Published in final edited form as:

Lancet Infect Dis. 2014 March ; 14(3): 175–177. doi:10.1016/S1473-3099(13)70356-6.

Reduction in antibiotic use, an added yet sometimes underappreciated benefit of pneumococcal conjugate vaccines

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Acute respiratory illnesses, especially acute otitis media-AOM, are leading causes of antibiotic use in children. However, antibiotic use, either necessary or unnecessary, facilitates the emergence of resistance and is a known risk factor for carriage, and spread of antibiotic-resistant bacteria to close contacts.¹ Several initiatives promoting judicious use of antibiotics have been launched and implemented to reduce the spread of resistant bacteria.

Although active educational efforts on the consequences of antibiotic overuse and the need for more accurate diagnosis before antibiotic use (especially AOM) have been associated with overall reductions in antibiotic use, these reductions have been modest, and increases in use of broad spectrum antibiotics, especially macrolides, have been noted. In addition to maintaining and expanding these necessary educational activities, other interventions are needed to effectively reduce unnecessary antibiotic use. Arguably, the best strategy to prevent unnecessary prescription of antibiotics in general and broad spectrum antibiotics in particular is to prevent the conditions that could trigger the antibiotic prescription.

Pneumococcal conjugate vaccines have modified the epidemiology of pneumococcal diseases with sustained reductions in invasive and non-invasive pneumococcal diseases.^{2–4} Once described as potential “*antiresistance vaccines*”¹, pneumococcal conjugate vaccines have also reduced disease due to antibiotic-resistant bacteria;^{5–8} and, through disease prevention, reduced antibiotic use. Previous randomized and observational studies have shown that vaccination with pneumococcal conjugate vaccines can reduce antibiotic use.^{5,9–11} Nevertheless, the reductions in antibiotic prescriptions, reductions in antimicrobial-resistance and their consequences have not been routinely included in cost-effectiveness evaluations of pneumococcal conjugate vaccination programs.¹²

In this issue of the journal, Arto Palmu and colleagues describe the effectiveness of vaccination with a ten-valent pneumococcal *Haemophilus influenzae* protein D conjugate vaccine (PHID-CV10) in reducing outpatient antibiotic purchases. They conducted a well-designed large cluster randomized controlled trial in Finland. The trial included arms for

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Potential conflicts of interest

CGG has received research support from the Centers for Disease Control and Prevention, the Thrasher Research Fund and Pfizer. CGG has served as consultant for Pfizer and GSK

3+1 and 2+1 vaccination schedules (with their respective controls), and included young infants <7 months old for the primary vaccination series and older infants and toddlers for catch-up doses. All schedules included a booster dose.¹³ Follow-up and outcome ascertainment was achieved through review of antibiotic purchases recorded in a national registry. The study demonstrated that vaccination with PHID-CV10 reduced outpatient purchases of antibiotics recommended for management of AOM by 8% relative to control vaccines. The evaluation of purchases of any antibiotic as a secondary outcome yielded similar results. The estimated effectiveness was almost identical between the 3+1 and 2+1 schedules. The overall effectiveness of vaccination was higher in preventing recurrent antibiotic purchases, and also higher for preventing purchases of amoxicillin combined with an enzyme inhibitor. The effectiveness was lower and not statistically significant for the catch-up schedules. Although the 8% relative reduction may appear small, the absolute burden of antimicrobial use was substantial and the investigators estimated that during the 2-year follow-up, vaccination of 5 children prevented 1 antibiotic purchase.

Outcome data for the trial were ascertained from existing records of antibiotic purchases gathered systematically as part of an existing comprehensive and fully linked data system. This assured that the outcome data were complete and gathered without regard to intervention information. Nevertheless, the specific reason for antibiotic purchase was known only for ~52% of purchases. Although the vast majority of antibiotic purchases with known indication were for AOM, it is unclear if there were defined diagnostic and treatment criteria standardized across the study clusters. One may expect however, that this potential outcome misclassification would likely favor the null hypothesis making the presented results conservative estimates of the true vaccination effectiveness. Although this powerful research strategy has been used by the study investigators and other groups in the past, the strategy has only recently generated substantial interest as an attractive model and innovative alternative to the follow-up of traditional randomized controlled trials.¹⁴

Findings from this important trial provide new evidence on the effectiveness of PHID-CV10 in reducing antibiotic use, and demonstrate the effectiveness of the 2+1 schedule in reducing antibiotic purchases. These findings add substantially to the growing body of evidence supporting the benefits of the shortened 2+1 schedule.¹³ This vaccination schedule is currently used in several countries with reported effectiveness in preventing disease outcomes very similar to those from countries using 3+1 schedules. The cost-effectiveness of switching from a 3+1 to a 2+1 vaccination schedule is undergoing detailed evaluation.¹⁵

Despite the encouraging findings of the trial, vaccination with pneumococcal conjugate vaccines is only a first step in reducing antibiotic resistance. As antibiotic use may even facilitate the emergence of resistant-bacteria not covered by the conjugate vaccines,^{1,5,16,17} additional and sustained efforts are needed to continue reducing unnecessary use of antibiotics. Effective campaigns that promote the judicious use of antibiotics, including antibiotic stewardship programs, are needed to support the added yet sometimes underappreciated benefit of pneumococcal conjugate vaccines in reducing antibiotic use.

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