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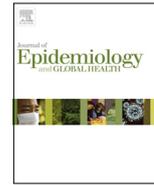
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ORIGINAL ARTICLE

Epidemiology of invasive pneumococcal disease in Saudi Arabian children younger than 5 years of age



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Abstract This study evaluated the incidence, serotype distribution, and antimicrobial susceptibility of invasive pneumococcal disease (IPD) in Saudi Arabian children. This multicenter, prospective, clinical surveillance study included children under 5 years of age, residents of one of the seven study health areas, who were brought to a study hospital with suspicion of IPD. Bacterial isolates from sterile site samples, collected less than 24 h after hospital visit/admission, were identified, serotyped, and tested for antibiotic susceptibility. Between June 2007 and January 2009, 631 episodes of suspected IPD were recorded, and 623 were included in the analysis. One child (0.2%) had previously received one dose of a pneumococcal vaccine. Forty-seven episodes were positive for *Streptococcus pneumoniae* and three for *Haemophilus influenzae*. The incidence of confirmed IPD cases was estimated to be 2.5–21.6 per 100,000 children (<5 years). Among the 46 *S. pneumoniae* isolates serotyped and tested for antibiotic susceptibility, the most common serotypes were 5 and 23F (20% each), 6B (17%), and 1 and 14 (11% each). Sixty-three percent of isolates were multidrug-resistant. Vaccination of Saudi Arabian children with expanded-coverage conjugate pneumococcal vaccines containing serotypes 1 and 5 could have a substantial impact to prevent IPD in this population. © 2015 Ministry of Health, Saudi Arabia, Production and hosting by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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1. Introduction

Invasive pneumococcal disease (IPD) caused by *Streptococcus pneumoniae* is a major cause of morbidity and mortality worldwide, especially in young children and elderly people; its most severe manifestations include bacteremia, septicemia, bacteremic pneumonia, and meningitis [1,2]. A previous study conducted in 1999–2003 in Saudi Arabia has estimated an average annual IPD incidence of 17.4/100,000 children younger than 5 years of age, a case fatality rate of 12.2%, and an almost fourfold higher incidence of IPD in the 1st year of life compared with the next 4 years [3]. That study may underestimate the true IPD burden in Saudi Arabia since only microbiologically confirmed IPD cases (meningitis or bacteremia) were included in the analyses [3]. Additionally, as the study focused only on hospitalized children, outpatient bacteremia was not assessed and blood cultures from pneumonia were frequently not performed [3].

Currently, more than 90 pneumococcal serotypes have been identified based on differences in capsular polysaccharides. The serotype distribution varies somewhat between different geographical regions, especially regarding the relative prominence of serotypes 1 and 5 [4,5]. In a study conducted in 2000–2004 on 350 isolates collected from children in different regions of Saudi Arabia, the most common invasive *S. pneumoniae* serotype was 14, followed by serotypes 23F, 6B, and 19F. These serotypes were shown to account for 80% of the invasive pneumococcal isolates resistant to widely used antibiotics (penicillin, erythromycin, and cefotaxime); in Saudi Arabia, different antibiotics are prescribed against these pathogens as there are no national guidelines [6].

Other studies conducted in Saudi Arabia have shown a high and increasing prevalence of multidrug-resistant *S. pneumoniae* isolates [6–14]. The emergence of antimicrobial resistance among pneumococcal isolates is a major health problem in many other countries and is mainly due to the extensive and inappropriate use of antibiotics [15].

Since certain serotypes occur with different frequencies due to outbreaks, temporal variability in serotype distribution can be observed. The existing data need to be updated and the relative value of expanded serotype conjugate vaccines needs to be understood. Moreover, the true IPD incidence rate in Saudi Arabia remains unclear, as does the geographical representativeness of previous studies. The current clinical study assesses the

incidence per health area (except Riyadh and Jeddah) of IPD in Saudi Arabian children younger than 5 years of age, along with the distribution of pneumococcal serotypes and antibiotic susceptibility of *S. pneumoniae* isolates, in both inpatient and outpatient populations that had not yet benefited from the introduction of pneumococcal conjugate vaccination. Additionally, this study attempted to provide information on other bacterial pathogens causing invasive disease in Saudi Arabian children, such as *Haemophilus influenzae* and *Neisseria meningitidis* and to describe antimicrobial drug resistance patterns of these pathogens in Saudi Arabian children suspected of having IPD.

2. Materials and methods

2.1. Study design and participants

This multicenter, prospective, national, clinical surveillance study was conducted in 12 hospitals located in seven health areas (Al Gassim, Al Baha, Al Jouf, Al Madeenah, Al Qateef, Riyadh City, and Jeddah City), to represent the epidemiology and disease burden across Saudi Arabia. The selected study hospitals from Riyadh and Jeddah do not accurately represent the catchment area for these two cities because of other private and public healthcare centers not included in this study; for this reason the two areas were excluded from the incidence calculation. The recruitment period was longer than 1 year to take seasonal variations into account (June 2007–January 2009). The study was conducted according to Good Clinical Practice, the Declaration of Helsinki, and the local rules and regulations of the country. The study protocol and the consent form were reviewed and approved by the Ministry of Health or the National Independent Ethics Committee. Before enrollment, informed consent was obtained from the parents/guardians of each study participant.

This study included children younger than 5 years of age suspected of having IPD, who were residents of the study areas and were brought to one of the study hospitals. Suspected IPD cases were identified by the local physicians according to their individual clinical judgment. IPD was suspected if at least one of the following pulmonary symptoms was present: dyspnea, chest discomfort, pleuritic pain, chest splinting, cough productive of purulent or blood-tinged sputum, tachypnea, or tachycardia. Other symptoms included fever (axillary temperature >37.5 °C), elevated white blood cells ($>15,000$), suspicion of meningitis, or systemic complaints. At each study hospital, attempts were

made to provide enhanced education to physicians regarding the value of blood culturing when IPD was suspected. IPD was confirmed if *S. pneumoniae* was isolated from a normally sterile site, regardless of the clinical symptoms.

Children were eligible if sterile site samples (blood, cerebrospinal fluid, pleural fluid, or synovial fluid) had been collected by the local clinician less than 24 h after the hospital visit/admission. If a child was enrolled more than once for the same *S. pneumoniae* infection, only the first episode was retained for analysis. A case was considered a new *S. pneumoniae* infection if symptoms occurred at least 21 days after the first episode with the same pathogen or if the serotype was different. As serotyping was not performed at the hospital, all children meeting the inclusion criteria were enrolled.

2.2. Study procedures

All children younger than 5 years of age with clinical symptoms of IPD were anonymously recorded in a screening logbook. Two different logbooks were used: one for the outpatients and emergency room patients (hereafter referred to as outpatient group) and another for the hospitalized patients who had at least one overnight stay in hospital before diagnosis (inpatient group).

For sterile site samples collected less than 24 h after hospital visit/admission, parents/guardians were asked to sign the informed consent, and inclusion criteria were checked to enroll the children in the study. Clinical and demographic characteristics, including risk factors (chronic pulmonary disease or asthma; immunosuppression or immunodeficiency; HIV positive or AIDS; malignancy, leukemia, or Hodgkin's disease; splenectomy or asplenia; sickle cell anemia; renal dysfunction; chronic cardiovascular disease or failure; cerebrospinal fluid leak; malnutrition; burns; or other), pneumococcal conjugate vaccination history, general symptoms, and antibiotic pretreatment were recorded in a case report form (CRF) for each enrolled child.

Samples were cultured and bacterial isolates identified at local laboratories. These bacterial isolates were shipped together with the CRF to the central laboratory at King Saud University for re-identification, serotyping, and antibiotic susceptibility testing. Samples were preferably collected before antibiotic administration, but if the child had received antibiotic at any point before taking the sterile site sample, this was stated in the CRF together with the type of antibiotic taken.

(The laboratory procedures are available in the [Supplementary material](#).)

2.3. Statistical analysis

The estimation of the expected annual incidence of IPD was based on incidences reported in hospital-based studies in Europe (20–40/100,000 children <5 years of age) [5,16]. Based on these estimates, a minimum of 37–75 episodes were expected in this study.

Calculations for the incidence rates of invasive disease due to *S. pneumoniae*, *H. influenzae*, or *N. meningitidis* were derived from the total number of new episodes of confirmed invasive disease caused by each pathogen, including those episodes for which no informed consent was obtained.

This was a descriptive study and no statistical comparisons were performed. Continuous variables were described with the number of nonmissing observations, mean, standard deviation, median, minimum and maximum, and number of missing observations. Categorical variables were described with frequency tables and absolute numbers and percentages for each level were given. All confidence intervals were two-sided 95% confidence intervals and were calculated from Proc StatXact. All statistical analyses were performed using SAS version 9.2.

3. Results

3.1. Demographic and baseline characteristics of enrolled individuals

Between June 2007 and January 2009, 1030 episodes were screened, 631 of which were recorded as suspected IPD. Six hundred and twenty-three episodes in 622 children were analyzed: 621 children who experienced a single infection and one child who had two infections.

Forty-five episodes (7.2%) were reported in infants <1 month of age, 290 episodes (46.5%) in infants aged 1 month–1 year, and the remaining 288 episodes (46.2%) in children 1–5 years of age (Table 1). Of the 623 episodes, 61.8% (385/623) were reported in the inpatient group and 38.2% (238/623) in the outpatient group. The mean age of the children was 15.0 ± 14.2 months; 45.3% (282/623) of episodes occurred in girls. In this study, one child (0.2%) had received pneumococcal vaccination prior to enrollment. Baseline characteristics of the enrolled children were similar to those of the screened children.

Table 1 Demographic characteristics and clinical information regarding children suspected of having IPD who were included in the study.

	Inpatients ^a	Outpatients ^b	Total
<i>N</i> ^c	385	238	623
Age (mo) (mean ± SD)	15.9 ± 14.8	13.4 ± 12.9	15.0 ± 14.2
Age category (mo) <i>n</i> ^d (%)			
<1	28 (7.3)	17 (7.1)	45 (7.2)
1–11	172 (44.7)	118 (49.6)	290 (46.5)
12–59	185 (48.1)	103 (43.3)	288 (46.2)
Gender <i>n</i> (%)			
Male	215 (55.8)	126 (52.9)	341 (54.7)
Pneumococcal vaccination <i>n</i> (%)			
Yes	1 (0.3)	0 (0.0)	1 (0.2)
Antibiotic pretreatment <i>n</i> (%)			
Yes	40 (10.4)	64 (26.9)	104 (16.7)
Unknown	16 (4.2)	25 (10.5)	41 (6.6)
Antibiotic taken in hospital prior to sample collection <i>n</i> (%)			
Yes	2 (0.5)	8 (3.4)	10 (1.6)
Hospitalization after diagnosis			
<i>n</i> (%)	385 (100)	236 (99.2)	621 (99.7)
Duration (d) (mean ± SD)	6.0 ± 7.4	7.6 ± 8.1	6.6 ± 7.7

IPD = invasive pneumococcal disease; SD = standard deviation.

^a Hospitalized patients with at least one overnight stay in hospital before diagnosis.

^b Outpatients and patients brought to emergency room.

^c Total number of episodes.

^d Number (percentage) of episodes in the specified category.

3.2. Clinical management

Pretreatment with antibiotics within the past 48 h before the hospital visit/admission was reported in 104/623 (16.7%) episodes (Table 1). Overall, 621/623 (99.7%) episodes were followed by hospitalization after diagnosis, and the mean duration of hospitalization was 6.6 days. The most frequent presentation leading to suspicion of IPD was pneumonia, reported in 387/623 (62.1%) episodes (Table 2). Pneumonia was confirmed only by using an X-ray in 97.9% (379/387) as opposed to cases confirmed by detection of pleural effusion/empyema in 2.1% (8/387) of these episodes.

Risk factors for IPD were present in 149/623 (23.9%) episodes. The most frequently reported condition was chronic pulmonary disease/asthma, present in 56/149 (37.6%) episodes, followed by chronic cardiovascular disease in 25/149 (16.8%) episodes, and sickle cell anemia in 18/149 (12.1%) episodes.

At discharge, 598/623 (96.0%) episodes had recovered. However, seven children (1.1%) died during this study; one episode (0.2%) was followed by sequelae, and two episodes (0.3%) resulted in neurological problems due to IPD.

3.3. Identification and incidence of pathogens

Only 50/623 (8.0%) blood samples tested positive for bacteria and were sent to the central laboratory for further testing (Table 3). Cerebrospinal fluid was collected for 125/623 (20.1%) episodes, out of which only eight samples (6.4%) tested positive for bacteria and were sent to the central laboratory. Two blood samples and one cerebrospinal fluid sample were lost and thus could not be further tested for antibiotic susceptibility and serotype determination. Out of the 50 episodes confirmed for invasive disease, 47 were positive for *S. pneumoniae* and three for *H. influenzae*, with no cases of co-infection. No samples were positive for *N. meningitidis*. Of the 47 episodes positive for *S. pneumoniae*, 22 were reported in infants younger than 1 year of age and 25 in children 1–5 years of age. Overall, the presence of *S. pneumoniae* was confirmed in 7.5% (47/623) of suspected IPD episodes.

Of the 48 samples tested by the central laboratory, 46 were positive for *S. pneumoniae* and were serotyped (26 in the inpatient group; 20 in the outpatient group). The most frequently isolated

Table 2 Clinical presentation of children suspected of having IPD.

Clinical presentation at the visit		Inpatients ^a N ^c =385	Outpatients ^b N = 238	Total N = 623
		n ^d (%)	n (%)	n (%)
Bacteremia without focus	Yes	99 (25.7)	36 (15.1)	135 (21.7)
Meningitis	Yes	29 (7.5)	16 (6.7)	45 (7.2)
Pneumonia	Yes	216 (56.1)	171 (71.8)	387 (62.1)
X-ray confirmed pneumonia	Yes	212 (98.1)	167 (97.7)	379 (97.9)
	Missing/NA	169 (–)	67 (–)	236 (–)
Pleural effusion/empyema	Yes	4 (1.9)	4 (2.3)	8 (2.1)
	Missing/NA	169 (–)	67 (–)	236 (–)
Otitis media	Yes	16 (4.2)	10 (4.2)	26 (4.2)
Bronchitis	Yes	8 (2.1)	0 (0.0)	8 (1.3)
Epiglottitis	No	385 (100)	238 (100)	623 (100)
Peritonitis	No	385 (100)	238 (100)	623 (100)
Pericarditis	Yes	0 (0.0)	2 (0.8)	2 (0.3)
Cellulitis	Yes	1 (0.3)	3 (1.3)	4 (0.6)
Septic arthritis	Yes	1 (0.3)	1 (0.4)	2 (0.3)
Osteomyelitis	Yes	1 (0.3)	0 (0.0)	1 (0.2)
Abscess (not skin)	Yes	2 (0.5)	0 (0.0)	2 (0.3)
Other	Yes	43 (11.2)	17 (7.1)	60 (9.6)

IPD = invasive pneumococcal disease; NA = not applicable.

^a Hospitalized patients with at least one overnight stay in hospital before diagnosis.

^b Outpatients and patients brought to emergency room.

^c Total number of episodes.

^d Number (percentage) of episodes in the specified category.

pneumococcal serotypes were 5 and 23F, which were each identified in 9/46 episodes (20%), followed by 6B in 8/46 episodes (17%), and 1 and 14, each in 5/46 episodes (11%) (Table 4). Serotype 23F was more frequently identified in the outpatient group than in the inpatient group (6/20 versus 3/26). Serotypes 1 and 5 seemed to be more frequently identified in the inpatient group (4/26 and 6/26) than in the outpatient group (1/20 and 3/20). Of note, serotype 19A was only identified in one sample (2.2%) in this study.

The point estimates for incidence of confirmed IPD cases, caused by *S. pneumoniae*, varied between 2.5/100,000 and 21.6/100,000 children <5 years of age in the different health areas included (Table 5).

Two of the three confirmed *H. influenzae* episodes were identified in infants <1 year of age. Both *H. influenzae* positive samples sent to the central laboratory were nontypeable (data not shown). The number of *H. influenzae* positive samples was too small to calculate incidences by region.

3.4. Antibiotic susceptibility

Among the *S. pneumoniae* isolates tested for antibiotic susceptibility, 78% (36/46) were multidrug resistant (Table 6). The majority of isolates

had low susceptibility to penicillin: 30% (14/46) showed intermediate resistance and 39% (18/46) were resistant. Additionally, 30% of isolates were resistant to chloramphenicol, while 43% showed intermediate resistance and 54% were resistant to trimethoprim–sulfamethoxazole. All isolates were sensitive to ceftriaxone.

The two tested *H. influenzae* isolates were sensitive to all antibiotics except cefuroxime, for which they showed intermediate resistance (data not shown).

4. Discussion

In this surveillance study, *S. pneumoniae* was confirmed in 7.5% of Saudi Arabian children <5 years of age suspected of having IPD who were brought to one of the study hospitals. Although the confidence intervals overlapped, the point estimates of the incidence of IPD varied between 2.5/100,000 and 9.6/100,000 in children younger than 5 years of age in the different health areas included in the study, with the exception of 21.6 in Al-Baha City. Interestingly, apart from this one exception, the incidence in these areas was lower compared with 17.4/100,000 children reported by a previous study conducted in children younger than 5 years of age admitted to hospitals in Riyadh and Jeddah [3].

Table 3 Bacterial etiology determined at local and central laboratories by sterile site sample.

Laboratory	Sample origin	Characteristics	Categories	Inpatients ^a	Outpatients ^b	Total
				<i>N</i> ^c = 385	<i>N</i> = 238	<i>N</i> = 623
				<i>n</i> ^d (%)	<i>n</i> (%)	<i>n</i> (%)
Local hospital	Blood	Sample collected	Yes	385 (100)	238 (100)	623 (100)
		Bacterial species identified	<i>Streptococcus pneumoniae</i>	27 (7.0)	20 (8.4)	47 (7.6)
			<i>Haemophilus influenzae</i>	3 (0.8)	0 (0.0)	3 (0.5)
			Other	354 (92.2)	218 (91.6)	572 (92.0)
			Missing/NA	1 (–)	0 (–)	1 (–)
	Cerebro-spinal fluid	Sample collected	Yes	80 (20.8)	45 (18.9)	125 (20.1)
		Bacterial species identified	<i>S. pneumoniae</i>	4 (5.1)	4 (8.9)	8 (6.5)
			Other	75 (94.9)	41 (91.1)	116 (93.5)
			Missing/NA	306 (–)	193 (–)	499 (–)
	Pleural fluid	Sample collected	Yes	1 (0.3)	1 (0.4)	2 (0.3)
		Bacterial species identified	Other	1 (100)	1 (100)	2 (100)
				Missing/NA	384 (–)	237 (–)
	Other ^c normally sterile site	Sample collected	Yes	4 (1.0)	13 (5.5)	17 (2.7)
		Bacterial species identified	Other	4 (100)	13 (100)	17 (100)
			Missing/NA	381 (–)	225 (–)	606 (–)
Central laboratory	Blood	Sample received	Yes	28 (7.3)	20 (8.4)	48 (7.7)
		Bacterial species identified	<i>S. pneumoniae</i>	26 (92.9)	20 (100)	46 (95.8)
			<i>H. influenzae</i>	2 (7.1)	0 (0.0)	2 (4.2)
			Missing/NA	357 (–)	218 (–)	575 (–)
	Cerebro-spinal fluid	Sample received	Yes	1 (0.3)	0 (0.0)	1 (0.2)
		Bacterial species identified	<i>S. pneumoniae</i>	1 (100)	0 (–)	1 (100)
				Missing/NA	384 (–)	238 (–)

NA = not applicable.

^a Hospitalized patients with at least one overnight stay in hospital before diagnosis.^b Outpatients and patients brought to emergency room.^c Total number of episodes. Bacterial species except *S. pneumoniae*, *H. influenzae* and *Neisseria meningitidis*.^d Number (percentage) of episodes in the specified category.

Table 4 Serotype distribution of *Streptococcus pneumoniae* isolates causing invasive pneumococcal disease in children <5 years of age.

Pneumococcal serotype	Inpatients ^a		Outpatients ^b		Total	
	N ^c = 26		N = 20		N = 46	
	n ^d	%	n	%	n	%
1	4	15.4	1	5.0	5	10.9
4	1	3.8	1	5.0	2	4.3
5	6	23.1	3	15.0	9	19.6
6B	4	15.4	4	20.0	8	17.4
9V	0	0.0	1	5.0	1	2.2
11A	1	3.8	0	0.0	1	2.2
14	3	11.5	2	10.0	5	10.9
15	2	7.7	0	0.0	2	4.3
19A	1	3.8	0	0.0	1	2.2
19F	1	3.8	2	10.0	3	6.5
23F	3	11.5	6	30.0	9	19.6

^a Hospitalized patients with at least one overnight stay in hospital before diagnosis.

^b Outpatients and patients brought to emergency room.

^c Total number of episodes.

^d Number (percentage) of episodes in the specified category.

The proportion of IPD cases in children younger than 5 years old occurring in the less than 1 year age group (335/623; 53.6%) in the present study was similar to that observed in 1999–2003 (39/82; 47.6%) in Saudi Arabian children [3]. Nonetheless, the true burden of IPD, and thus the potential impact of a pneumococcal conjugate vaccine (PCV) is likely to be substantially greater than these numbers would suggest. A randomized clinical trial demonstrated that at least three times more clinically suspected IPD cases can be prevented by pneumococcal vaccination than microbiologically confirmed cases [17].

Pneumococcal serotypes 5, 23F, 6B, 1, and 14 were the most frequently identified serotypes in Saudi Arabian children with IPD in this study. This

serotype distribution differs from that observed in 2000–2004, when serotype 14 was the most common serotype in Saudi Arabian children, followed by 23F, 6B, and 19F [6]. The serotype distribution in the present study, which enrolled children with clinical symptoms is, however, similar to that identified from isolates collected as routine surveillance in 2005–2010, when serotype 23F was the most common, followed by 6B, 5 and 1 [18]. In 2010, serotype 23F was the most prevalent in Saudi Arabia, followed by 19F, 19A, 6B, 7F, 5 and 1 [18]. Previously, serotypes 5 and 1 were infrequently identified (each in 1.4% of the isolates) [6], while in the present study, these serotypes were identified in 20% and 11% of the isolates, respectively. The differences in

Table 5 Incidence of confirmed invasive disease episodes by health area and pathogen for children <5 years of age.

Health area	Bacterial species	n ^a	N ^b	Incidence per 100,000 (95% CI)
Buraidah	<i>Haemophilus influenzae</i>	2	49,461	4.04 (0.49–14.61)
	<i>Streptococcus pneumoniae</i>	4	49,461	8.09 (2.20–20.71)
Al Baha City	<i>S. pneumoniae</i>	4	18,549	21.56 (5.88–55.21)
Sikaka Province	<i>S. pneumoniae</i>	1	17,685	5.65 (0.14–31.50)
Al Madeenah City	<i>S. pneumoniae</i>	9	94,246	9.55 (4.37–18.13)
Al Qateef Province	<i>S. pneumoniae</i>	1	39,613	2.52 (0.06–14.07)
Riyadh City	<i>S. pneumoniae</i>	26	—	—
Jeddah City	<i>H. influenzae</i>	1	—	—
	<i>S. pneumoniae</i>	2	—	—

The catchment area for Riyadh City and Jeddah City were not available.

CI = confidence interval.

^a Number of confirmed episodes of invasive pneumococcal disease.

^b Population of children <5 years of age in the given health area during 2007.

Table 6 Antibiotic susceptibility of *Streptococcus pneumoniae* isolates from children <5 years of age.

Characteristics	Categories	Inpatients ^a N ^c = 26		Outpatients ^b N = 20		Total N = 46	
		n ^d	%	n	%	n	%
Antibiotics susceptibility test performed	Yes	26	100	20	100	46	100
Multidrug resistance	Yes	16	61.5	13	65.0	29	63.0
	No	10	38.5	7	35.0	17	37.0
Penicillin	Intermediate	10	38.5	4	20.0	14	30.4
	Resistant	10	38.5	8	40.0	18	39.1
Azithromycin	Intermediate	2	7.7	0	0.0	2	4.3
	Resistant	10	38.5	6	30.0	16	34.8
Amoxicillin/clavulanate	Intermediate	0	0.0	3	15.0	3	6.5
Trimethoprim/sulfamethoxazole	Intermediate	9	34.6	11	55.0	20	43.5
	Resistant	16	61.5	9	45.0	25	54.3
Chloramphenicol	Resistant	6	23.1	8	40.0	14	30.4
Cefaclor	Intermediate	1	3.8	1	5.0	2	4.3
	Resistant	15	57.7	9	45.0	24	52.2
Cefuroxime	Intermediate	3	11.5	2	10.0	5	10.9
	Resistant	13	50.0	8	40.0	21	45.7

^a Hospitalized patients with at least one overnight stay in hospital before diagnosis.

^b Outpatients and patients brought to emergency room.

^c Total number of episodes.

^d Number (percentage) of episodes in the specified category.

serotype distribution between the two studies are in line with previous observations [19,20] that the seasonal peaks in IPD caused by serotypes 1 and 5 might occur following cyclical patterns every 3–4 years. In the present study, serotype 19A, which shows reduced susceptibility to antibiotics, was infrequently identified (1 single case representing 2.2% of the isolates), in line with previous findings in Saudi Arabia (2000–2004) [6]. However, in the post-PCV7 era, in 2009–2010, serotype 19A was considered to be responsible for 20% of IPD cases in the Western region of Saudi Arabia, possibly due to local antibiotic pretreatment practices, which could affect the serotypes isolated by blood culture [18]. The burden of IPD due to serotype 19A has been increasing in some countries around the world, especially in European and North American countries and in Australia [21,22]. Finally, serotype 3 was not identified in young Saudi Arabian children with IPD, confirming the results of other studies showing that this serotype is not a common cause of IPD in this age group [22]. Although the aforementioned study [18] reported antibiotic resistance and serotype distribution, our study additionally calculated incidence based on the samples collected from patients with clinical symptoms.

Local epidemiological data are useful to evaluate the impact of pneumococcal vaccines on IPD.

In the present study, the potential pneumococcal vaccine serotype coverage rates among Saudi Arabian children younger than 5 years of age were estimated to be 61% (28/46 isolates) for PCV7, and to be significantly higher for PHiD-CV (91%; 42/46 isolates) and PCV13 (93%; 43/46 isolates). However, these figures do not take into account potential cross-protection; evidence of cross-protection against serotype 6A has long existed for PCV7, and PHiD-CV is similarly immunogenic against that serotype; in addition, there is emerging evidence of cross-protection against serotype 19A for PHiD-CV [23].

In line with previous reports in Saudi Arabia, 63% of the *S. pneumoniae* isolates in this study showed multidrug resistance. The frequent occurrence of multidrug-resistant isolates may be partially explained by the high and inappropriate use of antibiotics in Saudi Arabia [6–14]. Of note, the proportion of isolates with decreased susceptibility to penicillin was higher in this study than in a previous study conducted in 2000–2004 (70% vs. 54%), using the same susceptibility criteria [6]. The proportion of fully resistant isolates was higher in our study compared with previous observations (39% vs. 12%), while that of isolates showing intermediate resistance to penicillin was lower (30% vs. 42%). It is important to note that we utilized the 2005 National Committee for Clinical Laboratory

Standards susceptibility criteria in order to facilitate comparisons with the previous studies; applying the cutoffs associated with more recent Clinical and Laboratory Standards Institute 2014 criteria, which only affect interpretation of the penicillin results, would tend to decrease somewhat the proportion of nonmeningitis isolates considered fully resistant.

Nontypeable *H. influenzae* (NTHi) was identified in two episodes of suspected IPD. The 11-valent PCV using NTHi protein D as carrier, which was the precursor of PHiD-CV, has shown some efficacy against acute otitis media caused by NTHi [24]. However, additional studies are needed to determine whether PHiD-CV itself has such efficacy and whether efficacy would extend to invasive disease caused by NTHi. In this study, *N. meningitidis* was not responsible for any invasive disease episodes.

Limitations of this study include low culture positivity rate, a previously reported problem that could be mitigated by using molecular detection techniques [25]. False-negative cultures may result from previous antibiotic use, insufficient sample volume, or inadequate storage and transportation conditions [26]. The reported antibiotic use was high in enrolled children, especially outpatients, and possibly underestimated, since no urine antimicrobial tests were performed.

In conclusion, this multicenter prospective clinical surveillance study conducted between June 2007 and January 2009 showed that *S. pneumoniae* was the most commonly identified pathogen in Saudi Arabian children younger than 5 years of age with confirmed invasive disease. The most common pneumococcal serotypes were 5, 23F, 6B, 1, and 14, with antibiotic resistance being a major issue. Although this study was conducted largely in the pre-PCV era, these data remain relevant as vaccine-type IPD can continue to circulate and potentially cause disease even after several years of universal mass vaccination PCV programs [23]. Therefore, vaccination of Saudi Arabian children with expanded coverage conjugate pneumococcal vaccines, especially PHiD-CV and PCV13, would have a substantial impact to prevent IPD in this population.

Conflicts of interest

W.P.H., S.A., W.K. and J.Y.P. are employees of the GSK group of companies. WPH has stock options of the GSK group of companies and is patent owner of the 13-valent PCV licensed to Pfizer/Wyeth for which he receives no royalties. Y.A., R.A. and A.M.S. have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.jegh.2015.08.002>.

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