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Is household antibiotic use a risk factor for antibiotic-resistant pneumococcal infection?

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SUMMARY

We used microbiology and pharmacy data from health-maintenance organizations to determine whether antibiotic use by a household member increases the risk of penicillin-non-susceptible pneumococcal disease. Though it has been well established that an individual's antibiotic use increases one's risk of antibiotic-resistant infection, it is unclear whether the risk is increased if a member of one's household is exposed to antibiotics. We therefore conducted a case-control study of patients enrolled in health maintenance organizations in Western Washington and Northern California. Cases were defined as individuals with penicillin-non-susceptible pneumococcal infection; controls were individuals with penicillin-susceptible pneumococcal infection. Socioeconomic variables were obtained by linking addresses with 1997 census block group data. One-hundred and thirty-four cases were compared with 798 controls. Individual antibiotic use prior to diagnosis increased the odds of penicillin non-susceptibility, with the strongest effect seen for β-lactam use within 2 months (OR 1·8, 95% CI 1·2, 2·8). When household antibiotic use by persons other than the patient were considered, at 4 months prior to diagnosis there was a trend towards an association between penicillin non-susceptibility and β-lactam antibiotic use, and a possible association in a small subgroup of patients with eye and ear isolates. However, no significant overall pattern of association was seen. We conclude that though antibiotic use of any kind within 2 months prior to diagnosis is associated with an increased risk of penicillin-non-susceptible pneumococcal disease, there is no significant overall pattern of association between household antibiotic use and penicillin-non-susceptible pneumococcal infection.

INTRODUCTION

Excessive antibiotic use is thought to be an important factor responsible for the increase in antibiotic-resistant *Streptococcus pneumoniae*. One recent multi-centre survey found nearly a quarter of all pneumococcal isolates to be penicillin-non-susceptible *Streptococcus pneumoniae* (PNSP) [1]. Previous studies have demonstrated that using antibiotics increases an individual's risk of either colonization or disease due to PNSP [2–7]. Furthermore, suburban residents have been shown to be at higher risk for antibiotic resistant infections, though they are at lower risk for

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infection overall [8]. This effect is thought to be due to their greater access to medical care and antibiotic prescription.

Prior to the emergence of antibiotic resistance in pneumococcus, researchers showed that bacterial colonization spreads within families [9–11]. Given that antibiotics increase the risk of PNSP carriage in individuals and that pneumococcal colonization is transmitted between household members, it is possible that antibiotic use by one person in a household could increase the risk that another person in the household will become infected by PNSP. A previous case-control study done in 1980 found that household antibiotic use did not increase the risk of penicillin-resistant infection, but this study was small with only 18 cases [12]. For a larger study, data from health maintenance organizations (HMOs) are well-suited for answering this question because their microbiology and pharmacy information are kept in computerized databases, they have unbiased case ascertainment, and their populations are large and relatively closed (i.e. most patients stay within their HMO for diagnosis, treatment, and prescriptions). We therefore sought to use HMO data to conduct a case-control study aimed at investigating the possible role of household antibiotic use in PNSP disease.

METHODS

Setting

The study was conducted at Group Health Cooperative of Puget Sound (Seattle, WA, USA) and at Kaiser Permanente Northern California (Oakland, CA, USA). Both are large health maintenance organizations with computerized microbiology, enrolment, and pharmacy databases. Human subjects review board approval was obtained prior to the study.

Identification of cases and controls

Patients with an isolate positive for *Streptococcus pneumoniae* were identified at each HMO through microbiology databases. At Group Health we looked for patients from 1991 to 1997 with at least one positive culture for *S. pneumoniae* from blood; cerebrospinal fluid (CSF); discharge of fluid from eyes or ears; or other body fluid. At Kaiser, a database of patients under 5 years of age with pneumococcal isolates from October 1995 to December 1997 was combined with a new database of patients of any age with a positive blood or CSF culture during 1996 or 1997. (Using earlier data from Kaiser would have been incomplete because CSF isolates were not recorded in Kaiser's electronic records until 1995.) At both HMOs we included only those patients 6 months and older whose households were continuously enrolled for at least 6 months prior to the date the first positive body fluid culture was ordered. We excluded those patients for whom we were unable to obtain census block level data.

Cases were defined as those individuals whose first pneumococcal isolate had a mean inhibitory concentration to penicillin of greater than 0·1 mcg/ml [13]. Controls were patients with penicillin-susceptible isolates. We calculated that if 4 controls were selected for each case and if 20 % of controls were exposed to household antibiotics, a study size of 555 would be sufficient to detect a doubling of risk with a power of 80 % ($\alpha = 0{\cdot}05$).

Data collection and definition of antibiotic exposure

Histories of oral antibiotic prescriptions for the infected individual and household members prior to the isolation of *S. pneumoniae* were obtained through the HMO's pharmacy databases. Because families often enrol in HMOs through an employed member of the household, a group of individuals sharing the same HMO subscriber number was considered to be a 'household'. Antibiotic use was defined as the presence in the pharmacy database of one or more prescriptions for an oral antibiotic (excluding antiviral, antifungal, and antituberculous medications) in the 6 months preceding diagnosis; both total antibiotic use and β-lactam use were analysed. 'Self antibiotic use' was defined as use by a patient in the group, while 'household antibiotic use' was defined as use by any individual in the patient's household other than the patient. Age and gender for each patient were obtained from the HMO's enrolment databases. Because data on household income and ethnicity were not available in HMO records, proxies for these variables were obtained for each patient by linking the patient's address as listed in the HMOs' enrolment databases to 1997 census block group estimates of median household income and racial composition.

Statistical analysis

In addition to the primary analysis, we also considered the subgroups of (1) patients with eye and ear

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Table 1. *Characteristics of cases and controls*

	Cases ($n=134$)	Controls ($n=798$)	P value
Mean age	35·6	40·7	0·087
Under 5 years old	57 (42%)	249 (31%)	0·010
Over 65 years old	40 (30%)	258 (32%)	0·569
Male	68 (51%)	408 (51%)	0·935
From Kaiser Permanente	99 (74%)	434 (54%)	<0·001
Source of isolate			0·001
Eye and ear	17 (13%)	32 (4%)	
Blood	114 (85%)	737 (92%)	
Cerebrospinal fluid	1 (1%)	8 (1%)	
Other body fluid	2 (1%)	21 (3%)	
Census block group*			
Percent white race	71·0%	75·2%	0·027
Median household income	$51 999	$50 874	0·512
Presence of household beta-lactam user			
<2 years	3 (2%)	27 (3%)	0·487
2–5 years	9 (7%)	41 (5%)	0·453
6–18 years	11 (8%)	75 (9%)	0·660
19–64 years	34 (25%)	170 (21%)	0·292
⩾65 years	4 (3%)	19 (2%)	0·677

* 1997 estimate of patient's census block group determined by the address listed in the HMO's enrolment databases.

isolates, and (2) those with isolates from normally sterile sites (e.g. blood and CSF). The rationale was that patients with eye and ear isolates were more likely to be younger children with otitis media, and therefore more likely to live in a household with antibiotic-using siblings. The Wilcoxon rank-sum test was used to compare continuous variables such as census block median household income. Univariate logistic regression models were constructed for exposure variables of interest to calculate unadjusted odds ratios (OR), and multivariate models including possible confounding covariates were constructed to calculate adjusted ORs. Fully adjusted models included age, sex, race, income, study site, and year of diagnosis. In these models age, income, and year of diagnosis were used as continuous covariates. For all analyses, a P value less than 0·05 was considered statistically significant. All analysis was done using Stata version 5.0 for Macintosh (Stata Corp., College Station, TX, USA).

RESULTS

From a total of 1009 patients with pneumococcal isolates, 77 (8%) were excluded for lack of census block data. Of the remaining 932 patients, 134 cases of PNSP were identified (Table 1). The other 798 patients served as controls. Cases tended to be younger than controls (mean age 35·6 *vs.* 40·7 years, $P=0·087$), and were more likely to be from Kaiser Permanente (74 *vs.* 54%, $P<0·001$). The proportion of children under age 5 years was 41% for cases, 32% for controls ($P=0·01$). There were also significant differences in the source of isolates: cases had a higher proportion of ear and eye isolates (13 *vs.* 4%, $P<0·001$) and a lower proportion of blood isolates (85 *vs.* 92%, $P=0·006$). As a group, the 40 patients with ear and eye isolates were younger than those with blood and CSF isolates (mean age 9·6 years, range 7 months to 86 years *vs.* 42 years, range 6 months to 99 years).

The proportion of PNSP isolates increased with time, from 0% in 1991, to 22% in 1997. This trend remained statistically significant when adjusted for study site.

Self antibiotic use

Cases were more likely to have used antibiotics in the 2 months prior to diagnosis than controls (unadjusted OR 1·6, 95% CI 1·1, 2·4). The association was strongest for β-lactam antibiotic use within 2 months prior to diagnosis (OR 1·8, 95% CI 1·2, 2·6). The association of PNSP with β-lactam use 2 and 4 months prior to diagnosis was statistically significant when adjusted for year of diagnosis, age, race, income, source of isolate, and study site (Table 2). When only those patients with isolates from normally sterile sites were considered, only the association of antibiotic use

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Table 2. *Odds ratios of penicillin non-susceptibility and antibiotic exposure*

Time of antibiotic exposure	Cases (%)	Controls (%)	Univariate OR (95% CI)	*P* value	Adjusted* OR (95% CI)	*P* value
Self use						
2 months	28·3	19·7	1·62 (1·07, 2·45)	0·02	1·85 (1·16, 2·96)	0·01
4 months	35·8	30	1·31 (0·89, 1·92)	0·17	1·44 (0·93, 2·22)	0·102
6 months	43·3	37·3	1·28 (0·88, 1·85)	0·19	1·32 (0·86, 2·02)	0·201
Self use, β-lactams only						
2 months	24·6	15·4	1·79 (1·16, 2·78)	0·01	1·84 (1·14, 2·95)	0·012
4 months	34·3	25·4	1·53 (1·04, 2·26)	0·03	1·57 (1·02, 2·42)	0·042
6 months	42·5	32·6	1·53 (1·05, 2·22)	0·03	1·48 (0·97, 2·25)	0·069
Household use						
2 months	17·2	14·4	1·23 (0·75, 2·01)	0·41	0·92 (0·53, 1·6)	0·762
4 months	27·6	22·8	1·29 (0·85, 1·95)	0·23	1·04 (0·65, 1·66)	0·875
6 months	32·8	27·8	1·27 (0·86, 1·88)	0·24	1·02 (0·65, 1·61)	0·922
Household use, β-lactams only						
2 months	11·9	9·5	1·29 (0·73, 2·28)	0·39	0·99 (0·52, 1·88)	0·978
4 months	20·9	14·7	1·54 (0·97, 2·44)	0·07	1·27 (0·76, 2·13)	0·362
6 months	24·6	19·3	1·37 (0·89, 2·1)	0·16	1·09 (0·67, 1·79)	0·718

* Adjusted for year of diagnosis, age, race, income, source of isolate, and study site.

2 months prior to diagnosis remained statistically significant (OR 1·7, 95% CI 1·1, 2·8). No associations were statistically significant for the subgroup of patients with eye and ear isolates (OR for β-lactam use at 4 months = 1·2, 95% CI 0·2, 6·3).

Household antibiotic use

Household antibiotic users of all ages were represented. Two percent of cases and 3% of controls had a household β-lactam antibiotic recipient under the age of 2 years. An adult household β-lactam recipient between the ages of 19 and 64 years was present in 25% of cases and 21% of controls; this difference was not statistically significant. Elderly household β-lactam recipients over 65 years old were present in 3% of cases and 2% of controls.

No overall significant pattern of increased risk was observed with household antibiotic use. The risk of PNSP infection was slightly but not significantly increased by household antibiotic use in the months prior to diagnosis (Table 2). When the analysis was restricted to β-lactam use only, cases tended to have been more likely to have had a household member use antibiotics within 4 months of diagnosis (unadjusted OR 1·5, 95% CI 1·0, 2·4, $P = 0·065$). This association also was not statistically significant in the fully-adjusted model (OR 1·3, 95% CI 0·8, 2·1, $P = 0·362$).

In the subgroup analysis, no statistically significant association between household antibiotic use and PNSP was found in patients with isolates from normally sterile sites (unadjusted OR for β-lactam use 4 months prior to diagnosis = 1·1, CI 0·7, 2·0, adjusted OR 1·0, 95% CI 0·6, 1·9).

When the subgroup with eye and ear isolates was considered, 12 of 17 cases (71%) *vs.* 16 of 32 controls (50%) had a household member use antibiotics of any kind within 4 months of diagnosis, a statistically significant difference in the fully adjusted model (OR 7·8, 95% CI 1·0, 60·2) but not the univariate model (OR 2·4, 95% CI 0·7, 8·4). At 4 months, household β-lactam use was present in 10 cases (59%) *vs.* 12 controls (37%), which also was statistically significant in the fully adjusted model (OR 24·4, 95% CI 1·4, 414) but not the univariate model (OR 2·4, 95% CI 0·7, 7·9). No statistically significant associations were observed at 2 or 6 months in the subgroup of eye and ear isolates.

Sociodemographic variables

There were univariate associations between PNSP and census block race and income (Table 1), but these differences were not statistically significant when adjusted for study site, nor when analysed by subgroup.

DISCUSSION

Household and environmental factors have long been known to play a role in the spread of pneumococcus,

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both penicillin-susceptible and resistant. Having a household member colonized with pneumococcus increases an individual's risk for acquiring the bacteria [14]. As a result, serotypes tend to cluster within families, spreading especially in situations of upper respiratory infections and crowding [15]. A study in a military population showed that pneumococcal carriers are also more likely to live with a health care worker than non-carriers. Recent studies in the age of antibiotic resistance have shown that persons with household members in day care are at particularly increased risk for carrying PNSP [16, 17]. On the community level as well, antibiotic use has also been shown to increase the spread of resistant pneumococci [18].

Siblings of patients with invasive pneumococcal disease may be colonized with the same serotype of pneumococcus [19]. This finding suggests a possible sequence of events that could lead to the association of household antibiotic use with PNSP: first a person develops PNSP colonization as a result of a course of oral β-lactam antibiotics, then asymptomatically transmits PNSP to other persons in the household who might be vulnerable to invasive disease. The very old and the very young would be especially susceptible, as they were in our study. An alternative model is also possible in which a person receives a course of oral antibiotics to treat a minor PNSP infection, and transmits that same strain to another family member who suffers a more serious invasive illness.

We replicated the findings of earlier studies that antibiotic use by an individual is associated with an increased risk of disease from PNSP. However we found no overall pattern of association with household antibiotic use. Because we used patients with penicillin-sensitive pneumoccocal disease as controls rather than a sample of patients without pneumococcal disease, the odds ratios presented here should be interpreted as conditional relative risks: given that one develops pneumococcal disease, the OR is the increase in the odds of an infection with a penicillin-non-susceptible strain.

It remains possible that there was a modest effect for which even this fairly large study had limited power to detect, or an effect limited to a particular subgroup. Though we found a statistically significant association between antibiotic use at 4 months and PNSP in the subgroup of patients with eye and ear isolates, the significance of this finding is unclear. The wide confidence intervals as well as the large variation in OR depending on the inclusion of age in the adjusted model suggest that this association was highly influenced by the small number of young patients with PNSP eye and ear isolates. We would expect that an association between PNSP and household antibiotic use would be weaker than with self-antibiotic use, yet in this subgroup the association with self-antibiotic use was smaller and not statistically significant.

Our inability to capture all antibiotic exposure might have biased our results: though we assumed that the use of non-HMO pharmacies by Group Health patients and their households was negligible [20], approximately 15% of Kaiser Permanente patients in California do not have prescription drug coverage and may not have filled their prescriptions at Kaiser.

The failure to duplicate the associations of PNSP with race and income noted in previous studies [21] could be explained by some of the limitations of our study. First, our study was restricted to households with health insurance, thus selecting for individuals more likely to be employed and with higher income. Another limitation is that we used census block data as proxies for race and income rather than the actual data from our study subjects, which may have allowed residual confounding by these factors. A third important limitation is that much of our data was from the early 1990s in the Pacific Northwest, which historically has had lower rates of antibiotic resistance than other parts of the country [22]. We found increasing levels of penicillin non-susceptibility outside of Washington state and with each year of the study. A larger study size would possible if we were to repeat this study now when PNSP is more prevalent, conduct a similar study in regions of the country with higher levels of antibiotic resistance, or combine our data with contemporary data from other centres. With a larger group of cases and controls would come greater power to detect modest effects, albeit of uncertain clinical or epidemiological significance.

Despite these limitations our study reinforces the importance of appropriate antibiotic use. With the advent of conjugate pneumococcal vaccine there is hope that the selective pressure of antibiotic use in young children may become less of an issue because vaccinated children have been observed to have lower rates of nasopharyngeal colonization [23, 24]. The heptavalent vaccine seems to have modest protective efficacy against otitis media [25], the illness accounting for most antibiotic use in children [26]. However,

reducing antibiotic use in children may not be enough. In our study, 28% of cases and 23% of controls had a household member older than 18 years old use β-lactam antibiotics within 6 months prior to diagnosis. Though much of the epidemiology of PNSP focuses on children in day care, judicious antibiotic use efforts should be targeted at adults as well.

In conclusion, our study agrees with previous findings that antibiotic use by an individual increases the risk of invasive disease due to PNSP. We found a trend towards an association between PNSP and household β-lactam use at 4 months prior to diagnosis. We also observed a possible association between PNSP and household antibiotic use at 4 months in the small subgroup of patients with eye and ear isolates. However no overall statistically significant pattern of association between PNSP and household antibiotic use was seen.

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