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Pneumococcal carriage in children and adults two years after introduction of the thirteen valent pneumococcal conjugate vaccine in England

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ABSTRACT

Background/Aims: In April 2010 the 7-valent pneumococcal conjugate vaccine (PCV7) was replaced by the 13-valent PCV. We investigated pneumococcal carriage in children eligible for PCV7 or PCV13 and their household contacts.
Methods: Eligible families in Hertfordshire and Gloucester were identified and a nasopharyngeal swab obtained from consenting household members between July 2012 and March 2013. Samples were cultured for *Streptococcus pneumoniae* and serotyped by standard methods. For each serotype the ratio of its prevalence in invasive pneumococcal disease (IPD) to its carriage prevalence (case:carrier ratio, CCR) was calculated. Results were compared with previous carriage studies in 2001/2002 and 2008/2009, before and after PCV7 introduction.
Results: 217 households were included. Among <5-year olds 47.7% (95% confidence interval 41.8–53.5) were carrying a pneumococcus compared with 51.0% (95% CI: 44.0–58.0) in 2008/2009 and 48.4% (95% CI: 44.1–52.7) in 2001/2002. The odds of carrying a PCV7 serotype was significantly reduced in 2008/2009 (0.07, 95% CI: 0.03–0.16) and 2012/2013 (0.01 95% CI: 0.00–0.07) relative to 2001/2002, while the odds of carrying any of the extra six PCV13 serotypes increased after PCV7 introduction (1.38, 95%CI: 0.73–2.59) but declined significantly after PCV13 introduction (0.05, 95%CI: 0.01–0.37). The CCRs for the frequently carried serotypes were relatively low, with the highest CCR observed for serotypes 7F, 19A, 3, 8, and 33F. Across the three carriage studies, CCR estimates were stable for nearly all serotypes.
Conclusion: Carriage of additional PCV13 serotypes has rapidly reduced post-PCV13 introduction in both vaccinated and unvaccinated individuals with a continued decline in transmission of PCV7 serotypes. Carriage rates in children remain unchanged, but the low CCRs of replacing serotypes would be expected to further reduce overall IPD across all age groups.

1. Introduction

Streptococcus pneumoniae is a Gram-positive diplococcus that colonises the human nasopharynx and is frequently carried (and transmitted) by children but less so among adults. While most carriers remain asymptomatic, the organism can sometimes spread locally to cause non-invasive mucosal infections such as sinusitis and otitis media or may invade the bloodstream to cause invasive pneumococcal disease (IPD), including septicaemia, meningitis and invasive pneumonia. The risk of developing IPD is dependent on both host susceptibility and invasiveness of the pneumococcus, which is largely determined by its polysaccharide capsule [1,2]. Pneumococci can be distinguished into >90 different serotypes based on specific antibody responses generated by their polysaccharide capsule.

In 2006, the UK introduced a conjugate vaccine against the seven most prevalent pneumococcal serotypes (PCV7) into the national childhood immunisation programme [3]. Unlike other countries, a reduced two-dose primary infant schedule (at two and four months of age) was recommended followed by a booster at 12/13 months. At the same time, a 12-month catch-up campaign offering PCV7 to all ≤2 years was initiated. The programme led to a rapid reduction

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in IPD caused by the PCV7 serotypes across all age groups [4]. The decline in PCV7-serotype IPD, however, was offset by an increase in IPD caused by non-PCV7 serotypes [4]. In April 2010 PCV7 was replaced in the infant immunisation schedule by a 13-valent pneumococcal conjugate vaccine (PCV13) that aimed to provide broader protection against IPD [5].

Conjugate vaccines not only protect against invasive disease but also reduce carriage among vaccinated individuals and, therefore, transmission to unvaccinated children and susceptible adults [6–9]. It is this indirect (herd) protection that makes conjugate vaccines so effective, both in terms of population health gain and economic worth [10].

The balance between herd protection and disease replacement by non-vaccine serotypes is critical in determining the effectiveness of national immunisation programmes. It is difficult to understand transmission and predict disease replacement by monitoring IPD alone and carriage studies alongside national IPD surveillance are essential to estimate carriage rates in vaccinated and unvaccinated age-groups and provide critical information on replacing serotypes [11]. Understanding the transmission dynamics of replacing serotypes both in carriage and disease can provide valuable insight into predicting the long-term impact of routine PCV13 immunisation. Replacement with pneumococcal serotypes that have a lower invasiveness potential (as measured by case:carrier ratios; CCRs) than the PCV13 serotypes should produce a net reduction in IPD, while emergence of highly invasive serotypes indicates the potential for replacement disease with non-vaccine serotypes. The invasiveness of different pneumococcal serotypes will therefore determine the extent to which serotype replacement in carriage will result in changes to IPD in the population [11,12].

The replacement of PCV7 with PCV13 has already resulted in a significant reduction in IPD across all age groups [13]. Its impact on serotype replacement in carriage, however, is not predictable. This study, therefore, aimed to investigate pneumococcal carriage in children eligible for PCV7 or PCV13 and their household contacts in order to estimate carriage rates and to identify serotypes replacing in carriage and their invasiveness two years after PCV13 introduction.

2. Methods

The methodology for the current nasopharyngeal carriage study was very similar to a previous cross-sectional carriage study we conducted in 2008/2009 [11]. For clarity we reiterate the methodology in the context of this study.

2.1. Study population

Children aged 1–5 years and their household members were recruited from general practices in Hertfordshire and Gloucestershire. Exclusion criteria were: immunosuppression; neurological disorders affecting swallowing; ear, nose and throat disorders affecting the anatomy of the ear; moderate to severe cerebral palsy or other debilitating condition; or immunosuppression. Swabbing was delayed for at least 4 weeks after completion of any antibiotic course for all participants. Participants with a respiratory tract infection at the time of swabbing were not excluded. The National Research Ethics Service approved the study protocol. Written informed consent was obtained from adult participants and from parents/guardians of children prior to enrolment. Information was collected on participants' age, gender, household size, number of smokers in household, hours in day-care and pneumococcal vaccination history.

To compare to pre-vaccination and post-PCV7 carriage in England we used the results from a longitudinal study performed in 2001/02 in families attending the same general practices in Hertfordshire where swabs were taken monthly over a ten-month period [14] and from a cross-sectional study undertaken in 2008/09 in Hertfordshire and Gloucestershire among children eligible for PCV7 and their household members [11]. At the time of the longitudinal study, serotype 6C could not be distinguished from 6A, but in 2009, 19 of the 122 serotype 6As from the earlier study were randomly re-tested and six were found to be 6C. We have assumed that this proportion (32%) holds for the rest of the 6A carriage isolates from the 2001/2002 study. In the 2008/2009 carriage study, some samples were typed as 11B and 11C [11]; these were re-typed and were all identified as serotype 11A. We worked with the updated serotype results.

2.2. Specimen testing

Nasopharyngeal swabs (calcium–alginate) were taken by trained nurses between July 2012 and March 2013 and placed directly in STGG broth. Samples collected at Hertfordshire were sent by same-day courier to the Respiratory & Vaccine Preventable Bacteria Reference Unit (RVPBRU) Microbiology Services at Public Health England, Colindale, stored overnight at 2–8 °C and frozen the next morning at −80 °C. Samples collected at Gloucestershire were stored locally at the Gloucester Vaccine Evaluation Unit at −80 °C and transferred to RVPBRU in batches on dry ice. On receipt, the batches were stored at −80 °C. The samples were cultured for *S. pneumoniae* at the end of the study as previously described [11,14] Any colonies resembling pneumococcus were subjected to normal identification methods and serotyped using standard laboratory protocol [15].

2.3. Statistical analysis

Descriptive data analysis was performed in R 3.0.2 [16] and Generalised Estimating Equations (GEE) models were analysed using STATA 12.1. Exact binomial 95% confidence intervals (CIs) were obtained for carriage rates in 2012/2013 and 2008/2009 by age-group (<5, 5–20, >20 years). To account for longitudinal design in the 2001/2002 study, we computed carriage rates using a GEE model with exchangeable correlation structure. When comparing overall and vaccine-specific carriage between periods, this comparison took account of the longitudinal design of the 2001/2002 study along with other covariates by using a GEE model with exchangeable correlation structure and factors for study period, age in years, gender, smoking status in the household, and the number of children and adults in the household. For this analysis, data were stratified into two age-groups (<5 and ≥5 years) to achieve better comparability with previously reported changes in carriage.

For calculating case:carrier ratios (CCR), the numbers of IPD cases caused by individual serotypes were extracted from the national surveillance database for England and Wales [17] for the epidemiological years 2001/2002, 2008/2009 and 2012/2013, and analysed alongside carriage data from studies conducted in the same years. Because of limited carriage data for ≥60-year olds, CCRs were calculated for <60-year olds using serotype-specific carriage prevalence as numerator. The 95%CI were calculated on the basis of the 95%CI of the serotype-specific prevalence assuming the national incidence data on IPD to be complete and not based on a population sample [17]. For the 2012/2013 season, only serotyped samples were available; therefore the overall number was inflated to adjust for non-serotyped IPD cases. Based on the serotyped/not-serotyped ratio in the 2011/12 season 20% of the samples were not available for serotyping.

Simpson's index for diversity was calculated to assess the change in diversity in the bacterial population corresponding to vaccination [18]. Ranked serotype distribution was compared to the

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