# Risk Factors for Invasive Pneumococcal Disease in Children: A Population-based Case–Control Study in North America

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**ABSTRACT.** *Objective.* **To identify risk factors for invasive pneumococcal disease, including penicillin-resistant infections, among children 2 to 59 months of age.**

*Design.* **Case–control study.**

*Participants.* **Patients with invasive pneumococcal infections identified by population-based surveillance ($n$ = 187) and controls identified through random-digit telephone dialing ($n$ = 280).**

*Outcome measures.* **Invasive pneumococcal disease was defined as isolation of *Streptococcus pneumoniae* from a normally sterile site. Patients 2 to 59 months of age who were residents of one of four active surveillance areas were included. *S pneumoniae* isolates were tested by broth microdilution. Isolates with a minimum inhibitory concentration to penicillin ≥2 μg/mL were considered resistant.**

*Results.* **Invasive pneumococcal disease was strongly associated with underlying disease and with day care attendance in the previous 3 months. Among 2- to 11-month-olds, current breastfeeding was associated with a decreased likelihood of invasive pneumococcal disease (odds ratio, 0.27; 95% confidence interval: 0.08, 0.90). Penicillin-resistant infections were independently associated with day care attendance, at least one course of antibiotics, and at least one ear infection in the previous 3 months.**

*Conclusions.* **This study shows the association of underlying illnesses, day care attendance, and lack of breastfeeding with risk of invasive pneumococcal disease in children. The association of recent antibiotic use and infection with penicillin-resistant *S pneumoniae* highlights the need to avoid unnecessary antibiotic use in children. *Pediatrics* 1999;103(3). URL: http://www.pediatrics.org/cgi/content/full/103/3/e28; *Streptococcus pneumoniae; prevention; risk factors; epidemiology.***

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ABBREVIATIONS. OR, odds ratio; CI, confidence interval.

The pneumococcus *Streptococcus pneumoniae* is the leading cause of severe bacterial infections in children in industrialized countries such as the United States. It is the predominant pathogen in acute otitis media, the most common reason for pediatric office visits in the United States. Incidence rates of pneumococcal bacteremia of more than 150 episodes per 100 000 children younger than 2 years of age have been reported from several sites.[1–3] With the successful control of *Haemophilus influenzae* type b meningitis through routine vaccination, *S pneumoniae* is now the most frequent agent identified from patients with bacterial meningitis in the United States.[3] Therefore, the emergence of strains of *S pneumoniae* that are no longer susceptible to first- and second-line antimicrobial agents is particularly concerning.[4]

Our ability to prevent pneumococcal infections in young children is quite limited. Available polysaccharide vaccines are not immunogenic in young infants, among whom the incidence is greatest.[5–7] Thus, identification of modifiable risk factors may yield other potential strategies for prevention or to identify groups for selective vaccination. However, there is limited information available on factors associated with an increased risk for pneumococcal infections in young children.[8,9] To identify risk factors for invasive pneumococcal disease (including penicillin-resistant infections), we conducted a population-based, case–control study comparing a sample of all patients with invasive pneumococcal infections identified through active surveillance with control subjects identified through random digit telephone dialing.

## METHODS

### Surveillance for Invasive Pneumococcal Disease

Cases of invasive pneumococcal disease were identified through active, laboratory-based surveillance between January 15, 1995, and June 14, 1996. Surveillance was conducted in four areas: metropolitan Atlanta, GA (8 counties); five counties in Tennessee (including the cities of Chattanooga, Knoxville, Memphis, and Nashville); metropolitan Baltimore. MD; and the Toronto–Peel region, Ontario, Canada. The surveillance area population included 10.2 million, including ~750 000 children younger than 5 years old. All hospitals and laboratories serving the residents of the surveillance population were contacted biweekly and audited semiannually to identify cases. A case of invasive *S pneumoniae* disease was defined as isolation of *S pneumoniae* from a normally sterile site (eg, blood, cerebrospinal fluid, synovial fluid, pericardial fluid, pleural fluid, or peritoneal fluid) in a surveillance area

resident 2 to 59 months of age. Penicillin resistance was defined using National Committee for Clinical Laboratory Standards criteria (minimum inhibitory concentration [MIC] ≥2 μg/mL).[10]

### Selection of a Sample of All Case-patients

Each month, all case-patients 2 to 23 months and 24 to 59 months of age were listed by chronologic order of first positive culture date, and a 25% sample was selected systematically from each list. Case-patients without a telephone number were excluded before sampling.

### Selection and Enrollment of Patients With Penicillin-resistant Infections

In addition to selecting a sample of all case-patients, we attempted to enroll all case-patients with an infection attributable to an *S pneumoniae* isolate that was resistant to penicillin. Each case-patient's isolate was screened initially for susceptibility to penicillin by the oxacillin disk method. Each patient with an isolate that had a zone of inhibition ≤19 mm was enrolled, and the isolate's susceptibility to penicillin was then determined by broth microdilution. For the analysis of risk factors for penicillin-resistant infections, those patients with a penicillin MIC ≥2 (National Committee for Clinical Laboratory Standards breakpoint for resistant) were considered resistant.

### Selection of Control Subjects

In each surveillance area, control subjects were identified by random-digit telephone dialing and frequency-matched to case-patients by age (in two age groups, 2 to 23 months and 24 to 59 months) and calendar month of first positive culture. For example, if there were 8 case-patients 2 to 23 months of age identified in a surveillance area in the month of December, we systematically selected two of these case-patients and then aimed to enroll 2 control subjects 2 to 23 months of age. Therefore, in each surveillance area, we aimed to enroll an equal number of control subjects and case-patients in each age stratum in each month.

From a computer-generated list of random telephone numbers, each was dialed in sequence. Four calls per telephone number were attempted. The first attempt was made on a weekday during regular business hours (9 AM to 5 PM) to eliminate nonresidential numbers. For maximum efficiency in reaching residences, the remaining three calls were placed during the week in the evening (Monday to Friday, 6 PM to 9 PM), and during the weekend. The telephone was allowed to ring 10 times before the household was considered unavailable. Telephones answered by machine also were considered unavailable.

### Collection of Interview Data

Experienced surveillance personnel contacted the household, explained the purpose of the study, obtained informed consent, and conducted the interview using a standard questionnaire. The interview was conducted with the person in the household who was primarily responsible for the eligible child's everyday care. This study was approved by the IRB at the Centers for Disease Control and Prevention and by the IRB at each of the sponsoring institutions.

### Analytic Methods

Odds ratios (ORs) were determined separately for the age groups 2 to 11, 12 to 23, and 24 to 59 months. This stratification reflects potential differences in the risk factors independently associated with invasive pneumococcal disease that may be age-dependent. Although case-patients and control subjects were matched by age groups (2 to 23 and 24 to 59 months), case-patients still were slightly younger than control subjects within each age stratum. Therefore, all subsequent analyses were adjusted for age.

Household crowding was defined as the ratio of the number of persons to the number of rooms in a house. Crowding then was categorized as a dichotomous variable with greater than the median value (0.6 persons per room) used as the cutoff. Day care attendance was defined as any setting outside of the home where a child regularly spent ≥4 hours per week with at least two unrelated children under adult supervision. Ear infections and antibiotic use were defined by parent/caretaker's recall. Recent day care, recent ear infections, and recent antibiotic use were defined as any of these in the 3-month period preceding illness onset or enrollment. Current breastfeeding (in the preceding 2 weeks) was determined by parent/caretaker's response and did not distinguish exclusive breastfeeding from mixed breastfeeding and formula feeding.

Logistic regression was used to assess the independent effect of various risk factors (Proc Logistic, SAS for Windows v6.12, Cary, NC). The stepwise function was used to identify the most parsimonious model. ORs with 95% confidence intervals (CIs) that do not include 1.00 and $P$ values $<.05$ were considered statistically significant.

## RESULTS

Surveillance identified 887 episodes of invasive pneumococcal disease among children 2 to 59 months old. We selected a sample of 228 case-patients and enrolled 187 of them; we also enrolled 280 control subjects. Of eligible case-patients 82% were enrolled, 5% refused, and the remainder were unreachable. The number of case-patients and control subjects enrolled varied by area, from 88 case-patients and 151 control subjects from the Atlanta site to 13 case-patients and 20 control subjects from the Tennessee site. The parents of <1% of eligible control subjects refused to participate.

Of the 187 case-patients enrolled, 137 (73%) were younger than age 2 years, 134 (72%) had nonfocal bacteremia, 81 (44%) were hospitalized, and only 1 (0.5%) died (Table 1). The sample of case-patients enrolled in the study was similar in these characteristics to the total population of case-patients in this age group identified by surveillance.

Underlying illnesses were identified in case-patients only. Although 18 (10%) of the case-patients reported an underlying illness, none of the 280 control subjects reported an underlying illness (defined as an immunosuppressive condition, sickle cell disease, cancer, kidney disease, or asplenia). Because of the strength of this association (OR, undefined; lower 95% CI: 8.08), additional analyses were restricted to the 169 case-patients without underlying disease.

Table 2 presents characteristics associated with invasive pneumococcal disease, stratified by age group. In each age group, invasive pneumococcal

**TABLE 1.** Comparison of Enrolled Case-patients ($n$ = 187) to the Population of All Case-patients with Invasive Pneumococcal Disease Identified ($n$ = 887)

| Characteristic | Enrolled Case-patients (%) | All Case-patients (%) |
|---|---|---|
| Age group | | |
| 2 to 11 Mo | 57 (30) | 266 (30) |
| 12 to 23 Mo | 80 (43) | 387 (44) |
| 24 to 59 Mo | 50 (27) | 234 (26) |
| Underlying illness* | 18 (10) | Not available |
| Nonfocal bacteremia | 134 (72) | 646 (73) |
| Pneumonia | 21 (11) | 136 (15) |
| Meningitis | 11 (6) | 34 (4) |
| Otitis media | 7 (4) | 55 (6) |
| Severity/Outcome: | | |
| Hospitalized | 81 (44%) | 343 (39%) |
| Died | 1 (0.5%) | 11 (1%) |

* Underlying illnesses included immunodeficiency disorder ($n$ = 12), sickle cell disease ($n$ = 5), cancer ($n$ = 3), kidney disease ($n$ = 2), asplenia ($n$ = 1). Some patients reported more than one underlying condition. Detailed information on underlying illness was not available on case-patients who were not enrolled in the case–control study.

**TABLE 2.** Univariate Analysis of Characteristics Associated With Invasive Pneumococcal Disease, 169 Case-patients and 280 Control Subjects, 1994–1996

| Characteristic | 2 to 11 Mo | | | 12 to 23 Mo | | | 24 to 59 Mo | | |
|---|---|---|---|---|---|---|---|---|---|
| | Cases ($n$ = 54) | Controls ($n$ = 73) | ORs (95% CI) | Cases ($n$ = 74) | Controls ($n$ = 117) | ORs (95% CI) | Cases ($n$ = 41) | Controls ($n$ = 90) | ORs (95% CI) |
| Day care attendance in the last 3 months | 48% | 21% | 3.20 (1.45, 7.06) | 55% | 28% | 3.08 (1.67, 5.70) | 54% | 36% | 2.43 (1.09, 5.42) |
| Ear infection in the last 3 months | 49% | 27% | 2.21 (1.03, 4.75) | 48% | 30% | 2.16 (1.17, 4.01) | 38% | 15% | 2.66 (1.08, 6.57) |
| At least one recent course of antibiotics | 34% | 11% | 3.42 (1.25, 9.39) | 30% | 13% | 3.10 (1.39, 6.93) | 64% | 30% | 3.62 (1.09, 12.10) |
| Black race | 44% | 27% | 1.93 (0.90, 4.13) | 36% | 32% | 1.23 (0.66, 2.28) | 51% | 29% | 2.73 (1.22, 6.10) |
| Current breastfeeding | 7% | 32% | 0.21 (0.07, 0.68) | 5% | 6% | 0.75 (0.21, 2.72) | 1% | 2% | 1.18 (0.07, 2.95) |
| Household income <$30 000/y | 69% | 53% | 1.93 (0.85, 4.38) | 58% | 52% | 1.25 (0.66, 2.38) | 72% | 60% | 1.75 (0.72, 4.26) |
| Crowding* | 63% | 48% | 1.45 (0.89, 2.37) | 59% | 55% | 1.13 (0.76, 1.68) | 68% | 51% | 1.71 (0.99, 2.95) |
| Male sex | 69% | 55% | 1.63 (0.76, 3.47) | 61% | 56% | 1.22 (0.67, 2.24) | 56% | 51% | 1.30 (0.59, 2.83) |
| Asthma | 15% | 10% | 1.27 (0.42, 3.88) | 8% | 10% | 0.93 (0.32, 2.65) | 7% | 14% | 0.45 (0.12, 1.75) |

disease was associated with recent day care attendance, recent ear infections, and recent antibiotic use. Among 2- to 11-month-olds, invasive pneumococcal disease also was associated with a decreased likelihood of current breastfeeding. Among 24- to 59-month-olds, invasive pneumococcal disease was associated with black race. Putative risk factors that were not associated with invasive pneumococcal disease by univariate analysis in any age group included the number of persons <18 years old in the household (data not shown), household income <$30 000 per year, male sex, and reported asthma.

Table 3 presents the results of a multivariate logistic regression analysis of risk factors for invasive pneumococcal disease, stratified by age group. Although invasive pneumococcal disease was independently associated with recent day care attendance in each age group, there were some differences by age. Not surprisingly in the age group in which breastfeeding is most common (infants 2 to 11 months of age), invasive pneumococcal disease was independently associated with not currently breastfeeding. In the 12- to 23-month age group, at least one recent course of antibiotics also was independently associated with invasive pneumococcal disease. Among children 24 to 59 months of age, household crowding and recent day care attendance were independently associated with invasive pneumococcal disease.

To determine whether any characteristics of day care attendance were associated with invasive pneumococcal disease, we conducted an additional analysis limited to recent day care attendees only. Among recent day care attendees, invasive pneumococcal disease was not associated with the type of day care center (day care center vs home day care), the number of children in the day care classroom or in the day care center, or the number of days per week or hours per week that the child attended day care ($P > .05$ for each). However, more recent initiation of day care use was associated with invasive pneumococcal disease. Even after adjusting for age, case-patients were more likely than control subjects to have attended day care for <12 months (OR, 4.16; 95% CI: 1.78, 9.70).

Recent day care attendance may influence the risk of invasive pneumococcal disease by its relation to other risk factors. Table 4 presents the relationship between day care attendance and other risk factors for invasive pneumococcal disease. This analysis includes 448 participants (case-patients and control subjects) for whom information on day care attendance was available. Children enrolled in day care were less likely to be currently breastfeeding and more likely to have had at least one recent ear infection and at least one recent course of antibiotics. Recent day care attendance was not associated with race or household income level.

To identify risk factors for penicillin-resistant infection, we compared the 52 case-patients with penicillin-resistant invasive pneumococcal disease with the 280 control subjects (Table 5). Because of the small number of cases, we did not analyze each age group separately. In a multivariate analysis of risk factors, penicillin-resistant *S pneumoniae* infections

**TABLE 3.** Multivariate Analysis of Risk Factors for Invasive Pneumococcal Disease, Stratified by Age Group

| Age Group | Covariate | Adjusted OR* | 95% CIs |
|---|---|---|---|
| 2–11 Mo | Recent day care attendance | 2.63 | 1.17, 5.93 |
| | Current breastfeeding | 0.27 | 0.08, 0.90 |
| 12–23 Mo | Recent day care attendance | 2.29 | 1.16, 4.50 |
| | At least one recent course of antibiotics | 2.42 | 1.05, 5.56 |
| 24–59 Mo | Recent day care attendance | 3.28 | 1.38, 7.80 |
| | Crowding | 2.02 | 1.12, 3.65 |

**TABLE 4.** Association of Day Care With Other Risk Factors, All Ages, Case-patients and Control Subjects Combined

| Characteristic | Recent Day Care Attendance | | $P$ Value* |
|---|---|---|---|
| | Yes ($n$ = 169) | No ($n$ = 279) | |
| At least one recent ear infection | 46% | 24% | <.001 |
| At least one recent course of antibiotics | 32% | 10% | <.001 |
| Current breastfeeding | 3% | 13% | .003 |
| Black race | 33% | 37% | .365 |
| Household income <$30 000/y | 53% | 63% | .067 |

* Adjusted for age.

**TABLE 5.** Multivariate Analysis of Risk Factors for Penicillin-resistant Invasive *S pneumoniae* Infections (52 Penicillin-resistant Cases, 280 Control Subjects)

| Age Group | Covariate | Adjusted OR* | 95% CIs |
|---|---|---|---|
| 2–59 Mo | Recent day care attendance | 3.79 | 1.85, 7.77 |
| | At least one recent course of antibiotics | 3.08 | 1.28, 7.40 |
| | At least one recent ear infection | 2.38 | 1.05, 5.42 |

* Adjusted for age.

were associated independently with recent day care attendance, at least one recent ear infection, and at least one recent antibiotic course.

## DISCUSSION

The primary findings of this study are a strong association between day care attendance and an increased risk of invasive pneumococcal disease, and confirmation of the importance of underlying disease as a risk factor in young children. In addition, this analysis demonstrated an association between antecedent antibiotic use and penicillin-resistant invasive pneumococcal disease.[11] This association supports the concept that unnecessary antibiotic use may be harmful to a child and emphasizes the need to promote judicious antibiotic use.[11]

The proportion of case-patients with an underlying disease in this population-based surveillance system (10%) was substantially lower than that observed recently from a national surveillance system based on patients from eight large children's hospitals (27% of episodes were associated with an underling illness).[12] This may reflect differences in blood culturing patterns or the tendency for children with underlying diseases to be overrepresented among the patient populations served by the referral children's hospitals. Although 10% of the case-patients in this study had an underlying illness, only half of these patients were ≥2 years of age. Thus, these data reinforce the recommendations to immunize children at ≥2 years old with pneumococcal polysaccharide vaccine and simultaneously highlight the limited impact that such vaccination would have on overall rates of invasive pneumococcal disease in a population.[7]

The association of invasive pneumococcal disease with day care attendance is consistent with the findings of studies from Finland and Alaska.[8,9] It is interesting to note that despite the fact that the epidemiologic pattern of pneumococcal disease varies substantially among Alaska, Finland, and the United States,[2,13,14] the association of day care attendance with invasive pneumococcal disease is observed consistently in these very different settings.

Day care attendance may increase a child's risk of invasive pneumococcal disease both directly and indirectly. Day care is an environment known to facilitate the transmission of infectious agents.[15] Because children attending day care centers come from different homes, it is likely that they are exposed to a greater number of pneumococcal serotypes. Also, children who attend day care may be exposed to a greater inoculum of pneumococci than are children who do not attend day care because of the intensity of contact that occurs in day care centers. In addition, the physical separation of a mother from her child makes providing a child with breast milk more demanding and, as a result, children in day care are less likely to breastfeed. In this way, day care attendance may increase indirectly the risk of invasive pneumococcal disease by reducing the likelihood that a child in day care will be protected by the effect of breastfeeding.

The strong protective effect of breastfeeding indicates the importance of this practice for preventing invasive pneumococcal disease. The low prevalence of current breastfeeding, even among control subjects, suggests that there is ample opportunity for prevention of invasive pneumococcal disease by increased breastfeeding. The findings of this study support the American Academy of Pediatrics recommendation that all infants should be breastfed through the first year of life.[16] The exact mechanisms for the impact of breastfeeding are unclear. Transfer of specific antibodies (eg, antibodies to specific pneumococcal serotypes) may play a role, but breast milk has been shown to inhibit colonization with other bacteria independent of the antibody concentration of the breast milk[17] and, thus, other general bacterial inhibitors such as casein may be responsible.[18]

The observed association of recent ear infections with invasive pneumococcal disease is consistent with findings from other studies.[8,9] In this study, as in others, day care attendance was associated with an increased risk of ear infections.[19] The association of recent ear infections with invasive pneumococcal disease may indicate that the middle ear is an important route of invasion for *S pneumoniae*. Recent ear infections also were associated with recent antibiotic use, and thus the independent association of invasive pneumococcal disease and recent antibiotic use among 1-year-olds is difficult to interpret.

Household crowding (defined as more than 0.6 persons per room) was associated with invasive pneumococcal disease among children 24 to 59 months of age in this study. In Finland, the presence of household siblings <7 years old was associated with invasive pneumococcal disease among 2- to 15-year-old children, but not among children <2 years old.[8] By contrast, in this study the number of children <18 years old in the household was not associated with invasive pneumococcal disease. Although higher rates of invasive pneumococcal disease among African-Americans have been identified repeatedly,[2] our data suggest that differences in other risk factors may account for these observations.

The association of penicillin-resistant invasive pneumococcal disease with antecedent antibiotic use is consistent with findings from other studies that have demonstrated a relationship between antibiotic use and penicillin-resistant *S pneumoniae* infections or carriage.[11,20] In collaboration with several partners (including the American Academy of Pediatrics), the Centers for Disease Control and Prevention has launched a nationwide campaign to promote the judicious use of antibiotics.[11] The success of this cam-

paign requires that clinicians and parents understand that unnecessary antibiotics can be harmful to a child. The findings of this study help to support the basis for efforts to curtail the unnecessary use of antibiotics.

Because this study was based on telephone interviews, it may not be generalizable to all populations. Although nearly 90% of the United States population has access to a telephone, this study design necessarily misses the 10% who do not. Furthermore, although the study population included children from three different areas of the United States and the metropolitan region of Toronto, Ontario, the population may not be representative of the entire population of the United States and Canada.

The findings of this study highlight the importance of day care, underlying illnesses, and recent antibiotic use as risk factors for invasive pneumococcal disease in children and the protective effects of breastfeeding. This study also shows that differences in the epidemiology of invasive pneumococcal disease between populations may be explained in part by differences in child care and breastfeeding practices.

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