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MAJOR ARTICLE

Bacteremic Community-Acquired Pneumonia in Ethiopian Children: Etiology, Antibiotic Resistance, Risk Factors, and Clinical Outcome

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Background. Community-acquired pneumonia (CAP) remains a leading cause of morbidity and mortality. We sought to determine the magnitude, etiology, and risk factors of CAP in children 5 years after introduction of pneumococcal conjugate vaccine (PCV) 10 in Ethiopia.

Methods. We conducted a prospective observational study on the bacterial etiology and risk factors of CAP among children aged 0–15 years in 2 pediatric emergency departments in Addis Ababa, Ethiopia. Blood culture, antibiotic susceptibility testing, and amplification of pneumococcal *lyt*A and *cps*B genes were performed. Serotypes of *Streptococcus pneumoniae* were determined by Quellung reaction and sequencing the *cps*B gene.

Results. Out of 643 eligible children, 549 were enrolled. The prevalence of bacteremic pneumonia was 5.6%. *Staphylococcus aureus* (26.5%) was the predominant pathogenic species, followed by *Enterococcus faecium* (11.8%), *Escherichia coli* (11.8%), and *Klebsiella pneumoniae* (11.8%). In univariate analysis, parental smoking and nonvaccination with PCV10 were associated with bacteremic CAP. In multivariable analysis, female sex (adjusted odds ratio [aOR], 2.3; 95% confidence interval [CI], 1.1–4.9), weight-for-age z-score (WAZ) <–2 SDs (aOR, 2.2; 95% CI, 1.1–4.8), and lower chest indrawing (aOR, 0.44; 95% CI, 0.2–0.95) were independently associated with bacteremic CAP. The overall in-hospital case fatality rate was 2.37% (13/549), and WAZ <–3 SDs (OR, 13.5; 95% CI, 3.95–46.12) was associated with mortality.

Conclusions. Five years after the introduction of PCV10 in Ethiopia, *S. aureus* was the main cause of bacteremic CAP in children, the contribution of *S. pneumoniae* was low, and there was a high level of antibiotic resistance among isolates.

Keywords. bacteremic community-acquired pneumonia; Ethiopia; PCV10; *Staphylococcus aureus*; *Streptococcus pneumoniae*.

Community-acquired pneumonia (CAP) remains a leading cause of morbidity and mortality worldwide. In 2015, there were an estimated 138 million (95% uncertainty interval [UI], 86–226 million) episodes of clinical pneumonia and 0.9 million (95% UI, 0.8–1.1 million) pneumonia deaths in children younger than 5 years. Half of all deaths occurred in India, Nigeria, Pakistan, Democratic Republic of Congo, and Ethiopia. The 5 countries with the highest mortality rates were all in sub-Saharan Africa [1].

The incidence of radiologically confirmed pneumonia has been substantially reduced as a result of the widespread introduction of pneumococcal conjugate vaccine (PCV) and *Haemophilus influenzae* type B (Hib) conjugate vaccine. The Hib vaccine has led to an 18% decrease in radiologically confirmed pneumonia [2], whereas the PCV efficacy trial in Gambia has indicated a 37% reduction in radiologically confirmed pneumonia cases [3].

Before the introduction of conjugate vaccines, *Streptococcus pneumoniae* and Hib were the leading bacterial causes of pneumonia, while *Staphylococcus aureus* and *Klebsiella pneumoniae* were associated with more severe cases. Due to an increased coverage of PCV and Hib conjugate vaccines, recent studies on the etiology of pneumonia indicate a changing profile of pathogens, which are mixed viral/bacterial infections [4].

Childhood pneumonia and associated severe clinical manifestations are a result of the complex interaction between the host, the pathogen, and environmental risk factors. The most common risk factors that affect the incidence of childhood CAP in developing countries are malnutrition, low birth weight, nonexclusive breastfeeding, lack of measles immunization, indoor air pollution, and crowding [5].

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Although only a minority of patients with pneumonia have documented blood stream infections, blood culture is still an important tool for diagnosis of pneumonia [6]. The World Health Organization (WHO) guidelines for the management of CAP in children recommend treatment of CAP and severe CAP with antibiotics to limit progression to severe or very severe CAP and the associated mortality [7]. Despite the challenges, it remains important to determine the etiology of CAP, considering the rise in antimicrobial resistance and the potential epidemiological impact of conjugate vaccines.

Most of the studies on childhood pneumonia in Ethiopia have focused on sociodemographic risk factors and the prevalence of CAP. Community-level prevalence rates of 16.1% [8] and 33.5% [9] have been reported. Risk factors associated with CAP in Ethiopian children are malnutrition, charcoal use for cooking, lack of exclusive breastfeeding in the first year of life, and overcrowding [8, 9]. There are, however, no data on the etiology of bacteremic CAP in Ethiopian children. PCV10 was introduced in Ethiopia in 2011 [10]. This study was therefore performed to determine the magnitude, etiology, and risk factors of bacteremic CAP in Ethiopian children and the role of *S. pneumoniae* in causing bacteremic pneumococcal CAP in children 5 years after the introduction of PCV10 in Ethiopia.

METHODS

Study Setting and Design

The study was carried out in the pediatric emergency departments (PEDs) of 2 large hospitals in Addis Ababa, Ethiopia: the Tikur Anbessa Specialized Hospital (TASH) and the Yekatit 12 Hospital.

Patient Recruitment, Data Collection, and Follow-up

We carried out a prospective observational study from September 1, 2016, to August 30, 2017. All children between the ages 0 to 15 years presenting to the 2 PEDs with CAP and who fulfilled the following criteria were recruited: (1) cough and/or dyspnea, and/or (2) radiological confirmation of pneumonia by the attending radiologist according to WHO guidelines [11], (3) first symptoms appearing within the last 2 weeks, and (4) no intake of antibiotics, with no hospital or health care admissions in the 2 weeks before the current admission. Tachypnea was defined as respiratory rate ≥60/min in children <2 months; ≥50/min in children 2–12 months; ≥40/min in children ≥1–5 years; and ≥20/min in children >5 years [12, 13]. Trained research nurses approached parents/guardians of children who fulfilled the criteria during the study period. A structured questionnaire was used to obtain sociodemographic and other relevant clinical data. The final outcome was registered, and length of stay in the hospital was recorded in days.

Laboratory Procedures

Sample Collection

At enrollment, venous blood (1 mL for <1-month-old and 2–5 mL for >1-month-old children) was drawn aseptically and transferred into 20 mL of Brain Heart Infusion (BHI) broth (Oxoid, Cheshire, England) bottles and mixed gently by inverting the bottle. In addition, 1–2 mL of blood, collected using ethylenediaminetetraacetic acid (EDTA) vials, was available for 273 children and was frozen at –80°C for polymerase chain reaction (PCR).

Culture and Identification

The inoculated BHI was cultured aerobically. After 24 hours of incubation, Gram stain was carried out, followed by subculture on blood agar, chocolate agar, and MacConkey agar (Oxoid). Culture bottles that did not show growth were further incubated for 7 days and subcultured before being reported negative. Initial identification of bacteria was carried out at the Armauer Hansen Research Institute (AHRI), Addis Ababa, Ethiopia, by Gram stain, hemolytic activity on sheep blood agar plates, optochin sensitivity, bile solubility, coagulase test, colony morphology on MacConkey agar, and growth on mannitol salt agar. Further identification was then performed on all isolates by Matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS) at Ghent University, Ghent, Belgium.

Antibiotic Susceptibility Testing

Antibiotic susceptibility testing on a selected panel of antibiotics that are used locally was done using the Kirby-Bauer disk diffusion method [14] and interpreted according to the Clinical and Laboratory Standard Institute (CLSI) criteria [15]. The following reference strains were used as controls: *Escherichia coli* ATCC 25922, *S. aureus* ATCC 25923, and *S. pneumoniae* ATCC 49619.

DNA Extraction

DNA extraction from *S. pneumoniae* isolates was carried out by alkaline lysis as described previously [16]. For DNA extraction from whole blood, initial pretreatment of the samples was performed as described elsewhere [17]. Briefly, 100 µL of whole-blood EDTA was added to 100 µL of Tris-EDTA buffer containing 75 U/mL of mutanolysin (Sigma Chemical Co., St. Louis, MO), and the mixture was incubated for 1 hour at 37°C. DNA extraction was then carried out with the DNeasy 96 Blood & Tissue Kit (Qiagen, Venlo, the Netherlands), according to the manufacturer's instructions.

Amplification of cpsB and lytA

Primers used to amplify 1061 bp of the *cps*B gene (encoding for phosphotyrosine phosphatase) were forward primer cps1-FP (5'-GCAATGCCAGACAGTAACCTCTAT-3') and 2 reverse primers, cps2-RP (5'-CCTGCCTGCAAGTCTTGATT-3') and cps-2538-RP (5'-CTTTACCAACCTT TGTAATCCAT-3'), and the PCR reaction was performed as described previously [18]. Amplification of a 101-bp fragment of the *lyt*A gene was carried out as previously described [19], using the primers

*lyt*A F (5'-ACGCAATCTAGCAGATGAAGCA-3') and *lyt*A R (5'-TCGTGCGTTTTAATTCCAGCT-3'). The PCR amplicons were analyzed with 1.0% agarose gel electrophoresis.

Sequencing and Serotyping

Twenty microliters of the amplicons was sent for sequencing to GATC Biotech (Constance, Germany), and sequencing was performed using the Sanger sequencing technique. *cps*B gene sequences were used to interrogate GenBank database (http://www.ncbi.nlm.nih.gov/blast). Serotype was assigned based on a BLAST bit score of >99% sequence identity of the query *cps*B nucleotide sequence with the reference sequences from GenBank. Serotyping was also performed by Quellung reaction using type-specific antisera.

Statistical Analysis

Data were initially entered in ReDCap (Vanderbilt University, Nashville, TN), exported into Excel, and analyzed using PASW Statistics 20 software (SPSS Inc., Chicago, IL). Descriptive statistics were used to analyze sociodemographic and clinical characteristics. Continuous variables were expressed in terms of mean ± SD and median (interquartile range [IQR]), whereas categorical variables were expressed in frequencies and percentages. The chi-square test for categorical variables and Mann-Whitney *U* test for continuous variables were performed to compare descriptive data between bacteremic and nonbacteremic children. To identify variables associated with bacteremic CAP, bivariate analysis using binary logistic regression was performed. Variables significant at $P < .1$ were then used in a multivariable model to identify independent associations. Variables in the multivariable model were considered significant at $P < .05$. Results from the logistic regression analyses are reported as odds ratios (ORs) and adjusted ORs (aORs) with 95% confidence intervals (CIs).

Ethical Approval

The study was approved by the AHRI/All Africa Leprosy Rehabilitation and Training Hospital (ALERT) Ethics Review Committee, Addis Ababa University Institutional Review Board, Yekatit 12 Medical College Ethics Committee, and the National Research Ethics Review Committee (No. 310/194/2017). The parents and/or guardians of all participants gave written informed consent.

RESULTS

Characteristics of the Study Population

Blood for culture and complete sociodemographic and clinical data were obtained from 549 out of the 643 children who fulfilled the inclusion criteria during the study period. Among the 549 children enrolled, 321 (58.5%) were males. Among children with bacteremia (31), most (61.3%) were females ($P = .022$) (Table 1). The median age of children (IQR) was 9 months (IQR 3–18), and most of the children (93.7%) were infants. Although parental smoking was reported in only 18 (3.3%) of the children, bacteremia was seen in a significantly higher percentage of the children who were exposed to smoking (16.7%) than in those who were not (5.3%; $P = .039$).

The most common clinical presentation of the children was cough (93.1%), followed by fever (92.3%) and tachypnea (87.4%) (Table 2). Bacteria were isolated from significantly more of the children without signs of lower chest indrawing (9.7%) than from those with signs of lower chest indrawing (4.3%; $P = .019$). A chest radiograph was performed in 68 children, and pneumonia was radiologically confirmed in 55 (80.9%) of them. Full-dose PCV10 vaccination had been given to 484 (88%) of the children. Bacterial pathogens were isolated in significantly more children who were unvaccinated with PCV10 than those who had received at least 1 dose of PCV10 (14.3% vs 5.2%; $P = .042$). Weight-for-age z-score (WAZ) was between –2 and –3 SDs in 49 (8.1%) and was less than –3 SDs in 71 (12.9%) of the children.

Etiology

A pathogen was identified in 34 of 549 (6.19%) blood cultures, of which 31 (91.18%) were positive for bacteria and 3 (8.82%) were positive for fungi (Table 3). The most commonly isolated pathogens were *S. aureus* (26.5%), *E. faecium* (11.8%), *E. coli* (11.8%), and *K. pneumoniae* (11.8%). *S. pneumoniae* was isolated from only 1 of the blood cultures. The following bacterial species, which we designated as probable pathogens, were isolated from 5.3% (29/549) of blood cultures: *Streptococcus oralis* (n = 8), *Kocuria* spp. (n = 5), *Micrococcus luteus* (n = 4), *Pantoea agglomerans* (n = 2), *Streptococcus parasanguinis* (n = 2), *Arthrobacter oxydans* (n = 1), *Bacillus cereus* (n = 1), *Brachybacterium faecium* (n = 1), *Enterococcus raffinosus* (n = 1), *Exiguobacterium aurantiacum* (n = 1), *Lysinibacillus fusiformis* (n = 1), *Streptococcus infantis* (n = 1), *Streptococcus mitis* (n = 1), *Streptococcus pseudopneumoniae* (n = 1). In addition, coagulase-negative staphylococci were isolated from 28 (5.1%) of the blood cultures.

Antibiotic Susceptibility Testing

Most of the bacterial isolates (64.5%) were Gram-negative, and all except *Proteus mirabilis* were resistant to 2 or more antibiotics (Table 4). All 4 *Enterococcus faecium* isolates were resistant to amoxicillin, penicillin, erythromycin, and tetracycline. All 3 *K. pneumoniae* isolates were resistant to amoxicillin, ceftriaxone, erythromycin, and gentamicin. Among Gram-positives, all 9 *S. aureus* isolates were resistant to penicillin, and 5 were resistant to tetracycline. Methicillin resistance, which was determined using cefoxitin discs, was observed in 3 of the *S. aureus* isolates.

Serotyping and *lyt*A PCR

Out of 273 whole-blood samples on which *lyt*A PCR was performed, a positive result was obtained in only 2 cases, 1 of which

Table 1. Comparison of Sociodemographic and Environmental Risk Factors Among Children Aged 0–15 Years With Bacteremic and Nonbacteremic CAP

Variable	Category	All Children (n = 549) No. (%)	Bacteremic (n = 31) No. (%)	Nonbacteremic (n = 518) No. (%)	*P*[a]
Gender	Male	321 (58.5)[b]	12 (3.7)	309 (96.3)	**.022**
	Female	228 (41.5)	19 (8.3)	209 (91.7)	
Age	<28 d	5 (0.9)	0 (0.0)	5 (0.9)	.441
	28 d–1 y	441 (80.3)	28 (6.3)	413 (93.7)	
	2–5 y	89 (16.2)	2 (2.2)	87 (97.8)	
	≥6 y	14 (2.6)	1 (7.1)	13 (92.9)	
Premature birth	Yes	93 (16.9)	4 (4.3)	89 (95.7)	.537
Birth weight	<2.5 Kg	62 (11.3)	6 (9.7)	56 (90.3)	.144
	≥2.5 Kg	487 (88.7)	25 (5.1)	462 (94.9)	
No. of household members	≤ 3	164 (29.9)	7 (4.3)	157 (95.7)	.659
	4–6	336 (61.2)	21 (6.2)	315 (93.8)	
	≥ 7	49 (8.9)	3 (6.1)	46 (93.9)	
No. of rooms in the house	1	157 (28.6)	8 (5.1)	149 (94.9)	.723
	≥ 2	392 (71.4)	23 (5.9)	369 (94.1)	
Has siblings aged <5 y	Yes	108 (19.7)	7 (6.5)	101 (93.5)	.675
Day care/preschool attendance	Yes	57 (10.4)	3 (5.3)	54 (94.7)	.895
Breastfeeding	Yes	337 (61.4)	22 (6.5)	315 (93.5)	.259
Mothers age, median (IQR), y		29 (26–33)	31 (28–34)	29 (26–33)	.597
Mother's level of education	Illiterate	92 (16.8)	3 (3.3)	89 (96.7)	.713
	Primary	163 (29.7)	11 (6.7)	152 (93.3)	
	Secondary	158 (28.8)	9 (5.7)	149 (94.3)	
	College and above	136 (24.8)	8 (5.9)	128 (94.1)	
Fathers level of education	Illiterate	42 (7.7)	2 (4.8)	40 (95.2)	.378
	Primary	128 (23.3)	4 (3.1)	124 (96.9)	
	Secondary	151 (27.5)	12 (7.9)	139 (92.1)	
	College & above	228 (41.5	13 (5.7)	215 (94.3)	
Monthly income	<1000 birr (45 $)	91 (16.6)	7 (7.7)	84 (92.3)	.572
	(45–136 $)	321 (58.5)	15 (4.7)	306 (95.3)	
	(136–227 $)	93 (16.9)	7 (7.5)	86 (92.5)	
	(227 $)	44 (8)	2 (4.5)	42 (95.5)	
Parental smoking	Yes	18 (3.3)	3 (16.7)	15 (83.3)	**.039**
Cooking fuel	Firewood	99 (18)	2 (2)	97 (98)	.084
	Charcoal	335 (61)	21 (6.3)	314 (93.7)	.430
	Electricity	311 (56.6)	19 (6.1)	292 (93.9)	.591
	Gas	37 (6.7)	2 (5.4)	35 (94.6)	.948
Cooking performed in living rooms	Yes	317 (57.7)	19 (61.3)	12 (38.7)	.68

Abbreviation: CAP, community-acquired pneumonia.

[a] *P* value of chi-square test for categorical variables and Mann-Whitney *U* for continuous variables; those in bold are significant at $P < .05$.

was also blood culture–positive. The pneumococcus isolated from blood culture could not be assigned to a specific serotype on the basis of PCRSeqTyping and was 35A/B/C/F, 33A/C/F. It was then assigned to serotype 33A by means of the Quellung reaction. The serotype of the additional pneumococcus that was detected by *lyt*A PCR was serotype 24, as determined by PCRSeqTyping.

Predictors of Bacteremic Community-Acquired Pneumonia

Female children were more likely to have bacteremic CAP than males (aOR, 2.3; 95% CI, 1.1–4.9; $P = .032$). Children who were malnourished (WAZ <–2 SDs) were more likely to have bacteremic CAP than those who were well-nourished (aOR, 2.2; 95% CI, 1.1–4.8; $P = .047$). Children with signs of lower chest indrawing were less likely to have bacteremic CAP than those without signs of lower chest indrawing (aOR, 0.44; 95% CI, 0.2–0.95; $P = .037$) (Table 5).

Mortality

The overall in-hospital case fatality rate was 2.37% (13/549). The etiology of fatal pneumonia was determined in only 3 of these cases. The organisms that were isolated from the children who died were *S. aureus, K. pneumoniae,* and *Kocuria kristinae*. The median length of stay of the children who died (IQR) was

Table 2. Comparison of Clinical Characteristics and Risk Factors Among Children Aged 0–15 Years With Bacteremic and Nonbacteremic CAP

Variable	Category	All Children (n = 549) No. (%)	Bacteremic (n = 31) No. (%)	Nonbacteremic (n = 518) No. (%)	P^a
URTI in the last 3 mo	Yes	89 (16.2)	6 (6.7)	83 (93.3)	.625
LRTI in the last 3 mo	Yes	105 (19.1)	9 (8.6)	96 (91.4)	.149
Previous hospital admission	Yes	92 (16.8)	5 (5.4)	87 (94.6)	.923
Days since onset of symptoms	≤3	260 (47.4)	11 (4.2)	249 (95.8)	.336
	4–6	249 (45.4)	18 (7.2)	231 (92.8)	
	≥7	40 (7.3)	2 (5)	38 (95)	
Sign and symptoms	Fever	507 (92.3)	30 (5.9)	477 (94.1)	.340
	Cough	511 (93.1)	27 (5.3)	484 (94.7)	.177
	Dyspnea	310 (56.5)	22 (7.1)	288 (92.9)	.094
	Tachypnea	480 (87.4)	25 (5.2)	455 (94.8)	.241
	Chest pain	119 (21.7)	9 (7.6)	110 (92.4)	.306
	Rales	317 (57.7)	15 (4.7)	302 (95.3)	.278
	Wheezing	346 (63)	18 (5.2)	328 (94.8)	.556
	Lower chest indrawing	415 (75.6)	18 (4.3)	397 (95.7)	**.019**
	Nasal flaring	383 (69.8)	22 (5.7)	361 (94.3)	.881
	Inability to breastfeed	129 (23.5)	9 (7)	120 (93)	.454
	Vomiting	264 (48.1)	15 (5.7)	249 (94.3)	.973
	Convulsion	16 (2.9)	2 (12.5)	14 (87.5)	.228
	Lethargy	42 (7.7)	5 (11.9)	37 (88.1)	.067
Radiologically confirmed		55 (80.9)[b]	2 (3.6)	53 (96.4)	.496
Vaccination with PCV10	Vaccinated[c]	521 (94.9)	27 (5.2)	494 (94.8)	**.042**
	1st dose	8 (1.5)	0 (0.0)	8 (100)	
	2nd dose	29 (5.3)	2 (6.9)	27 (93.1)	
	3rd (full) dose	484 (88.2)	25 (5.2)	459 (94.8)	
	Nonvaccinated	28 (5.1)	4 (14.3)	24 (85.7)	
Nutritional[d] status	Malnourished[d]	120 (21.9)	11 (9.2)	109 (21.0)	.059
	Moderately	49 (8.9)	4 (8.2)	45 (91.8)	
	Severely	71 (12.9)	7 (9.9)	64 (90.1)	
	Well-nourished	429 (78.1)	20 (4.7)	409 (95.3)	
Length of stay, median (IQR), d		2 (1–3)	2 (2–3)	2 (1–3)	.788
Final outcome	Died	13 (2.4)	2 (15.4)	11 (84.6)	.124
	Discharged or transferred	536 (97.6)	29 (5.4)	507 (94.6)	

Abbreviations: CAP, community-acquired pneumonia; LRTI, lower respiratory tract infection; PCV, pneumococcal conjugate vaccine; URTI, upper respiratory tract infection.

[a] *P* value of chi-square test for categorical variables and Mann-Whitney *U* for continuous variables; those in bold are significant at $P < .05$.

[b] Radiologically confirmed cases; for 55 (80.9%) out of the 68, a chest radiograph was performed.

[c] Vaccinated with at least 1 dose of PCV10.

[d] World Health Organization child growth standard of weight-for-age z-score was used to determine nutritional status. Accordingly, well-nourished: z-score ≥ –2.0 <; moderately malnourished: –3.0 < z-score < –2.0; severely malnourished: z-score < –3.0.

2 days (IQR 1–3). Nutritional status was the only variable that was associated with mortality. Children who were severely malnourished (WAZ <–3 SDs) were 13.5 times more likely to die than those who were not (95% CI, 3.95–46.12; $P < .001$).

DISCUSSION

To our knowledge, this is the first study in Ethiopia that describes bacteremic CAP in children. The main findings of the study are (1) the prevalence of bacteremic CAP was 5.6% (out of 549 cases of CAP); (2) the most common isolate was *S. aureus*, and there was only 1 *S. pneumoniae* isolate, with 1 additional case as determined by *S. pneumoniae*–specific PCR; (3) in univariate analysis by chi-square, parental smoking and nonvaccination with PCV10 were associated with bacteremic CAP; (4) multivariable analysis revealed that female sex and malnutrition were associated with an increased bacteremic CAP, whereas lower chest indrawing was associated with decreased bacteremic CAP; and (5) malnutrition was positively associated with mortality.

In this study, the prevalence of bacteremic pneumonia in a population of Ethiopian children, of whom 88.2% were fully PCV-vaccinated, was 5.6%. Other reports mention prevalences of 4.1% in a PCV-vaccinated population in Austria [20], and 6.7% in Mali [21] and 6.9% in Kenya [22] for nonvaccinated populations.

In our study, *S. aureus*, at 26.5% (9/34), was the most common isolate. A study on the vaccine-naïve pediatric population

Table 3. Etiology of Community-Acquired Pneumonia in Children Aged 0–15 Years

Species	No.	%
Known pathogens	34	
Bacteria	31	
Staphylococcus aureus	9	26.5
Enterococcus faecium	4	11.8
Escherichia coli	3	8.8
Klebsiella pneumoniae	3	8.8
Pseudomonas spp.	3	5.9
Moraxella catarrhalis	2	5.9
Acinetobacter baumanni	1	2.9
Burkholderia cepacia	1	2.9
Citrobacter koseri	1	2.9
Haemophilus influenzae	1	2.9
Proteus mirabilis	1	2.9
Staphylococcus lugdunensis	1	2.9
Streptococcus pneumoniae	1	2.9
Fungi	3	
Candida albicans	1	2.9
Candida parapsilosis	2	5.9

in India also identified *S. aureus* (33.3%, 15/45) as the most common cause of bacteremic CAP [23]. Results of a study on nonbacteremic CAP in Ethiopian children before the introduction of PCV10 indicated that *S. pneumoniae* (14.3%) and *Streptococcus pyogenes* were the most common isolates, followed by *S. aureus* (12.5%) [24]. Although it is difficult to extrapolate findings from bacteremic CAP into nonbacteremic CAP and vice versa, some inferences could be made. In a pre-PCV study on the etiology of CAP in Kenya by Hammit and colleagues, *S. pneumonie* was the most common isolate from both blood culture and induced sputum (IS). Blood culture was positive in only 6 (10%) of 63 children with a positive IS culture, and of 5 children with pneumococcal bacteremia, *S. pneumoniae* was isolated in the IS culture of only 2 [22]. It has not been elucidated whether a similar trend exists for *S. aureus*. A recent report by Hammit and colleagues indicated an 85% decline in the incidence of bacteremic pneumococcal pneumonia in Kenya [25]. It is therefore important to assess the role of *S. aureus* in both bacteremic and nonbacteremic CAP in Ethiopia in relation to a possible decline in the incidence of pneumococcal bacteremic and nonbacteremic CAP in the post-PCV period.

We ascertained the distinction between CAP and hospital-acquired pneumonia (HAP) using Centers for Disease Control and Prevention criteria [26]. *S. pneumoniae, H. influenzae, S. aureus,* and *K. pneumoniae,* which cause CAP [4], can also cause early-onset (occurring within the first 4 days of hospitalization) HAP and its subtype, ventilator-associated pneumonia (VAP). Late-onset HAP/VAP, which are associated with high rates of morbidity and mortality, are often caused by multidrug-resistant (MDR) pathogens such as *S. aureus*, *Pseudomonas aeruginosa*, *K. pneumoniae,* and *Enterobacter* spp. [27].

We were able to isolate *S. pneumoniae* from only 1 blood culture, and *lyt*A PCR detected 1 more case. Before the introduction of PCV, a bacteremic pneumococcal pneumonia prevalence of up to 7.2% was reported in Mali [28]. Moïsi and colleagues have been able to show a 3-fold increase in detection of pneumococcal bacteremia using *lyt*A PCR compared with blood culture

Table 4. Antibiotic Susceptibility of Pathogenic Bacterial Blood Culture Isolates From Children With Community-Acquired Pneumonia

Antibiotics		P	AML	AMC	CRO	E	TE	SXT	CN	C	CIP	FOX
Species	Total No.	No.[a]	No.[a]	No.[a]	No.[a]	No.[a]	No.[a]	No.[a]	No.[a]	No.[a]	No.[a]	No.[a]
Gram-positive												
Staphylococcus aureus	9	9	-	-	-	3	5	1	2	0	1	3
Staphylococcus lugdunensis	1	1	-	-	-	1	1	0	0	0	1	-
Streptococcus pneumoniae	1	0	-	-	-	0	1	1	-	0	-	-
Gram-negative												-
Enterococcus faecium	4	4	4	-	-	4	4	-	-	1	0	-
Escherichia coli	3	-	0	0	0	1	1	0	0	0	0	-
Klebsiella pneumoniae	3	-	3	1	3	3	1	2	3	2	2	-
Pseudomonas spp.	3	-	3	2	2	2	0	2	0	1	0	-
Moraxella cattarhalis	2	-	-	0	1	2	0	0	-	1	0	-
Acinetobater baumanni	1	1	1	1	1	-	0	1	0	-	0	-
Burkholderia cepacia[b]	1	-	-	-	-	-	-	-	-	-	-	-
Citrobacter koseri	1	-	1	1	1	1	1	1	0	-	0	-
Haemophilus influenzae	1	-	1	1	1	1	1	0	-	1	1	-
Proteus mirabilis	1	-	0	0	0	0	1	0	0	0	0	-

Abbreviations: -, not tested; AML, amoxicillin; AMC, amoxicillin, clavulanate; C, chloramphenicol; CIP, ciprofloxacin; CN, gentamicin; CRO, ceftriaxone; E, erythromycin; FOX, cefoxitin; P, penicillin; SXT, trimethoprim/sulfamethoxazole; TE, tetracycline.

[a]Number of resistant isolates.

[b]Has been performed, but disc diffusion interpretative breakpoints are not available.

Table 5. Factors Associated With Bacteremic Community-Acquired Pneumonia in Children Aged 0–15 Years

	Bivariate		Multivariable	
Variable	OR (CI)	*P*	aOR (CI)	*P*[a]
Female sex	2.34 (1.1–4.9)	.025	2.3 (1.1–4.9)	**.032**
Malnourished	2.1 (0.96–4.4)	.064	2.2 (1.1–4.8)	**.047**
Lower chest indrawing	0.42 (0.2–0.89)	.023	0.44 (0.2–0.95)	**.037**
Vaccination with PCV10	0.33 (0.11–1.01)	.053	2.6 (0.8–8.1)	.11
Parental smoking	3.6 (0.98–13.1)	.053	3.2 (0.83–12.4)	.91

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio; PCV, pneumococcal conjugate vaccine.

[a]*P* value of multivariable logistic regression analyses; those in bold are significant at $P < .05$.

during the prevaccination period in Mali [17]. Our results, which indicate only insignificant enhancement of detection by *lyt*A PCR, might be a reflection of the current prevalence of bacteremic pneumococcal pneumonia 5 years after the introduction of PCV10 in Ethiopia. Unfortunately, due to the lack of pre-PCV vaccination data on the prevalence of bacteremic pneumococcal pneumonia in Ethiopia, comparisons could not be made.

Our findings indicate that most of the bacterial isolates were resistant to first- and second-line antibiotics used to treat CAP in children. There was also a high level of multidrug resistance, with *E. faecium* and *K. pneumoniae* being 100% resistant to 4 antibiotics each. Studies indicate that there is a trend of increasing antimicrobial resistance in Ethiopia [29]. The standard treatment guideline in Ethiopia suggests the use of chloramphenicol in case of lack of response to trimethoprim-sulphamethaxozole, amoxicillin, and bezylpenicillin. With only 25% resistance of *E. faecium* against chloramphenicol in our study, it could still be used as a treatment option [30]. In the case of MDR *K. pneumoniae,* the use of piperacillin-tazobactam, moropenem, and impenem-cilastatin has been suggested [31]. Our results highlight the need for incorporation of improved diagnostic tools and antimicrobial resistance surveillance to aid the choice of antibiotics.

The case fatality rate in our study (2.37%) was lower than results from a non-PCV population in Mali (4.2%) [21] and a multihospital, retrospective cohort study in Kenya (5%) 3 years after introduction of PCV10 in the country [32].

Several risk factors associated with bacteremic CAP in Ethiopian children have been identified in our study through univariate and multivariable analyses. A significantly higher percentage of children who had a parent that smokes had bacteremic CAP than those without. Although there are no studies that describe the relationship between parental smoking and bacteremic CAP, parental smoking and environmental tobacco exposure have been associated with pneumonia [33].

Bacteremic CAP was observed in significantly more of the children who were not vaccinated with PCV10 compared with those who had received at least 1 dose of PCV10. Tagarro and colleagues have been able to show that due to the introduction of PCV13 in Madrid, Spain, bacteremic CAP declined from 7.9/100 000 children in 2009 to 2.1/100 000 children in 2012. The incidence of bacteremic CAP then increased again to 5.4/100 000 children in 2014, 2 years after the withdrawal of PCV13 from the universal vaccination program [34].

Female sex was significantly associated with isolation of pathogenic bacteria from blood cultures of children with CAP, with female children being 2.3 times more likely to have bacteremic CAP than male children. Although male sex has been associated with higher pneumonia incidence and hospitalization [35], there is no evidence in the literature for the association between gender and bacteremic pneumonia in children. However, Isaacman and colleagues have reported increased risk of bacteremia in febrile female children [36].

In this study, children with signs of lower chest indrawing were less likely to have bacteremic CAP than those without. Lower chest indrawing is one of the main signs that is used to classify pneumonia [12] and has been identified as a sign of potentially fatal pneumonia [32]. In a study performed by De Santis and colleagues in Tanzania, lower chest indrawing was found to be associated with viral disease [37]. Although clinical presentation of viral diseases is thought to be milder than that of bacterial diseases, at present most acute respiratory infections in children in well-vaccinated populations are due to viruses rather than bacteria, even in children with a more severe presentation [37, 38].

In our study, children with pneumonia who were malnourished were 2.2 times more likely to have bacteremic pneumonia, and those who were severely malnourished were 13.5 times more likely to die due to pneumonia than well-nourished children. WAZ <–3 SDs has been identified as a clinically important risk of death in a recent report from Kenya [32].

Our study had some limitations. Although we only tried to include children who did not receive antibiotics during the 2 weeks preceding sampling, there might still have been cases of empiric antibiotic treatment. The low volume of blood obtained in some children might also have affected culture positivity. Limitations in proper transport and storage of whole blood might have also affected the results of *lyt*A PCR. Although both emergency departments accept patients coming from home, many of the cases in the hospitals are referrals, and our results might not be representative of the true prevalence of CAP in Addis Ababa.

CONCLUSIONS

This study has described the sociodemographic and clinical predictors of bacteremia in Ethiopian children with CAP. Five years after the introduction of PCV10 in Ethiopia, *S. aureus* was the main etiological agent of bacteremic CAP, and the contribution of *S. pneumoniae* was low. Most of the bacterial isolates were resistant to first- and second-line antibiotics to treat CAP, which indicates a need for incorporation of improved diagnostic tools and antimicrobial resistance surveillance to aid the choice of antibiotics. Parental smoking, nonvaccination with PCV10, female sex, malnutrition, and absence of chest indrawing were associated with bacteremic CAP. Malnutrition was associated with mortality due to CAP.

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