Burden of *Streptococcus pneumoniae* sepsis in children after introduction of pneumococcal conjugate vaccines - a prospective population-based cohort study

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Summary:

Shortly following introduction of PCV-13 in Switzerland, blood culture-proven pneumococcal sepsis accounted for 25% of community-acquired sepsis in children, with an 8% case fatality rate. Presence of meningitis and infection by serotype 3 were associated with severe disease.

Abstract

Background: Population-based studies assessing the impact of pneumococcal conjugate vaccines (PCV) on burden of pneumococcal sepsis in children are lacking. We aimed to assess this burden following introduction of PCV-13 in a nationwide cohort study.

Methods: The Swiss Pediatric Sepsis Study (09/2011-12/2015) prospectively recruited children <17 years of age with blood culture-proven sepsis due to *Streptococcus pneumoniae,* meeting criteria for systemic inflammatory response syndrome. Infection with vaccine serotype in children up to date with PCV immunization was defined as vaccine failure. Main outcomes were admission to pediatric intensive care unit (PICU) and length of hospital stay (LOS).

Results: Children with pneumococcal sepsis (n=117) accounted for a crude incidence of 2.0 per 100,000 children (95% CI 1.7-2.4) and 25% of community-acquired sepsis episodes. Case fatality rate was 8%. 42 (36%) patients required PICU admission. Children with meningitis (29; 25%) were more often infected by serotypes not included in PCV (69% vs 31%; *p<0.001*). 16 (26%) of 62 children up to date with PCV immunization presented with vaccine failure, including 11 infected with serotype 3. In multivariable analyses, children with meningitis (OR 6.8; 95% C.I 2.4-19.3; p<0.001), or infected with serotype 3 (OR 2.8; 95% C.I 1.1- 7.3; *p=0.04*) were more often admitted to PICU. Children infected with serotype 3 had longer LOS (β coefficient 0.2, 95% CI 0.1-1.1; *p=0.01*).

Conclusions: The incidence of pneumococcal sepsis in children shortly after introduction of PCV-13 remained substantial. Meningitis mostly due to non-vaccine serotypes and disease caused by serotype 3 represented significant predictors of severity.

Keywords: sepsis, child, bacteremia, *Streptococcus pneumonia*, serotype 3

Abbreviations: CAP: community-acquired pneumonia; IPD: invasive pneumococcal disease; LOS: length of hospital stay; PCV: pneumococcal conjugate vaccine; PICU: pediatric intensive care unit; SIRS: systematic inflammatory response syndrome, ST: serotype.

Introduction

Streptococcus pneumoniae is a leading cause of sepsis, meningitis and community-acquired pneumonia (CAP) resulting in significant mortality in children worldwide.[1, 2] Invasive pneumococcal disease (IPD), defined as all clinical phenotypes in which *S. pneumoniae* was isolated from blood, cerebrospinal fluid, pleural fluid or any other normally sterile site by culture, antigen testing or molecular assays was significantly reduced after the implementation of pneumococcal conjugate vaccines (PCV). Surveillance studies conducted in the United States and in the United Kingdom reported 91% -97% effectiveness of 7-valent PCV (PCV-7, Prevenar7®) and 13-valent PCV (PCV-13, Prevenar13®), respectively, among children < 5 years of age against IPD caused by serotypes included in PCV herein defined as vaccine serotypes [1, 2]. A previous study [4] identified underlying co-morbidities as a major risk factor for IPD among children vaccinated with PCV-7 , whereas limited data suggested an association between pneumococcal serotype 3 and death among children with bacteremic pneumonia [5]. For the incidence of pneumococcal disease most studies refer to IPD, while less is known on the rate of blood culture-proven sepsis, meeting the criteria for systemic inflammatory response syndrome (SIRS), herein defined as pneumococcal sepsis.

There is a lack of recent population-based studies determining the burden and outcomes of pneumococcal sepsis in children. In Switzerland, the Federal Office of Public Health (FOPH) recommended the immunization of all children under 2 years of age (with a catch-up dose up to 5 years of age) with PCV-7 in 2006 followed by a switch to PCV-13 in 2011 [6]. In the present study, we assessed incidence, clinical presentation, risk factors for severity of pneumococcal sepsis in children using a nationwide prospective sepsis cohort [1, 2, 7].

Materials and Methods

Participants and definitions

The Swiss Pediatric Sepsis Study (SPSS) [8, 9] is a prospective national observational multicenter cohort study investigating blood culture-proven sepsis in children under 17 years of age from all ten major children's hospitals in Switzerland from September 1, 2011, to December 31, 2015. Based on data of the mandatory hospital statistics, the 10 participating centers during the study period cared for 78% of all children < 17 years of age with an ICD-10 code for pathogen-specific sepsis admitted to a hospital in Switzerland, and for 98% of all children admitted to the intensive care unit with this code [9].

Details of the study design and the study protocol have been published elsewhere [9]. In brief, children with blood culture-proven sepsis meeting the criteria for SIRS, as defined by the 2005 pediatric consensus definition [7] at the time of blood culture sampling were included. SIRS required the presence of at least two of the following four criteria, one of which had to be abnormal temperature or leukocyte count: a core temperature > 38.5°C or < 36°C, Tachycardia, tachypnea, and abnormal white cell count. Severe sepsis was defined by the presence of cardiovascular or respiratory failure, or two or more other organ dysfunctions (hepatic, renal, hematologic, central nervous system). Septic shock was defined as sepsis in the presence of cardiovascular failure [7]. Ethics approval was obtained from all local ethics committees of participating centers, including a waiver from informed consent to record anonymized epidemiological data [9]. For the present study, only sepsis episodes due to *S. pneumoniae* bacteremia, were included. Admission to the pediatric intensive care unit (PICU) and length of hospital stay (LOS) were defined as outcomes.

Collection of clinical information and specimens

Information on patient demographics, baseline characteristics and outcomes were collected prospectively [9]. For this analysis we grouped co-morbidities into the following categories: asplenia, sickle cell disease, and immunodeficiency, neurological, cardiac, respiratory and metabolic conditions, which represent distinct high-risk groups for IPD [6] and compared this group to so far healthy children without any known risk for IPD. The clinical focus was prospectively categorized into pneumonia, complicated pneumonia (any pneumonia with effusion), meningitis, other infection site (infections of bone and joint, ENT or skin), or primary bloodstream infection otherwise. Blood cultures were processed according to standard operating procedures of the local microbiology laboratory using an automated alert process.

All *S. pneumoniae* isolates were serotyped at the national reference center for IPD in Berne, Switzerland, according to the standard procedure known as the Quellung reaction [10].

Information on pneumococcal immunization status at the time of admission for sepsis was extracted from written personal vaccination cards. Vaccination with 7-valent (PCV-7, Prevenar®) or 13-valent pneumococcal conjugate vaccine (PCV-13, Prevenar 13®) was categorized in “up to date”, “not up to date” for age at sepsis or “unimmunized” along the criteria shown in Table 1 with protection being achieved 2 weeks after the 2nd dose [6]. Vaccine failure was defined as an infection with a vaccine serotype while being immunized ~~fully~~ up to date for age with PCV-7 or PCV-13.

Incidence calculation

To calculate the crude incidence of pneumococcal sepsis, we included only episodes recorded in full study years (2012-2015), as measured in the ten participating study centers. We calculated the age-specific incidence of pneumococcal sepsis by dividing the annual number of blood culture-proven

pneumococcal sepsis episodes recruited in the study by the end-of-year resident population in Switzerland in the respective age-groups and age standardized it to the European standard population [9, 11]. We calculated the age-specific incidence of IPD in children in Switzerland (2012-2015) based on the number of IPD cases by age group using the same methodology. These data, which were collected in the frame of the mandatory notification of invasive pneumococcal diseases, were provided by the Swiss Federal Office of Public Health.

Statistical analyses

The χ^2 test or Fisher's exact test were used to compare categorical variables between groups as appropriate. Multivariable logistic regression was used to assess clinical, epidemiologic and socio-demographic correlates of admission to the PICU. We derived medians and the interquartile range (IQR), used the Mann-Whitney test for comparisons of non-normally distributed continuous data, and used a transformation using the natural logarithm (ln) of LOS when performing multivariable linear regression. All available predictors including age, meningitis as clinical focus vs any other focus, infection with serotype 3 versus any other serotype, vaccine failure and the presence of any co-morbidity previously reported to be associated with adverse outcomes on the basis of the literature were included *a priori* in the initial models. Significant variables *(p<0.05)* were then added to multivariable models. In addition, an interaction variable between serotype 3 and vaccine failure was created given the potential interaction between both predictors with the outcomes of interest. All tests were two-sided and a p-value < 0.05 was considered to be statistically significant. Data were analyzed using SPSS statistical software (version 20.0, SPSS Inc, Chicago, IL, USA).

Results

Burden and presentation of pneumococcal sepsis

In the 4.3-year study period, 117 children experiencing 118 pneumococcal sepsis episodes (one patient had recurrent pneumococcal infection) were recorded. *S. pneumoniae* accounted for 10% (118/1181) of all bacterial sepsis episodes in the Swiss Paediatric Sepsis Study (SPSS) and ranked fourth most frequent pathogen after *Escherichia coli, Staphylococcus aureus* and coagulase-negative staphylococci [9]. *S. pneumoniae* was the leading pathogen of sepsis among previously healthy children, causing 25% of community-acquired sepsis episodes (97/382). Among all children with pneumococcal sepsis, 57% were males. 83% were so far healthy without any risk while 20 (17%) suffered from an underlying disease at risk for IPD of whom 9 with an immune-compromising condition. Sixty children (51%) presented with pneumonia including 18 (15%) complicated by pleural effusion, 29 (25%) with meningitis, 19 (16%) with primary bloodstream infection and 9 (8%) with any other clinical focus. The median age was 3.6 years (interquartile range (IQR) 1.8-6.0). Meningitis was more common in infants than in older children (14/29; 48% vs. 10/88; 11%; Table 2).

The crude incidence of blood culture-proven pneumococcal sepsis was 2.0 per 100'000 children (95% CI 1.7 - 2.4), which translated into an age-standardized incidence of 2.1 per 100'000 children (95% CI 1.7 - 2.5). It was highest in infants (6.7 per 100'000 (95% CI 4.2-10.1)) and toddlers (3.6 per 100'000 (95% CI 2.7-4.8)) and decreased in older children (Figure 1).

Sepsis severity and outcomes

The median duration of hospital stay of children with pneumococcal sepsis was 9 days (IQR 4-14 days). Forty-two (36%) children were admitted to PICU of whom 22 (52%) required mechanical ventilation. Fourteen children (12%) presented with septic shock. Nine children died resulting in a case fatality rate

of 8%. Eight deaths were directly related to sepsis, and one child died due to an underlying metabolic condition with acute encephalopathy, which may have been triggered by sepsis. The fatal cases included 7 previously healthy patients (median age 3.7 years (IQR 1.4-6.2)) of which 4 patients presented with meningitis (Table 2).

Serotype distribution and immunization status

Information on pneumococcal serotype was available in 112 of 117 (96%) children. The vaccine serotypes 3 (n=27; 24%), 19A and 7F (n=11; 10% each) were most frequently detected, followed by the non-vaccine serotypes 15 and 24 (n=7, 6% each). Sixty-four episodes (57%) were caused by PCV-13 serotypes. Twenty of the 29 children (69%) with meningitis were infected with non-vaccine serotypes of whom 7 (35%) were diagnosed with serotype 15, which was not detected in children without meningitis. Seven (78%) of the 9 fatal sepsis episodes were due to infection with non-vaccine serotypes (Figure 2, Table 3).

Children infected with vaccine serotypes were older than those infected with non-vaccine serotypes (median 4.7 versus 2.2 years; *p<0.001*). Ten children (5/64 infected with PCV serotypes, 5/48 infected with non-vaccine serotypes) were too young (< 130 days of life) to be protected by immunization with PCV.

Data on history of immunization with PCV was available from 102/117 (87%) children with pneumococcal sepsis of whom 33 (32%) children with known serotype were unvaccinated. These 33 unvaccinated children included 4/7 children (57%) with sepsis due to PCV-7 serotypes, 19/51 (37%) with sepsis due to a serotype contained in PCV-13 but not in PCV-7 and 10/44 (23%) with sepsis due to non-vaccine serotypes. A higher rate of unvaccinated children infected by pneumococcal serotypes included

in PCV-13 but not in PCV-7 was recorded compared with those infected by pneumococcal non-vaccine serotypes (19/51 (37%) versus 10/44 (23%); *p<0.001*).

A total of 62 children were immunized "up to date" for age with respect to time of introduction of PCV and age. Immunization failure was recorded in 16 episodes, including 11 episodes due to serotype 3, three due to 19A, and one each due to serotypes 14 and 6B (Table 3). All children with vaccine failure and sepsis with serotype 3 had received two priming and a PCV-13 booster dose.

Predictors of admission to the PICU and LOS

Children with meningitis were more likely to be admitted to PICU compared to those without meningitis (20/29; 69% versus 22/88, 25%, *p<0.001;* Table 1). Children with sepsis with serotype 3 represented 31% (13/42) of children requiring PICU compared to 20% (14/70 among pneumococcal sepsis episodes not requiring PICU, and the overall LOS was longer compared to children infected by any other serotype (14 days (IQR 9-18.5) versus 7 days (IQR 3-12), *p=0.009*). In multivariable analyses the presence of meningitis (OR 6.8; 95% C.I 2.4-19.3 *p<0.001*) and sepsis by serotype 3 (OR 2.8; 95% C.I 1.1-7.3; *p=0.04*) represented significant independent predictors of admission to the PICU. In addition, children infected with serotype 3 (β coefficient 0.2, 95% CI 0.1-1.1; *p*=0.01) presented with a longer hospital stay compared to those infected with any other serotype (Table 4).

Discussion

Our study demonstrates the ongoing burden of pneumococcal sepsis among children in Switzerland, shortly after the introduction of PCV-13. Over half of the episodes were caused by serotypes included in PCV-13, predominantly serotype 3.

In this nationwide prospective study conducted between 2011 and 2015, just after the switch from PCV-7 to PCV-13, *S. pneumoniae* accounted for 25% of community-acquired blood culture-proven sepsis episodes. The estimated 3 doses coverage with PCV-13 among children under 2 years of age in Switzerland ranged from 75 to 80% in this period [12]. Pneumococcal sepsis predominantly affected previously healthy children under 5 years of age (83%) without known risk factors for IPD similar to reports before the introduction of PCV-13 [9, 10]. Infants had a three times higher incidence of pneumococcal sepsis compared to older children and were more likely to suffer from meningitis.

The severity of pneumococcal sepsis was substantial. More than a third of children required admission to PICU and 12% presented with septic shock. In addition to meningitis, infection with serotype 3 was a significant independent predictor for admission to the PICU. Over one third of PICU admissions was related to serotype 3, translating into prolonged LOS. The need for PICU admission and the presence of meningitis put these children at a substantially higher risk for long-term sequelae including neurodevelopmental delay [13]. While our study was not powered to detect differences in mortality, the reported case fatality rate (8%) was comparable to a recent large Australian and New Zealand pediatric sepsis cohort (reporting data between 2002 and 2013) [14] but amongst the highest, i.e. twice as high, as the mean case fatality rate 3.5% reported for IPD in Europe (data reported between 1998 and 2008) [15]. These discrepancies are likely related to different case definitions. Most reported data refers to the epidemiology of IPD among which bacteremia in children may represent 40-50% [1],

not all fulfilling sepsis criteria. IPD beside sepsis includes many non-septic children with pneumonia or arthritis while our study focused on blood culture-proven sepsis applying the 2005 Pediatric Sepsis Consensus Definitions [7] representing the most severe phenotype compared to all IPD.

Pneumococcal serotypes contained in PCV-13, mostly serotype 3, were responsible for more than half of the pneumococcal sepsis episodes in our study. We observed a lower rate of children being immunized up to date with PCV in our cohort compared to national data (66% vs 75-80%) [6, 12] which may reflect a selection of susceptible unprotected individuals in our cohort. Importantly, our study was started in the first year of introduction of PCV-13 into the general vaccine schedule in Switzerland. In the study period, the incidence rates of IPD among children under 5 years of age in Switzerland (7.5 per 100'000 children per year) [6] were similar to those given by US population-based reports (6.4 per 100'000 children) [16] and higher compared to reports from the UK (4.1 per 100'000 children) [2]. These discrepancies likely result from differences in timing of PCV-13 introduction, PCV-13 catch-up policies, vaccination coverage, and the period during which surveillance studies were conducted. Between 2011 and 2015 vaccination coverage rates with 3 doses of PCV-13 of up to 93.5% have been reported in the UK, compared to 75-80 % in Switzerland [12, 17]. Herd protection from PCV-13 was probably not yet achieved in our cohort unlike in the UK [17]. In addition, the inclusion of a large number of children who did not qualify for PCV vaccination because of their age (> 5 years) were not or (age < 5 months of age) not yet fully protected, or who did not follow the recommendations may account for this finding. Recent national surveillance data [6, 18] reported a 50% decrease in IPD among children under 5 years of age between 2009 and 2017, that may be increasing to 80-90% as seen in other countries [1, 2, 17], thus supporting the efficacy of PCV-13 vaccination.

However, 11 of 16 (69%) vaccine failures were caused by infection with serotype 3, supporting previous reports on the low immunogenicity of PCV-13 for serotype 3 [5, 6]. All children with vaccine

failure infected with serotype 3 had received a PCV-13 booster dose. This finding warrants considerations for more effective vaccines and immunization schedules given the impact of serotype 3 observed in our cohort. The importance of serotype 3 in pneumococcal sepsis is supported by experimental studies, demonstrating significant cortical necrosis and abscess formation in meningitis among rats infected with serotype 3 compared to those infected with serotype 1 [5, 19-22] and a systematic review [5] which reported increased case-fatality rates amongst children and adults with bacteremic community-acquired pneumonia infected with serotype 3 compared to serotype 14.

The strengths of this study are the population-based design and detailed prospectively collected information including serotyping and vaccination status. Based on mandatory hospital statistics the study centers cared for 78% of all children with ICD-10 coded for pathogen-specific sepsis admitted to a hospital in Switzerland [9]. By comparing data on blood culture-proven pneumococcal sepsis from our prospective study cohort with administrative data on IPD provided by the Swiss Federal Office of Public Health, we estimated that 40% of IPD episodes were represented in the study. This estimate is in line with bacteremia representing 48% of IPD cases among children in the US [1]. In addition, clearly defined criteria for the inclusion of children with bacteremia and SIRS resulted in a population of patients with an unequivocal phenotype. Limitations refer to SIRS-based sepsis definitions[25, 26], which recently have been revised in the adult population [23, 24]. Finally, we cannot report on the impact of PCV vaccination on the burden of pneumococcal sepsis in Switzerland because of the lack of data before the introduction of PCV vaccination.

In conclusion, the burden of disease of pneumococcal sepsis among young, mostly previously healthy children, still remains significant in Switzerland shortly after the introduction PCV-13. Pneumococcal serotype 3 infections accounted for a substantial proportion of cases in our cohort, were commonly seen in up to date for age vaccinated children, and were associated with more severe

disease. Our data support the need for vaccines with better protection against serotype 3 as well as the need for ongoing surveillance of IPD, and sepsis in particular, as the burden of sepsis by pneumococcal serotypes not included in PCV already in this study is relevant.

Acknowledgement

We would like to thank the Federal Office of Public Health for providing aggregated IPD data and linking them to the blood-culture positive pneumococcal sepsis data collected within this study.

Disclaimer

The funding sources had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript. The authors have no conflicts of interest to disclose. The authors had no financial or other forms of conflicts of interest.

Funding

This work was supported by grants from the Swiss National Science Foundation (342730_153158/1), the Swiss Society of Intensive Care, the Bangerter Foundation, the Vinetum and Borer Foundation and the Foundation for the Health of Children and Adolescents.

Conflicts of Interest

Dr. Heininger reports personal fees from Sanofi, Takeda, Seqirus, and Pfizer, outside the submitted work. All other authors have no conflicts of interest to disclose.

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Legends to figures

Figure 1

Black horizontal lines show the crude incidence of blood culture-proven pneumococcal sepsis during full study years (2012 – 2015) by age group, as measured in the ten participating study centers; x show the national incidence of all invasive pneumococcal disease in Switzerland for each age-group given (data provided by the Swiss Federal Office of Public Health). Vertical lines represent the 95% CIs around the point estimates for each age-group.

Figure 2

Pneumococcal serotypes isolated from blood from children with pneumococcal sepsis. Information on serotypes was available from 112 of 117 sepsis episodes (serotype not available in 5 episodes). Sepsis in is indicated by grey bars, black bars illustrate episodes with sepsis and meningitis.

Figure 1

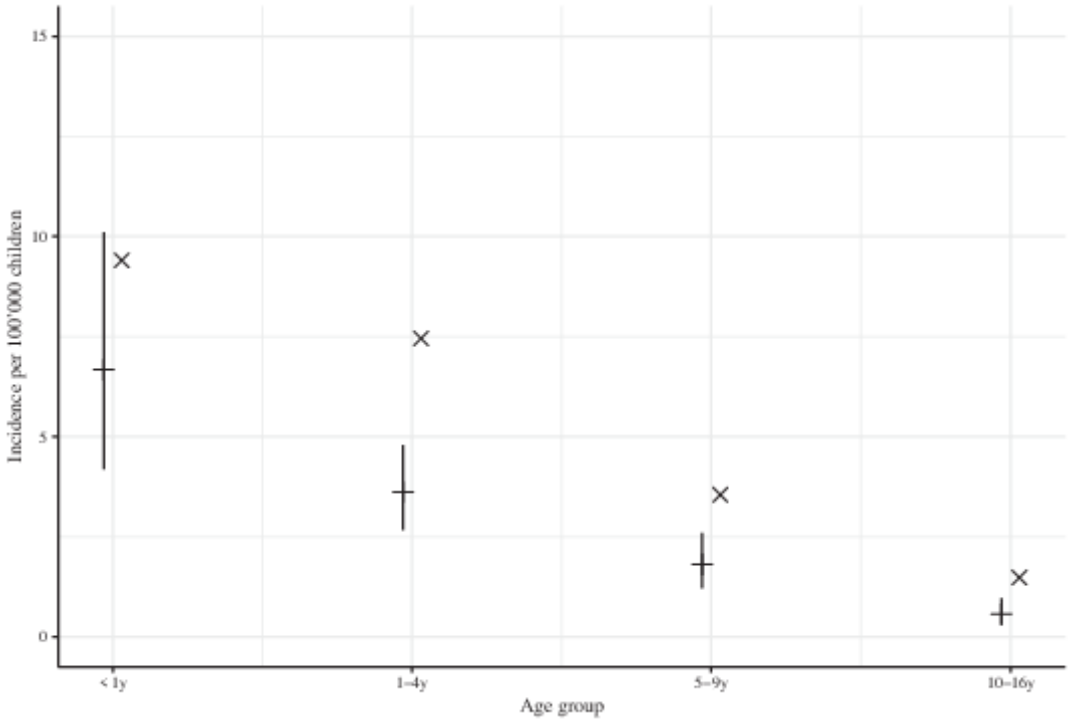

Figure 2: Serotype distribution in children with pneumococcal sepsis

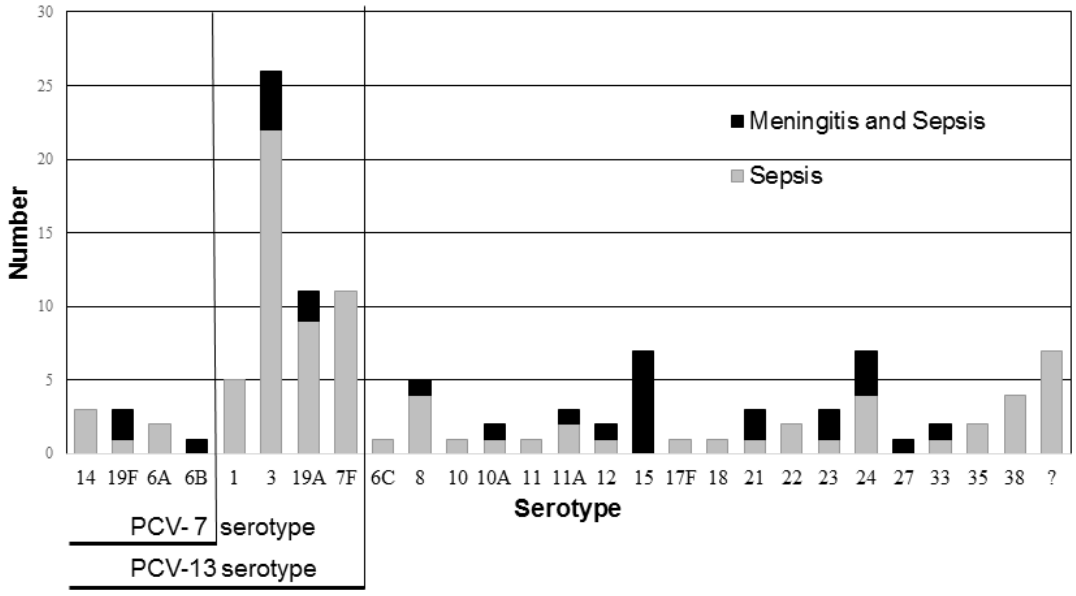

TABLE 1: Definitions for vaccination up to date for age with 7-valent or 13-valent pneumococcal conjugate vaccine

Age groups	Complete vaccination: up to date for age	Vaccination not up to date for age
Children <12 months of age	From 2 weeks after the second dose and onwards	Received ≥ 1 dose without meeting criteria for complete vaccination
Children 12-15 months of age	• ≥2 doses before 12 months of age • and/or from 2 weeks after the second dose and onwards, regardless of age when the doses were administered	Received ≥ 1 dose without meeting criteria for complete vaccination
Children >15 months of age and <24 months of age	• ≥2 doses documented before 12 months of age AND 1 dose from 12 months of age onwards administered ≥ 2 weeks ago	Received ≥ 1 dose without meeting criteria for complete vaccination
Children ≥24 months of age	• ≥2 doses documented before 12 months of age AND 1 dose from 12 months of age onwards administered ≥ 2 weeks ago • OR from 2 weeks after the second dose onwards when these 2 doses were administered from age 12 months onwards AND the second dose was administered ≥ 2	Received ≥ 1 dose without meeting criteria for complete vaccination

	weeks ago • OR ≥ 1 dose documented ≥24 months of age AND the first (or only) dose was administered ≥ 2 weeks ago	

TABLE 2: Baseline characteristics and clinical outcomes of children presenting blood culture-proven pneumococcal sepsis

	All patients N=117	**Meningitis N=29**	**Non-meningitis N=88**	***P values***
A) Baseline characteristics				
Age; median years (IQR[a])	3.6 (1.8-6.0)	1.7 (0.6-6.5)	3.8 (2.2-5.9)	0.385
< 2 months; N (%)	**6 (5.1)**	**2 (7)**	**4 (4.5)**	***<0.001***
2-12 months; N (%)	**18 (15.4)**	**12 (41.4)**	**6 (6.8)**	***<0.001***
12 months-4 years; N (%)	**50 (42.7)**	**6 (20.7)**	**44 (50.0)**	***0.009***
≥ 5 years; N (%)	43 (36.8)	9 (31.0)	34 (38.6)	0.503
Gender; N male (%)	67 (57.3)	19 (65.5)	48 (54.5)	0.388
Ethnicity; N caucasian (%)	92 (88.5)	24 (88.9)	68 (88.3)	0.247
No underlying comorbidity; N (%)	97 (82.9)	26 (89.7)	71 (80.7)	0.145
B) Clinical outcomes				
Severe sepsis; N (%)	**27 (23.1)**	**12(41.4)**	**15 (17)**	***0.009***

Septic shock; N (%)	14 (12)	5 (17.2)	9 (10.2)	0.331
Death at 30 days of admission; N (%)	9 (8.1)	4 (14.3)	5 (6)	0.226
Admission in PICU; N (%)	**42 (36)**	**20 (69)**	**22 (25)**	***0.001***
Invasive ventilation; N (%)	22 (18.8)	8 (27.6)	14 (15.9)	0.260
Length of stay in PICU; median days (IQR)	4 (1.5-10)	3 (1-6)	5 (2-10)	0.313
Length of hospital stay; median days (IQR[a])	9 (4-14)	10 (8.3-14.8)	7 (3.0-14)	0.210

LEGEND [a]IQR interquartile range; p-values compare children with pneumococcal sepsis with to those without meningitis; significant p values (P<0.05) are indicated in bold. Severe sepsis included in addition presence of cardiovascular organ dysfunction or acute respiratory distress syndrome or two or more other organ dysfunctions. Septic shock was defined as sepsis and cardiovascular organ dysfunction [1].

Table 3. ***S. pneumoniae*** **serotype distribution by immunization status in children with pneumococcal sepsis**

		Infection by vaccine serotype				**Infection by non-vaccine serotype**	**unknown**	**Total**
	Immunization status	**in PCV13**	in PCV7	in PCV13 but not PCV7	ST 3	**Non PCV13**		
	Total	**64**	7	57	27	**48**	5	117
	Up to date for age immunization failure*	***16***	***2***	***14***	***11***			16
		16		16	5	**29**	1	46

	Up to date for age as recommended but not against serotype of sepsis							
	Not up to date for age as recommended	**3**	1	2	1	**5**	1	9
	No immunization	**23**	4	19	9	**10**	3	36
	No data on immunization	**6**	0	6	1	**4**		10

*immunization failure (as defined in table 1): infection with vaccine serotype and PCV immunized up to date for age.

**serotype 3: n=11, 19A: n=3, serotype 14: n=1; serotype 6B: n=1

Note: 32 children had a pneumococcal sepsis due to a serotype included in PCV and were immunized as recommended. Among those, 16 were immunized up to date for age with PCV against the serotype causing sepsis and were counted as vaccine failures. The other 16 children were immunized as recommended with PCV but at time of sepsis were not protected against the serotype causing sepsis (received PCV7 while the serotype causing sepsis was only included in PCV13 but not in PCV7).

TABLE 4: Predictors of admission in the PICU and length of hospital stay for children with pneumococcal sepsis

	PICU admission (n=42)				Length of hospital stay (n= 117)			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	OR (95 %C.I)	**P value**	**OR (95 %C.I)**	**P value**	**ß coefficient (95 %C.I)**	**P value**	**ß coefficient (95 %C.I)**	**P value**
Infants (< 12 months of age) vs older children	2.6 (1.04, 6.5)	**0.04**	1.4 (0.5,4.2)	0.559	0.1 (-0.2, 0.8)	0.225	0.1 (-0.2, 0.8)	0.258
Meningitis vs no meningitis	6.7 (2.6, 16.8)	**<0.001**	6.8 (2.4,19.3)	**<0.001**	0.2 (0.04,0.9)	**0.034**	0.2 (-0,05,0.9)	0.08
Infection with serotype 3 vs any other serotype	1.8 (0.8, 4.3)	0.192	2.8 (1.1,7.3)	**0.04**	0.2 (0.005,0.9)	**0.03**	0.2 (0.1,1.1)	**0.01**
Vaccine failure in children PCV immunized up to date for age (1)	0.8 (0.2, 2.2)	0.637	-	-	0.01 (-0.05, 0.6)	0.923	-	-
Interaction variable serotype 3x vaccine failure*	1.4 (0.4, 5.1)	0.568	-	-	0.09 (-0.4, 1.0)	0.353	-	-
Presence of any co-morbidity	0.4 (0.1, 1.3)	0.142	-	-	0.032 (-0.1, 0.2)	0.735	-	-

(1) Infection with vaccine serotype and immunized up to date for age with PCV-7 or PCV-13 vs infected with non-vaccine serotype or with a vaccine serotype AND not immunized at all

* An interaction effect occurs when the effect of one variable depends on the value of another variable. As vaccine failure might depend on serotype 3,

an interaction variable between serotype 3 and vaccine failure was created

OR: Odds ratio; C.I: Confidence interval