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Prevalence of carriage of antimicrobial resistant strains of *Streptococcus pneumoniae* in primary school children in Hong Kong

M. V. BOOST[1]*, M. M. O'DONOGHUE[1] AND J. S. DOOLEY[2]

[1] *Department of Nursing & Health Sciences, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong*
[2] *School of Environmental Studies, University of Ulster, Coleraine, Northern Ireland*

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SUMMARY

A cross-sectional survey was conducted to determine prevalence and assess risk factors for carriage of antibiotic resistant strains of *Streptococcus pneumoniae* in healthy school children in Hong Kong. Throat swabs were collected from 1455 subjects and written questionnaires providing demographic data and medical history were completed by parents. The overall carriage rate of *Streptococcus pneumoniae* was 3·5%, of which 49% were penicillin resistant. High levels of resistance to tetracycline (73%), erythromycin (52%), trimethoprim (66%) and ciprofloxacin (57%) were observed. Carriage was associated with presence of a younger sibling (OR = 1·79) and use of antibiotics (OR = 2·31). High use of day care and small size of housing units did not result in a high rate of carriage. The low rate of carriage may be linked to high use of antibiotics, geographical factors or ethnicity. High rates of antibiotic resistance reflect heavy use of antibiotics by general practitioners.

INTRODUCTION

Streptococcus pneumoniae is the most important bacterial cause of pneumonia, bacteraemia and otitis media in children and is the third most common cause of meningitis [1–3]. The emergence of antibiotic resistant strains of pneumococci over the last 20 years, has made management of these infections more difficult [4]. Early resistant isolates showed intermediate levels of resistance to penicillin (minimum inhibitory concentration (MIC) 0·12–1 μg/ml) but later, highly resistant isolates (MIC 4–8 μg/ml) [5], and multiply-resistant pneumococci were reported [6]. Reports show a progressive increase in prevalence once resistant strains are introduced into an area, as observed in Spain between 1980 and 1987 [7, 8]. Resistance to penicillin has been reported in clinical isolates in South East Asia including Japan [9], Taiwan [10, 11], and China [12], and an increasing prevalence of penicillin-resistant clinical isolates of pneumococci has been observed in Hong Kong [13]. Resistance rates increased from zero in 1987–8 to 10% in 1993 [13]. Another study reported 17% incidence of resistance in pneumococcal isolates [14]. High carriage rates of penicillin-resistant pneumococci in the community have been associated with an increased incidence of clinical infection with resistant strains [4, 15–17]. Healthy children may act as an important reservoir of resistant strains of the organism [18]. Several risk factors for carriage of antibiotic-resistant strains in children have been described including recent hospital admission, recent antibiotic use and attendance at day-care centres [19–21]. Small size of housing unit and overcrowding have also been identified as risk factors for carriage of pneumococci

* Author for correspondence.

[21, 22]. The overcrowding and day care risk factors are of particular relevance in Hong Kong, where housing units are small in size and where there is a high rate of use of child care facilities. In addition, antibiotic use by general practitioners is high [23]. There has only been one limited community-based survey of carriage of pneumococci in Hong Kong [23]. The prevalence of antibiotic-resistant strains carried by healthy children in the community in Hong Kong has not been reported. Knowledge of the levels of penicillin resistance in the community would be useful in the management of pneumococcal disease.

The aim of this study was to establish the carriage rate of *Streptococcus pneumoniae*, and the prevalence of antibiotic-resistant strains in Hong Kong primary school children. It also attempted to determine risk factors associated with carriage of antibiotic resistant strains.

MATERIALS AND METHODS

Study population

The reference population was defined as children attending the first year of primary school (primary one) in Hong Kong. As 98% of the population in Hong Kong is Chinese, the sample was restricted to those of Chinese ethnic origin. The schools used were situated in traditional urban areas, areas of older public housing and in new towns in the New Territories, to provide a representative sample in terms of both locations and socio-economic status. Informed consent to screen the children was sought from parents, who were asked to complete a simple questionnaire on family size, age of siblings of the index child, housing type as an indicator of socio-economic status, recent travel out of Hong Kong, hospital admissions in the past year, and visits to the doctor and antibiotic use in the preceding 3 months. The questionnaire had been translated into Chinese and validated by a pilot study. Housing type used the definitions of the Census and, in general, families living in private flats or in home ownership schemes would have higher incomes. Public housing indicates rented government owned properties which are only available to those on lower incomes. The temporary housing category indicates homes in government provided housing of small size with very limited facilities. Families may have to stay in these premises for several years whilst waiting for places in public housing.

Study design

The study was a cross-sectional survey. A representative sample of the primary one school population were screened for carriage of *Streptococcus pneumoniae* and the prevalence of antibiotic resistance determined in these isolates. The investigation was approved by the Human Subjects Ethics Committee of the Hong Kong Polytechnic University.

Microbiological methods

Throat swabs collected from each child were placed in transport media and delivered to the laboratory within 1 h. The swabs were inoculated on 5% blood agar supplemented with 1% crystal violet and the plates incubated at 37 °C in 5% CO_2 for 24 h. *Streptococcus pneumoniae* were identified by colonial morphology, optochin sensitivity and bile solubility. Screening for antibiotic resistance was performed on Mueller Hinton agar with 5% lysed horse blood by dis-diffusion techniques using antibiotic concentrations and breakpoints as specified by the National Committee for Clinical Laboratory Standards (NCCLS) [24]. Susceptibility to the following antibiotics was determined: erythromycin, tetracycline, vancomycin, teicoplanin, rifampicin, trimethoprim, ciprofloxacin, and imipenem. For teicoplanin, trimethoprim, ciprofloxacin and imipenem, interpretation criteria of the Swedish Reference Group for Antibiotics was used [25]. Susceptibility to benzyl penicillin was determined using 1 μg oxacillin disks [26]. Isolates with a zone of inhibition $\leqslant$ 19 mm were considered resistant and the MICs to penicillin and cefotaxime were then determined by E-test. Cefotaxime is currently used in Hong Kong to treat cases with penicillin resistance.

Statistical methods

Results were analysed using the SPSS statistical package and Pearson chi square test was performed and odds ratios with 95% confidence intervals were calculated. Multivariate logistic regression was also performed with carriage of pneumococci as the dependent variable and inclusion of younger siblings, travel, hospitalization, visits to the doctor and use of antibiotics as covariates. This analysis was repeated using carriage of antibiotic resistant strains as the dependent variable.

It was calculated that for the sample size of 1455, with a carriage rate of 3·5% and by setting alpha to

Table 1. *Antimicrobial resistance of isolates of* Streptococcus pneumoniae

Antimicrobial agent	No. of strains resistant (%) (penicillin-sensitive strains) $n = 26$	No. of strains resistant (%) (penicillin-sensitive strains) $n = 25$	No. of strains resistant (%) (all strains) $n = 51$
Sensitive to all drugs	5 (19)	—	5 (10)
Penicillin (IR)	—	9 (36)	9 (18)
Penicillin (R)	—	14 (56)	14 (27)
Tetracycline	17 (65)	20 (80)	37 (73)
Erythromycin	10 (38)	17 (68)	27 (52)
Trimethoprim	17 (65)	17 (68)	34 (66)
Ciprofloxacin	17 (65)	12 (48)	29 (57)
1 agent	6 (23)	—	6 (12)
2 agents	8 (31)	3 (12)	11 (22)
3 agents	9 (34)	8 (32)	17 (33)
4 agents	3 (12)	9 (36)	12 (24)
Cefotaxime*	—	9 (36)	9 (18)

* (MIC $\geqslant$ 1·0 mg/ml).

0·05 and power to 0·8, the minimum odds ratio detectable was 1·67.

RESULTS

Study population

1970 children from 19 schools were invited to participate. 1470 parents completed the consent form and questionnaire, and samples were collected from 1455 children, a response rate of 73 %. Nine children were absent on the day of sampling and six refused to have a swab taken. Participation rates differed little between schools (range 68–80 %) and were not linked to location. Some parents who had declined to participate completed the questionnaire. 50 of these were analysed and there appeared to be no difference between those who participated and those who refused. A few who refused gave the reason of previous unpleasant experience with throat swab, but most simply declined. Between 17 and 121 children were screened in each school (mean 77). The mean age was 77 months, median 72 months. The sex distribution was approximately equal (51 % girls, 49 % boys).

Carriage of *Streptococcus pneumoniae*

The prevalence of carriage of *Streptococcus pneumoniae* was 3·5 % (49 out of 1455). A total of 51 strains were isolated as 2 children carried 2 strains. 25 (49 %) of the 51 strains were resistant to penicillin, of which, 14 (27·5 %) were highly resistant to penicillin. Cefotaxime MIC was determined and of strains displaying high level penicillin resistance, 9 (64 %) showed resistance (MIC $\geqslant$ 1·0 μg/ml). Only 5 strains (10 %) were sensitive to all drugs tested and all penicillin resistant strains displayed resistance to at least one other drug. Resistance to tetracycline, ciprofloxacin and trimethoprim was observed alone, but erythromycin resistance was always in combination (Table 1). Although there was some reduction in zone size, no strains showed resistance to imipenem using the Swedish Reference criteria [25].

Epidemiological characteristics

Several factors appeared to be associated with carriage, but the relatively small numbers of carriers resulted in wide confidence intervals (Table 2). Only the presence of younger sibling(s) in the family was clearly associated with increased risk of carriage (OR 1·88, CI 1·04–3·40; $P = 0{\cdot}036$). The presence of only older siblings appeared to be protective, with confidence intervals just above the value for significance (OR 0·56, CI 0·30–1·02; $P = 0{\cdot}056$).

There did not appear to be a relationship between the age of the child and the risk of carriage within the age range sampled, as prevalence in those > 77 months was 3·4 % and in those > 72 months, 3·5 %.

There was no significant association between housing type and either carriage of pneumococci or presence of resistant strains of *Streptococcus pneumo-*

Table 2. *Associations between family size, siblings, travel, hospitlization, visits to the doctor and antibiotic usage and carriage of* Streptococcus pneumoniae

Variable	*Streptococcus pneumoniae* Present (%) $n = 49$	Absent (%) $n = 1406$	Crude OR, 95% CI	Adjusted OR, 95% CI
Older siblings	16 (32)	645 (46)	0·56 (0·30–1·02)	—
No siblings	11 (22)	366 (26)	0·81 (0·41–1·58)	—
Has siblings	38 (77)	1025 (74)	1·23 (0·61–2·34)	—
Younger siblings	24 (49)	484 (35)	1·79 (1·01–3·15)	1·88 (1·04–3·40) (carriage of pnc)
Travel	11 (23)	292 (21)	1·15 (0·51–2·27)	1·13 (0·57–2·27) (carriage of pnc)
Hospitalization	2 (4·2)	22 (1·6)	2·76 (0·63–12·02)	3·56 (0·77–16·42) (carriage of pnc)
Visit to doctor*	15 (33)	546 (39)	0·73 (0·39–1·38)	0·71 (0·23–2·13) (carriage of pnc)
Visit to doctor†	10 (43)	551 (39)	1·92 (0·60–6·15)	2·49 (0·13–46·27) (carriage of PRSP)
Use of antibiotic*	14 (34)	473 (30)	1·12 (0·72–1·75)	1·17 (0·637–2·21) (carriage of pnc)
Use of antibiotic†	9 (39)	478 (34)	2·31 (0·63–8·39)	1·93 (0·58–6·38) (carriage of PRSP)

* All isolates, † Penicillin-resistant isolates.
Older siblings = child has older siblings only. Younger siblings = child has younger siblings. Hospitalization = hospitalization within last year for any reason. Visit to doctor = parent reported visit within last 3 months. Use of antibiotic = parent reported antibiotic prescribed for the child within last 3 months.
pnc = pneumococcus; PRSP = Penicillin resistant *Streptococcus pneumoniae*.

Table 3. *Relationship between housing type and carriage of* Streptococcus pneumoniae

Housing type	Prevalence of carriage (%)	Percentage of penicillin restraint strains (%)
Private flat	4·7	43
Home Ownership Scheme	3·0	66
Public	2·6	45
Temporary	6·9	25

niae (Table 3). The sample closely matched the percentages living in the four housing types reported by the most recent census. The highest isolation of pneumococci was from children living in temporary housing, but numbers of children living in this type of housing was only 4% of the total tested.

The rate of carriage differed between individual schools ranging from 0–13% and there appeared to be clustering of carriage of *Streptococcus pneumoniae* in some schools ($\chi^2 = 67{\cdot}71$; $P = < 0{\cdot}001$). In schools where carriage was found, both sensitive and resistant strains were isolated.

DISCUSSION

This study showed a low rate of carriage of *Streptococcus pneumoniae* in primary one schoolchildren in Hong Kong (3·5%). This figure is lower than the carriage rate of 10·8% reported in the limited study performed by Sung et al. [23]. However, their study population ranged in age from 2 months to 5 years, and previous workers have shown that higher carriage rates are found in younger children [27].

The association observed in this study between carriage and younger siblings may reflect the higher rates of carriage usually seen in the younger age group. However, an increase of carriage in early school years has been reported [28], which may reflect contact with other children who are carriers. Having no siblings or only older siblings would tend to reduce exposure to younger children explaining the lower carriage rates. Although many studies have reported higher rates of carriage in children in pre-school and primary school [16, 19], a low carriage rate in young children was reported in a recent large study in Italy [28]. These authors suggested the low rate may be due to sampling of healthy children. This may also explain the low carriage rate in our study, as sampling was performed on children attending school. Few children in either the Italian or the present study had been hospitalised.

Many studies [7, 8, 14, 29, 30] have reported an increase in the prevalence of antibiotic resistance of laboratory isolates in the last 20 years. These studies fail to address the prevalence of antibiotic-resistant pneumococci in the general population. Several studies described as population-based studies were connected to outbreaks or were associated with one institution. Variations in study design make it difficult to compare prevalence rates between countries. Studies performed in Spain [16], Australia [31] and Canada [27] have reported prevalence rates of penicillin resistance in pneumococcal strains to be 35·9%, 30% and 17%. In contrast, a UK study of similar design to this study, found a much lower rate of resistant strains (2·8%) [19]. This may reflect lower rates of antibiotic use in UK. The results of the present survey have shown that 49% of strains are antibiotic resistant, which is one of the highest reported rates in a community study. The proportion of strains with high level resistance was 28·5% which is much higher than that of the UK study [19] and that of Australian children in day care [31]. Penicillin-resistance was reported as 17·4% in clinical isolates of *Streptococcus pneumoniae* in Hong Kong but this was not differentiated into high and intermediate levels of resistance [14].

Levels of resistance to other antimicrobials were also high and all penicillin resistant strains were resistant to at least one other agent. The high level of resistance to erythromycin in the isolates (52%) reflects that seen in clinical isolates in Hong Kong (68%) [29].

Some studies have reported that carriage of pneumococci, in particular resistant strains [19], is associated with travel overseas. In this current study, travel did not seem to be associated with pneumococcal carriage or antibiotic resistance. However, as the number of children who had travelled was relatively small, and mainly to nearby Southern China, the effect of travel may have been missed. Hospitalization has been shown to be associated with carriage of penicillin-resistant strains in children [20], but although there was an indication of increased risk of carriage associated with hospitalization (OR 3·56), this did not achieve significance as only 24 children (1·6%) had been hospitalized. Several studies have shown an association between antibiotic use and carriage of resistant strains of *Streptococcus pneumoniae* [22, 32]. Investigation of this association was made difficult because many of the parents were unaware of the types of drugs prescribed for their children. Of those reporting antibiotic use, there did appear to be an association (OR 1·17 for all isolates, OR 1·93 for resistant isolates) but this did not reach statistical significance due to the small numbers.

Socio-economic factors and poor housing conditions have been shown to be associated with higher rates of carriage of *Streptococcus pneumoniae* [27, 33], but there were no significant associations with any housing type although rates did appear higher in temporary housing. It is possible that the lower level of resistant strains in children living in temporary housing reflects lower use of antibiotics. The percentage of resistant strains was highest in home ownership scheme housing. This may be due to the higher socio-economic status and ease of access to doctors of this group, who may seek medical attention more often. However, small numbers of isolated pneumococci prevented any valid statistical testing. Other studies on Vietnamese children living in detention camps in Hong Kong [23] in very overcrowded conditions, have shown higher rates of carriage. The effect of socioeconomic factors in the current study may be masked, as the carriage rate was low overall and, although overcrowding has decreased, there is still a high density of people in most housing units in Hong Kong. The low rate of carriage reported here is in contrast to the situation elsewhere, where high rates of carriage have been associated with small size of housing units [33].

Use of child care facilities has been identified as a risk factor for carriage in other studies [20, 27, 34], but although virtually all children in this study had attended kindergarten, there was a low rate of carriage.

It is difficult, therefore, to explain the low rate of carriage of pneumococci in Hong Kong. Genetic factors have been suggested as of possible importance in determining carriage, and were suggested as a possible additional factor in the comparison of Hong Kong and Vietnamese children [23]. Further studies of other groups of children living in Hong Kong should be performed to determine if the environment or ethnicity affect carriage in this area.

It has been suggested that high rates of antibiotic use may eradicate carriage of pneumococci from most children, but may select for resistant strains when these are present [35]. It is generally considered that there is a high rate of prescription of antibiotics in Hong Kong [23, 36]. This may account for the change in direction of the risk factor for visits to the doctor in carriage of antibiotic resistant strains, and the low rate of carriage together with a high level of antibiotic resistance observed in this study. Longitudinal studies on the effect of antibiotics on carriage of pneumococci may reveal this relationship. Restrictive strategies on antibiotic usage may be considered to reduce the high rates of carriage of resistant pneumococci.

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