, routine immunizations have made bacteremia in the previously healthy toddler a rare event. As the incidence of pneumococcal bacteremia has decreased, *E coli*, *Salmonella* spp, and *S aureus* have increased in relative importance. New guidelines are needed to approach the previously healthy febrile toddler in the outpatient setting.

[a]*Division of Infectious Diseases, Department of Pediatrics, Kaiser Permanente Northern California, San Francisco, California;* [b]*Division of Research, Kaiser Permanente Northern California, Oakland, California; and* [c]*Division of Infectious Diseases, Department of Pediatrics, Kaiser Permanente Northern California, Hayward, California*

Dr Greenhow conceptualized and designed the study and drafted the initial manuscript; Dr Hung carried out the initial analyses and reviewed and revised the manuscript; Dr Herz conceptualized the study and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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Address correspondence to Tara L. Greenhow, MD, Department of Pediatrics, Division of Infectious Diseases, Kaiser Permanente Northern California, 2200 O'Farrell St, San Francisco, CA 94115. E-mail: tara.greenhow@kp.org

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**WHAT'S KNOWN ON THIS SUBJECT:** After routine immunization with pneumococcal conjugate vaccine, pneumococcal bacteremia rates have decreased. *Escherichia coli*, *Salmonella* spp, and *Staphylococcus aureus* have become the leading causes of bacteremia in children 3 to 36 months old.

**WHAT THIS STUDY ADDS:** Implementation of routine immunization with 13-valent pneumococcal conjugate vaccine resulted in a 95.3% reduction in pneumococcal bacteremia. After implementation, *Escherichia coli*, *Salmonella* spp, and *Staphylococcus aureus* caused 77% of bacteremia, and 76% of bacteremia occurred with a source.

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Before the introduction of the 7-valent pneumococcal conjugate vaccine (PCV7) (Prevnar 7; Wyeth, now Pfizer, New York, NY) in April 2000, the risk of bacteremia for febrile children 3 to 36 months old in an ambulatory setting was 1.6% to 4.3%.[1–6] After its introduction, bacteremia became a rare event, occurring in 0.16% to 0.37% of febrile children.[7,8] Furthermore, the rate of *Streptococcus pneumoniae* bacteremia decreased,[1,9–16] with a range of 0.09% to 0.27%.[9]

In a post-PCV7 patient population, the distribution of pathogens found in blood cultures markedly changed. Bacteremia was increasingly caused by *Escherichia coli*, nonvaccine serotypes of *S pneumoniae*, *Salmonella* spp, *Staphylococcus aureus*, and *Streptococcus pyogenes*.[1,17]

As pneumococcal rates decreased, regional variability and trends in rates of *Salmonella* spp, *S aureus*, and *Neisseria meningitidis* bacteremia have become increasingly important. Rates of gastrointestinal illness from *Salmonella* spp from 1998 to 2014 have been nearly constant, averaging 15 cases per 100 000 people.[18] With significant worldwide variability, recent estimates of *S aureus* bacteremia range from 6 to 20 per 100 000 children.[19,20] A growing rate of *S aureus* bacteremia attributable to a rise in methicillin-resistant *S aureus* (MRSA)[21,22] has been occurring for decades,[19,22–25] but this increase may have stabilized in the last several years.[19] *N meningitidis* bacteremia rates have been steadily declining in the United States since the late 1990s to a current estimate of 0.3 per 100 000 children.[26]

In June 2010, Kaiser Permanente Northern California (KPNC) introduced universal immunization with the 13-valent pneumococcal conjugate vaccine (PCV13). Several studies predicted the continued decline in invasive pneumococcal disease post-PCV13.[27,28] Initial trends through 2012 demonstrated continued decline in pneumococcal infections, with the biggest impact in children <5 years old.[17,29–32] Our objectives were to compare the incidence rate of, proportion of pathogens of, and risk factors for bacteremia in children 3 to 36 months old by 3 time periods: pre-PCV7, post-PCV7/pre-PCV13, and post-PCV13.

## METHODS

### Study Design

This retrospective cohort study analyzed the electronic medical records (EMRs) of all blood cultures collected from September 1, 1998 to August 31, 2014 on previously healthy children age 3 to 36 months in the clinic, in the emergency department (ED), or in the first 24 hours of hospitalization at KPNC. Previously healthy was defined as children without underlying immunocompromising conditions, oncologic diagnoses, or genetic disorders (as defined by International Classification of Diseases, Ninth Revision codes) diagnosed before blood culture acquisition but during the child's lifetime, obtained from encounter diagnosis or problem list; or current central venous catheters before blood culture acquisition, obtained from encounter diagnosis or problem list.[33,34] Data extraction from EMRs identified subject medical record number, sex, date of birth, date of visit, site of blood acquisition, organisms identified in blood culture, and receipt of pneumococcal conjugate vaccine (PCV7 or PCV13). If the blood culture was positive with a pathogen, urine and stool culture results within 3 days of blood culture acquisition were reviewed. Urinalysis results were considered positive if the specimen contained leukocyte esterase or had >5 white blood cells per high-powered field.

In June 2010, KPNC introduced universal immunization with PCV13. Previously, from April 2000 to May 2010, children received PCV7. All pneumococcal vaccines given after July 1, 2010 were PCV13. Routine immunization was administered at 2, 4, and 6 months, with a booster between 12 and 15 months. The number and type of pneumococcal conjugate vaccine were recorded.

To analyze clinically significant bacteremia, we classified all organisms identified in blood cultures as either a likely contaminating organism or a potential pathogen.[1] Although some organisms could be considered clinically significant pathogens in unusual circumstances, based on usual clinical presentation, pathogenicity in a previously healthy host, and review of the EMR by author T.L.G., some organisms were identified as likely blood culture contaminants. Bacterial isolates such as *Staphylococcus epidermidis*, *Micrococcus*, and diphtheroids were considered contaminants unless they were isolated from ≥2 bacterial cultures. The charts of children with viridans group *Streptococcus*-positive blood cultures were reviewed to determine whether the isolate was a contaminant. Blood culture contaminants were not included in our analysis of bacteremia and were reported separately.

### Study Setting

From 1998 to 2014, KPNC had >3 million members each year and >40 pediatric clinics, 19 EDs, and 10 pediatric hospital wards. At several facilities, a pediatric consult was available for in-person evaluation in the ED.

### Statistical Methods

We compared the incidence rate of all bacteremia in children 3 to 36 months old during 3 time periods: pre-PCV7 (September 1998–March 2000), post-PCV7/pre-PCV13 (April 2000–May 2010), and post-PCV13 (June 2010–August 2014).

The numbers of blood cultures and cases of bacteremia per KPNC member ages 3 to 36 months per year were calculated. The cases of bacteremia per blood culture

**TABLE 1** Characteristics of Children With Bacteremia and Blood Cultures Obtained From 1998 to 2014

| | All Blood Cultures, *n* (%) | All Bacteremia, *n* (%) | *S pneumoniae*, *n* (%) | *E coli*, *n* (%) | *Salmonella* spp, *n* (%) | *S aureus*, *n* (%) | *N meningitidis*, *n* (%) |
|---|---|---|---|---|---|---|---|
| | *n* = 57 733 | *n* = 538 | *n* = 237 | *n* = 131 | *n* = 57 | *n* = 54 | *n* = 11 |
| Age, mo | | | | | | | |
| 3–11 | 22 624 (39) | 253 (47) | 74 (31) | 104 (79) | 19 (33) | 19 (35) | 8 (73) |
| 12–23 | 23 979 (42) | 188 (35) | 116 (49) | 21 (16) | 15 (26) | 21 (39) | 2 (18) |
| 24–36 | 11 130 (19) | 97 (18) | 47 (20) | 6 (5) | 23 (41) | 14 (26) | 1 (9) |
| Female sex | 27 019 (47) | 253 (47) | 99 (42) | 85 (65) | 21 (37) | 25 (46) | 6 (55) |
| Site of culture | | | | | | | |
| Outpatient clinic | 33 391 (58) | 328 (61) | 137 (58) | 91 (69) | 45 (79) | 22 (41) | 7 (64) |
| ED | 20 978 (36) | 172 (32) | 91 (38) | 35 (27) | 8 (14) | 21 (39) | 2 (18) |
| Hospital | 3364 (6) | 38 (7) | 9 (4) | 5 (4) | 4 (7) | 11 (20) | 2 (18) |
| Vaccine dose, no. | | | | | | | |
| 4 | 19 052 (33) | 124 (23) | 46 (19) | 13 (10) | 30 (53) | 21 (39) | 1 (9) |
| 3 | 16 165 (28) | 97 (18) | 26 (11) | 33 (25) | 14 (24) | 12 (22) | 0 (0) |
| 2 | 5773 (10) | 59 (11) | 11 (5) | 28 (21) | 5 (9) | 4 (7) | 3 (27) |
| 1 | 4619 (8) | 64 (12) | 7 (3) | 38 (29) | 0 (0) | 9 (17) | 1 (9) |
| 0 | 12 124 (21) | 194 (36) | 147 (62) | 19 (15) | 8 (14) | 8 (15) | 6 (55) |

obtained per year were calculated. A comparison of the relative incidence rate of bacteremia by organism was performed. Poisson regression was used to model quarterly rates of all bacteremia and *S pneumoniae* bacteremia. An interrupted time series analysis was conducted.

Comparisons involving categorical variables were performed via the $\chi^2$ or Fisher's exact test. Normally distributed continuous variables were compared via Student's *t* test or analysis of variance. Comparisons of non–normally distributed continuous variables were conducted via the Wilcoxon rank-sum test or Kruskal–Wallis test. Time series analysis was performed in SAS version 9.3 (SAS Institute, Inc, Cary, NC).

## RESULTS

During this 16-year study (1998–2014), the annual total population of children age 3 to 36 months at KPNC ranged from 94 269 to 103 474 (average, 98 447; SD 2640). A total of 74 665 blood cultures were obtained from all children age 3 to 36 months; 61 563 of these cultures were taken in healthy toddlers. After removal of 1251 cultures obtained >1 day into hospitalization and 2579 duplicate cultures (ie, >1 blood culture obtained during single episode of illness), 57 733 blood cultures were obtained. Cultures were acquired from outpatient clinics (33 391 [58%]), from EDs (20 978 [36%]), and in the first 24 hours of hospitalization (3364 [6%]) (Table 1). Of these cultures, 538 (1%) grew a pathogen, 1173 (2%) grew a contaminant, and 56 022 (97%) were negative. Between 1998 to 1999 and 2013 to 2014, the total number of annual blood cultures dropped by 68% overall and 45% in the ED (Cochran–Armitage trend test $P < .001$).

From 1998 to 2014, more blood cultures were obtained in children 12 to 23 months old, the post-PCV7/pre-PCV13 study period, and the outpatient clinic. In contrast, more bacteremia occurred in children 3 to 11 months old because of the preponderance of *E coli* in this age group. In all types of bacteremia except *S aureus*, the blood culture was more likely to be obtained in the outpatient setting. More cases of *E coli* bacteremia occurred in girls (Table 1).

### Etiology of Bacteremia

Bacteremia varied by age. Before the routine use of pneumococcal vaccine, *E coli* was the most common cause of bacteremia in children 3 to 5 months of age, whereas at older ages the incidence of pneumococcal bacteremia dwarfed all others. In the years after routine use of PCV13, *E coli* was the most common organism causing bacteremia in children 3 to 11 months old, occurring almost 4 times more frequently than *S pneumoniae*.

During the post-PCV13 study period, 21 total pathogens (95% confidence interval [CI], 13.5–30.3) per 100 000 children per year were identified in blood cultures (Table 2). *E coli*, *Salmonella* spp, and *S aureus* accounted for 77% of overall pathogens (Figs 1 and 2). Of the children with *E coli* bacteremia, 93% had a urinary tract source. A total of 76% of bacteremia occurred with a source, including 34% urinary tract infections, 17% gastroenteritis, 8% pneumonias, 8% osteomyelitis, 6% skin and soft tissue infections, and 3% other. The post-PCV13 annual incidence rate of bacteremia with a source was 15.9 (95% CI, 9.4–23.5) per 100 000 children. A total of 24% of bacteremia occurred without a source, including *Salmonella typhi*, *S pneumoniae*, *E coli*, *Streptococcus agalactiae*, *N meningitidis*, and nontypable *Haemophilus influenzae*. The post-PCV13 annual incidence rate of bacteremia without a source was 5 (95% CI, 1.6–11.3) per 100 000 children.

### Time Series Analysis

The rate of all bacteremia per 100 000 children per year decreased

**TABLE 2** Incidence Rate of Bacteremia by Study Period

| | Rate per 100 000 Children per Year (95% CI) | | | Rate per 10 000 Blood Cultures (95% CI) | | |
|---|---|---|---|---|---|---|
| | Pre-PCV7 | Post-PCV7/Pre-PCV13 | Post-PCV13 | Pre-PCV7 | Post-PCV7/Pre-PCV13 | Post-PCV13 |
| All bacteremia | 97 (79.4–117) | 29 (20.4–38.9) | 21 (13.5–30.3) | 168 (144–195) | 75 (59–94) | 96 (78–117) |
| *S pneumoniae* | 74.5 (59–93) | 10 (5–18) | 3.5 (1.1–8.7) | 129 (108–153) | 26 (17–38) | 16 (9–26) |
| *E coli* | 9.4 (4.8–17) | 8.2 (4.1–15.7) | 8.4 (4.1–15.7) | 17 (10–27) | 21 (13–32) | 37 (26–51) |
| *Salmonella* spp | 3.8 (1.1–8.7) | 3.2 (1.1–8.7) | 4.5 (1.6–10.2) | 7 (3–14) | 8 (3–16) | 20 (12–31) |
| *S aureus* | 3.1 (1.1–8.7) | 4.6 (1.6–10.2) | 3.5 (1.1–8.7) | 6 (2–13) | 9 (4–17) | 16 (9–26) |
| *N meningitides* | 2.5 (0.6–7.2) | 0.6 (0–3.7) | 0.2 (0–3.7) | 4.5 (2–10) | 1.5 (0–6) | 1 (0–6) |
| Contaminated blood culture | 100 (82.1–120) | 75.6 (60.3–93) | 45 (33–59.8) | 174 (151–199) | 196 (172–222) | 205 (180–231) |

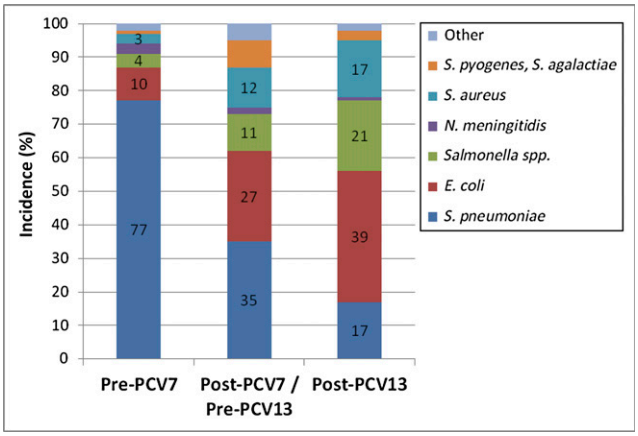


**FIGURE 1**
Relative incidence of bacteremia by organism per study period (pre-PCV7, post-PCV7/pre-PCV13, and post-PCV13).

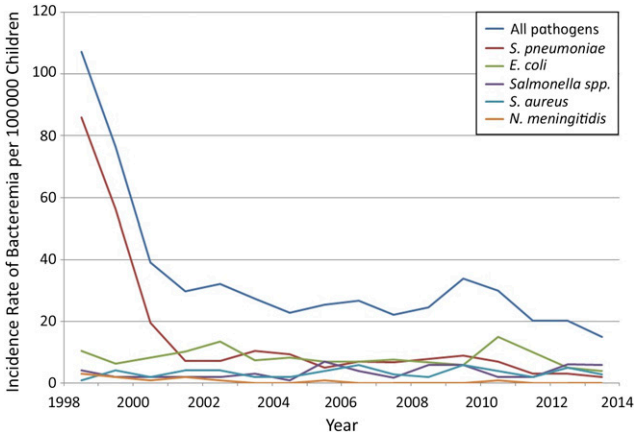


**FIGURE 2**
Rate of all bacteremia by organism per 100 000 children per year between 1998 and 2014.

from 97 (95% CI, 79.4–117) in the pre-PCV7 study period to 21 (95% CI, 13.5–30.3) in the post-PCV13 study period. The rate of pneumococcal bacteremia per 100 000 children per year dropped from 74.5 (95% CI, 59–93) in the pre-PCV7 study period to 3.5 (95% CI, 1.1–8.7) in the post-PCV13 study period (Table 2). This was a decrease of 86.6% and 95.3% in study periods 2 and 3, respectively. Poisson regression modeling the observed rate of bacteremia revealed a trend over time to decreasing rates of all bacteremia ($P < .001$) and *S pneumoniae* bacteremia ($P < .001$) (Fig 3). When incorporated into the regression model, both PCV7 and PCV13 led to a significant reduction in all and *S pneumoniae* bacteremia rates. *S pneumoniae* bacteremia was highly seasonal, with the majority occurring in the winter ($P = .01$). Site of blood culture acquisition was not a predictor of all bacteremia.

The relative incidence of *E coli*, *Salmonella* spp, and *S aureus* bacteremia increased as the absolute incidence of *S pneumoniae* and *N*

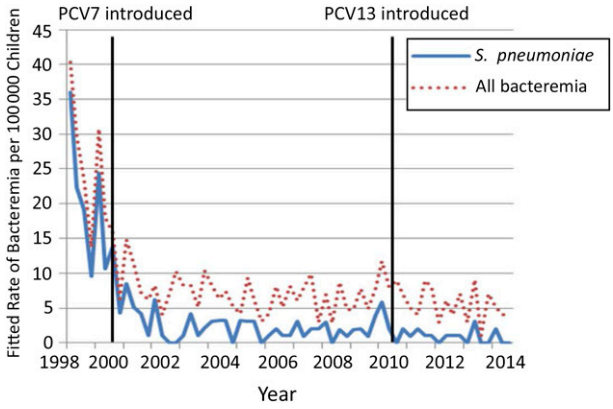


**FIGURE 3**
Fitted rate of *S pneumoniae* and all bacteremia per 100 000 children per year between 1998 and 2014.

*meningitidis* bacteremia decreased. The incidence rate of *E coli*, *Salmonella* spp, and *S aureus* bacteremia stayed constant over the 16 years (Table 2, Fig 2). In the pre-PCV7 period, 78% of all significant cases of bacteremia were caused by *S pneumoniae*; this proportion dropped to 35% in the post-PCV7/pre-PCV13 period and to 17% in the post-PCV13 period.

The rate of all bacteremia per 10 000 blood cultures decreased from 168 (95% CI, 144–195) in the pre-PCV7 period to 75 (95% CI, 59–94) in the post-PCV7/pre-PCV13 period, then increased to 96 (95% CI, 78–117) in the post-PCV13 period. Rates of *S pneumoniae* and *N meningitidis* declined per 10 000 blood cultures, whereas rates of *E coli*, *Salmonella* spp, and *S aureus* bacteremia increased (Table 2).

### Contaminants

Contaminant organisms were grown from 1.9% of blood cultures and remained constant during the 3 study periods (range, 1.7%–2.4%). As the number of blood cultures obtained decreased, the rate of contaminated blood cultures per 100 000 children per year decreased from 100 (95% CI, 82.1–120) pre-PCV7 to 45 (95% CI, 33–59.8) (Table 2). The contamination rate for the youngest children (3 to 11 months old) was higher than at 12 to 23 months or 24 to 36 months ($P < .001$). Compared with outpatient blood cultures, cultures from the ED and the first 24 hours of hospitalization were more likely to be a contaminant ($P < .001$). Of the 1173 total contaminants isolated over the 16 study years, 319 children had 325 additional blood cultures in the 1 to 3 days after the contaminant was identified.

## DISCUSSION

After the introduction of universal PCV13 immunization, bacteremia has become a rare event in previously healthy children 3 to 36 months old. Between 1998 to 1999 and 2013 to 2014, the annual number of cases of all bacteremias dropped by 78%, and the annual number of pneumococcal cases dropped by 95.3%. As shown by time series analysis, the dramatic decline in *S pneumoniae* bacteremia rates was clearly related to the impact of immunization, as the incidence decreased from 74.5 (95% CI, 59–93) pre-PCV7 to 3.5 (95% CI, 1.1–8.7) post-PCV13 per 100 000 children per year.

Our post-PCV13 rates of *S pneumoniae* bacteremia in northern California were lower than those reported in New York City from 2007 to 2009 and from 2011 to 2012 in children <5 years old. In the post-PCV7/pre-PCV13 and post-PCV13 periods, Farnham et al[29] reported a rate of 21 and 6.4 cases per 100 000 children <5 years old, respectively. In contrast, our rates in northern California were 10 and 3.5 per 100 000 children 3 to 36 months old, respectively. The lower rates at KPNC probably reflected a combination of regional variability, a continued decline in *S pneumoniae* bacteremia rates after the introduction of PCV13, including only a previously healthy population, and collecting fewer blood cultures and not capturing transient bacteremia.

In the post-PCV13 period, bacteremia was increasingly caused by *E coli* (39%), *Salmonella* spp (21%), and *S aureus* (17%). This changing distribution of pathogens has also been observed in the United Kingdom[17] and Israel.[35] It is unclear how the northern California incident rates of *E coli*, *Salmonella* spp, and *S aureus* are generalizable to other regions of the United States. Overall *Salmonella* spp infections are highest in the southeastern United States, in boys, and in children <1 year old. Rates of *Salmonella* spp infections in California are similar to those of other western states with the exception of *S typhi* rates, which are much higher in northern California. Many counties in northern California report rates of >0.47 cases per 100 000 population.[18] Our incidence rate of 0.95 per 100 000 children per year for *S typhi* and *S paratyphi* bacteremia is higher than the national and regional rates, probably because of regional variability and the

young age of our study population. The incidence of *S aureus* bacteremia in healthy children 3 to 36 months old has not been fully described; however, recent estimates of *S aureus* bacteremia range from 6 to 20 per 100 000 children.[19,20] In contrast, at KPNC our rates of *S aureus* bacteremia were 3.5 (95% CI, 1.1–8.7) per 100 000 children per year. Our lower rates are probably multifactorial. We included only previously healthy children with blood collected in an outpatient clinic, in an ED, or in the first 24 hours of hospitalization. Rates of MRSA are lower in northern California compared with other parts of the United States.[36] At KPNC only 10% of pediatric *S aureus* bacteremia cases are due to MRSA. Our *N meningitidis* bacteremia rates of 0.2 per 100 000 children are consistent with the national estimate of 0.3 per 100 000 children.[26]

As rates of all bacteremia per 100 000 children per year in the post-PCV13 study period decreased, there was an increase in all bacteremia per 10 000 blood cultures compared with the post-PCV7/pre-PCV13 period. Rates of *S pneumoniae* bacteremia steadily declined per 10 000 blood cultures over the 3 study periods. In contrast, rates of *E coli*, *Salmonella* spp, and *S aureus* bacteremia per 10 000 blood cultures increased. Changes to the former were associated with the impact of immunization, but changes to the latter were associated with the impact of changing practices, most notably the trend toward fewer blood cultures.

In the final study period (post-PCV13), 76% of bacteremia occurred with a source, most frequently urine, gastrointestinal, lung, bone, or skin and soft tissue. Ribitzky-Eisner et al[35] in Israel found a similar post-PCV13 rate, with 80% of bacteremia occurring with a source. Because bacteremia in the post-PCV13 era is more likely to occur with a source, a focused examination should be performed and appropriate studies obtained at the time of a blood culture collection.

Given the low frequency of bacteremia in children 3 to 36 months old, several authors have recommended obtaining fewer blood cultures in young febrile children.[1,4,37] The total number of blood cultures obtained in outpatient clinics at KPNC declined by more than one-third from 1998 to 2003.[1] But over the same period, similar to Simon et al,[38] we found no decline in blood culture acquisition rates in children presenting to the ED. In contrast, from 1998 to 2014, physicians in both the outpatient clinic and ED changed their behavior. The total number of annual blood cultures dropped 68%, including a drop of 45% in the ED. It is likely that this reduction in blood culture acquisition was caused by both a decrease in bacteremic (ie, "sick appearing") children and a decreased suspicion of bacteremia as a result of the physicians' knowledge about the effectiveness of the current immunizations.

Site of culture acquisition (outpatient clinic, ED, or first 24 hours of hospitalization) was not a predictor for bacteremia. Several publications have focused on rates of bacteremia in children presenting to the ED,[6–9,17] with few publications focusing on children with blood cultures collected in both the outpatient clinic and the ED.[1,4] These findings highlight the need for vigilance about bacteremia in all settings and suggest that many previously healthy children with bacteremia are not so sick as to need initial care in the ED. Although site of culture acquisition was not a predictor of all bacteremia, we continued to find that compared with outpatient blood cultures, cultures from the ED and the first 24 hours of hospitalization were more likely to be contaminants ($P < .001$). We suspect the higher rates of contamination are due to technique and less familiarity with pediatric blood draws.

Our study had some limitations. Our denominator was not febrile children presenting for care. Instead, we used the surrogates of rate per study population per year and rate per number of blood cultures acquired. Although most KPNC members receive all their care from a KPNC facility, a small proportion of children (estimated at <1% [A. Herz, personal communication, December 15, 2016]) may have been seen elsewhere. If a child was ill, the child would probably return to a KPNC facility for follow-up. KPNC members were similar to the insured population and general population in northern California with regard to sociodemographic and health characteristics, but they differ in several ways from a population that includes those with Medi-Cal coverage and the uninsured.[39–43] Despite these limitations, given the occurrence of bacteremia in this age group and the large population of KPNC, it is likely that our study accurately reported incidence rates of and risk factors for bacteremia in the general population.

## CONCLUSIONS

Bacteremia in healthy children 3 to 36 months old is rare in the post-PCV13 era. The most common pathogens identified in blood cultures today are *E coli*, *Salmonella* spp, and *S aureus*. Because bacteremia in the post-PCV13 era is more likely to occur with a source, a focused examination should be performed and appropriate studies should be obtained at the time of a blood culture collection.

### ABBREVIATIONS

CI: confidence interval
ED: emergency department
EMR: electronic medical record
KPNC: Kaiser Permanente Northern California
MRSA: methicillin-resistant *Staphylococcus aureus*
PCV7: 7-valent pneumococcal conjugate vaccine
PCV13: 13-valent pneumococcal conjugate vaccine

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