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CLINICAL POSTER HIGHLIGHTS

Nasopharyngeal Carriage of *Streptococcus pneumoniae*: Epidemiology and Influence of Vaccination

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TOPIC HIGHLIGHTS

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INTRODUCTION

Nasopharyngeal Carriage of *Streptococcus pneumoniae*: Epidemiology and Influence of Vaccination

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The nasopharynx (NP) typically harbors several species of bacteria, including pathogenic and avirulent bacteria. Colonization of the NP with potentially pathogenic bacteria begins in infancy and continues throughout childhood, most prominently with *Streptococcus pneumoniae* (the pneumococcus), *Haemophilus influenzae* (mostly nontypable), *Moraxella catarrhalis*, and to a lesser degree *Neisseria meningitidis* and *Staphylococcus aureus*.[1-3] The composition of the NP bacterial flora varies throughout life, depending on exposure, host susceptibility, age, geographical area, antibiotic use, and crowding.[1,3-5] Interactions among the bacterial flora also influence the types of bacteria resident in the NP.[1,3] For example, inverse relationships in the likelihood of cocolonization have been found between pneumococcus and *S aureus*, and between *N meningitidis* and pneumococcus or *H influenzae*, suggesting that these bacteria may interfere with each other.

Nasopharyngeal Pneumococcal Carriage

NP carriage of the pneumococcus is of particular concern. Although NP pneumococcal carriage is usually asymptomatic, it can lead to serious infectious diseases in children, including pneumonia, acute otitis media (AOM), meningitis, and bacteremia.[2,6] Studies have shown that pneumococcal disease is preceded by NP colonization with pneumococcus bearing the same serotype as the disease-causing bacteria. In addition, NP pneumococcal carriage in children is a source of horizontal disease transmission in the community, particularly among family members and in day care centers.[4,7]

NP pneumococcal carriage is widely prevalent in healthy children. Up to 81% of children aged <3 years harbor at least one strain of pneumococcus.[8] Age is significantly associated with NP pneumococcal carriage. NP pneumococcal colonization rates peak during the first 3 years of life and decline thereafter.[1] Other factors that increase the risk of NP pneumococcal carriage include day care center attendance, previous antibiotic use, and crowding.[1,3,5,9]

Effects of Vaccination on Nasopharyngeal Pneumococcal Carriage

The 7-valent pneumococcal conjugate vaccine (PCV7; Prevenar®, Wyeth Pharmaceuticals Inc, Philadelphia, PA) is recommended by the American Academy of Pediatrics Committee on Infectious Diseases for routine administration in infants in a 3-dose series followed by a booster in toddlers, with catch-up schedules for children aged 24 to 59 months at high risk of invasive pneumococcal disease.[10] PCV7 has demonstrated significant efficacy against invasive pneumococcal disease, pneumonia, and AOM.[11-15]

PCV7 and an investigational 9-valent PCV have been shown to reduce the rate of NP carriage of pneumococcal vaccine serotypes (VTs).[9,16,17] A replacement effect has been reported, with increased rates of NP carriage of nonvaccine serotypes occurring in conjunction with decreased rates of carriage of VTs. Of note, NP pneumococcal colonization with VTs has been shown to be reduced in unvaccinated household members in homes where children were vaccinated with PCV7.[18] In addition, vaccination with PCV7 has been shown to reduce NP carriage of antibiotic-resistant *S pneumoniae* VT strains.[8,9,19] The effects

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Nasopharyngeal Carriage of *Streptococcus pneumoniae*: Summaries of Six Clinical Studies

Risk Factors for Bacterial Nasopharyngeal Carriage and the Effect of PCV7

Authors

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This was a randomized, controlled trial that assessed the effects of abbreviated schedules of vaccination with PCV7 on NP bacterial carriage in 1003 healthy infants in the Netherlands. Infants received PCV7 on 2-dose (2 and 4 months) or 2+1-dose (2, 4, and 11 months) schedules, or no vaccine (controls). NP swabs were taken at 6 weeks and 6, 12, 18, and 24 months and were cultured for *S pneumoniae, H influenzae, M catarrhalis,* and *S aureus*. Demographics and risk factors were assessed at the same time points.

Two primary doses of PCV7 significantly reduced NP carriage of VT *S pneumoniae* by 12 months and at each time point thereafter. At 6 weeks, prior to vaccination, NP carriage of VT *S pneumoniae* was observed in <10% of children in each group. By 6 months, following 2 doses, approximately 20% of children in each group were positive for VT *S pneumoniae*. By 12 months and thereafter, NP carriage of VT *S pneumoniae* had increased to approximately 40% in the control group, but remained at approximately 20% in both the 2-dose group and the 2+1-dose group ($P<0.05$ versus controls). The 2-dose group and 2+1-dose group differed significantly only at 18 months, when carriage rates were lower in the 2+1-dose group than in the 2-dose group ($P<0.05$). This booster effect at 18 months was temporary and was not seen at 24 months.

Temporal patterns of NP carriage differed for the other bacterial species. NP carriage rates of *S aureus* were higher in early infancy than at later time points, declining from approximately 50% in each group at 6 weeks to approximately 10% or less by 12 months. Notably, at 12 months, carriage rates of *S aureus* were significantly higher in the 2+1-dose group than in the controls ($P<0.05$). Carriage rates of *H influenzae* increased from approximately 15% at 6 weeks to approximately 60% at 18 months. At 12 months, the 2-dose group had significantly higher *H influenzae* carriage rates than the control group. *M catarrhalis* carriage rates increased from approximately 25% at 6 weeks to approximately 65% at 6 months; there were no significant differences among groups.

On multivariate analysis, day care center attendance was the most important factor increasing risk of NP carriage of *S pneumoniae, H influenzae*, and *M catarrhalis* in unvaccinated children in the second year of life. Other factors that increased risk of NP carriage of these pathogens included current symptoms of upper respiratory tract infections (URTIs) and presence of siblings. In contrast, risk of *S aureus* carriage was increased in boys and was decreased among children in day care. Use of antibiotics within 1 month significantly reduced risk of NP carriage of *S pneumoniae*, but it did not influence carriage of other pathogens.

Commentary by Dr Dagan

This study showed that an abbreviated schedule of vaccination with PCV7, using 2 primary doses in infancy, significantly reduced NP carriage of *S pneumoniae* compared with no vaccine. However, this study lacked a comparison with the "standard" and more frequently studied schedule of 3 primary doses plus 1 booster dose. The transient but significant increase of NP carriage of *S aureus* and *H influenzae* at 12 months in children who received PCV7 bears further evaluation. As demonstrated in previous studies, day care center attendance was the most significant risk factor for NP carriage of *S pneumoniae* and other pathogens.

Reference: van Gils EJM, Hak E, Veenhoven RH, et al. Risk factors for bacterial nasopharyngeal carriage and the effect of PCV7. Poster presented at: 27th Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID); June 9-13, 2009; Brussels, Belgium. Poster #9.

Changes in Carriage of *Streptococcus pneumoniae* in Children Attending Day Care Centres (DCCs) in Coimbra, Portugal

Authors

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In this cross-sectional study, NP swabs were obtained from 560 children aged 6 months to 6 years who attended day care centers in an urban setting in Coimbra, Portugal. Vaccination status and demographic data were obtained as well.

On univariate analysis, age was significantly associated with NP carriage of *S pneumoniae* ($P<0.0001$). NP carriage rates of *S pneumoniae* were highest (73.3%) in the youngest age group (aged 6–12 months), declining to 41.8% in children aged >60 months. In contrast, NP colonization with other pathogens was lowest in children aged 6 to 12 months (26.7%) and increased to 58.2% in children aged >60 months. Antibiotic use in the previous month was associated with a significantly lower rate of NP carriage of *S pneumoniae* (use vs nonuse: 41.9% vs 60.6%) and a higher rate of colonization with other pathogens (use vs nonuse: 58.1% vs 39.4%) ($P<0.0001$). In addition, smoke exposure at home was associated with an increased rate of carriage of *S pneumoniae* (yes vs no: 65.1% vs 52.0%) and a decreased rate of carriage of other pathogens (yes vs no: 34.9% vs 48.0%) ($P=0.006$).

A total of 459 children (82%) had been partially or completely vaccinated with PCV7; 404 children (72%) had received all doses appropriate to their age. Vaccination status was not associated with overall NP carriage rates of *S pneumoniae* or other pathogens.

A total of 311 *S pneumoniae* isolates were resistant to antibiotics. VT isolates were significantly more likely to be resistant to penicillin, cefotaxime, erythromycin, clindamycin, and tetracycline than were nonvaccine types ($P<0.00001$). Vaccinated children were significantly more likely than unvaccinated children to carry strains resistant to oral penicillin (13.2% vs 4.3%; $P=0.039$); however, vaccination status was not associated with resistance to other antibiotics. Nonvaccine serotypes 6A and 19A were more likely than other nonvaccine types to be antibiotic resistant.

The most common serotypes of *S pneumoniae* were 19A, 15B/C, 6A, nontypable, and 11A. A total of 7.4% of isolates were VTs, including 19F (n=20), 14 (n=2), and 6B (n=1). Children with NP carriage of serotype 19F were mostly aged >2 years (90%), had received ≥1 dose of PCV7 (65%), and were age-appropriately vaccinated (60%); 80% carried isolates that were resistant to erythromycin, clindamycin, and tetracycline, 50% with decreased susceptibility to penicillin, and 20% with decreased susceptibility to cefotaxime.

Carriage of VTs was approximately the same (19F) or lower (14, 6B) in 2008 than in 2007. Carriage rates of serotypes 6B, 15A, 23A, and 17F declined by >1%, while carriage of serotypes 19A, 15B/C, 6A, and 11A increased by >6%; additional serotypes with increased carriage from 2007 to 2008 at rates >2% included nontypable, 23B, 22F, and 35B.

Commentary by Dr Dagan

The absence of 4 VTs (4, 9V, 18C, and 23F) and the decline in 2 others (14 and 6B) supports the effectiveness of PCV7 in this population. The authors suggested that the continued carriage of serotype 19F might indicate that a higher concentration of antibodies is required for protection against this serotype compared with other serotypes. Further evaluation is needed. The increase in carriage of serotypes 19A and 6A is concerning, given the high rates of antibiotic resistance in these serotypes in this region. Of note, serotypes 19A and 6A are both included in the 13-valent PCV that is currently being developed.

Reference: Rodrigues R, Gonçalves G, Finn A, et al. Changes in carriage of *Streptococcus pneumoniae* in children attending day care centres (DCCs) in Coimbra, Portugal. Poster presented at: 27th Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID); June 9-13, 2009; Brussels, Belgium. Poster #116.

Dynamic Epidemiology of Nasopharyngeal Flora in Kindergarten Children

Authors

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This 2-year prospective study evaluated NP carriage and antibiotic resistance of *S pneumoniae*, *S aureus*, *H influenzae*, *M catarrhalis*, and *Streptococcus pyogenes* in 346 children attending kindergarten in Brussels, Belgium, from October 2006 to May 2008. Three NP samples per child were obtained during the school year. Information regarding antibiotic consumption and demographics was obtained from the parents.

The median age of the children was 50.5 months (range: 22.4–84.2 months). Only 18.7% had received ≥1 dose of PCV7. A total of 746 NP samples and 84 nasal samples were obtained. Global carriage rates were 43.3% for *S pneumoniae*, 31.4% for *S aureus*, 60.1% for *H influenzae*, 41.3% for *M catarrhalis*, and 2.9% for *S pyogenes*. Cocolonization carriage rates were 13.1% for *S pneumoniae*/*S aureus*, 16.3% for *S pneumoniae*/*H influenzae*, 20.8% for *S aureus*/*H influenzae*, and 2.9% for *S pneumoniae*/*S aureus*/*H influenzae*.

The 10 most common *S pneumoniae* serotypes/serogroups were 6B, 19F, 23F, 6A, nontypable, 23A, 11, 19A, 3, and 15; 29.9% of the serotypes were covered by PCV7. Serotypes/serogroups 6B, 19F, and 15 declined in frequency and serotypes 6A and 23A increased in frequency from autumn to spring, while the other 5 common serotypes/serogroups were detected at relatively constant rates during the school year.

A total of 361 strains of *S pneumoniae* were antibiotic resistant, of which 86 (23.6%) were resistant to erythromycin, 46 (12.7%) were intermediately resistant to penicillin, and 51 (16.7%) were resistant to trimethoprim-sulfamethoxazole. In addition, 20 strains were resistant to both penicillin and erythromycin, 20 to erythromycin and trimethoprim-sulfamethoxazole, 4 to penicillin and trimethoprim-sulfamethoxazole, and 11 to all 3 antibiotics.

S aureus carriage patterns varied among children. A total of 45.5% were noncarriers, 42.6% were intermittent carriers, and 11.8% were persistent carriers. Notably, 88.6% of *S aureus* samples were resistant to penicillin; fewer samples were resistant to erythromycin (28.7%), clindamycin (5.3%), ciprofloxacin (1.8%), or methicillin (4.9%).

Commentary by Dr Dagan

At the time of the study, only 18.7% of subjects had received ≥1 dose of PCV7. Thus, it is not surprising that VTs were among the most common serotypes detected. Cocolonization with 2 species of bacteria was detected in up to 21% of samples. Antibiotic resistance was present in up to 23.6% of *S pneumoniae* strains, whereas 88.6% of *S aureus* strains were resistant to penicillin. Because PCV7 was introduced in 2004 in Belgium, with universal reimbursed vaccination beginning in 2007, vaccine coverage should increase over time in the age group evaluated in this study. Thus, further monitoring of carriage rates, cocolonization, and resistance may be informative.

Reference: Jourdain S, Sputael V, Malaviolle X, et al. Dynamic epidemiology of nasopharyngeal flora in kindergarten children. Poster presented at: 27th Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID); June 9-13, 2009; Brussels, Belgium. Poster #171.

Prevalence of *Streptococcus pneumoniae* Nasal Carriage Among Children With Community Acquired Respiratory Tract Infections

Authors

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This retrospective study evaluated data from medical files of all children (N=398) who underwent nasal swabs at a primary health care clinic in Bucharest, Romania, from January to October 2008. The children were aged 2 months to 14 years.

A total of 106 children (26.6%) aged 6 months to 6 years carried *S pneumoniae*. NP carriage rates increased with age to a maximum of >30% in the 3- to 4-year age group, and declined in subsequent years to <10% in the 5- to 6-year age group. None of the children who were *S pneumoniae* carriers had been immunized against *S pneumoniae*.

NP carriage of *S pneumoniae* occurred most frequently in children with URTIs (approximately 30%) or adenoid vegetations/chronic rhinitis (approximately 20%), and less frequently (<10%) in children with recurrent respiratory tract infections, AOM, or lower respiratory tract infections. Cocolonization with both *S pneumoniae* and *M catarrhalis* was most common among children with URTIs; cocolonization with both *S pneumoniae* and *H influenzae* was most common among children with URTIs or with adenoid vegetations/chronic rhinitis. More than 50% of *S pneumoniae* strains showed high levels of resistance to macrolides (erythromycin, azithromycin), tetracycline, and trimethoprim-sulfamethoxazole and showed high levels of intermediate susceptibility to penicillins and cephalosporins.

Commentary by Dr Dagan

NP carriage of *S pneumoniae* occurred at the highest rates in toddlers and preschool-aged children, supporting the authors' suggestion that horizontal transmission is likely to occur in these age groups. NP carriage of *S pneumoniae* and cocolonization with *M catarrhalis* and *H influenzae* were most common in children with URTIs. High levels of resistance and intermediate resistance to commonly used antibiotics are of concern and justify the authors' recommendation to increase vaccination efforts. However, more information is needed on serotypes associated with high antibiotic resistance rates in Romania.

Reference: Bogdan R, Oros M, Codleanu C, et al. Prevalence of *Streptococcus pneumoniae* nasal carriage among children with community acquired respiratory tract infections. Poster presented at: 27th Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID); June 9-13, 2009; Brussels, Belgium. Poster #244.

Effect of a Reduced Dose Infant Schedule of the 7-Valent Pneumococcal Conjugate Vaccine (PCV7) on Nasopharyngeal Pneumococcal Carriage (NP-PNC-CARR)

Authors

N. Givon-Lavi, D. Greenberg, and R. Dagan, all from Ben-Gurion University of the Negev and Soroka University Medical Center, Beer-Sheva, Israel

This was an open-label, randomized, controlled study that compared the effects of 3 different schedules of immunization with PCV7 on the immunogenicity and NP carriage of *S pneumoniae* in 690 infants and toddlers. Subjects were randomized to receive PCV7 on a 3+1 schedule (primary series at 2, 4, and 6 months and a booster at 12 months; n=352), a 2+1 schedule (primary series at 4 and 6 months and a booster at 12 months; n=171), or a 0+2 schedule (no primary series, toddler doses at 12 and 18 months; n=167). Subjects received concomitant DTaP-IPV-PRPT (GlaxoSmithKline, Rixensart, Belgium) at 2, 4, 6, and 12 months, and MMR (GlaxoSmithKline, Rixensart, Belgium) at 12 months. NP samples were obtained at 2, 4, 6, 7, 12, 13, 18, 19, 24, and 30 months. Serum samples were drawn at 2, 7, 13, and 19 months. Significance values were corrected for ethnicity.

Following the primary series, the proportion of subjects with immunoglobulin G (IgG) geometric mean concentrations (GMCs) ≥0.35 µg/mL (the World Health Organization threshold for protective levels of antibody for invasive pneumococcal disease) at 7 months ranged from 85.1% (serotype 23F) to 98.3% (serotype 4) in the 3+1 group and from 61.1% (serotype 6B) to 96.8% (serotype 4) in the 2+1 group. The proportion of subjects with IgG GMCs ≥0.35 µg/mL was significantly higher in the 3+1 group than in the 2+1 group for 5 of the 7 serotypes: 6B (86.4% vs 61.1%; $P<0.001$), 9V (96.4% vs 93.0%; $P=0.047$), 14 (94.7% vs 89.8%; $P=0.026$), 18C (96.4% vs 91.1%; $P=0.013$), and 23F (85.1% vs 70.1%; $P<0.001$), with a trend for serotype 19F (93.0% vs 89.2%; $P=0.064$). IgG GMCs were significantly higher in the 3+1 group than in the 2+1 group for 4 serotypes: 6B (2.07 µg/mL [95% confidence interval (CI), 1.73–2.47 µg/mL] vs 0.57 µg/mL [95% CI, 0.46–0.71 µg/mL]; $P<0.001$), 14 (5.12 µg/mL [95% CI, 4.43–5.91 µg/mL] vs 3.57 µg/mL [95% CI, 2.85–4.47 µg/mL]; $P=0.004$), 18C (1.62 µg/mL [95% CI, 1.45–1.81 µg/mL] vs 1.22 µg/mL [95% CI, 1.06–1.41 µg/mL]; $P=0.003$), and 23F (1.14 µg/mL [95% CI, 0.99–1.31 µg/mL] vs 0.63 µg/mL [95% CI, 0.52–0.77 µg/mL]; $P<0.001$).

Following the booster dose, the proportion of subjects with IgG GMCs ≥1.0 µg/mL was similarly high in both the 3+1 group and the 2+1 group, ranging from 89.0% (serotype 19F) to 98.6% (serotype 14) in the 3+1 group and from 88.4% (serotypes 6B and 18C) to 98.1% (serotype 14) in the 2+1 group. GMCs were significantly higher in the 3+1 group than in the 2+1 group for 3 serotypes: 6B (10.99 µg/mL [95% CI, 8.78–13.77 µg/mL] vs 6.93 µg/mL [95% CI, 5.36–8.95 µg/mL]; $P=0.009$), 18C (3.70 µg/mL [95% CI, 3.17–4.30 µg/mL] vs 2.80 µg/mL [95% CI, 2.45–3.20 µg/mL]; $P=0.008$), and 23F (5.64 µg/mL [95% CI, 4.72–6.72 µg/mL] vs 3.87 µg/mL [95% CI, 3.32–4.52 µg/mL]; $P=0.002$).

In contrast, 1 month following the first toddler dose in the 0+2 group, the proportion of subjects with IgG GMCs ≥1.0 µg/mL ranged from 25.3% (serotype 6B) to 78.6% (serotypes 4 and 9V). One month after the second toddler dose, IgG GMCs increased to levels that approximated those of the 3+1 and 2+1 groups 1 month after their booster dose.

Cumulative new NP acquisition of PCV7 serotypes was greater in the 2+1 group than in the 3+1 group during the first year of life ($P=0.015$); however, in the second year of life, new acquisition was greater in the 3+1 group than in the 2+1 group ($P=0.040$). Cumulative incidence of new NP acquisition of PCV7 serotypes was greater in the 0+2 group than in the other groups throughout the study period. Notably, cumulative new acquisition of serotypes 6B and 6A was greater in the 2+1 group than in the 3+1 group both in the first and second years; this difference was significant only in the first year (6B: $P=0.004$; 6A: $P=0.042$). Cumulative new acquisition of non-PCV7 serotypes and of all serotypes occurred at similar rates in all 3 treatment groups.

Commentary by Dr Dagan

Compared with the 3+1 schedule, the 2+1 schedule resulted in lower immunogenicity and higher rates of NP acquisition of VTs following the primary series in infants, demonstrating superiority of the 3+1 schedule for this age group. In contrast, in the second year of life, the 3+1 and 2+1 schedules showed similar levels of immunogenicity and NP acquisition, despite inferior antibody concentrations to serotypes 6B, 18C, and 23F, and a slightly higher level of new PCV7 serotype NP acquisition in the 3+1 group. The authors concluded that a 2+1 schedule with a high coverage rate and extensive catch-up is likely to be effective and provide extensive herd immunity.

Reference: Givon-Lavi N, Greenberg D, Dagan R. Effect of a reduced dose infant schedule of the 7-valent pneumococcal conjugate vaccine (PCV7) on nasopharyngeal pneumococcal carriage (NP-PNC-CARR). Poster presented at: 27th Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID); June 9-13, 2009; Brussels, Belgium. Poster #261.

Nasopharyngeal Microbiota During Upper Respiratory Infection: Comparison Between Children With and Without Acute Otitis Media

Authors

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In this study, NP specimens were obtained from children aged 6 to 35 months who presented with URTIs and parental suspicion of AOM. Of a total of 503 children, 317 were diagnosed with AOM, and 186 were diagnosed with URTIs, but no AOM at entry and follow-up.

Respiratory viruses were detected in NP samples at similar rates in the AOM and non-AOM groups. The most common respiratory virus was rhinovirus, followed by human bocavirus, respiratory syncytial virus, enterovirus, human metapneumovirus, influenza A/B virus, adenovirus, and parainfluenza 1-3 virus.

NP samples from children with AOM were significantly more likely than those from children without AOM to have ≥1 type of bacterial pathogen typically associated with AOM ($P<0.001$). In particular, the incidence of each bacterial pathogen was significantly greater in children with AOM than in those without AOM ($P<0.005$ for each). *M catarrhalis* was the most common pathogen, occurring in >70% of children with AOM, followed by *S pneumoniae* (>60%), *H influenzae* (>20%), and *S pyogenes* (<5%). In contrast, bacterial nonpathogens were found significantly less often in children with AOM than in those without AOM ($P<0.001$).

Commentary by Dr Dagan

As expected, NP carriage of respiratory viruses was common in children with URTIs, both with and without AOM. Similarly, NP carriage of bacterial pathogens associated with AOM was more common in children with URTIs and AOM than in those with URTIs but no AOM, most likely representing the dominance of pathogenic over nonpathogenic bacterial colonization during acute bacterial infection.

Reference: Ruohola A, Lindholm L, Vainionpää R, et al. Nasopharyngeal microbiota during upper respiratory infection: Comparison between children with and without acute otitis media. Poster presented at: 27th Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID); June 9-13, 2009; Brussels, Belgium. Poster #575.

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of increased vaccine coverage on the prevalence of nonvaccine serotypes, antibiotic resistance, and ecology of the NP bacterial flora need further monitoring.

The following studies, presented as posters at the 27th Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID) held in Brussels, Belgium, from June 9–13, 2009, provide updated information on the epidemiology of NP carriage of the pneumococcus and other bacterial flora, and the effects of PCV7 on NP pneumococcal carriage in children.

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