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Clinical trials play an important role in the development of new medical treatments. The purpose of this study is to describe patients participating in a clinical trial and to analyze the socio-demographic characteristics of patients with susceptible and multi-drug resistant *Streptococcus pneumoniae* ear infections. At the conclusion of this study, a socio-demographic description of clinical trial participants was obtained and the results of the study indicated that multi-drug resistant patients were slightly younger than patients with susceptible *S. pneumoniae* ear infections and were more likely to attend day care.

FACTORS ASSOCIATED WITH MULTI-DRUG RESISTANCE AMONG PATIENTS WITH STREPTOCOCCUS PNEUMONIAE EAR INFECTIONS

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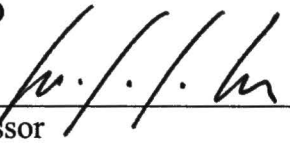

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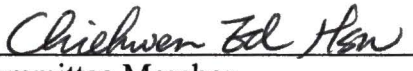

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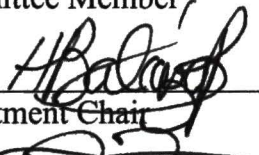

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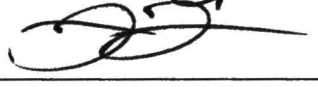

Dean, School of Public Health

FACTORS ASSOCIATED WITH MULTI-DRUG RESISTANCE AMONG PATIENTS WITH STREPTOCOCCUS PNEUMONIAE EAR INFECTIONS

THESIS

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURE

INTRODUCTION

New drugs are developed through a rigorous process that includes clinical trials. The data gathered from these studies assist the Food and Drug Administration in making decisions regarding new drug applications. The purpose of this study is to provide a socio-demographic description of pediatric patients participating in an ear infection clinical trial. The description includes age, sex, ethnicity, otitis media risk factors, vaccine history, and the occupation of the patient's caregiver.

The research study will also describe patients with: 1) susceptible *Streptococcus pneumoniae* ear infections and 2) multi-drug resistant *Streptcoccus pneumoniae* ear infections using the same descriptive variables as mentioned previously. A closer look at ear infections caused by *S. pneumoniae* is of interest because these infections were once highly treatable with penicillin, but now many are resistant to penicillin and other antibiotics (multi-drug resistant). Antibiotic resistance has quickly become an important public health issue. A better understanding of the socio-demographic characteristics of individuals at risk for multi-drug resistant *S. pneumoniae* ear infections will be of benefit to public health professionals.

BACKGROUND

Clinical trials play a vital role in the development of new medical treatment. Clinical trials are "organized studies that provide large bodies of data for statistically valid evaluation of treatments" (K.N. Anderson, L.E. Anderson, Glanze, 1994). It is important to obtain data on all populations that may benefit from new therapies in order to have a complete medical assessment of effectiveness. Clinical trials throughout the years have had under representation of women and minorities for various reasons, including lack of opportunity, distrust of medical treatment, financial barriers, investigator preferences, illiteracy, and lack of awareness (Noah, 2003). There is little documentation about the representation of minority children in clinical trials. A socio-demographic description of the patients involved in this clinical trial will provide data on the issue.

The clinical trial of interest examined children suffering from acute otitis media with tympanostomy tubes (AOMT). Acute otitis media is an infection of the middle ear. It is the primary reason children visit the doctor and is responsible for 25% of pediatrician visits amounting to 5 billion dollars in health care expenses each year (Tan, 2002). Symptoms of acute otitis media include irritability and inconsolable crying in children. Other possible symptoms include fever, sore throat, headache, and ringing noise in the ear (Allina Hospital and Clinics, 2003). Treatment for repeated middle ear infections is often the insertion of tympanostomy tubes. Ear tubes serve to relieve pressure by providing a means for fluid to drain (Staffel, 2001).

Patients with ear infections are commonly children because the passageway from the nose and throat to the middle ear is immature (Alcon, 2004). Approximately 85% of children experience at least one episode of acute otitis media by age 3 (Carson-Dewitt, 2003). Along with age, other risk factors for ear infections include: male gender, exposure to cigarette smoke, day care attendance, number of children exposed to, and short duration of breastfeeding (Bechtel, 2003).

The bacteria most commonly associated with ear infections include: *S. pneumoniae*, *Haemophilus influenzae*, and *Moraxella cattarrhalis* (Dhooge, van Kempen, Sanders, Rijkers, 2003). *S. pneumoniae* is responsible for 6 million cases of otitis media each year, the majority of bacterial ear infections (Centers for Disease Control and Prevention [CDC], 2003). Treatment for ear infections often involves the use of antibiotics. *S. pneumoniae* was once highly treatable with penicillin but has become resistant to this antibiotic as well as others.

Antibiotic resistance has become a major public health threat. Penicillin resistant *S. pneumoniae* was first reported in 1974, by 1989 the prevalence of penicillin resistant *S. pneumoniae* in North America was 5%, this quickly increased to more than 50% in 1999 (Doern et al., 2001 & Zhanel et al., 2003). It is evident bacteria have found a way to mutate and become resistant to antibiotics rather quickly. Public health experts believe the emergence of resistant bacteria is widely attributed to the misuse and overuse of antibiotics. Infections caused by this new generation of antibiotic resistant organisms costs an estimated 4 to 5 million dollars each year according to the Institute of Medicine (McGowan, 2001).

This impact is felt by patients, health care providers, the pharmaceutical industry, and by the public.

The issue of antibiotic resistance has become more apparent as complications and deaths due to resistant microorganisms have increased. Throughout the years organizations have come together to discuss the public health threat of infections resistant to antibiotic treatments. In 1999, the Alliance for the Prudent Use of Antibiotics (APUA) sponsored a meeting with physicians and infectious disease specialists at the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) to outline a plan for action against antibiotic resistance. The plan outlined actions physicians and patients could take to address the misuse and overuse of antibiotics including: antibiotic education, identify the causative agent, prescribe antibiotics when appropriate, preventive vaccination, promote new drug development, and complete full course of antibiotic treatment (Hooton, Levy, Sloan, 2001). In 2001, another plan was developed to focus on the action public health must take to combat antibiotic resistance. The development of this plan was organized by an interagency task force made up of the Centers of Disease Control and Prevention, the Food and Drug Administration, and the National Institutes of Health (CDC, Food and Drug Administration [FDA], National Institute of Health [NIH], 2001). The focused areas of the domestic action plan included surveillance, prevention and control, research, and product development. The interagency task force is now joining forces with the World Health Organization and other partners to address the development of a global public health action plan to combat antimicrobial resistance.

METHODS

Alcon Laboratories conducted the clinical trial with the proper approvals and subsequently provided the data for this study. The purpose of this study was to describe the socio-demographic characteristics of participants in an ear infection clinical trial conducted from February 2001 through May 2002. This study went on to describe and analyze the socio-demographic characteristics of patients with: 1) susceptible *Streptococcus pneumoniae* and 2) multi-drug resistant *Streptococcus pneumoniae* ear infections.

Subjects

The clinical trial was conducted across the United States and two sites in Canada. The cities across the United States included: Austin, Avon Lake, Bellaire, Bloomington, Boise, Bossier City, Bountiful, Bridgeport, Burlington, Chaska, Colorado Springs, Erie, Fort Worth, Fresno, Indianapolis, Johnson City, Kalamazoo, Las Vegas, Little Rock, Missoula, Monroe, Murfreesboro, Naples, New Haven, Orlando, Pasadena, Pelham, Portland, Princeton, Raleigh, Richmond, San Antonio, Shreveport, Southfield, Southhaven, Statesville, Voorhees, Wayne, Wenatchee, White Plains, Wichita, Wilmington, and Winson-Salem. The two Canada sites included: Calgary and Barrie. Approximately 600 patients were enrolled in the clinical trial. This enrollment number was determined considering factors such as a 20-30% culture negative rate, type of comparison study, and the statistical significance of efficacy variables. In order for patients to participate in the clinical trial their caregiver must have given consent and agreed to the clinical trial protocol including three physician visits, maintaining a patient diary, and keeping the patient's ears dry. Other

criteria patients had to meet included: age, unobstructed tympanostomy tubes, visible otorrhea, otorrhea for less than 21 days, certain typanostomy tube types, no fungal infection, no active case of herpes simplex, no menstruating females, no HIV positive patients, no diabetic patients, could not have cleft pallet, could not have down syndrome, no use of topical antibiotic in past 3 days, no use of systemic antibiotic in past 7 days, no use of stringent wash in past 24 hours, no use of other medications throughout the study (anti-inflammatory), could not have allergy to quinolones or steroids, could not have previously enrolled in an ear study, one patient per family, and the patient could not be a family member or connected with the investigator site.

Data Sources

Socio-demographic data (database 1) were requested from Alcon Laboratories Clinical Trial Department. These data included age, sex, ethnicity, otitis media risk factors, vaccine history, and caregiver's occupation. Socio-demographic information was collected at the clinical site once consent to participate in the clinical trial was given by the patient's caregiver. The patient's caregiver answered questions pertaining to the child's illness and socio-demographic information. The principal investigator or sub-investigator recorded responses while the clinical site coordinator oversaw the entire process.

The microbiology data (database 2) were requested from Alcon Laboratories Anti-Infective Microbiology Department. These data included bacterial isolate identification and susceptibility to the antibiotics: penicillin, tetracycline, erythromycin, and trimethoprim. In order to collect data for the microbiology database (database 2) ear specimens were collected from patients. The specimens were initially processed by North Coast Clinical

Labortories (Sandusky, OH) using conventional microbiology methods. Characterization to the species level was performed at Alcon Research Ltd. (Fort Worth, TX). Automated ribotyping analysis was performed using a Riboprinter system (Qualicon, Wilmington, DE). Ribotyping involves enzymatic digestion of chromosomal DNA followed by hybridization using probes for genes that encode ribosomal RNA. Identification is based on the unique strain pattern (Forbes, Sahm, Weissfeld, 1998). Phenotypic analysis was performed using GN2 MicroPlates (Biolog, Heywood, CA). Identification is based on 95 tests involving unique reduction of tetrazolium results (BIOLOG, 2001). End point Minimal Inhibitory Concentrations (MICs) were determined following the National Committee for Clinical Laboratory Standards procedure (National Committee for Clinical Laboratory Standards [NCCLS], 2003). Minimal inhibitory concentration is defined as the lowest antimicrobial concentration that completely inhibits visible bacterial growth (Forbes, Sahm, Weissfeld, 1998). Resistance was determined using acquired resistance break points. This "breakpoint" is set at a level of 16 fold above the typical MIC for *S. pneumoniae.*

Data Management

Database 1 was initially in SAS format and database 2 was in an Access Database, the data was combined to an Excel spread sheet, and finally transferred to SPSS (version 11.0.1 for Windows; SPSS, Inc., Chicago, IL) format for analysis. In order to maintain patient confidentiality database 1 and 2 did not use any patient identifiers. The master list of patient identifiers will be retained in client files at clinical sites. The investigators do not have access to these files. All reports and potential publications will report aggregate information only and subjects will not be identified.

Data Analysis

Data analysis included descriptive statistics for all of the clinical trial patients and variables of interest. An independent samples t test was used to evaluate the statistical significance of the difference in mean age between: 1) susceptible *S. pneumoniae* and 2) multi-drug resistant *S. pneumoniae* groups. The same test was run to evaluate the statistical significance of the difference in mean number of siblings between the two groups. Odds ratio for ethnicity, otitis media risk factors, and vaccine history was determined using SPSS software.

RESULTS

Description of All Clinical Trial Patients

A total of 599 patients participated in the ear infection clinical trial. The ages of patients included a range from less than 1 year old through 12 years of age. The majority, 222 (37.1%), of participants were 1 year old. A minority, 3 (0.5%), of participants were 11 years of age and 3 participants were 12 years of age as well. Percentages decreased as age increased with the exception of participants less than 1 year old (Table 1).

Three hundred and seventy-three (62.3%) of participants were male and 226 (37.7%) were female (Table 2). The majority of participants in this clinical trial were Caucasian, 486 (81.1%). Other populations represented in this study included Hispanic, 54 (9%), Black, 33 (5.5%), Other, 23 (3.8%), and Asian, 3 (0.5%) (Table 2).

The most common occupation for participant's caregivers was homemaking, 172 (28.7%), followed by professionals with no management responsibilities, 109 (18.2%), then administrative support, 90 (15%). The least common occupation for caregivers were ones in precision production, craft, and repair, 9 (1.5%) (Table 3).

The majority of participants received the haemophilus vaccine, 369 (61.6%) and had not received the pneumococcal vaccine, 316 (52.8%) (Table 4).

A majority of participants had siblings, 420 (70.1%), attended daycare, 356 (59.4%), and were primarily bottle fed as infant (breast fed <2 months), 348 (58.1%). The least common otitis media risk factor was passive exposure to cigarette/cigar smoke, 139 (23.2%) (Table 5).

Description and Analysis of Patients with 1) Susceptible *S. pneumoniae* and 2) Multi-Drug Resistant *S. pneumoniae* Ear Infections

Patients with multi-drug resistant *S. pneumoniae* ear infections were slightly younger than patients with susceptible *S. pneumoniae* ear infections. The mean age (+/- standard deviation) of patients with multi-drug resistant infections was .8824 (+/- .91336) years while the mean age for patients with susceptible infections was 1.8406 (+/- 1.89134). A statistically significant (p=.004) mean difference of .9582 years was found (Table 1).

A significant difference between patients with multi-drug resistant and susceptible *S. pneumoniae* ear infections was not found when considering sex and ethnicity (Table 2).

The most common occupations for caregivers with children infected with multi-drug resistant *S. pneumoniae* were homemaking, 8 (23.5%), professional specialty with management responsibilities, 6 (17.6%), and professional specialty with no management responsibilities, 5 (14.7%). The most common occupations for caregivers with children infected with susceptible *S. pneumoniae* were homemaking, 14 (20.3%), professional specialty with no management responsibility, 14 (20.3%), and administrative support, 12 (17.4%) (Table 3). These data are also presented in Figure 1.

An association between patients with multi-drug resistant and susceptible *S. pneumoniae* ear infections was not found when considering the haemophilus vaccine. A significant difference was found when considering the pneumococcal vaccine: patients who had received the vaccine are 3.25 times more likely to be infected with multi-drug resistant pneumococcus than those who had not received the vaccine (OR, 3.254; CI_{95}, 1.278 to 8.284; p = .012) (Table 4).

No association was found between patients with multi-drug resistant and susceptible *S. pneumoniae* when considering the following otitis risk factors: passive exposure to cigarette/cigar smoke, pacifier use, frequent upper respiratory infections (> 1 URI in 6 month period), primarily bottle fed as infant (breast fed <2 months), and siblings. A significant difference was found when considering the otitis media risk factor of daycare attendance. Patients who attend daycare are 2.634 times more likely to be infected with a multi-drug resistant pneumococcus (OR, 2.634; CI_{95}, 1.008 to 6.881; p = .044) (Table 5). A mean difference of number of siblings between the multi-drug resistant and susceptible *S. pneumoniae* groups was not found, (mean difference, .2485; p= .093) (Table 6).

DISCUSSION

Having access to clinical trial data provided an opportunity to describe pediatric participants of an ear infection clinical trial. This also provided the opportunity to take a closer look at multi-drug resistant *S. pneumoniae* ear infections and the factors associated with this infection.

As expected the age range of clinical trial patients was less than 1 through 12 years of age. This age range was expected due to the enrollment criteria of ages between 6 months to 12 years. In view of ear infections being most common in children between 6-18 months it was not surprising that the majority of the children in this study were 1 year olds (Dhooge, van Kempen, Sanders, Rijkers, 2002). When comparing patients with multi-drug resistant and susceptible *S. pneumoniae* infections there was a difference in age. Patients with multi-drug resistant *S. pneumoniae* ear infections were younger than patients with susceptible *S. pneumoniae* ear infections. This result coincides with young age being a risk factor for multi-drug resistant *S. pneumoniae* infections (Kaplan, Mason, 1998).

The majority of participants were male also as expected considering ear infections are more common in males than females. A difference in sex between patients with multi-drug resistant and susceptible *S. pneumoniae* ear infections was not observed.

In this study the majority of participants were Caucasian. Minority children were under represented in this clinical trial. This result is in parallel with minorities in general being under represented in clinical trials. This result is in contrast to a review of the literature that found an over representation of Black children in clinical trials (Walsh, Ross,

2003). A representation of more Black children was expected due to African Americans being at more risk for pneumococcal disease that made up about 17% of the ear infections in this study (Morbidity and Mortality Weekly Report, 2000). The minority population most represented in the clinical trial was Hispanic children. The reason for this finding is unclear. Alcon did not actively recruit certain populations. The result may simply be due to the clientele of the physicians participating in the clinical trial. A difference in ethnicity between patients with multi-drug resistant and susceptible *S. pneumoniae* ear infections was not observed. Future clinical trials may consider the recruitment of clinical sites with more minority patients in order to have an improved minority representation.

The caregiver's occupation data was not analyzed because of the data collection method utilized in the clinical trial. The caregiver present at the time of the office visit was interviewed about their occupation. Family information on this topic was not obtained leaving an incomplete picture of family income. Future clinical trials may consider attaining more detailed information on economics because its effects on health are significant.

Vaccine history was examined for all clinical trial participants. The majority of participants in the study had received the haemophilus vaccine but had not received the pneumococcal vaccine. The low rate of pneumococcal vaccination may be due to the recent approval, 2000, of the pneumococcal vaccine Prevnar for children under 2 years of age (CDC, 2001a). A difference in pneumococcal vaccine between patients with multi-drug resistant and susceptible *S. pneumoniae* ear infections was observed. Participants who received the pneumococcal vaccine were 3.25 times more likely to be infected with a multi-drug resistant pneumococcus. The type of vaccine and the dose number was not examined

during the analysis of these data. For these reasons this result may be questionable. There has been much controversy over the pneumococcal vaccine. The vaccine includes the majority of antibiotic resistant serotypes therefore it should protect against resistant *S. pneumoniae* (Brown, 2001). Vaccine results have indicated a 7% decrease in ear infections while other studies have found vaccinated children have an increase of infections due to *S. pneumoniae* serotypes not included in the vaccine (CDC, 2001b & Russel, Mulholland, 2002).

Otitis media risk factors were evaluated for all clinical trial participants as well. Passive exposure to cigarette/cigar smoke was examined. Some studies have documented a relationship between otitis media and exposure to tobacco smoke while others have not (Paradise et al., 1997). The differences in results may be due to the methodology in measuring the exposure. This study found passive exposure to smoke as the least common risk factor among participants. Specific information such as the amount of cigarettes and duration of exposure was not collected, making the measurement of exposure vague.

Frequent upper respiratory infections are a risk factor for acute otitis media because infections originally in the respiratory tract may migrate to the ear. This risk factor was the second least common risk factor in this study. A difference in upper respiratory infections between patients with multi-drug resistant and susceptible *S. pneumoniae* ear infections was not observed.

Pacifier use is also a risk factor for acute otitis media. The risk is due to the alteration of pressure between the middle ear and the nasopharynx during pacifier use. In this study pacifier use was the third least common risk factor. A difference in pacifier use

between patients with multi-drug resistant and susceptible *S. pneumoniae* ear infections was not observed.

Primarily bottle fed as an infant was another otitis media risk factor examined in this study. Breast fed children receive antibodies from their mother strengthening their immune system until they can build their own (Paradise et al., 1997). A difference in being bottle fed as an infant between patients with multi-drug resistant and susceptible *S. pneumoniae* ear infections was not observed.

The most common risk factors for participants included having siblings and day care attendance. Both of these risk factors are associated with the exposure to large numbers of children. The time spent in a day care is not as important as the amount of children exposed to at day care or at home (Huffman, 2000). A difference in day care attendance between patients with multi-drug resistant and susceptible *S. pneumoniae* ear infections was observed. Participants who attended day care were 2.634 times more likely to be infected with a multi-drug resistant pneumococcus. Through the years the use of day care facilities has escalated providing a channel for the transmission of resistant pneumococcal infections (Jacobs, Dagan, Appelbaum, Burch, 1998). Previous studies have documented day care attendance, recent antibiotic use, and young age as major risk factors for resistant *S. pneumoniae* (Kaplan, Mason, 1998).

Recent antibiotic use was not directly examined in this clinical trial but in order to be enrolled in the study a patient could not have taken systemic antibiotics within the last 7 days and topical antibiotics within the past 3 days. Future clinical trials may consider

obtaining information on recent antibiotic use because it is a major risk factor for multi-drug resistance.

Although access to clinical trial data provided a unique opportunity to examine susceptible and multi-drug resistant *S. pneumoniae* ear infections the clinical trial was not designed to specifically examine this topic. Another limitation to this study is the number of patients with *S. pneumoniae* infections, 103. Future research may consider combining *S. pneumoniae* data from several ear infection clinical trials with similar designs to increase this number.

Surveillance is vital for identifying and monitoring antimicrobial resistance. Data gathered from this study contributes to the surveillance of *S. pneumoniae* infections as well as the surveillance of multi-drug resistant *S. pneumoniae* infections. The data presented in this study may serve as an information tool about the public health threat of antibiotic resistance for physicians, public health professionals, parents, and communities.

Table 1

Age distribution of all clinical trial patients, patients with susceptible *S. pneumoniae*, and multi-drug resistant *S. pneumoniae* ear infections

Age (years)	Clinical Trial Patients (n=599)	Susceptible *S .pneumoniae* Patients (n=69)	Multi-Drug Resistant *S. pneumoniae* Patients (n=34)	Mean Difference	*p*
0	12% (72)	13% (9)	35.3% (12)	.9582	.004*
1	37.1% (222)	50.7% (35)	50% (17)		
2	16.2% (97)	14.5% (10)	8.8% (3)		
3	11.2% (67)	8.7% (6)	2.9% (1)		
4	6.2% (37)	2.9% (2)	2.9% (1)		
5	5.8% (35)	2.9% (2)			
6	4.8% (29)	2.9% (2)			
7	1.5% (9)	1.4% (1)			
8	1.5% (9)	1.4% (1)			
9	1.7% (10)	1.4% (1)			
10	1% (6)				
11	.5% (3)				
12	.5% (3)				

* $p<.05$

Table 2

Sex and ethnicity of all clinical trial patients, patients with susceptible *S. pneumoniae*, and multi-drug resistant *S. pneumoniae* ear infections

Characteristic	Clinical Trial AOMT Patients (n=599)	Susceptible *S. pneumoniae* AOMT Patients (n=69)	Multi-Drug Resistant *S. pneumoniae* AOMT Patients (n=34)	OR (CI_{95})	*p*
Sex					
Male	62.3% (373)	63.8% (44)	55.9% (19)	.720 (.312-1.661)	.440
Female	37.7% (226)	36.2% (25)	44.1% (15)		
Ethnicity					
Caucasian	81.1% (486)	78.3% (54)	85.3% (29)	1.0	
Asian	.5% (3)	1.4% (1)	2.9% (1)	.537 (.032-8.905)	.660
Black	5.5% (33)	1.0% (7)	5.9% (2)	1.880 (.366-9.641)	.443
Hispanic	9% (54)	7.2% (5)	2.9% (1)	.372 (.042-3.341)	.361
Other	3.8% (23)	2.9% (2)	2.9% (1)	.931 (.081-10.708)	.954

Table 3

Caregiver's occupation of all clinical trial patients, patients with susceptible *S. pneumoniae*, and multi-drug resistant *S. pneumoniae* ear infections

Occupation of Caregiver	2000 National Compensation Survey	Clinical Trial Patients (n=599)	Susceptible *S. pneumoniae* Patients (n=69)	Multi-Drug Resistant *S. pneumoniae* Patients (n=34)
Service Occupation	$9.59	5.8% (35)	4.3% (3)	5.9% (2)
Operators, Fabricators, and Laborers	$10.15	4.3% (26)	4.3% (3)	2.9% (1)
Administrative Support	$12.55	15% (90)	17.4% (12)	14.7% (5)
Sales Occupation	$13.40	6.8% (41)	7.2% (5)	5.9% (2)
Precision production, Craft, and Repair	$17.01	1.5% (9)	1.4% (1)	2.9% (1)
Professional –no management responsibilities	$25.57	18.2% (109)	20.3% (14)	14.7% (5)
Professional -management responsibilities	$28.37	10.9% (65)	11.6% (8)	17.6% (6)
Homemaking	—	28.7% (172)	20.3% (14)	23.5% (8)
Other	—	5.8% (35)	10.1% (7)	5.9% (2)
Technologist or Technician	—	2.8% (17)	2.9% (2)	5.9% (2)

Table 4

Vaccine history of all clinical trial patients, patients with susceptible *S. pneumoniae*, and multi-drug resistant *S. pneumoniae* ear infections

Vaccine History	Clinical Trial Patients (n=599)	Susceptible *S. pneumoniae* Patients (n=69)	Multi-Drug Resistant *S. pneumoniae* Patients (n=34)	OR (CI_{95})	*p*
Haemophilus Vaccine					
Yes	61.6% (369)	62.3% (43)	79.4% (27)	3.349 (.891-12.583)	.062
No	20.9% (125)	23.2% (16)	8.8% (3)		
Unknown	17.5% (105)	14.5% (10)	11.8% (4)		
Pneumococcal Vaccine					
Yes	28.7% (172)	27.5% (19)	50% (17)	3.254 (1.278-8.284)	.012*
No	52.8% (316)	57.8% (40)	32.3% (11)		
Unknown	18.5% (111)	14.5% (10)	17.6% (6)		

* $p < .05$

Table 5

Otitis media risk factors of all clinical trial patients, patients with susceptible *S. pneumoniae*, and multi-drug resistant *S. pneumoniae* ear infections

Otitis Media Risk Factors	Clinical Trial Patients (n=599)	Susceptible *S. pneumoniae* Patients (n=69)	Multi-Drug Resistant *S. pneumoniae* Patients (n=34)	OR (CI_{95})	*p*
Siblings	70.1% (420)	68.1% (47)	67.6% (23)	.979 (.406-2.357)	.962
Daycare Attendance	59.4% (356)	59.4% (41)	79.4% (27)	2.634 (1.008-6.881)	.044*
Bottle fed as infant (breast fed <2 mo.)	58.1% (348)	53.6% (37)	64.7% (22)	1.586 (.679-3.701)	.285
Pacifier use	41.7% (250)	44.9% (31)	44.1% (15)	.968 (.423-2.212)	.938
Frequent Upper respiratory infections (> 1 URI in 6 month period)	37.4% (224)	46.4% (32)	35.3% (12)	.631 (.270-1.472)	.285
Passive exposure to cigarette/cigar	23.2% (139)	17.4% (12)	17.6% (6)	1.018 (.346-2.995)	.974

* $p < .05$

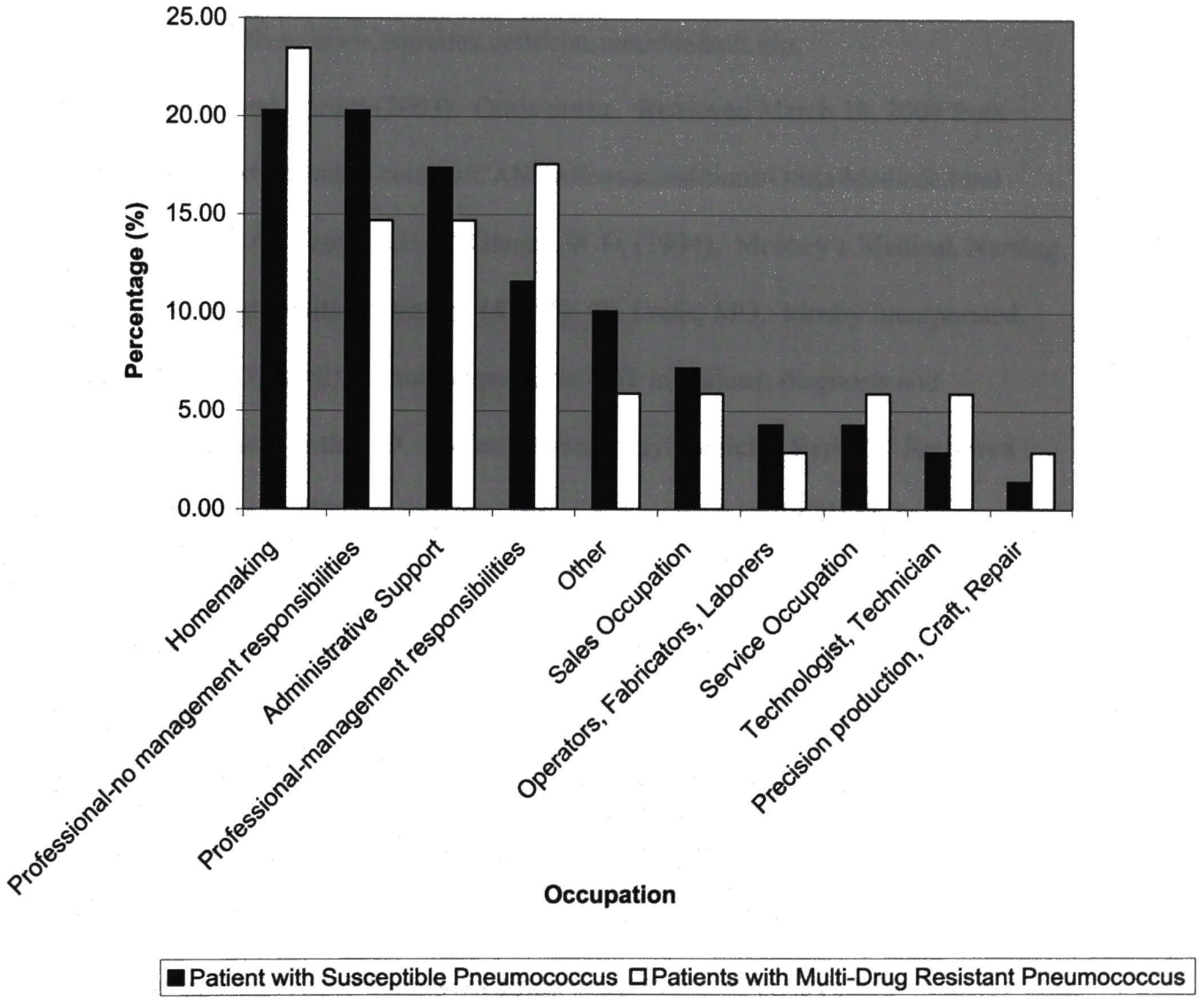
Table 6

Sibling number of all clinical trial patients, patients with susceptible *S. pneumoniae*, and multi-drug resistant *S. pneumoniae* ear infections

Sibling number within household	Clinical Trial Patients (n=599)	Susceptible *S. pneumoniae* Patients (n=69)	Multi-Drug Resistant *S. pneumoniae* Patients (n=34)	Mean Difference	*p*
0	29.9% (179)	31.9% 22	32.4% 11	.2485	.093
1	39.2% (235)	44.9% (31)	50% (17)		
2	20.4% (122)	10.1% (7)	17.6% (6)		
3	7.5% (45)	7.2% (5)			
4	2.3% (14)	5.8% (4)			
5	.3% (2)				
8	.2% (1)				
10	.2% (1)				

Figure 1

Caregiver's occupation of patients with susceptible *S. pneumoniae* and multi-drug resistant *S. pneumoniae* ear infections



REFERENCES

Alcon, Inc. (2004). Ciprodex otic consumer and patient information. Retrieved February 23, 2004 from www.ciprodex.com/consumer/default.asp.

Allina Hospital and Clinics (2003). Otitis media. Retrieved March 18, 2004 from www.medformation.com/ac/CAM.nsf/consconditions/Otitis Mediacc.html.

Anderson, K.N., Anderson, L.E., & Glanze, W.D. (1994). Mosbey's Medical, Nursing, and Allied Health Dictionary (4th ed.). St. Louis, MO.: Mosby Incorporated.

Bechtel, K. (2003, April). Common pediatric ENT infections: diagnosis and management in the ED. Pediatric Emergency Medicine Reports. Retrieved December 15, 2003 from www.findarticles.com/cf_0/m0KHL/4_8/ 99908967/print.jhtml.

Biolog (2001). GN2 mircroplate instructions for use. Hayward, CA: Biolog Incorporated.

Brown, A. (2001). Prevnar: a pneumococcal conjugate vaccine for infants and young children. Issues in Emerging Health Technologies, number 14.

Carson-Dewitt (2003). Otitis media. Gale Encyclopedia of Medicine. Retrieved December 15, 2003 from www.findarticles.com/cf_0/g2601/0010 /2601001001/print.jhtml.

Centers for Disease Control and Prevention (2003). Drug-resistant *Streptococcus pneumoniae* disease. Retrieved January 26, 2004 from www.cdc.gov/ncidod/dbmd/diseaseinfo/drugresisstreppneum_t.htm.

Centers for Disease Control and Prevention (2001a). Pneumococcal cojugate vaccine. Retrieved December 15, 2003 from www.vaccineworld.com.

Centers for Disease Control and Prevention (2001b). Pneumococcal disease. Retrieved December 11, 2003 from www.cdc.gov/nip/diseases/pneumo/pneumo-faqs.htm.

Centers for Disease Control and Prevention, Food and Drug Administration, & National Institutes of Health (2001). A public health action plan to combat antimicrobial resistance. Retrieved December 15, 2003 from www.cdc.gov/drugresistance /actionplan/aractionplan.pdf.

Dhooge, I.J., van Kempen, M.J.P., Sanders, L.A.M., & Rijkers, G.T. (2002). Deficient IgA and IgG2 anti-pneumococcal antibody levels and response to vaccination in otitis prone children. International Journal of Pediatric Otorhinolaryngology, 64, 133-144.

Doern, G.V., Heilmann, K.P., Huynh, H.K., Rhomberg, P.R., Coffman, S.L., & Brueggemann, A.B. (2001). Antimicrobial resistance among clinical isolates of *Streptococcus pneumoniae* in the United States during 1999-2000, including a comparison of resistance rates since 1994-1995. Antimicrobial Agents and Chemotherapy, 45(6), 1721-1729.

Forbes, B.A., Sahm, D.F., & Weissfeld, A.S. (1998). Diagnostic microbiology. St. Louis, MO: Mosby Incorporated.

Hooton, T.M., Levy, S.B., & Sloan, R.W. (2001). Antimicrobial resistance: a plan for community practice. American Family Physician. Retrieved December 15, 2003 from www.findarticles.com/cf_0/m3225/6_63/71579792/print.jhtml.

Huffman, G.B. (2000). Respiratory infections in children attending day care. American Family Physician. Retrieved December 15, 2003 from www.findarticles.com/cf_0/m3225/5_61/61432768/print.jhtml.

Jacobs, M.R., Dagan, R., Applebaum, P.C., & Burch, D.J. (1998). Prevalence of antimicrobial-resistant pathogens in middle ear fluid: multinational study of 917 children with acute otitis media. Antimicrobial Agent and Chemotherapy, 42(3), 589-595.

Kaplan, S. L. & Mason, E.O. (1998). Management of infections due to antibiotic-resistant *Streptococcus pneumoniae*. American Society for Microbiology, 11(4), 628-644.

McGowan, J.E. (2001). Economic impact of antimicrobial resistance. Emerging Infectious Diseases, 7(2).

Morbidity and Mortality Weekly Report (October 6, 2000). Preventing pneumococcal disease among infants and young children. Retrieved March 25, 2004 from www.cdc.gov/mmwr/PDF/RR/RR4909.pdf.

National Committee for Clinical Laboratory Standards (2003). Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard (6^{th} ed.). Wayne, PA: NCCLS.

Noah, B.A. (2003). The participation of underrepresented minorities in clinical research. American Journal of Law and Medicine. Retrieved February 12, 2004 from www.findarticles.com/cf_0/m6029/2-3_29/105518895/print.jhtml.

Paradise, J.L., Rockette, H.E., Colborn, D.K., Bernard, B.S., Smith, C.G., Kurs-Lasky,

M., & Janosky, J.E. (1997). Otitis media in 2253 Pittsburgh-area infants: prevalence and risk factors during the first two years of life. Pediatrics, 99(3), 318-333.

Russell, F. & Mulholland, K. (2002). Prevention of otitis media by vaccination. Drugs, 62(10), 1441-1445.

Staffel, J.G. (2001). Ear Disease. The University of Texas Health Science Center at San Antonio Otolaryngology Head and Neck Surgery. Retrieved March 18, 2004 from www.uthscsa.edu/oto/ear.html.

Tan, T.Q (2002). Update on pneumococcal infections of the respiratory tract. Seminars in Respiratory Infections, 17(1), 3-9.

Walsh, C. & Ross, L.F. (2003). Are minority children under- or overrepresented in Pedicatric research? Pediatrics, 112 (4), 890-895.

Zhanel, G.G., Palatnick, L., Nichol, K.A., Bellyou, T., Low, D.E., & Hobar, D.J (2003). Antimicrobial resistance in respiratory tract *Streptococcus pneumoniae* isolates: results of the Canadian respiratory organism susceptibility study, 1997 to 2002. Antimicrobial Agents and Chemotherapy, 47(6), 1867-1874.