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The descriptive epidemiology of *Streptococcus pneumoniae* and *Haemophilus influenzae* nasopharyngeal carriage in children and adults in Kilifi District, Kenya

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Abstract

Background—Transmission and nasopharyngeal colonization are necessary steps en route to invasive pneumococcal or *Haemophilus influenzae* disease but their patterns vary geographically. In East Africa we do not know how these pathogens are transmitted between population sub-groups nor which serotypes circulate commonly.

Methods—We did two cross-sectional nasopharyngeal swab surveys selecting subjects randomly from a population register to estimate prevalence and risk-factors for carriage in 2004. *H. influenzae* type b vaccine was introduced in 2001.

Results—Of 450 individuals sampled in the dry season, 414 were resampled during the rainy season. Among subjects 0–4, 5–9 and 10–85 years old pneumococcal carriage prevalence was 57%, 41% and 6.4%, respectively. *H. influenzae* prevalence was 26%, 24% and 3.0%, respectively. Prevalence of *H. influenzae* type b in children <5 years was 1.7%. Significant risk factors for pneumococcal carriage were rainy season (OR 1.65), coryza (OR 2.29) and co-culture of non-capsulate *H. influenzae* (OR 7.46). Coryza was also a risk factor for *H. influenzae* carriage (OR 1.90). Of 128 *H. influenzae* isolates 113 were non-capsulate. Among 279 isolates of *Streptococcus pneumoniae* 40 serotypes were represented and the distribution of serotypes varied significantly with age; 7-valent vaccine-types, vaccine-related types and non-vaccine types comprised 47%, 19% and 34% of strains from children aged <5 years. Among older persons they comprised 25%, 28% and 47%, respectively ($p=0.005$).

Conclusions—The study shows that pneumococcal carriage is common up to 9 years of age and that the majority of serotypes carried at all ages, are not covered specifically by the 7-valent pneumococcal conjugate vaccine.

Keywords

Nasopharyngeal carriage; *Streptococcus pneumoniae*; *Haemophilus influenzae*; developing country; children; adults; serotypes

INTRODUCTION

In Kilifi, Kenya, community-acquired bacteraemia is responsible for at least a third of all hospital deaths in infants and a quarter of deaths in children aged <1 year; *Streptococcus pneumoniae* is the commonest invasive isolate [1]. Before introduction of *Haemophilus influenzae* type b (Hib) vaccine *H. influenzae* was the commonest cause of bacterial meningitis at Kilifi District Hospital [2]. Now it is *S. pneumoniae*. Pneumococcal conjugate vaccine was efficacious in two populations studied in Africa [3, 4] and there is growing international pressure to introduce this vaccine in developing countries [5].

In addition to direct protection against the serotypes in the vaccine pneumococcal conjugate vaccine (PCV) has two complex epidemiologic effects, which derive from its capacity to reduce the prevalence of nasopharyngeal carriage [6, 7]. Among unvaccinated individuals it reduces the incidence of invasive disease caused by serotypes in the vaccine (herd protection) and among vaccinated individuals it facilitates colonization and disease by serotypes not included in the vaccine (serotype replacement disease). The magnitude of these effects varies in different studies. For example, among Native Americans in the South Western USA the combination of direct protection and herd protection was no greater than the direct protection alone observed in Californian infants [8, 9]. By contrast, the herd protection effect is substantially greater than the direct protective effect in the American population as a whole [10]. In America the rise in the incidence of non-vaccine serotype disease has been small when compared with the fall in incidence of vaccine serotype disease [10] but among Alaskan Natives the two effects are virtually in balance [11]. The epidemiology of transmission and disease varies significantly by geography and ethnic group and this is likely to explain much of the variation in vaccine program effectiveness. Our anticipation of vaccine success in Kenya is based on its programmatic use in America [10, 12] but the experiences of populations more akin to people in the developing world, the indigenous ethnic groups of America, show that a simple extrapolation may not be unjustified.

If the success of the vaccine is likely to be determined by the underlying epidemiology of transmission and carriage it is important to describe that epidemiology. Little is known of the patterns of carriage and transmission of *S. pneumoniae* in East Africa. In this study we describe the effects of age, sex, season and urbanization on the prevalence of nasopharyngeal carriage and describe the serotypes of pneumococci circulating in a community in coastal Kenya where invasive disease incidence is high [1, 13].

MATERIALS AND METHODS

We did a cross-sectional survey of nasopharyngeal carriage prevalence among healthy subjects of all ages during the dry season and repeated it three months later in the rainy season in the same individuals. The sampling frame for the study was the population register of the Kilifi Demographic Surveillance System (DSS). The DSS began in 2000 with a population census of all households within a predefined area of 891 km² surrounding Kilifi District Hospital. Vital status was subsequently updated in the population register by questionnaires administered at household visits conducted approximately twice a year. In 2005 Kilifi DSS was admitted to the INDEPTH network (www.indepth-network.net) a network of DSS sites with common data reporting standards. In January 2003 the population register numbered 220 000 individuals and we used this register to generate lists of randomly selected individuals within 64 age-sex-location strata aiming to recruit 480 individuals, 7-8 from each stratum. The strata were composites of two sexes, 4 locations and 8 age groups (<1, 1-2, 3-4, 5-9, 10-19, 20-39, 40-49, ≥50 years.) For logistic reasons we restricted selection to two semi-urban locations from township settings (Kilifi, Roka) and two rural locations (Marere, Pinglikani). In Kilifi District Hib vaccine was introduced into

the routine childhood immunization program in 2001. At 12 months of age 87% of children have received three doses of the vaccine [14]. Pneumococcal carriage prevalence is higher among HIV-infected than HIV-uninfected individuals [15], however, we chose not to test study subjects for HIV status because the prevalence of HIV in Coastal Kenya is low at 4.8% in men and 6.6% in women [16].

In Kilifi there is a long rainy season in May-July and a short rainy season in October-November. The climate between January and March is very dry. To select dates for our rainy and dry season surveys we aggregated daily rainfall data from a meteorologic recording station at Kilifi Agricultural Research Institute in Kilifi town into weekly rainfall means for the preceding 10 years, 1994-2003. The dates of sampling selected were 2-24 March 2004 and 2 June-3 July 2004. The survey in the rainy season took longer to conduct because the rains impeded transport throughout the study area.

A nasopharyngeal specimen was collected from each consenting individual by trained field workers according to the WHO guidelines [17]. A rayon-tipped flexible aluminium-shaft (Medical Wire and Equipment Company, Town, UK) was passed via the anterior nares to the posterior nasopharynx to a depth predefined by the external distance from the tip of the nose to the external auditory canal. It was left in place for approximately 2 seconds and rotated through 180 degrees before removal. Swabs were immediately placed in STGG transport medium and transported to the laboratory within 8 hours. Putative risk factors for nasopharyngeal colonization, including cigarette smoking, coryza in the last two weeks, use of antibiotics or folate synthesis inhibitors (sulfadoxine/pyrimethamine or sulfamethoxazole/trimethoprim) in the preceding two weeks and number of children aged <5 years resident in the house, were ascertained by questionnaire at the same time. Those who had taken medications were asked to remember the name, describe the package and, if possible, produce the package for verification.

STGG swab specimens were processed at the Wellcome Trust/Kenya Medical Research Institute microbiology laboratories according to the WHO guidelines [17] either immediately (fresh) or after a period of freezing at -80°C for up to two months. Fresh or thoroughly thawed specimens were vortexed for 10 seconds and 10µl was inoculated directly onto 7% horse blood agar with gentamicin 2.5 µg/ml and 7% chocolate agar. Media were incubated overnight at 37°C in 5% CO₂. *S. pneumoniae* was identified by colony morphology, α-haemolysis, optochin susceptibility, bile solubility and serotyping. Four morphologically distinct colonies were sub-cultured for typing from each primary plate. Pneumococci were serogrouped by latex agglutination and serotyped by the Quellung reaction using polyclonal rabbit antisera (Statens Serum Institute, Copenhagen, Denmark). *Haemophilus* species were identified by growth on chocolate agar alone, colony morphology, X and V factor dependency and serotype. Swabs from children aged <5 years were also cultured on media containing Hib antiserum to increase the sensitivity of detection of Hib carriage by identification of precipitation haloes [18]. Serotype results for *H. influenzae* isolates were confirmed in England by polymerase chain reaction-based capsular genotyping using primers designed to amplify the type-specific regions of the *cap* loci in each of the 6 (a-f) capsular types [Falla 1994]. [19]

STATA (version 8.2) was used for statistical analyses. The prevalence of nasopharyngeal carriage of *S. pneumoniae* and *H. influenzae* was presented as proportions of individuals in different age, sex and location strata. The effect of season on carriage was calculated as a matched odds ratio and tested with McNemar's χ^2 tests. Logistic regression was used to analyze risk factors for carriage entering subject identity as a random effect to take account of the correlation of response variables from the same individual in the two surveys. The contribution of each variable to the model was determined by Likelihood Ratio Tests and

only those with a p value <0.05 were retained in the final model except for age, in 8 strata, which was retained as an *a priori* confounder.

The study was approved by the Kenya Medical Research Institute/National Ethical Review Committee and The Oxford Tropical Research Ethics Committee and written informed consent was obtained for all participants.

RESULTS

Four-hundred and sixty of the selected individuals were identified in the community and of these 450 (98%) agreed to participate and were sampled during the dry season; 227 (50%) were female and the numbers recruited from each of four locations ranged from 111-114. The age distribution of subjects is shown in table 1. When these 450 subjects were sought again in the rainy season 1 had died, 14 declined to participate further and 21 were lost to follow-up leaving 414 (92%). Among 864 swabs cultured, 648 (75%) were processed after a period of freezing lasting no longer than 2 months.

The mean weekly rainfall during the three weeks of the first survey was 0.24 mm and during the four weeks of the second survey it was 8.1 mm. Carriage prevalence of *S. pneumoniae* in the dry and rainy seasons was 27% (123/450) and 35% (146/414), respectively. Carriage prevalence of *H. influenzae* in the dry and rainy seasons was 12% (54/450) and 18% (74/414), respectively. In the dry season 40 (9%) of subjects carried both *S. pneumoniae* and *H. influenzae*, in the rainy season 62 (15%) of subjects carried both organisms. Variation in the carriage prevalence of *S. pneumoniae* and *H. influenzae* by age is shown in Table 1.

Among 414 individuals sampled in both surveys the number of *S. pneumoniae* carriers was 116 (28%) in the dry season and 146 (35%) in the rainy season. The numbers of carriers of *H. influenzae* were 50 (12%) and 74 (18%) respectively. Carriage prevalence was significantly higher in the rainy season for both *S. pneumoniae* (OR 1.65, p=0.007) and for *H. influenzae* (OR 1.8, p=0.009). The prevalence of carriage did not vary significantly by sex or location (rural vs. semi-urban) for either organism and there was no significant interaction between season, age or sex with carriage prevalence. Risk factors associated with nasopharyngeal carriage of *S. pneumoniae* and *H. influenzae* derived from the logistic regression analysis are shown in table 2. The positive association between the two pathogens was independent of age; for example, in children aged <5 years the prevalence of *H. influenzae* carriage was 37% (74/198 swabs) among those who carried *S. pneumoniae* and 11% (16/151 swabs) among those who did not.

In the dry season survey 127 strains of *S. pneumoniae* were isolated from 123 swabs; 4 individuals were infected simultaneously with two serotypes. Two strains were untypable and the remaining 125 strains expressed 36 capsular types. In the rainy season survey 152 strains, expressing 31 different serotypes, were isolated from 146 individuals; 6 individuals were infected simultaneously with two serotypes. Seventeen individuals carried the same serotype in the two studies, of whom sixteen were aged <5 years. These strains were of serotypes 19F (n=4), 6B (4), 6A (3), 23B (2), 9V (2), 18F (1) and 15A (1). Overall, 40 different pneumococcal serotypes were identified in the two surveys (Table 3).

Vaccine types (VT) are the 7 serotypes contained in PCV7, vaccine-related types (VRT) are serotypes within serogroups that are immunologically cross-reactive with VT pneumococci and all other serotypes are non-vaccine types (NVT). Of 207 pneumococci isolated from children aged <5 years, 97 (47%) were VT, 40 (19%) were VRT and 70 (34%) were NVT. Of 72 pneumococci isolated from older persons, 18 (25%) were VT, 20 (28%) were VRT and 34 (47%) were NVT. The distributions of VT, VRT and NVT among the two age groups were significantly different (p=0.005). Between the 46 isolates from children aged

5-9 years and the 26 isolates from subjects aged 10-85 there was no significant difference in the distribution of VT, VRT and NVT ($p=0.35$).

In the two surveys combined, 90 isolates of *H. influenzae* were cultured in swabs from children aged <5 years. Of these, 78 were non-capsulate, 6 were of type b, 3 were of type a, 2 were of type e and 1 was of type c. The prevalence of Hib carriage in children <5 years was 1.7% (6/349). Thirty-eight isolates of *H. influenzae* were cultured from swabs from persons aged 5 years; 35 were non-capsulate, 1 was type a, 1 was type c and 1 was type e.

DISCUSSION

This is the first population-based survey of nasopharyngeal (NP) carriage of *S. pneumoniae* and *H. influenzae* conducted in East Africa. The prevalence estimate for pneumococcal carriage in children less than 5 years (50-61%) does not conform with the perception that carriage of the pneumococcus is almost invariable in African children. Much of the variation in carriage prevalence estimates in Africa is attributable to differences in the sampling frames. Studies in Ghana, Zambia, Malawi, and Mozambique have reported the colonization prevalence at 51%, 72%, 84% and 87%, respectively [20-23] but each of these studies sampled sick children presenting to hospital. Estimates of carriage prevalence among well children are lower, at 22% in Kenya [24], 48% in Malawi [25] and 62% in Uganda [26] but even in these studies the children were selected because they attended a health facility. In The Gambia in 1989-91 the prevalence of nasopharyngeal carriage in the under-fives was 90% among children who were hospitalized with invasive pneumococcal disease, and 76% among healthy location-matched controls [27]. More recently in a study of selected villages it was estimated at over 90% [28]. The carriage prevalence in unselected children aged <5 years in our study was 51-60%. It does appear that the colonisation prevalence in East and Southern Africa is substantially lower than that in The Gambia underlining the premise that pneumococcal epidemiology varies widely by geography.

Previous studies of children have mostly been restricted to those aged <5 years. Our study shows that children aged 5-9 years also have a high prevalence of nasopharyngeal carriage of both *S. pneumoniae* and *H. influenzae*. In a demographic structure where half of the population is aged <15 years [16] those in the age group 5-9 years old represent a sizeable fraction of the total population and one that is likely to interact frequently with young children who are most susceptible to disease, facilitating transmission of respiratory pathogens. The distribution of pneumococcal serotypes found in this group with a much lower representation of vaccine serotypes differs substantially from that in younger children.

In our analysis, coryza and rainy season sampling were associated with carriage of *S. pneumoniae* and *H. influenzae*, independently of the effect of age. It is difficult to determine whether coryza, a marker of viral upper respiratory tract infection, is truly associated with carriage or whether it simply facilitates mucous sampling and thus enhances detection. The interpretation of a seasonal effect is limited by the fact that the survey observed only two short time periods within the annual cycle and because there are numerous hypothetical mechanisms by which season may affect carriage. Rains, like cold weather in temperate climates, encourage indoor living leading to temporary crowding in poorly ventilated structures. In Hong Kong, Vietnamese refugee children with a mean living area of 1.75m² were compared to Chinese children with a mean living area of 10.2m²; carriage prevalence of *S. pneumoniae* was 56% and 11%, respectively [29]. The contention that a humid environment better sustains the growth of bacterial pathogens on the mucosal surface is not borne out by evidence from other bacterial pathogens; in West Africa the prevalence of *H. influenzae* (and *N. meningitidis*) carriage does not vary by season [30, 31].

We observed a positive interaction between the presence of one species of pathogen in the nasopharynx and the presence of the other that was independent of age, season and coryza. In the mouse model of colonization by contrast, pre-existing carriage of one serotype of pneumococcus reduced the probability of colonization by a second serotype, indicating a negative interaction, although this was not consistently found [32]. Although there may be competition between species at the nasal mucosa there is probably also a degree of host susceptibility to colonisation, which is not specific for either pathogen.

Among children aged <5 years the carriage prevalence of *H. influenzae* in Kilifi (26%) was within the range observed in Central African Republic (20%) and South Africa (40%) [33, 34]. Freezing of STGG media has negligible effect on pneumococcal culture sensitivity [17] but in our hands it reduced the per-swab sensitivity for *H. influenzae* by half. As three-quarters of the swabs were processed after freezing, the mean sensitivity of study swabs for *H. influenzae* was only approximately 63%. However, even if we take this degree of insensitivity into account, the prevalence of Hib carriage in the population aged <5 years was low and this is likely to be attributable to the Hib vaccine program. In The Gambia introduction of Hib vaccine was associated with a decline in Hib carriage among young children from 12% to 0.25% [35]. Carriage of non-capsulate *H. influenzae* was common in our survey though it should be noted that there has been no concomitant increase in the incidence of non-capsulate invasive disease since the introduction of Hib vaccine [36].

In developing countries there are few studies describing the proportion of episodes of invasive pneumococcal disease caused by vaccine serotypes nor describing the extent to which this may be approximated by using nasopharyngeal isolates. Among invasive isolates from children aged <5 years in Kilifi in 1998-2002 the vaccine serotype coverage for the 9-valent vaccine (PCV9), which also includes serotypes 1 and 5, was 70% [1]. In the same age group the coverage in carried isolates was 47% for both PCV7 and PCV9. We observed only one carried isolate of serotype 1, though it accounts for 23% of all invasive disease episodes in children [1], and we did not detect serotype 5 at all. For PCV7 therefore, the carried isolates predict the vaccine serotype coverage accurately; for PCV9 they are grossly inaccurate.

A second question of current interest regarding pneumococcal serotypes is whether the direct benefits of introducing PCV7 into routine childhood immunization programs in developing countries would be undermined by an increase in the incidence of non-vaccine type disease. The risk of serotype replacement disease is a function of the exposure frequency and virulence of non-vaccine types in the population. In the USA serotypes 3 and 19A and serogroups 15 and 33 are those that have increased most significantly following vaccine introduction [11, 37-39]. Only 9% (18/207) of the carried isolates from young children in Kilifi fell into these groups. However, across all ages there were at least 40 circulating serotypes in a relatively small population sample in Kilifi and 164 (59%) of the carried pneumococci were from serotypes that are not included in PCV7. Operational use of conjugate pneumococcal vaccines in Kenya, justified by strong evidence of efficacy [3, 4] will provide a natural test of virulence for the many non-vaccine serotypes circulating in this population.

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Table 1Prevalence of nasopharyngeal carriage of *S. pneumoniae* and *H. influenzae* by age

Age group	No. sampled*	<i>S. pneumoniae</i>			<i>H. influenzae</i>		
		No. positive	% positive	95% CI	No. positive	% positive	95% CI
<1 y	98	58	59	49-69	28	29	20-39
1-2 y	130	79	61	52-69	36	28	20-36
3-4 y	121	61	50	41-60	26	21	15-30
5-9 y	109	45	41	32-51	26	24	16-33
10-19 y	104	10	9.6	4.7-17	4	3.8	1.1-9.6
20-29 y	102	8	7.8	3.4-15	4	3.9	1.1-9.7
30-49 y	93	3	3.2	0.7-9.1	1	1.1	0.03-5.8
50 y	107	5	4.7	1.5-11	3	2.8	0.6-8.0

* Thirty-two individuals moved up one age category between the two surveys.

Table 2Risk factors for detection of prevalent nasopharyngeal carriage of *S. pneumoniae* and *H. influenzae*

Risk factor	Adjusted Odds Ratio	95% CI
For <i>S. pneumoniae</i> carriage		
Rainy season	1.65	1.11 – 2.43
Coryza	2.29	1.48 – 3.56
Culture of <i>non-capsulate H. influenzae</i>	7.46	3.94 – 14.1
Taken amoxicillin/ampicillin in the last 2 weeks	0.15	0.03 – 0.76
For <i>H. influenzae</i> carriage		
Swab cultured after freezing	0.53	0.30 – 0.91
Coryza	1.90	1.06 – 3.40
Culture of 1 pneumococcal serotype	8.24	4.53 – 15.0
Culture of 2 pneumococcal serotypes	57.8	9.77 – 342

Risk-factors tested but excluded from the final model included: sex, rural or semi-urban location, cigarette smoking, history of exposure to sulfadoxine/pyrimethamine or sulfamethoxazole/trimethoprim during the preceding two weeks and number of children aged <5 years in the household. Age, in 8 strata, was included in the final model as an *a priori* confounder.

Table 3

Number of isolates of *S. pneumoniae* by serotype isolated from the nasopharynx of children aged <5 years and of older children and adults in the two surveys combined. The serotypes are ranked in their order of frequency in children aged <5 years

serotype	aged <5 years	age 5 years	Total
19F *	34	5	39
6B *	21	1	22
6A	20	4	24
23F *	20	3	23
23B	11	4	15
14 *	9	3	12
9V *	8	2	10
11A	8	2	10
13	6	3	9
15A	5	6	11
16F	5	2	7
35B	5	1	6
15C	4	0	4
19A	4	1	5
4 *	3	1	4
10A	3	2	5
15F	3	1	4
15B	3	2	5
17F	3	0	3
20	3	2	5
29	3	2	5
34	3	3	6
3	2	0	2
7C	2	1	3
10B	2	1	3
18C *	2	3	5
19B	2	5	7
23A	2	2	4
37	2	2	4
non-typable	2	0	2
other †	7	8	15
total	207	72	279

* indicates a serotype that is included in the commercially available 7-valent pneumococcal conjugate vaccine.

† Other serotypes among children aged <5 years include one each of types 1, 8, 9N, 12F, 21, 31 and 35A; among older individuals these include two isolates of serotypes 18F and 19C and one isolate each of serotypes 1, 21, 11F and 22F.