Epidemiol. Infect. (2004), **132**, 159–166. © 2004 Cambridge University Press
DOI: 10.1017/S0950268803001791 Printed in the United Kingdom

Prevalence of *Streptococcus pneumoniae* and *Staphylococcus aureus* nasopharyngeal colonization in healthy children in the United States

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(*Accepted 21 October 2003*)

SUMMARY

This study documents the colonization of *Staphylococcus aureus* (SA), *Streptococcus pneumoniae* (SP) and specific resistant forms of these organisms among healthy children and identifies risk factors associated with these pathogens. Prospective point prevalence survey of nasopharyngeal specimens were obtained from 291 healthy children seeking routine well-child care at a university-based ambulatory paediatric clinic in a large urban city in the United States. A total of 291 children less than 5 years were enrolled during a 1-year period. Fifty-four (18·6%) were colonized with SA and 47 (16·2%) were colonized with SP. Among the 54 SA isolates, five (9·2%) were methicillin resistant (MRSA) and among the SP isolates, three (6·4%) were intermediate to penicillin (DRSP). Eighty per cent of all children enrolled reported no underlying medical condition. Care outside their home was more common among colonized (40·8%, 40/98) than non-colonized children (25·4%, 49/193), $P=0·007$. Healthy children from households of four or more people were also more likely to be colonized. The colonization rate of SA and SP among healthy children is consistent with what has been reported in the literature. The prevalence of MRSA and DRSP among healthy children colonized with SA or SP is low in this population of children attending a university-based ambulatory care centre in the United States.

INTRODUCTION

Nasopharyngeal colonization by certain bacteria is an important risk factor for specific infections. In the case of *Streptococcus pneumoniae* (SP), colonization of the nasopharyngeal mucosa is believed to precede the development of certain infections such as otitis media and pneumonia [1–4]. Factors identified to be associated with colonization include young age, attendance in day-care settings, winter season, parental smoking, and prior use of antibiotic therapy [5]. Pneumococci colonize most of the upper respiratory tract but are recovered most frequently from the nasopharynx [5]. There is geographic variation in the carriage and resistance rates of SP in the United States. Reported carriage rates of SP range from 11 to 76% [6, 7], whereas resistance rates to penicillin are dependent tremendously on geographic regions and different population subgroups [5]. Infections caused

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by resistant SP isolates (DRSP) have increased worldwide [8]. Development of pneumococcal resistance is related to frequency of antibiotic usage; however, the exact mechanisms are not clearly identified [9, 10].

Staphylococcus aureus (SA) is also a potential pathogen and is known to colonize healthy adults at rates of 10–30% [11, 12]. Carriage detection by sampling anterior nares has been demonstrated to be an efficient method [13, 14]. Little data are available on colonization rates in healthy children [15, 16]. Previously identified risk factors include hospitalization, chronic skin conditions, history of in-dwelling catheter or other medical device [12]. One study of newborns suggested that it may be as high as 35% [16]. Antibiotic resistance in SA began with the development of resistance to penicillin by the organism's production of β-lactamase [17]. Of recent concern is the observation that the prevalence of methicillin-resistant SA (MRSA) has steadily increased overall [18–21], especially among healthy children without the usual predisposing risk factors [13, 22, 23]. Risk factors of MRSA carriage, e.g. frequent exposure to medical care facility, underlying illnesses, and prior antimicrobial use, have been well documented [11, 12, 24] and colonization of MRSA has been shown to increase the risk for SA infections [11].

The objective of this study was to determine the colonization rates of staphylococci and pneumococci and document the rate of specific resistant forms (DRSP and MRSA) of these pathogens among healthy children. Most of the paediatric literature on SA or SP colonization report on sub-populations known to be at risk for colonization, e.g. day-care attendees. Our study is unique in that we looked at a general population of healthy children who came for routine 'well-child' or maintenance care and tried to identify risk factors that might be associated with colonization.

METHODS

This was a prospective study of children 5 years old and younger who attended a university-based paediatric outpatient clinic in a large urban city in the United States from January 1998 to the end of January 1999. All children enrolled were seen for routine health maintenance care in our paediatric resident physician clinics. Parents of eligible children were asked to participate in the study after they were examined. Children were enrolled only if parents were told they were not ill. Exclusion criteria included current antibiotic use and any diagnosed illness at the time of the visit. Response rate was 75%. Reasons for refusal to participate included not wanting to stay longer in the clinic and not wanting to participate in research. A consent form was presented and signed by the parent.

Parents of children enrolled were then asked to complete a questionnaire, which was administered by one of the investigators (L.C.I., S.K.). All questions were administered verbally and responses recorded by the investigator. The questionnaire included information on demographics (see Table 1), history of past and current antimicrobial use, past medical history including hospitalizations, surgeries and episodes of acute otitis media, and child-care arrangements (day care, in-home child care, etc.). Parents were also asked whether their child had 'any illnesses' and if they responded positively, they were then asked to specify what those illnesses were. Other potential risk factors explored included antibiotic use by, and hospitalization of, household members, number of people living in households and exposure to persons residing in nursing homes, chronic care facilities, shelters, or correctional facilities. In addition, all enrollees' outpatient medical records were reviewed to assist with information that the parent was unable to provide.

A nasopharyngeal swab (NP) was then obtained from the naris of each participant. An investigator (L.C.I., S.K.) obtained a NP specimen by introducing a sterile calcium alginate-tipped swab on an aluminium shaft (Calgiswab Type 1; Spectrum Laboratories, Houston, TX, USA) in one of the patient's nares to the point of meeting resistance. Both the posterior and anterior portions of the naris were included in this single swab. The swab was then placed directly into a transport tube containing liquid Stuart's medium (BBL™ CultureSwab™, Becton Dickinson and Company, Sparks, MD, USA) and transported to the University of Illinois at Chicago Microbiology Laboratory within 8 h for processing. The swabs were plated onto mannitol salt agar (MSA) and colistin, nalidixic acid agar (CNA) containing 5% sheep's blood (Remel, Lenexa, KS, USA) and incubated for up to 48 h at 35 °C in ambient air. MSA plates were examined for the presence of colonies typical of SA and CNA plates were examined for colonies typical of SA and SP. Identification of SA was confirmed using rapid latex agglutination (Staphaurex™, Murex Biotech Limited, Dartford,

https://doi.org/10.1017/S0950268803001791 Published online by Cambridge University Press

Table 1. *Demographic information*

Demographics	Non-colonizer 193 (%)	Colonizer 98 (%)	*Staphylococcus aureus* (SA) 54 (%)	*Streptococcus pneumoniae* (SP) 47 (%)
Gender				
Male	93 (32)	49 (16·8)	29 (10)	20 (6·9)
Female	100 (68)	49 (16·8)	25 (8·6)	27 (9·2)
Age (months)				
Mean	17·2	20·4	16·1	25·4
Median	12	12	6·5	20
Race/Ethnicity				
Black	108 (37)	69 (23·4)	35 (12)	34 (11·7)
Hispanic	70 (24)	30 (10·3)	17 (5·8)	13 (4·5)
White	11 (3·9)	2 (0·69)	2 (0·69)	0
Asian/Pacific islander	1 (0·34)	0	0	0
Socioeconomic				
<$14 000	126 (43·2)	64 (22)	29 (10)	37 (12·7)
Public assistance	144 (49·5)	71 (24·4)	37 (12·7)	37 (12·7)
WIC	140 (48·1)	56 (19·2)	33 (11·3)	24 (8·2)
Private insurance	33 (11·3)	21 (7·2)	13 (4·5)	8 (2·8)

Characteristics of enrollees. No demographic variable was statistically significant among the groups except age and WIC. Percentages are based on total number of enrollees ($n=291$).

Kent, UK). Identification of SP was confirmed by the Optochin disk test (Remel). If an isolate was determined to be SP or SA disk diffusion susceptibility testing was performed following National Committee for Clinical Laboratory Standards (NCCLS) recommendations [25]. For SP the following antibiotics were tested: chloramphenicol, clindamycin, erythromycin, oxacillin, tetracycline, trimethoprim–sulphamethoxazole, and vancomycin. For any SP isolate that had an oxacillin zone size $\leqslant 20$ mm, minimum inhibitory concentration (MIC) testing was performed for penicillin and ceftriaxone using either the *E* test (AB Biodisk, Solna, Sweden) or a microbroth dilution method (Pasco, Becton Dickinson and Company). SA isolates were tested for susceptibility to cefazolin, clindamycin, erythromycin, gentamicin, penicillin, ofloxacin, oxacillin, rifampin, trimethoprim–sulphamethoxazole, and vancomycin. For any SA that tested oxacillin-resistant by disk diffusion, confirmatory MIC testing was performed using a microbroth dilution method (Dade Microsan Inc., West Sacramento, CA, USA).

A sample size of 270 subjects was found to be sufficient to detect a difference of at least 18% between colonized and non-colonized children using Fisher's exact test at $P<0{\cdot}05$ with 80% power, assuming that one-third of the subjects would be colonized. That sample size is also sufficient to detect a difference of 22% between children colonized with either SA or SP and all other children, under the same assumptions and the additional assumption that approximately half of colonized children would be colonized with SA, and half with SP. A database was created based on the questionnaire and results from the microbiological analyses, using Epi-Info 6.04b (Centers of Disease Control and Prevention, Atlanta, GA). The age of each patient was converted into months and then grouped into eight age ranges, which were then stratified according to colonization status (ages were grouped by 2-month intervals until 6 months and thereafter yearly intervals). Logistic regression analysis and χ^2 analysis were performed using the SAS version 8.1 program (SAS Institute, Cary, NC, USA) and SPSS version 10.0 (SPSS Inc., Chicago, IL, USA) statistical software. Univariate analyses of potential risk factors for SA or SP colonization were performed. Bivariate analysis was conducted using χ^2 (Fisher's exact test was used for cells less than 5) and multivariate analysis was conducted using logistic regression. Those predictors of colonization that were found on univariate analysis to be significant at an α level of 0·10 for either SA or SP colonization were introduced into a stepwise multiple logistic regression model to predict SA or SP colonization. The study

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Table 2. *Risk factors*

Risk factor	Total *n* (%)	Colonized *n* (%)	SA *n* (%)	SP *n* (%)
Hospitalizations	120 (41)	36 (37)	19 (35)	17 (36)
Surgeries	83 (29)	30 (31)	18 (33)	13 (28)
Ear infections	5 (2)	2 (2)	0 (0)	2 (4)
Antibiotics use	120 (41)	38 (39)	16 (30)	22 (47)
Household member using antibiotics	66 (23)	25 (26)	14 (26)	12 (26)
Prolonged antibiotic use	5 (2)	2 (2)	2 (4)†	0 (0)
Hospitalization of household member	58 (20)	16 (16)	11 (20)	6 (13)
Day care or Nursery	38 (13)	17 (17)	8 (15)	9 (19)
Day care $\geqslant$5 days/week	60 (21)	31 (32)*	16 (30)†	17 (36)*
Any childhood illnesses	58 (20)	25 (26)	11 (20)	15 (32)*
Any care outside the house	89 (31)	40 (41)*	22 (41)	20 (43)†
Chronic care or correctional facility/shelter	9 (3)	3 (3)	3 (6)	0 (0)
Medication within 2 weeks	6 (2)	0 (0)†	0 (0)	0 (0)
Medication within 2–4 weeks	33 (11)	10 (10)	4 (7)	6 (13)
Medication within 1–6 months	48 (17)	18 (18)	9 (17)	9 (19)
Medication within 6–12 months	34 (12)	11 (11)	4 (7)	7 (15)

Summary of possible factors related to colonization by SA or SP. * Denotes a significance of $<0{\cdot}05$ and † denotes a significance of $<0{\cdot}1$.

was approved by the University of Illinois Institutional Review Board and all participants were informed that participation in the study was voluntary and caregivers provided informed consent before enrolment into the study.

RESULTS

Demographics

A total of 291 children were enrolled in the study, of which 149 (51%) were females. The race/ethnicity of those patients enrolled reflected the population of patients seen in our hospital-based clinic: 60·8% Black, 34·4% Hispanic, and 4·5% White (Table 1). During the study period, approximately 1362 patients were seen in our clinic of which approximately 50% were dedicated to well-child visits. The majority of the patients came from families that earned less than $14000 per year (65·3%) and received public assistance (73·9%); only 18·6% had private insurance. There were 67·4% of patients who were enrolled in the Women and Infant Children assistance programme (WIC), an assistance programme which provides nutritional services to single parents and their children who are financially disadvantaged. Overall, the mean age of enrolment was 18·3 months with the median being 12 months (range <1–60 months). Although the median age of children who visit the clinic is also 12 months, the distribution of children who attend the clinic was significantly different between our enrolled population and the population who visit the clinic ($P<0{\cdot}01$). Fifty-four (18·6%) were colonized with SA and 47 (16·2%) were colonized with SP. We compared the demographic profiles of the 98 colonized with either SA or SP to those who were not colonized.

Risk factors

Overall, 80% of parents reported that their child had no underlying medical conditions and the remainder of parents reported illnesses such as asthma, anaemia, and eczema (Table 2). There were 41% and 29% who reported having been hospitalized or having some type of surgery respectively. We then asked specifically about possible risk factors for colonization with either SA or SP. For example, when asked about recurrent otitis media, only 2% (5) reported more than two ear infections in the past 6 months (2 of the 5 were colonized with SP, none were colonized with SA).

Colonization *vs.* non-colonization

Among the 291 children, 54 [18·6% (14·5–23·4)] and 47 [16·2% (12·4–20·8)] were colonized with SA and SP respectively. There was no statistical difference in terms of gender, race/ethnicity, type of insurance, or income between those colonized and those who

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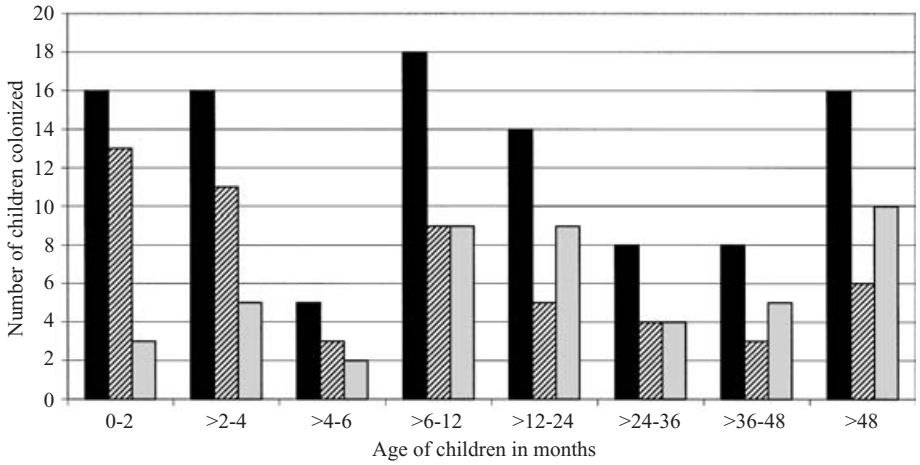

Fig. Age and colonization. Solid bars (■) reflect total population colonized with *Staphylococcus aureus* and *Streptococcus pneumoniae*. Hatched bars (▨) reflect *Staphylococcus aureus* colonization and grey bars (▭) reflect *Streptococcus pneumoniae*.

were not. Enrolment in WIC was significantly associated with colonization ($P=0{\cdot}012$). However, among the possible risk factors addressed, care outside the home was positively associated with colonization with either SA or SP. Forty-one per cent (40/98) of colonizers received some form of care outside their home compared to 25·4% (49/193) of non-colonizers ($P=0{\cdot}007$). In fact, those who were colonized were 2·30 (95% CI 1·17–3·51) times more likely to report some care outside the home than those who were not colonized ($P=0{\cdot}007$). There was also a trend toward colonization with greater numbers of people living in households ($\chi^2_{\text{trend}}=5{\cdot}46$, $P=0{\cdot}019$). Specifically, households with four or more people (44·1%) were 2·54 times (1·48–4·34) more likely to be colonized with either SA or SP ($P<0{\cdot}001$). However, colonizers (25·5%) were not significantly more likely than non-colonizers (17·1%) to have some underlying medical condition ($P=0{\cdot}12$).

SA colonization *vs.* SP colonization

Among those colonized, we found that both SA and SP were significantly associated with age group, but in opposite directions: Younger children, less than 6 months of age, were associated with SA colonization ($P=0{\cdot}028$) and older children, greater than 36 months old, were associated with SP ($P=0{\cdot}080$) (Fig.). Two-thirds of children colonized with SA were less than 12 months old with only 35% being older than 24 months. This compares to 62% of children colonized with SP who were older than 24 months.

In order to determine whether or not time of the year was associated with colonization, we stratified month of enrolment against those colonized with either SA or SP. Overall, there was no significant difference between those colonized and those not colonized. However, 60% of children colonized with SP were enrolled during the months of February and April whereas, only 42% of children colonized with SA were enrolled during this same time period.

In stepwise regression analyses, we found no single risk factor to be associated with increased SA colonization. In fact, antibiotic use was found to be protective of SA colonization [OR 0·433 (0·201–0·932)]. Day care for 5 or more days was associated with a greater likelihood overall colonization [OR 2·46 (1·18–5·15)] and also with a greater likelihood of SP colonization [OR 2·56 (1·08–6·07)]. Additionally, increasing age (in years) was associated with increasing risk of SP colonization [OR 1·37 (1·07–1·75)]. Although there was a trend towards increased likelihood of SP colonization for those with a positive response to 'Does your child have any illnesses?' [OR 2·27 (0·962–5·34)], it did not reach statistical significance.

In order to address whether or not colonizers were clustered in specific geographic locations, we identified the community area where each child lived. A large urban city, Chicago, is divided into 77 community areas based on location. We found no difference in colonization based on geographic location. However, among the community areas of all enrollees, there were significant differences between colonized and non-colonized community areas in terms

https://doi.org/10.1017/S0950268803001791 Published online by Cambridge University Press

of positive reporting of household members using antibiotics ($P=0{\cdot}004$) or history of more than 2 weeks of antibiotic use ($P=0{\cdot}04$). When we looked at only community areas that had colonizers, the only risk factor that was statistically significant was household member using antibiotics ($P=0{\cdot}011$).

Microbiology of isolates

Among the 54 SA isolates, we found that five (9·2%) were MRSA. All five isolates were susceptible to vancomycin, rifampin, trimethoprim–sulphamethoxazole. All five isolates were resistant to penicillin. Three of the five were resistant to erythromycin. One isolate was multiply resistant to penicillin, cefazolin, and erythromycin and one was intermediate to clindamycin. The patient with the multiply resistant isolate had listed only two risk factors: previous hospitalization and someone living in the home using antibiotics for more than 2 weeks. Four of the five patients with MRSA reported having had a previous hospitalization. All of these children were less than 1 year old and in fact, three of the four were $\leqslant$3 months. Three of the four were also hospitalized at birth and two of these were reported to be 'premature' (these two were also hospitalized for more than 2 weeks); the fourth was hospitalized for 1 month for 'rickets'. When we compared prolonged hospitalization (more than 2 weeks) to SA colonization and MRSA colonization, we found that only 15 out of 49 colonized with SA reported prolonged hospitalization compared to 4 out of 5 colonized with MRSA ($P=0{\cdot}047$). Only one parent of an MRSA child reported having care outside of the home. Ninety-one per cent (49/54) of SA isolates were resistant to penicillin and almost one-third (16/54) were resistant to erythromycin. All methicillin-sensitive isolates (MSSA) were susceptible to vancomycin, cefazolin, ofloxacin, rifampin, clindamycin, and trimethoprim–sulphamethoxazole.

Among the 47 SP isolates, we determined only three (6·4%) isolates were intermediate to penicillin. Two isolates were intermediate or resistant to erythromycin and nine (19·1%) were intermediate or resistant to trimethoprim–sulphamethoxazole. All isolates were susceptible to ceftriaxone, vancomycin and tetracycline. At our own institution during the study period, 22% of SP were non-susceptible to penicillin (19% intermediate, 3% resistant); these isolates came from blood, CSF, or other sterile body fluid. Specifically, among paediatric patients, 16% were non-susceptible to penicillin (all were intermediate). However, presumably these isolates were obtained from patients who came to the hospital for illnesses.

Of the three patients in the study with intermediate penicillin isolates, two reported having asthma and receiving care outside the home of 5 or more days. Only one reported having previous surgery. None of them had history of recurrent ear infections, prolonged use of antibiotics, or the other risk factors.

DISCUSSION

The carriage rates for both SA and SP have been documented in the paediatric population. However, the prevalence of resistant forms of these two pathogens have mostly been described in populations with previously identified risk factors or among children who have been hospitalized. Our study included only healthy children who were attending a health-care facility for a 'well-child' visit. Because of the increasing prevalence of DRSP and community-acquired MRSA documented in the large urban city of Chicago in the United States among children who have been hospitalized for serious bacterial infections, we wanted to document the prevalence among healthy children in this heavily populated region of the country. We found that the prevalence of colonization of both MRSA and DRSP to be relatively low, 1·7 and 1% respectively. Among the SP colonizers, we did not identify any isolate that was completely resistant to penicillin. This is in contrast to the latest data from the Chicago Department of Public Health, reporting an intermediate rate of 11·8% among invasive SP isolates from hospitalized patients (adults and children) at acute care hospitals [26].

Although all five children with MRSA were healthy and had no chronic illnesses at the time of presentation, four of the five MRSA patients had reported previous hospitalization with three hospitalized for more than 2 weeks. Our baseline colonization for SA and SP prevalence also concurs with what has been reported in the paediatric literature.

Although the age distribution between the enrolled children was significantly different than the children who accessed the clinic, it is not surprising. Almost 75% of the children who were enrolled were less than 2 years of age and this reflects the national health policy which recommends well-child visits occur at 1, 2, 4, 6, 9, 12, 15, 18 and 24 months of age. In contrast, the overall clinic includes children who are also acutely ill, which might account for the differences

in age distribution. Interestingly, we did not find a statistical difference in those children with an underlying respiratory condition, e.g. asthma, who were colonized with SA compared to SP ($P=0{\cdot}262$). This may be misleading due to our relatively small population of those with underlying respiratory conditions ($n=33$, 6 SA and 1 SP). Although enrolment in the WIC programme was negatively associated with SP colonization, this is most likely a function of age rather than a true association. (Most of the WIC participants were young children and SP colonization was seen more with older children.) We also found that if we controlled for all other variables, e.g. day care, WIC, etc. then we found no significance between age and those colonized with SA. Although we found that certain community areas were more likely to have household members who used antibiotics, we cannot fully explain why. An area to explore that might explain this association would be to assess the degree and ease of accessibility and frequency to health-care facilities, including neighbourhood walk-in clinics, in these community areas. Additionally, it may be worthwhile to also investigate the economic factors of various communities to see if they might explain increased antibiotic use. Along this line, factors to investigate include a more detailed look at housing conditions and actual distance to clinics; it is possible that close physical location might positively impact colonization with non-susceptible SA and/or SP. Obviously, a larger sample size would be needed to identify differences between colonized and non-colonized based on these variables. (Possible confounders that would be difficult to sort include accessibility to transportation, socioeconomic barriers not readily identifiable.) It would also be interesting to determine the prevalence of MRSA of DRSP among household members of those patients who were colonized with these organisms as well as document the duration of colonization for all those who were colonized with either SA or SP. Further epidemiology studies on prevalence of resistant forms of both SA and SP in children need to be performed in order to better address the carriage and subsequent transmission of these pathogens, as well as to address methods to control their spread in the community.

Limitations

Our study reflects the children who attended an urban clinic in Chicago, where the population is 2·89 million people with approximately 12·2% being 5 years and younger [27]. Although the racial/ethnic makeup in our enrollees is similar to the community surrounding the hospital, it is different than those in Chicago as a city: We have a higher black population and fewer Hispanics in the neighbourhoods around our inner city hospital. Similarly, the proportion of our patients at the poverty level is higher than for the city as a whole. These demographic features may impact the ability and frequency to access health care and receive antibiotics; both of these factors could also impact colonization rates for non-susceptible bacteria. Additionally, the number of patients sampled is approximately 57% of those patients who accessed our clinic during the study period for healthy visits. Our exclusion criteria limited us to seeing only healthy children, who make up approximately half of the population who visit the clinic. It would be interesting to compare the prevalence of colonization for susceptible and non-susceptible bacteria in not only healthy children but children who were sick during their visit.

ACKNOWLEDGEMENTS

The authors thank Dominik Starosta, B. S. and Julie Choi, for their helpful assistance in data entry, Jane Stevens and Joyce Tjhio for their technical assistance with the analyses of the bacterial isolates and Jack DeBoer for gathering the demographic information for the clinic population.

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