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# Age- and Serogroup-Related Differences in Observed Durations of Nasopharyngeal Carriage of Penicillin-Resistant Pneumococci▽

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**Using data from an ongoing Swedish intervention project, the observed durations of nasopharyngeal carriage of penicillin-nonsusceptible *Streptococcus pneumoniae* (PNSP) (MIC of penicillin G of ≥0.5 μg/ml) stratified by both pneumococcal serogroup and age of the carrier were compared. The means and 95% confidence intervals (CIs) were estimated by fitting a gamma distribution to the observed duration of carriage for each age and serogroup stratum. The mean observed duration of carriage for all cases was 37 days (95% CI, 35 to 38 days). Children below the age of 5 years carried PNSP for significantly longer periods (43 days; 95% CI, 41 to 45 days) compared with older individuals (25 days; 95% CI, 24 to 27 days). There were also differences within the group of cases below the age of 5 years, as the duration of carriage became significantly shorter for each increasing age step: <1, 1 to 2, and 3 to 4 years. In addition, patients <5 years of age carried serogroups 9 and 14 for significantly shorter periods than groups 6 and 23. Serogroup 9 was also carried for significantly shorter periods than group 19. For patients aged 5 years or older, no significant difference in carriage duration for different ages or serogroups could be noted. As young children have the longest duration of PNSP carriage, interventions aiming to reduce the prevalence in this group are of great importance. The results highlight the importance of taking both serogroup and age of the carriers into account when studying the dynamics of pneumococcal transmission in young children.**

Nasopharyngeal carriage is an important feature in the epidemiology of *Streptococcus pneumoniae* (the pneumococcus). Colonization precedes the development of disease in the individual (9, 11), and the nasopharynx acts as the main reservoir from which the bacteria are spread between individuals in the community (3, 4). As high penicillin resistance levels are reported in pneumococci today (13), modeling trends and evaluating the effect of interventions are of great interest. Since prevalence is a composite of both the incidence and the duration of carriage, an understanding of this relationship requires a separation of the two components.

Large variations in the duration of nasopharyngeal pneumococcal carriage have been observed. Age has been reported to be an important determinant, with the longest duration of carriage seen in the youngest individuals (7, 19, 25). Previous studies have also shown that serogroups 6, 19, and 23 are carried for longer periods than other serogroups (11, 25). However, as these serogroups are more common among the youngest children, age-related bias cannot be excluded (7). To our knowledge, durations of carriage adjusted for both the age of the carrier and the pneumococcal serogroup in order to avoid this bias have not been described previously.

In the Skåne Region of Sweden, all identified cases of pneumococci with an MIC to penicillin G (PcG) of ≥0.5 μg/ml (designated penicillin-nonsusceptible *Streptococcus pneumoniae* [PNSP]) are monitored with repeated nasopharyngeal (NP) cultures as a part of an ongoing communicable disease control project (8, 18). Detailed data on a large number of cases since the project started in 1995 offer a unique opportunity to study various aspects of the spread and carriage of PNSP. In this study, we used data from more than 2,000 PNSP cases identified in the region between 1995 and 2003 to evaluate whether there are significant differences in the duration of PNSP carriage when stratified by both pneumococcal serogroup and age of the carrier.

## MATERIALS AND METHODS

**Study area.** The Skåne Region is situated in the southernmost part of Sweden, with a population constituting approximately 13% of Sweden's total population. In the year 2000, the region had a population of 1,129,424 inhabitants, approximately 5% of whom were children below the age of 5 years.

An intervention program with the aim to reduce the spread of pneumococci with reduced susceptibility to penicillin in day care centers (the South Swedish Pneumococcal Intervention Program) has been running in the area since 1995. Whenever an individual carrying *Streptococcus pneumoniae* with an MIC to PcG of ≥0.5 μg/ml (henceforth designated PNSP) is identified when seeking medical care due to symptoms of infection (index case), all close contacts of the individual are screened by NP culture in order to identify additional, often asymptomatic cases (contact cases). Repeated weekly to biweekly NP cultures are obtained

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TABLE 1. PNSP cases per age group and serogroup

| Serogroup | No. of PNSP cases (no. of index cases) | | | | | | |
|---|---|---|---|---|---|---|---|
| | <1 yr | 1–2 yr | 3–4 yr | 5–6 yr | 7–18 yr | >18 yr | All cases |
| All serogroups | 79 (61) | 715 (358) | 632 (157) | 339 (45) | 153 (51) | 256 (119) | 2,174 (791) |
| 6 | 9 (6) | 90 (43) | 53 (12) | 13 (1) | 12 (6) | 15 (7) | 192 (75) |
| 9 | 22 (12) | 314 (139) | 335 (70) | 202 (27) | 96 (29) | 156 (67) | 1,125 (344) |
| 14 | 9 (7) | 51 (24) | 44 (11) | 13 (2) | 10 (3) | 20 (9) | 147 (56) |
| 15 | 8 (7) | 41 (23) | 48 (17) | 36 (8) | 11 (4) | 12 (8) | 156 (67) |
| 19 | 13 (13) | 108 (55) | 78 (20) | 32 (0) | 10 (3) | 24 (14) | 265 (105) |
| 23 | 13 (11) | 79 (55) | 50 (19) | 20 (4) | 7 (3) | 14 (9) | 183 (101) |

from all PNSP patients until they have submitted two consecutive PNSP-negative samples. Preschool children are restricted from attending day care centers until they are PNSP negative. The follow-up is performed by trained nurses at local health centers and coordinated by the Regional Centre for Communicable Disease Control of Skåne. A central database with epidemiological and microbiological information on all PNSP cases identified in the region since the intervention started is housed at the Regional Centre.

**Microbiological methods.** Nasopharyngeal carriage was determined by cultures of nasopharyngeal swab samples. All nasopharyngeal specimens were analyzed at the departments of clinical microbiology in Lund, Malmö, Helsingborg, and Kristianstad, all situated in the Skåne Region, Sweden. The specimens were inoculated onto blood agar plates supplemented with gentamicin (5 mg/liter) within 24 h of collection, and the isolates were identified as being *Streptococcus pneumoniae* on the basis of colony morphology and susceptibility to optochin.

Antibiotic susceptibility was determined using the disk diffusion method according to guidelines of the Swedish Reference Group for Antibiotics (27). Strains were inoculated onto Iso Sensitest agar (Oxoid Ltd., United Kingdom) supplemented according to the recommendations, and a 1-μg oxacillin disk (Oxoid Ltd.) was applied. Inhibition zone diameters were read to the nearest millimeter and interpreted according to Swedish Reference Group for Antibiotics guidelines. For pneumococci with a zone of <18 mm with a 1-μg oxacillin disk, the MIC of benzylpenicillin was determined using the Etest (AB Biodisk, Solna, Sweden) (23). Serotyping to the group level was performed by the quellung reaction using antisera from the Statens Seruminstitut, Copenhagen, Denmark (15).

**Study participants.** We obtained data on age, serogroup, duration of carriage, and reason for culture (index/contact case status) on all PNSP cases identified in the Skåne Region between March 1995 and December 2003 from the database at the Regional Centre for Communicable Disease Control in Skåne. All cases were subject to the South Swedish Pneumococcal Intervention Program and followed up with weekly to biweekly NP cultures. The duration of carriage was defined as the period from the day of the first PNSP-positive culture to the day of the first of the two consecutive PNSP-negative cultures. The age of the patient was recorded at the first PNSP-positive culture.

In total, 2,621 PNSP-positive cases (1,065 index cases and 1,556 contact cases) were identified in the region during the study period. Of these, 441 cases were excluded, as no information on either serogroup or duration of carriage was available. Furthermore, six cases were excluded because they carried more than one serogroup at the same time. The final data set used for this study consisted of 2,174 cases (791 index cases and 1,383 contact cases). There was no significant difference in age distribution between the 2,174 cases included in the final study database and the 447 cases that were excluded.

Cases were stratified according to pneumococcal serogroup (serogroups 6, 9, 14, 15, 19, and 23) and age of patient. Stratification for age was done in two steps. A detailed analysis with narrow age strata (<1 year, 1 to 2 years, 3 to 4 years, 5 to 6 years, 7 to 18 years, and >18 years) was supplemented with analysis with a cruder stratification to two groups (0 to 4 years and ≥5 years), as the narrower age strata sometimes included very few individuals.

**Statistics.** Previous studies have demonstrated a skewed distribution of the duration of pneumococcal carriage (6, 7). Our data showed the same highly positive skew with a few individuals carrying PNSP for extended lengths of time, indicating that the data might not be normally distributed. We used the Kolmogorov-Smirnov goodness-of-fit test, which can be applied to continuous distributions, to decide if our samples came from a population with a gamma distribution with the specified parameters. As the *P* values for the tests were higher than 0.05, we could not reject the null hypothesis that the sample data belonged to a gamma distribution with specific shape and rate parameters. To account for this, we fitted gamma distributions to the durations of carriage for each age-serogroup stratum. The mean of the gamma distribution, corresponding to the mean duration of carriage in days in our model, was estimated by fitting the parameters in the model with a 95% confidence interval (CI) (21).

The estimates do not include any corrections for the left-censored duration of carriage (period of PNSP carriage before a case is identified as a case), nor do they account for the interval censoring arising from the fact that carriage may have ended any time between the last positive swab and the first negative swab.

## RESULTS

The majority of the patients were children below the age of 5 years (Table 1). The index cases had a median age of 2 years, while the contact cases had a median age of 4 years. Fifty-four percent of the cases were males, and 46% were females. There were no differences in the mean duration of carriage between males and females (38 and 39 days, respectively). The large majority of the cases (86%) carried pneumococcal strains with an MIC to PcG of between 0.5 and 1 μg/ml. Fourteen percent had an MIC to PcG of 2 μg/ml, while only two cases had an MIC to PcG of 4 μg/ml.

The observed duration of carriage ranged between 2 and 368 days, with a mean length of 37 days (95% CI, 35 to 38 days). The distribution was skewed, with a majority of the cases (62%) carrying PNSP for 1 month or less. After 2 months, 81% of the cases were free of PNSP, and after 3 months, 92% of the cases were no longer PNSP carriers. Only 8% (182 cases) carried PNSP for 4 months or longer. Index cases had a significantly longer duration of carriage than did contact cases (45 days [95% CI, 42 to 48 days] versus 33 days [95% CI, 31 to 35 days]).

Children below the age of 5 years carried PNSP for significantly longer periods (43 days; 95% CI, 41 to 45 days) than did older individuals (25 days; 95% CI, 24 to 27 days). In addition, there were age-associated differences within the group of cases <5 years of age. As seen in Table 2, the estimated mean duration for PNSP carriage was the longest for children aged <1 year (mean, 74 days; 95% CI, 61 to 93 days), followed by significantly shorter periods for children 1 to 2 years old (mean, 47 days; 95% CI, 44 to 51 days) and 3 to 4 years old (mean, 34 days; 95% CI, 31 to 37 days). There were no significant differences between the mean carriage durations for children aged between 5 and 6 years and any of the older age groups.

Six serogroups accounted for 95% of the cases: serogroups 6 (9%), 9 (52%), 14 (7%), 15 (7%), 19 (12%), and 23 (8%). There were significant serogroup-specific differences in durations of carriage among cases younger than 5 years of age, while no significant differences in carriage duration between

TABLE 2. Observed duration of nasopharyngeal carriage of PNSP for all cases

| Serogroup | Mean duration (days) (95% CI) | | | | | | |
|---|---|---|---|---|---|---|---|
| | <1 yr ($n$ = 79) | 1–2 yr ($n$ = 715) | 3–4 yr ($n$ = 632) | 5–6 yr ($n$ = 339) | 7–18 yr ($n$ = 153) | >18 yr ($n$ = 256) | All cases ($n$ = 2,174) |
| All ($n$ = 2,174) | 74 (61–93) | 47 (44–51) | 34 (31–37) | 26 (23–28) | 26 (22–30) | 25 (22–28) | 37 (35–38) |
| 6 ($n$ = 192) | 143 (80–298) | 62 (51–77) | 55 (43–73) | 19 (12–35) | 28 (17–52) | 27 (17–47) | 56 (49–65) |
| 9 ($n$ = 1125) | 51 (35–80) | 37 (33–41) | 31 (28–34) | 26 (23–30) | 20 (17–25) | 23 (20–27) | 30 (28–32) |
| 14 ($n$ = 147) | 49 (28–102) | 41 (31–54) | 30 (23–40) | 23 (14–42) | 43 (23–93) | 24 (16–38) | 34 (29–40) |
| 15 ($n$ = 156) | 82 (44–180) | 49 (37–67) | 35 (27–47) | 24 (18–34) | 42 (23–94) | 35 (21–65) | 39 (34–46) |
| 19 ($n$ = 265) | 96 (57–184) | 54 (45–65) | 34 (27–42) | 23 (16–32) | 36 (20–74) | 31 (21–48) | 43 (39–49) |
| 23 ($n$ = 183) | 74 (45–133) | 67 (54–84) | 35 (27–47) | 30 (20–47) | 27 (14–61) | 25 (15–44) | 50 (43–58) |

serogroups could be noted when cases aged 5 years or older were analyzed. Among cases aged <5 years, significantly shorter mean durations of carriage could be noted for serogroup 9 (34 days; 95% CI, 32 to 37 days) and serogroup 14 (37 days; 95% CI, 31 to 45 days) than for serogroup 6 (64 days; 95% CI, 55 to 76 days) and serogroup 23 (56 days; 95% CI, 48 to 67). The mean carriage duration for serogroup 9 was also significantly shorter than that for serogroup 19 (49 days; 95% CI, 42 to 56 days). The mean duration of carriage for serogroup 15 (45 days; 95% CI, 37 to 55 days) did not differ significantly from those of any of the other studied serogroups. Figure 1 illustrates the estimated mean durations of carriage with 95% confidence intervals per serogroup for children aged <5 years.

The serogroup-specific differences in carriage durations remained significant for serogroups 6 and 9 in each successive smaller age stratum, <1 year, 1 to 2 years, and 3 to 4 years (Table 2). For children below the age of 1 year, the mean carriage duration for serogroup 9 was almost 3 months shorter than that for serogroup 6 and slightly less than a month shorter for 1- to 4-year-old children.

When index cases were analyzed separately, a similar pattern of a decrease in carriage duration with increasing age was seen (Table 3). In individual strata, the numbers of observations were sometimes small (Table 1), and hence, the confidence intervals became wider.

## DISCUSSION

The present study is, to our knowledge, the first study to compare the durations of NP pneumococcal carriage adjusted for both the pneumococcal serogroup and the age of the carrier. Our findings highlight the importance of taking both factors into account when studying the dynamics of pneumococcal transmission in young children. We found that among cases younger than 5 years, serotypes 9 and 14 had significantly shorter durations of carriage than serotypes 6 and 23. This serogroup-related difference remained in the smaller age strata (<1, 1 to 2, and 3 to 4 years), although the small number of cases in some strata made estimations more imprecise.

Although the objective of the present study was not to report exact carriage durations, our estimates were in accordance with those reported by previous studies. We estimated a crude mean carriage length of 37 days for all cases (ranging between 19 and 143 days depending on age and serogroup). A previous Swedish study based on a limited portion of the same study database (7) had mean estimates that overall were slightly smaller than ours, possibly due to a smaller number of observations. Similar to our estimated crude mean carriage duration of 67 to 74 days for children below 24 months of age, a Finnish study of young children reported a mean estimate of 2.3 months (95% CI, 1.5 to 3.3 months) (2). A United Kingdom-based study could also demonstrate a significant age-related difference between carriage durations for children younger than 5 years of age (mean, 51 days; 95% CI, 42 to 64 days) and older family members (mean, 19 days; 95% CI, 14 to 24 days) (19). However, none of these studies reported serogroup-specific carriage durations for different age groups.

Serogroups 6, 19, and 23 have previously been reported to cause longer durations of carriage than other serogroups (11, 25), although those studies did not take the age of the patients

TABLE 3. Observed duration of nasopharyngeal carriage of PNSP for index cases

| Serogroup | Mean duration (days) (95% CI) | | | | | | |
|---|---|---|---|---|---|---|---|
| | <1 yr ($n$ = 61) | 1–2 yr ($n$ = 358) | 3–4 yr ($n$ = 157) | 5–6 yr ($n$ = 45) | 7–18 yr ($n$ = 51) | >18 yr ($n$ = 119) | All cases ($n$ = 791) |
| All ($n$ = 791) | 77 (61–100) | 50 (46–56) | 37 (32–44) | 40 (30–54) | 34 (26–45) | 26 (22–32) | 45 (42–48) |
| 6 ($n$ = 75) | 147 (65–440) | 61 (46–84) | 74 (44–138) | —[a] | 40 (19–101) | 15 (8–36) | 63 (51–80) |
| 9 ($n$ = 344) | 51 (30–94) | 37 (32–44) | 28 (23–36) | 47 (33–69) | 26 (19–38) | 25 (20–32) | 33 (30–37) |
| 14 ($n$ = 56) | 49 (26–114) | 42 (29–64) | 37 (22–71) | 11 (3–77) | 110 (41–330) | 28 (16–58) | 42 (33–52) |
| 15 ($n$ = 67) | 84 (43–200) | 47 (32–72) | 51 (33–85) | 19 (10–42) | 44 (15–249) | 39 (21–85) | 47 (38–61) |
| 19 ($n$ = 105) | 96 (57–184) | 60 (47–79) | 44 (29–72) | —[a] | 7 (3–27) | 34 (21–63) | 56 (47–69) |
| 23 ($n$ = 101) | 79 (47–152) | 70 (55–92) | 28 (19–45) | 44 (18–130) | 45 (17–188) | 29 (16–60) | 58 (48–70) |

[a] —, two cases or less.

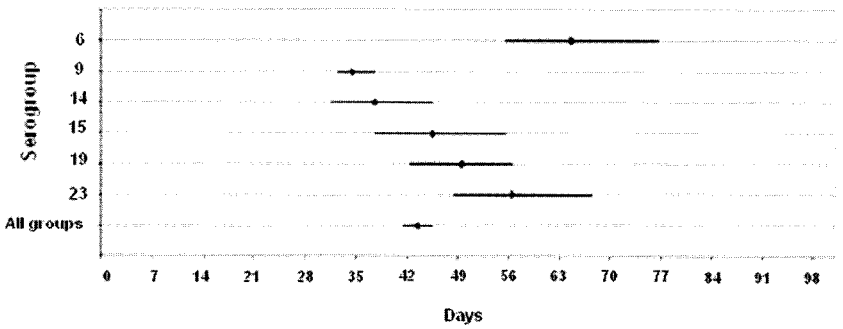


FIG. 1. Observed mean duration of carriage (days) with 95% confidence intervals for all PNSP cases per age group and serogroup for patients younger than 5 years of age.

into account. In our study, we could confirm only that serogroups 6 and 23 had a longer duration of carriage than did serogroups 9 and 14 among the youngest children. In patients older than 5 years of age, no significant differences in the duration of carriage could be noted for any studied serogroup. Our findings fit well with previous knowledge of the relatively poor immunocompetence of young children and the poor immunogenicity of many pneumococcal serotypes. Children below the age of 5 years lack the ability to mount a specific antibody response to several pneumococcal serotypes (5), and it has been shown that nasal carriage of serotypes 6, 19, and 23 especially does not elicit a humoral immune response in young children (24, 30).

Our study was based on a large number of cases that were followed up systematically in short intervals (weekly to biweekly). It should, however, be noted that like many other longitudinal studies, our estimates might be affected by two types of censoring. First, our data are left-censored, as the exact time for PNSP acquisition remains unknown. While contact cases might have carried their PNSP asymptomatically for a long period before being identified as a case through screening activities, index cases (the majority seeking medical care for upper respiratory tract symptoms) are probably identified in the beginning of their carriage period, since symptomatic pneumococcal infection often occurs soon after the acquisition of a new strain (11). As the index case estimates are probably closer to the true carriage durations, we have therefore chosen to report data for index cases separately, although the smaller number of observations in each stratum gives more uncertain estimates. The consistency of the index case estimates and the overall estimates supports our conclusions. The interval censoring arising from the fact that carriage might have ended any time between the last positive culture and the first negative culture (our end point) might slightly overestimate carriage duration. Here, no differences between index and contact cases can be expected, and the impact of the interval censoring is kept to a minimum by the short intervals between cultures.

We had no information on individual case characteristics such as antibiotic use, disease symptoms, or immunological status. However, due to the large number of cases included in this study, it is unlikely that these factors have biased our results in a systematic way. In a previous Swedish study, a history of acute otitis media before the age of 1 year or more than six episodes of acute otitis media was a significant risk factor for an extended duration of carriage, possibly due to both immunogenic and nonimmunogenic (anatomic and environmental) factors (7). An additional analysis of a subset of cases within that study showed no relationship between longer durations of carriage and antibiotic consumption during the 3-month period preceding the PNSP carriage or during the carriage period (12).

What accounts for the decline in the duration of pneumococcal carriage in the first 4 years of life? The mechanisms behind the immune response to pneumococci in young children are not well understood. It is clear that exposure to pneumococci induces antibody responses against the capsule (10, 26) and against other, conserved determinants (1, 22). However, animal studies have called into question the mechanistic importance of such antibodies in protection against carriage (16, 28, 29), and human studies have had mixed results regarding the importance of anticapsular (10, 14) antibodies or antibodies against other, more conserved determinants in protection against carriage or disease (17, 20). The differences in the observed carriage durations between serogroups within the same age group show that neither the age effect nor the serogroup effect accounts entirely for the other.

As the pediatric NP flora is considered the main ecological reservoir for pneumococci, the duration of NP carriage plays an important part in the transmission dynamics of the bacteria. With the longest duration of carriage seen among young children, and as pneumococci carried by this group are often associated with antibiotic resistance, interventions aimed at reducing the prevalence in this group are of great importance. However, our results highlight the importance of taking both serogroup and age of the carriers into account when studying the dynamics of pneumococcal transmission in young children.



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## REFERENCES

1. **Adrian, P. V., D. Bogaert, M. Oprins, S. Rapola, M. Lahdenkari, T. Kilpi, R. de Groot, H. Kayhty, and P. W. Hermans.** 2004. Development of antibodies against pneumococcal proteins alpha-enolase, immunoglobulin A1 protease, streptococcal lipoprotein rotamase A, and putative proteinase maturation protein A in relation to pneumococcal carriage and otitis media. Vaccine **22:**2737–2742.
2. **Auranen, K., E. Arjas, T. Leino, and A. K. Takala.** 2000. Transmission of pneumococcal carriage in families: a latent Markov process model for binary longitudinal data. J. Am. Stat. Assoc. **95:**1044–1053.
3. **Bogaert, D., R. De Groot, and P. W. Hermans.** 2004. Streptococcus pneumoniae colonisation: the key to pneumococcal disease. Lancet Infect. Dis. **4:**144–154.

4. **De Lencastre, H., and A. Tomasz.** 2002. From ecological reservoir to disease: the nasopharynx, day-care centres and drug-resistant clones of Streptococcus pneumoniae. J. Antimicrob. Chemother. **50**(Suppl. 2)**:**75–81.
5. **Douglas, R. M., J. C. Paton, S. J. Duncan, and D. J. Hansman.** 1983. Antibody response to pneumococcal vaccination in children younger than five years of age. J. Infect. Dis. **148:**131–137.
6. **Dowling, J. N., P. R. Sheehe, and H. A. Feldman.** 1971. Pharyngeal pneumococcal acquisitions in "normal" families: a longitudinal study. J. Infect. Dis. **124:**9–17.
7. **Ekdahl, K., I. Ahlinder, H. B. Hansson, E. Melander, S. Mölstad, and K. Persson.** 1997. Duration of nasopharyngeal carriage of penicillin-resistant Streptococcus pneumoniae: experiences from the South Swedish Pneumococcal Intervention Project. Clin. Infect. Dis. **25:**1113–1117.
8. **Ekdahl, K., H. B. Hansson, S. Mölstad, M. Söderström, M. Walder, and K. Persson.** 1998. Limiting the spread of penicillin-resistant *Streptococcus pneumoniae*: experiences from the South Swedish Pneumococcal Intervention Project. Microb. Drug Resist. **4:**99–105.
9. **Faden, H., L. Duffy, R. Wasielewski, J. Wolf, D. Krystofik, and Y. Tung.** 1997. Relationship between nasopharyngeal colonization and the development of otitis media in children. J. Infect. Dis. **175:**1440–1445.
10. **Goldblatt, D., M. Hussain, N. Andrews, L. Ashton, C. Virta, A. Melegaro, R. Pebody, R. George, A. Soininen, J. Edmunds, N. Gay, H. Kayhty, and E. Miller.** 2005. Antibody responses to nasopharyngeal carriage of Streptococcus pneumoniae in adults: a longitudinal household study. J. Infect. Dis. **192:**387–393.
11. **Gray, B. M., G. M. Converse III, and H. C. Dillon, Jr.** 1980. Epidemiologic studies of Streptococcus pneumoniae in infants: acquisition, carriage, and infection during the first 24 months of life. J. Infect. Dis. **142:**923–933.
12. **Gunnarsson, O., and K. Ekdahl.** 1998. Previous respiratory tract infections and antibiotic consumption in children with long- and short-term carriage of penicillin-resistant Streptococcus pneumoniae. Epidemiol. Infect. **121:**523–528.
13. **Jacobs, M. R., D. Felmingham, P. C. Appelbaum, R. N. Gruneberg, and the Alexander Project Group.** 2003. The Alexander Project 1998–2000: susceptibility of pathogens isolated from community-acquired respiratory tract infection to commonly used antimicrobial agents. J. Antimicrob. Chemother. **52:**229–2246.
14. **Lipsitch, M., C. G. Whitney, E. Zell, T. Kaijalainen, R. Dagan, and R. Malley.** 2005. Are anticapsular antibodies the primary mechanism of protection against invasive pneumococcal disease? PLoS Med. **2:**e15.
15. **Lund, E., and J. Henricsen.** 1978. Laboratory diagnosis, serology and epidemiology of *Streptococcus pneumoniae*, p. 241–262. *In* T. Bergan and J. R. Norris (ed.), Methods in microbiology. Academic Press, New York, NY.
16. **Malley, R., K. Trzcinski, A. Srivastava, C. M. Thompson, P. W. Anderson, and M. Lipsitch.** 2005. CD4+ T cells mediate antibody-independent acquired immunity to pneumococcal colonization. Proc. Natl. Acad. Sci. USA **102:**4848–4853.
17. **McCool, T. L., T. R. Cate, G. Moy, and J. N. Weiser.** 2002. The immune response to pneumococcal proteins during experimental human carriage. J. Exp. Med. **195:**359–365.
18. **Melander, E., H. B. Hansson, S. Mölstad, K. Persson, and H. Ringberg.** 2004. Limited spread of penicillin-nonsusceptible pneumococci, Skane County, Sweden. Emerg. Infect. Dis. **10:**1082–1087.
19. **Melegaro, A., N. J. Gay, and G. F. Medley.** 2004. Estimating the transmission parameters of pneumococcal carriage in households. Epidemiol. Infect. **132:**433–441.
20. **Musher, D. M., D. A. Watson, and R. E. Baughn.** 1990. Does naturally acquired IgG antibody to cell wall polysaccharide protect human subjects against pneumococcal infection? J. Infect. Dis. **161:**736–740.
21. **Pawitan, Y.** 2001. In all likelihood: statistical modelling and inference using likelihood. Oxford University Press, New York, NY.
22. **Rapola, S., V. Jantti, R. Haikala, R. Syrjanen, G. M. Carlone, J. S. Sampson, D. E. Briles, J. C. Paton, A. K. Takala, T. M. Kilpi, and H. Kayhty.** 2000. Natural development of antibodies to pneumococcal surface protein A, pneumococcal surface adhesin A, and pneumolysin in relation to pneumococcal carriage and acute otitis media. J. Infect. Dis. **182:**1146–1152.
23. **Skulnick, M., G. W. Small, P. Lo, M. P. Patel, C. R. Porter, D. E. Low, S. Matsumura, and T. Mazzulli.** 1995. Evaluation of accuracy and reproducibility of E test for susceptibility testing of *Streptococcus pneumoniae* to penicillin, cefotaxime, and ceftriaxone. J. Clin. Microbiol. **33:**2334–2337.
24. **Sloyer, J. L., Jr., J. H. Ploussard, L. J. Karr, and G. D. Schiffman.** 1980. Immunologic response to pneumococcal polysaccharide vaccine in infants. Ann. Otol. Rhinol. Laryngol. Suppl. **3:**351–356.
25. **Smith, T., D. Lehmann, J. Montgomery, M. Gratten, I. D. Riley, and M. P. Alpers.** 1993. Acquisition and invasiveness of different serogroups of Streptococcus pneumoniae in young children. Epidemiol. Infect. **111:**27–39.
26. **Soininen, A., H. Pursiainen, T. Kilpi, and H. Kayhty.** 2001. Natural development of antibodies to pneumococcal capsular polysaccharides depends on the serotype: association with pneumococcal carriage and acute otitis media in young children. J. Infect. Dis. **184:**569–576.
27. **Swedish Reference Group for Antibiotics and Its Subcommittee on Methodology.** 5 June 2006, accession date. The principles behind SRGA breakpoints. Swedish Reference Group for Antibiotics, Stockholm, Sweden. http://www.srga.org/.
28. **Trzcinski, K., C. Thompson, R. Malley, and M. Lipsitch.** 2005. Antibodies to conserved pneumococcal antigens correlate with, but are not required for, protection against pneumococcal colonization induced by prior exposure in a mouse model. Infect. Immun. **73:**7043–7046.
29. **van Rossum, A. M., E. S. Lysenko, and J. N. Weiser.** 2005. Host and bacterial factors contributing to the clearance of colonization by *Streptococcus pneumoniae* in a murine model. Infect. Immun. **73:**7718–7726.
30. **Wright, P. F., S. H. Sell, W. K. Vaughn, C. Andrews, K. B. McConnell, and G. Schiffman.** 1981. Clinical studies of pneumococcal vaccines in infants. II. Efficacy and effect on nasopharyngeal carriage. Rev. Infect. Dis. **3:**S108–S112.