PREVALENCE OF NASOPHARYNGEAL ANTIBIOTIC-RESISTANT PNEUMOCOCCAL CARRIAGE IN CHILDREN ATTENDING PRIVATE PAEDIATRIC PRACTICES IN JOHANNESBURG

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Objectives. To determine the nasopharyngeal carriage rate, serogroups/types, and antibiotic resistance of *Streptococcus pneumoniae* in children attending paediatric practices in the private sector in Johannesburg and to relate patterns of resistance to antimicrobial exposure and other demographic characteristics in individual children.

Design. A total of 303 children aged from 1 month to 5 years were recruited from eight private paediatric practices in northern Johannesburg. Nasopharyngeal samples were taken and parent interviews were conducted.

Results. Pneumococci were isolated from 121 children (40%). The most common serotypes were 6B, 19F, 6A, 23F, 14, and 19A. Carriage was significantly associated with prior hospital admission (odds ratio 1.89) and day care attendance (odds ratio 2.31) and was negatively associated with antibiotic use within the previous 30 days. Antibiotic resistance was found in 84 isolates (69.4%); 45 (37.2%) were multiply resistant. One-third of the pneumococci showed intermediate level resistance to penicillin and 12.4% were highly resistant. There was a high level erythromycin resistance in 38% of the isolates. A total of 94/214 children (42%) had recently used antibiotics and were four times more likely to carry antibiotic-resistant pneumococci ($P < 0.05$).

Conclusion. Pneumococcal resistance was significant in this group of children with easy access to paediatric services and antibiotic use. The implication of such high resistance for the treatment of pneumococcal diseases is that high-dose amoxicillin is the preferred empirical oral therapy for treatment of otitis media. Ceftriaxone or cefotaxime should be used in combination with vancomycin for the treatment of meningitis until a cephalosporin-resistant pneumococcal cause is excluded. Intravenous penicillin or ampicillin will successfully treat pneumococcal pneumonia in this population. Antimicrobial resistance among pneumococci colonising children in the private sector has increased dramatically in recent years.

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Isolates of *Streptococcus pneumoniae* were first described as being fully resistant to penicillin and resistant to multiple other antibiotics among children attending public sector institutions in South Africa in 1978.[1] Studies over the last 15 years have shown that these strains have spread among countries in Africa, Asia, Europe and America,[2] creating major problems in the treatment of pneumococcal meningitis[3] and otitis media.[4] South African data refer almost entirely to the public sector; the only study published to date conducted in the private sector was carried out 13 years ago.[5] In that study, conducted in day care centres in Johannesburg, penicillin-resistant strains were detected in only 2% of children. Anecdotal evidence from private laboratories suggests that the proportion of penicillin-resistant strains in children attending private practitioners has dramatically increased in the past few years, indicating a need for re-evaluation of antibiotic resistance in this population. Data from South Africa[3] and elsewhere[6-8] have shown clearly that the prevalence of resistant pneumococci in the nasopharynx of children attending outpatient facilities closely matches the resistance rate found in systemic (blood, cerebrospinal fluid and middle ear) isolates. An estimation of the prevalence of pneumococcal antibiotic resistance can, therefore, be determined by obtaining nasopharyngeal specimens from children and examining the resistance patterns of isolated organisms. In this study we sought to determine the nasopharyngeal carriage rate and serogroups/types of antibiotic-resistant *S. pneumoniae* in children attending paediatric practices in the private sector in Johannesburg, and to relate patterns of resistance to antimicrobial exposure and other demographic characteristics in individual children.

METHODS

Study recruitment

All children aged from 1 month to 5 years attending eight private paediatric practices in northern Johannesburg during the study period were eligible for participation. Parents were informed of the study either by the paediatrician or the trained nursing sister; less than 5% of the parents refused to give consent for study participation. Siblings brought to the

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paediatrician's office who were within the specified age range were also sampled. Nasopharyngeal sampling and parent interviews were done by the study nurse. The reason for the visit to the paediatrician was recorded, as well as the child's age, sex, number of siblings, suburb of residence, and day care attendance. Exposure to antibiotics or other medications by individual children were determined from parents and by review of the paediatrician's medical records.

Ethical approval for the study was obtained from the Committee for Studies on Human Subjects of the University of the Witwatersrand.

Microbiological testing

Nasopharyngeal specimens were taken by inserting a small calcium alginate swab into the posterior nasopharynx. The swabs were placed in cryotubes containing 1 ml glycerol/skim milk storage medium and kept at room temperature until transport to the South African Institute of Medical Research (SAIMR) laboratory. At the SAIMR the storage medium was planted onto blood agar plates containing 5 µg/ml of gentamicin and incubated at 37°C overnight. Isolates were identified as pneumococci by colony morphology, optochin sensitivity and bile solubility. Disc diffusion susceptibility tests were performed on all strains, with confirmation of antibiotic resistance and determination of minimum inhibitory concentrations (MICs) by the National Committee for Clinical Laboratory Standards (NCCLS) microdilution method at SAIMR central.[9] NCCLS criteria were used for the classification of resistance. Serotyping was performed on resistant pneumococcal strains using antisera from the Statens Seruminstitut, Copenhagen.

Analysis of data

Data were analysed using the EpiInfo[10] and SAS[11] software programs. The carriage rate, percentage resistance in relation to age, day care attendance, presence of siblings, and exposure to antibiotics were determined. Unadjusted odds ratios (ORs) were calculated and the significant variables (P-value < 0.05) in the univariate analyses were evaluated using an unconditional logistical regression model.

RESULTS

A total of 303 children aged from 1 to 60 months (mean age 22.8 months) were tested; 154 children (51%) were male and 149 were female (49%). The majority of children had come to the paediatrician for a routine check-up, were accompanying a sibling (52%), or had come for treatment of an upper respiratory tract infection, otitis media, sinusitis, or tonsillitis (24%).

Pneumococci were isolated from 121 children (40%). The antibiotic resistance patterns of the isolates are given in Table I.

Table I. Antibiotic resistance patterns of *Streptococcus pneumoniae* isolates from children attending private practitioners in northern Johannesburg ($N = 121$)

Resistance pattern*	Number of isolates (%)
Sensitive to all drugs	37 (30.6)
Pen^R	3 (2.5)
Tet^R	3 (2.5)
Ery^R	1 (0.8)
Cot^R	10 (8.3)
Pen^RTet^R	1 (0.8)
Pen^RCot^R	13 (10.7)
Tet^RCot^R	1 (0.8)
Ery^RCd^R	1 (0.8)
$Pen^RTet^RCot^R$	2 (1.6)
$Pen^REry^RCot^R$	3 (2.5)
$Tet^REry^RCd^R$	6 (5.0)
$Tet^REry^RCot^R$	1 (0.8)
$Pen^RChl^RTet^RCot^R$	5 (4.1)
$Pen^REry^RCd^RCot^R$	3 (2.5)
$Pen^RTet^REry^RCd^R$	2 (1.6)
$Pen^RTet^REry^RCot^R$	1 (0.8)
$Tet^REry^RCd^RCot^R$	5 (4.1)
$Pen^RChl^RTet^REry^RCot^R$	4 (3.3)
$Pen^RChl^RTet^REry^RCd^R$	1 (0.8)
$Pen^RTet^REry^RCd^RCot^R$	10 (8.3)
$Chl^RTet^REry^RCd^RCot^R$	1 (0.8)
$Pen^RChl^RTet^REry^RCd^RCot^R$	7 (5.8)

*Pen^R = resistant to > 0.06 µg/ml penicillin; Tet^R = resistant to > 2.00 µg/ml tetracycline; Ery^R = resistant to > 0.25 µg/ml erythromycin; Cot^R = resistant to > 0.5/9.5 µg/ml co-trimoxazole; Chl^R = resistant to > 4 µg/ml chloramphenicol; Cd^R = resistant to 0.25 µg/ml clindamycin.

Only 37 isolates (30.6%) were susceptible to all six antibiotics tested, and 45 (37.2%) were resistant to at least three classes of antibiotics. Resistance to co-trimoxazole alone, resistance to penicillin and co-trimoxazole, and simultaneous resistance to penicillin, tetracycline, erythromycin, clindamycin, and cotrimoxazole was found in 10 (8.3%), 13 (10.7%), and 10 (8.3%) isolates, respectively. Almost 6% of the isolates were resistant to six antibiotics.

High-level resistance to erythromycin was found in 38% of the isolates and half of the isolates were highly resistant to co-trimoxazole (Table II). The 47 erythromycin-resistant organisms were tested for susceptibility to azithromycin and clarithromycin; high-level resistance to these antibiotics was found in 46 and 47 isolates, respectively. Resistance to penicillin was primarily at an intermediate level, although 12% of isolates showed high-level resistance. The pneumococci resistant or intermediately resistant to penicillin were also tested for resistance to amoxicillin, co-amoxyclav, and the cephalosporins ceftriaxone, cefuroxime, cefaclor, cefixime, and cefpodoxime. These results are shown in Table III. More than 60% of the isolates fully or intermediately resistant to penicillin were highly resistant to cefaclor and cefixime, and one-third were highly resistant to cefuroxime. There was only intermediate-level resistance to ceftriaxone. Very few of the

Table II. Levels of antibiotic resistance of *Streptococcus pneumoniae* isolates from children attending private practitioners in northern Johannesburg (*N* = 121)

Antibiotic	Number (%) of isolates resistant at: Intermediate level*	High level†	Range of MICs (µg/ml)
Tetracycline	3 (2.5)	47 (38.4)	4.00 - 64.00
Penicillin	40 (33.0)	15 (12.4)	0.12 - 4.00
Co-trimoxazole	5 (4.1)	60 (49.6)	1.00/19.00 - 8.00/152.00
Chloramphenicol	NA‡	18 (14.9)	8.00 - 64.00
Clindamycin	0 -	36 (29.7)	16.00 - 64.00
Erythromycin	2 (1.6)	45 (37.2)	0.5 - 64.0

*Intermediate level defined as resistance to 0.12 - 1.0 µg/ml penicillin; 4 µg/ml tetracycline; 1/19 - 2/38 µg/ml co-trimoxazole; 0.5 - 1.00 µg/ml clindamycin; 0.5 - 1.00 µg/ml erythromycin.
† High level defined as resistance to ≥ 2 µg/ml penicillin; ≥ 8 µg/ml tetracycline; ≥ 4/76 µg/ml co-trimoxazole; ≥ 8 µg/ml chloramphenicol; ≥ 1 µg/ml clindamycin; ≥ 1 µg/ml erythromycin.
‡ Not applicable; there is no intermediate level of resistance to chloramphenicol.
MIC = minimum inhibitory concentration.

Table III. Antibiotic resistance to beta-lactam and cephalosporin antibiotics of penicillin-resistant pneumococci isolated from children attending private practitioners in northern Johannesburg (*N* = 55)

Antibiotic	Number (%) of isolates resistant at: Intermediate level*	High level†	Range of MICs (µg/ml)
Amoxicillin	2 (3.6)	3 (5.4)	1.00 - 2.00
Co-amoxyclav	2 (3.6)	-	1.00/0.5
Ceftriaxone	14 (25.4)	-	1.00
Cefuroxime	3 (5.4)	17 (31.0)	1.00 - 6.00
Cefaclor	NA	35 (63.4)	1.00 - 64.00
Cefixime‡	NA	34 (62.0)	2.00 - 32.00
Cefpodoxime	NA	5 (9.1)	2.00

*Intermediate level defined as resistance to 1.00 µg/ml amoxicillin; 1.0 µg/ml ceftriaxone, cefuroxime; 1/0.5 µg/ml co-amoxyclav; 2.00 µg/ml cefaclor; 1.00 µg/ml cefpodoxime.
† High level defined as resistance to ≥ 2 µg/ml amoxicillin, ceftriaxone, cefuroxime, or cefpodoxime; ≥ 4 µg/ml cefaclor.
‡ As no cutpoints are available, the breakpoints for cefaclor were used for cefixime.
MIC = minimum inhibitory concentration.

isolates showed simultaneous resistance to both penicillin and either amoxicillin or co-amoxyclav.

The most common serotype isolated was 6B, followed by 19F, 6A, 23F, 14, and 19A (Table IV).

Demographic variables and clinical history were used to identify risk factors for pneumococcal carriage and antibiotic resistance (Table V). The odds of isolating pneumococci were 1.89 times and 2.31 times higher in children who had ever been admitted to hospital and who attended day care, respectively. Antibiotic use within the previous 30 days was negatively associated with pneumococcal carriage (OR 0.45); however, those children who had used antibiotics and who were carriers of pneumococci were four times more likely to carry antibiotic-resistant organisms. Resistance was not found to be associated with use of any particular class of antibiotic.

Discussion

In 1986, 254 children under 5 years of age from six day care centres in Johannesburg were sampled for presence of nasopharyngeal pneumococci.[5] In that study, the overall carriage rate of 44.4% (113 children) was similar to that in the present study (40%). Penicillin or tetracycline resistance was found in 4.4% and 12.4% of the pneumococci, respectively. Pneumococcal resistance to erythromycin, clindamycin, or co-trimoxazole was found in 13.3% of the isolates, and multiple resistance in 17.7%.

In the 13-year interval between the previous and current study, antibiotic resistance in the private sector has increased dramatically. Antibiotic resistance was found in 69.4% of the pneumococci isolated in our study; 37.2% were multiply resistant organisms. Resistance to erythromycin or clindamycin has at least doubled (38.8% and 30%, respectively) in the private sector to levels far exceeding the 2.7% resistance observed in the public sector in South Africa from 1987 to 1996.[12] The percentage of children carrying co-trimoxazole-resistant pneumococci has almost quadrupled and nearly half of the isolates were resistant to penicillin.

What is the cause of this increase and what does it mean for the treatment of pneumococcal diseases in children in the

Table IV. Serogroups/types of *Streptococcus pneumoniae* isolates from children attending private practitioners in northern Johannesburg (N = 121)

Serogroups/types	Number of pneumococci (%)
3	2 (1.7)
6A	15 (12.4)
6B	25 (20.7)*
9V	2 (1.7)*
10	1 (0.8)
11	1 (0.8)
14	11 (9.1)*
15	4 (3.3)
16	1 (0.8)
18C	3 (2.5)*
19A	10 (8.3)
19F	20 (16.5)*
21	1 (0.8)
23A	4 (3.3)
23B	1 (0.8)
23F	13 (10.7)*
27	1 (0.8)
28	1 (0.8)
33	1 (0.8)
34	2 (1.7)
35	1 (0.8)
37	1 (0.8)

*Serogroups/types found in the nonavalent pneumococcal conjugate vaccine.

private sector? Antibiotic resistance in the pneumococcus is increasing globally. In 1987, penicillin resistance rates of 10% or more could be found in only six countries, including South Africa.[13] More recently, 33.5% of isolates from the USA were not susceptible to penicillin.[14] These organisms are spread person-to-person through respiratory secretions, and with the increased mobility of the world's population, there is the potential for importation of strains. A variant of the multiply resistant serotype 23F pneumococcus originating in Spain was isolated in 1991 from the throat of a South African child with otitis media and from the nasopharynx of five healthy siblings and classmates.[15] Further investigation revealed that the aunt of the index case had lived in Spain for a year and had returned to South Africa within the previous 6 months.

An essential factor in the increase in antibiotic resistance, however, is the availability and use of paediatric services and antibiotics in children in the private sector. In a study in Lesotho,[16] children from Maseru were more likely than their rural counterparts to have been hospitalised or to have received antibiotics and were also more likely to carry antibiotic-resistant pneumococci. A total of 57% of the children in our study had had at least one course of antibiotics in the previous 90 days, and at least 26% had taken antibiotics within the previous 30 days. Recent antibiotic use, particularly within the previous 2 - 7 weeks, has been shown to be associated with pneumococcal resistance in Icelandic children.[17]

In our study, antibiotic use was negatively associated with carriage, representing an inhibitory effect of the antibiotic on bacteria growing in the nasopharynx; however, the majority of organisms that remained were resistant. Continued selection of antibiotic resistance through repeated courses of antibiotics could create a pool of resistant organisms circulating through this population of children.

The implication of this level of resistance for the treatment of pneumococcal diseases is significant. Pharmacodynamic models[18] have accurately predicted the failure of oral therapy for otitis media caused by antibiotic-resistant pneumococci. A recent consensus paper concludes that high-dose amoxicillin (90 mg/kg/day) is the preferred empirical therapy for otitis media in the USA.[19] Our data would support that conclusion for the management of children with otitis media in the private sector in South Africa. The best alternatives for oral empirical therapy are co-amoxyclav, followed by cefuroxime axetil, or cefpodoxime. Children in whom that regimen fails require 3 days of intramuscular ceftriaxone.[20] The very high levels of macrolide resistance suggest that empirical therapy using that class of agent might not be successful.

The implication of these findings for the management of pneumonia in children is more hopeful. Data from South Africa[21] suggest that intravenous management of pneumonia with penicillin or ampicillin will successfully treat these resistant strains.

Penicillin therapy for meningitis is definitely contraindicated in South Africa.[22] Empirical therapy with cefotaxime or ceftriaxone plus vancomycin is appropriate for this group of children in South Africa. No fully ceftriaxone-resistant strains were detected in this study. Intermediately cephalosporin-resistant pneumococci are less common in the public sector (KK — personal communication), so empirical therapy with these cephalosporins alone may still be appropriate in public sector hospitals.

More than 95% of children will carry pneumococci asymptomatically in the nasopharynx at some time before 2 years of age,[23] and carriage rates as high as 70 - 85% have been reported in other studies in southern Africa.[24,25] As found in our study, acquisition of organisms can be influenced by day care attendance[5] and hospital admission,[26] settings where there are groups of children with prolonged interaction. Hospitalisation has also been shown to be a risk factor for antibiotic resistance;[26] however, we could detect no such association in our study as hospitalisation within the previous 6 weeks was rare (24 children).

Nasopharyngeal carriage studies such as ours are a quick and relatively easy way to determine the level of pneumococcal resistance in a population, and if conducted periodically, can be used to monitor trends in antibiotic resistance for the modification of empirical treatment guidelines.

A 9-valent pneumococcal conjugate vaccine has been shown

Table V. Univariate and multivariate relations between carriage and antibiotic resistance of *Streptococcus pneumoniae*, and demographic variables and clinical history of children attending private practitioners in Johannesburg

Variable (*N*)	Children with *S. pneumoniae* (%)	Odds ratio (95% CI) Unadjusted	Odds ratio (95% CI) Adjusted‡	% of carriers with resistance	Odds ratio (95% CI) Unadjusted	Odds ratio (95% CI) Adjusted‡
Age						
≤ 12 months (116)	32.7	–	–	71.0	–	–
> 12 months (187)	44.4	1.64 (0.98 - 2.74)*	1.16 (0.60 - 2.23)	78.0	0.89 (0.35 - 2.23)	
Gender						
Female (149)	41.6	1.15 (0.71 - 1.87)	–	77.4	2.19 (0.92 - 5.23)	–
Male (154)	38.3	–		61.0	–	
Has at least one sibling < 5 years						
Yes (147)	43.5	1.34 (0.82 - 2.18)	–	60.9	0.42 (0.17 - 1.00)*	0.48 (0.21 - 1.12)
No (156)	36.5	–		80.3	–	–
Sleeps in room with other children						
Yes (58)	44.8	1.28 (0.69 - 2.38)	–	69.2	0.99 (0.35 - 2.82)	–
No (245)	38.8	–		69.5	–	
Antibiotic use in previous 30 days†						
Yes (90)	30.0	0.49 (0.26 - 0.90)*	0.45 (0.24 - 0.84)*	88.9	4.21 (1.06 - 24.13)*	4.19 (1.15 - 15.24)*
No (124)	46.8	–	–	65.5	–	–
Prior hospitalisation						
Yes (119)	47.9	1.72 (1.05 - 2.84)*	1.89 (1.00 - 3.56)*	70.2	1.07 (0.46 - 2.50)	–
No (184)	34.8	–	–	68.7	–	
Attends day care						
Yes (148)	52.0	2.74 (1.66 - 4.53)*	2.31 (1.21 - 4.42)*	75.3	2.11 (0.89 - 5.04)	–
No (155)	28.3	–	–	59.1	–	

*Statistically significant, $P < 0.05$.
†Children without a specific date of antibiotic use were excluded from the analysis.
‡The variables for age, antibiotic use in the previous 30 days, and prior hospitalisation were fitted in the model to obtain the adjusted odds ratios for carriage. The variables for antibiotic use in the previous 30 days and siblings were used to determine the adjusted odds ratios for antibiotic resistance.

to reduce significantly the nasopharyngeal carriage of penicillin- and co-trimoxazole-resistant pneumococci by 50% and 34%, respectively.[27] A total of 61% of these serogroups/types are included in the 9-valent pneumococcal conjugate vaccine; 75% of the antibiotic-resistant organisms are potentially covered by the vaccine. Vaccines may ultimately be the answer to the increasing antibiotic resistance problem in that they will not only reduce the transmission of antibiotic-resistant strains, but they will also reduce the likelihood of a pneumococcal aetiology of otitis media, thus potentially reducing the need for antibiotic prescriptions for otitis media.

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