

A Retrospective Study of the Impact of Pneumococcal Conjugate Vaccine-13 Immunization in a Northern Israel Hospital

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ABSTRACT: **Background:** The introduction of pneumococcal conjugate vaccine-13 (PCV-13) has reduced the burden of invasive pneumococcal disease.

Objectives: To characterize true positive blood cultures of children who presented to our hospital following implementation of the PCV-13 vaccine.

Methods: A retrospective study was conducted on positive blood cultures of children presenting with fever from 2010–2017. Subjects were divided into two age groups: a younger group 3–36 months and an older group 3–18 years. Patients were classified as either having a focus of infection at the time of their bacteremia or not. Pneumococcal isolates were typed at Israel's Streptococcal Reference Laboratory.

Results: The samples included 94 true positive blood cultures. Focal infection with concomitant bacteremia was more common than bacteremia without a focus both overall: 67/94 (71%) vs. 27/94 (28.7%), $P < 0.001$ as well as in the two groups: 32/48 (66%) vs. 16/48 (33%), $P = 0.02$ in the younger group and 35/46 (76%) vs. 11/46 (24%), $P = 0.001$ in the older group. *Streptococcus pneumoniae* was the most common pathogen overall, 27/94 (29%), and in the younger group, 21/48 (44%), but rare in the older group, 6/46 (13%). In the latter, *Brucella* species predominated, 12/46 (26%), along with *Staphylococcus aureus* 12/46 (26%).

Conclusions: Our findings are consistent with other studies reporting decreased pneumococcal bacteremia, bacteremia primarily accompanying focal infection, and changing etiological agents among PCV-13-vaccinated children. *Brucella* species was prominent in older children with osteoarticular infections. Ongoing surveillance is warranted to better understand the implications of PCV-13.

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KEY WORDS: bacteremia, blood culture, *Brucella*, focal infection, occult bacteremia

The conjugated pneumococcal vaccine has evolved over several years to include an increasing number of serotypes with various invasive capacities or being prone to antimicrobial resistance. Multiple studies report a decreasing rate of pneumococcal bacteremia following the introduction of routine immunization with pneumococcal conjugate vaccine (PCV) [1–7]. In Israel, the pneumococcal conjugate vaccine PCV-7 was included in the national immunization plan from July 2009 to November 2010, and then replaced by PCV-13. Concomitantly, rates of invasive pneumococcal infection in the country have declined, as have rates of bacteremia without a focus of infection [2–4]. The decrease in serotype pneumococcal vaccine disease in the United States was associated with a change in epidemiology of clinical diagnoses and etiology [1].

The aim of this study was to characterize the clinical and laboratory features of children presenting with acute febrile illness with positive bacterial cultures in the PCV era in a secondary medical center in northern Israel.

PATIENTS AND METHODS

This retrospective study comprised children aged 3 months to 18 years who presented with a febrile illness to a medical center in northern Israel between the years 2010 and 2017. Demographic, clinical, and laboratory data, including blood culture results, were collected.

The patients were divided into two age groups: 3 months to 3 years of age and from older than 3 years to 18 years. Patients with risk factors for bacteremia, such as a central line or known immunodeficiency, were excluded. The study was performed in accordance with the Declaration of Helsinki and was approved by the institutional review board of Bnai Zion Medical Center.

STATISTICAL ANALYSIS

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 19 (SPSS, IBM Corp, Armonk, NY, USA).

Categorical data were presented as numbers and percentages and continuous data as median ± interquartile range (IQR). Chi-square test or Fisher’s exact test were used to compare categorical variables. Normally distributed continuous variables were compared via Student’s *t*-test or analysis of variance. The Kolmogorov–Smirnov test was used to analyze the data distribution. A *P* value of < 0.05 was considered statistically significant.

RESULTS

Overall, 902 (2.65%) of the 34,066 samples showed bacterial growth, but 562 (1.6%) were deemed contaminants and 246 (0.7%) of the patients did not meet inclusion criteria. The remaining 94 true positive blood cultures were approximately evenly divided between the younger and older groups [Figure 1]. In the 94 samples analyzed, focal infection with concomitant bacteremia was more common than bacteremia without a focus, both overall 67/94 (71%) vs. 27/94 (28.7%), *P* < 0.001, and in the two age groups, 32/48 (66%) vs. 16/48 (33%), *P* = 0.02, in the younger group, and 35/46 (76%) vs. 11/46 (24%), *P* = 0.001, in the older group [Table 1].

Figure 1. The study algorithm

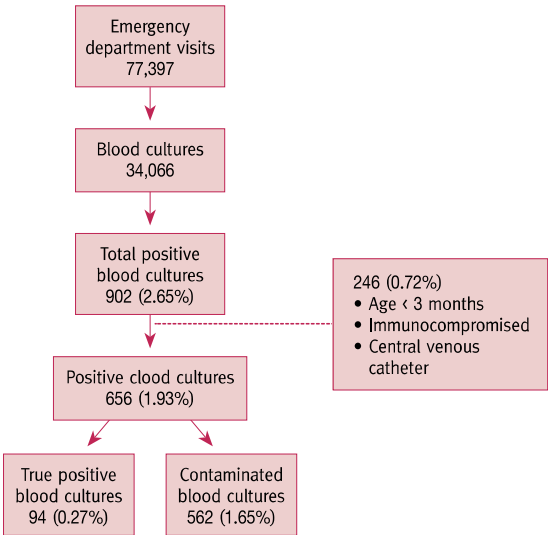


Table 1. Bacteremia without focus compared to bacteremia with a focal infection according to age groups

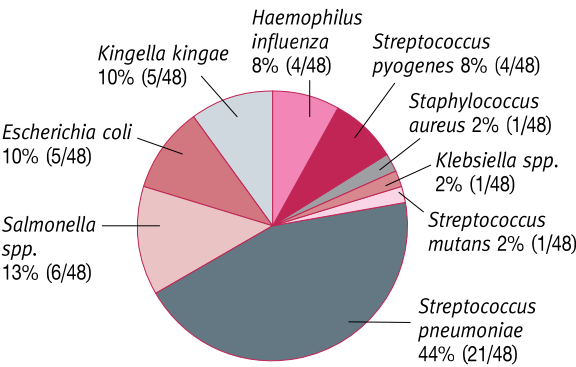
Age	Bacteremia N	Bacteremia without focus N (%)	Focal infection N (%)	P value
All	94	27 (28.7)	67 (71.2)	< 0.001
3 months ≤ age ≤ 3 years	48	16 (33)	32 (66)	0.02
3 years < age ≤ 18 years	46	11 (24)	35 (76)	0.001

Streptococcus pneumoniae was the most common pathogen overall, 27/94 (29%), and in the younger group, 21/48 (44%), but was relatively rare in the older group, 6/46 (13%). The second most common pathogen overall was *Staphylococcus aureus*, 13/94 (13.8%), followed by *Brucella* spp. (12.7%), *Salmonella* spp. (11.7%), *Escherichia coli* (9.5%), *Haemophilus influenzae* (7.4%), and *Kingella kingae* (5.3%). In total, more gram-negative pathogens were observed as the cause of bacteremia than gram-positive pathogens [Figure 2].

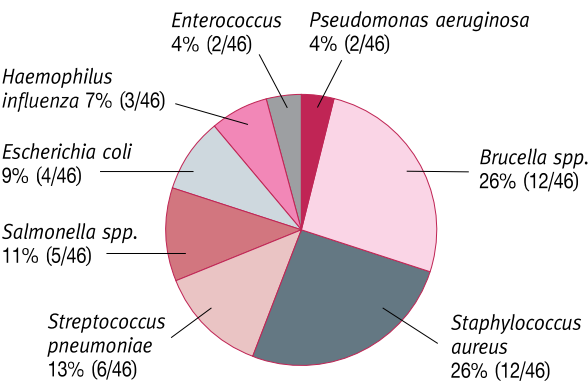
In the younger group, *Streptococcus pneumoniae* was the leading cause of bacteremia both with a focus, 11/32 (34%), and without a focus, 10/16 (62.5%). The most common pathogens after *Streptococcus pneumoniae* in this group were, in decreasing order, *Salmonella* spp., *Escherichia coli*, and *Kingella kingae*. In the older group, *Brucella* spp. and *Staphylococcus aureus* predominated, 12/46 (26%), with the former mainly causing osteoarticular focal infections, 9/35 (25%).

Figure 2. Distribution of pathogens according to age group

Distribution of pathogens in the younger group (n=48)



Distribution of pathogens in the older group (n=46)



To examine the effect of the pneumococcal conjugate vaccine on the incidence of *Streptococcus pneumoniae* bacteremia, we compared *Streptococcus pneumoniae* cases as a proportion of the true positive cultures during the pre- and post-PCV years (2007–2009 and 2010–2017, respectively). The mean ratio decreased from 36.1% pre-PCV to 15.45% post-PCV, $P < 0.001$ [Figure 3]. We also examined the serotypes of *Streptococcus pneumoniae* isolated in the blood cultures. In the younger group, pneumococcal bacteremia with serotype strains was not uncommon, especially in children who were not fully immunized with PCV-13. Serotype 19A was the most common non-PCV serotype isolated in the post-vaccination period. The serotypes most likely to cause focal infection in the post-vaccination period were 19A, 12F, 10B, 12E, 7B, 2, and 33F. The serotypes most likely to cause infection without focus were 23F and 18C.

In this study, the blood culture contaminants were coagulase-negative *Staphylococcus* (60.8%), *Streptococcus viridans* (15.4%), and *Micrococcus* species (7.4%).

DISCUSSION

In the current study, we examined true bacteremia over the last decade in 94 children in northern Israel coincident with PCV-13 vaccination becoming an integral component of Israel's national immunization program. The findings confirmed previous research showing a significant reduction in the incidence rate of invasive pneumococcal disease with vaccination. In addition, the findings showed changes in pathogen epidemiology. Bacteremia with an apparent focus of infection predominated in children up to 3 years, similar to previously published studies from Israel [8].

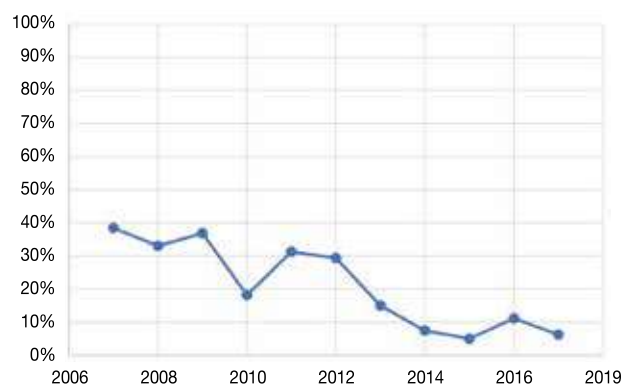
The rate of true positive blood cultures was 0.27% and the contamination rate was 1.6%. *Streptococcus pneumoniae* was the most common pathogen overall, and was most prevalent in the younger group, followed by *Salmonella* and *Escherichia*

coli. However, *Streptococcus pneumoniae* was rare in the older group, where *Brucella spp.* and *Staphylococcus aureus* predominated. The most common contaminant pathogen is coagulase-negative *Staphylococcus*. Similar data have been reported in a study from Israel [9].

Brucellosis is a major health problem for specific minorities in Israel, and particularly for Bedouin in rural settings. Since 2013, the prevalence of brucellosis has reached outbreak proportions, a development attributed mainly to the consumption of unpasteurized dairy products [11]. In 2016 Megged et al. [12] described a brucellosis outbreak among children and adults in two medical centers in Israel, and found that children had higher rates of hospitalization and osteoarticular symptoms. Fruchtman and colleagues [10] showed that in southern Israel, nearly 50% of brucellosis cases were accompanied by brucella bacteremia (128/252). More recently Ghanem-Zoubi et al. [13] described an increased incidence of brucella in the overall Israeli population from 1.9 per 100,000 in 2009 to 7.3 per 100,000 in 2014, and in the Arab population from 10 per 100,000 to 33.5 per 100,000 over the same period of time. Notably, in our study population, *Brucella spp.* was the most common etiological agent causing bacterial arthritis, and 92% of the brucellosis bacteremia patients were Moslem Arabs. It should be noted that although the short-term spike in *Brucella* bacteremia corresponded with the PCV-vaccine-related reduction in rates of pneumococcal bacteremia, given the pathogenesis of *Brucella* bacteremia the two events are unlikely to be related.

Worldwide, there has been a decrease in *Streptococcus pneumoniae* prominence, with a coincident rise in primarily gram-negative pathogens. In the United States, Greenhow and co-authors [1] found that the incidence rate of *Streptococcus pneumoniae*, previously the most common cause of bacteremia, now ranked below that of *Escherichia coli* and *Salmonella*. Regardless of the overall decline in *Streptococcus pneumoniae*, it is prudent to examine specific strains in terms of inclusion in the PCV-13 vaccine, and perhaps virulence and resistance patterns. In a study by Ribitzky-Eisner et al. [2] none of the *Streptococcus pneumoniae* serotypes isolated during 2011–2012 belonged to the 13-valent PCV vaccine, and there was an increase in non-PCV-13 serotypes. More recently, a study by Ben-Shimol and colleagues [4] on the impact of PCV-7/PCV-13 on invasive pneumococcal infection in young children showed an overall 70% decrease in invasive pneumococcal disease from 2004 to 2013. They ascertained that serotypes 12F, 15B/C, 24F, and 27 were the most common serotypes in both meningitis and non-meningitis invasive pneumococcal disease, with 12F the most prevalent overall. We also found an increase in non-PCV-13 serotypes compared to the pre-vaccination era, but in our study population 19A was the most prominent serotype cultured in partially-immunized infants. This serotype was also noted by Leibovitz and co-authors [7], in bacteremia among

Figure 3. Annual incidence ratio of *Streptococcus pneumoniae* cultures out of total positive cultures



febrile infants. These changing trends may be attributed to the pathogen community, patient age, diet, and most significantly to PCV-13 vaccination.

In addition to changes in the predominance of *Streptococcus pneumoniae*, we found significant changes in the clinical presentation of patients up to 3 years of age with bacteremia. Bacteremia occurred most commonly in conjunction with focal infection, specifically pneumonia in the younger group and osteoarticular infection in the older group. This trend was reported with 76% of bacteremia cases occurring in the presence of a urinary, gastrointestinal, lung, or bone infection [1]. These findings may justify a new approach toward the febrile child, namely stratification of high- and low-risk patients based on PCV-13 coverage with ensuing differential laboratory and antibiotic coverage.

LIMITATIONS

This retrospective study was conducted at a single center in northern Israel during a period of relatively high brucellosis activity. Therefore, the findings may not be generalized to other populations. It is also important to note that PCV-7 and PCV-13 were introduced in 2009 and 2010, respectively, and the study period was between 2010 and 2017. Therefore, the study population may be affected by gaps in PCV immunization.

CONCLUSIONS

The introduction of the pneumococcal conjugate vaccine has led to a decline in the incidence rate of pneumococcal bacteremia. Focal infections are more common in children than bacteremia without focus in all age groups. Temporarily corresponding with this decline in *Streptococcus pneumoniae* bacteremia, a rising prevalence rate of *Brucella spp.* morbidity has been found. However, given the pathogenesis of *Brucella* bacteremia, it is unlikely that there is a relation between these two trends. Regardless, ongoing surveillance is warranted to better understand the widespread implications of PCV-13 vaccination.

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Capsule

Fast and slow recycling of synaptic vesicles

The function of microtubules and filamentous actin in mature synapses is not fully understood. Using confocal and stimulated emission depletion microscopy on a giant auditory synapse of the rat nervous system, termed the calyx of Held, Babu et al. found that microtubules extended into terminal swellings and were partially colocalized with synaptic vesicles. Depolymerization of microtubules in calyceal terminals prolonged the recovery of excitatory postsynaptic currents from short-term depression, whereas

fast recovery from short-term depression was prolonged by depolymerization of filamentous actin. These results reveal distinct contributions of filamentous actin and microtubules to synaptic neurotransmission and indicate that these cytoskeletal elements independently contribute to different aspects of the recycling of synaptic vesicles.

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