Otitis media and its consequences: beyond the earache

An international group of multidisciplinary experts on middle-ear and paediatric infections met to explore where consensus exists on the management of acute otitis media. After informal discussions among several specialists of paediatric infectious disease, the group was expanded to include a larger spectrum of professionals with complementary expertise in middle-ear disease. Acute otitis media is a very common bacterial infection in children worldwide, leading to excessive antibiotic consumption in children in most countries and to a substantial burden of deafness and supplicative complications in developing countries. The group attempted to move beyond the existing controversies surrounding guidelines on acute otitis media, and to propose to clinicians and public health officials their views on the actions needed to be taken to reduce the disease burden caused by acute otitis media and the microbial antibiotic resistance from the resulting use of antibiotics. Definition of acute otitis media and diagnostic accuracy are crucial steps to identify children who will potentially benefit from treatment with antibiotics and to eliminate unnecessary prescribing. Although the group agreed that antibiotics are distributed indiscriminately, even to children who do not seem to have the disease, no consensus could be reached on whether antibiotics should be given to all appropriately diagnosed children, reflecting the wide range of practices and lack of convincing evidence from observational studies. The major unanimous concern was an urgent need to reduce unnecessary prescribing of antibiotics to prevent further increases in antibiotic resistance. Prevention of acute otitis media with existing and future viral and bacterial vaccines seems the most promising approach to affect disease burden and consequences, both in developed and developing countries.

Introduction

Crucial topics regarding acute otitis media, such as disease definition and diagnosis, indications for the prescription of antibiotics, acceptance of treatment guidelines, and effectiveness of preventive interventions remain unresolved. Scientific societies, specialists in otitis media, and evidence-based medicine experts have proposed many recommendations for the management of the disease. However, no real consensus practices exist and there is evidence that worldwide most physicians systematically prescribe antimicrobial drugs for the treatment of children with otitis media.1 In March, 2008, international experts on infectious diseases in children participated in a masterclass on bacterial infections of the respiratory tract. After the debates held during that meeting over the numerous unresolved issues on acute otitis media, we proposed to broaden and rationalise the discussion with an extended group including specialists in epidemiology, otorhinolaryngology, diagnosis and management of acute otitis media, microbiology, pharmacoeconomics, prevention, and global health. Three more formal meetings took place between September, 2008, and January, 2009. The meetings were funded by an unrestricted educational grant from GlaxoSmithKline through LMS-Group, a medical education company. In this paper, our international multidisciplinary group focus on the consensus that was reached for the practical management of acute otitis media in the context of increasing antimicrobial resistance among bacterial pathogens and the perspective of evolving interventions for reducing the burden of disease. Our intention is that this analysis will help decision making by clinicians and raise the awareness of public health authorities to the need to develop approaches for reducing direct and indirect consequences of acute otitis media.

A common infection in children worldwide

More than 80% of children will have developed acute otitis media at least once before 3 years of age,2,3 and 40% will have six or more recurrences by the age of 7 years.4 This frequent illness among children represents the most common cause of physician visits for sick children and the major reason for the prescription of antibiotics for children in developed countries,5 where infants and toddlers spend a mean of 42 days on antibiotics in the first year of life and 49 days on antibiotics in the second year of life.6 Over the past decade, efforts have been made in several countries to reduce the use of antibiotics,7 but the effect on the proportion of acute otitis media treated with antibiotics has been limited.7 In a recent US study,8 analysing data from 1995 to 2005, a stable proportion of 80% of cases were initially treated with antimicrobial drugs; however, an overall decrease in antibiotic prescribing was seen paralleling the reduction in diagnoses—from 760 to 484 prescriptions per 1000 children (relative risk 0.64; 95% CI 0.54–0.75).

As with many infectious diseases, the nature of the burden of otitis media differs greatly between developed and developing countries. The main differences seem to be the frequency of complications and sequelae such as hearing loss due to chronic supplicative otitis media (defined by WHO as 2 weeks of persistent ear discharge), rather than the incidence of acute otitis media.9,10 WHO estimates that 51000 deaths every year in children younger than 5 years are attributable to complications of acute otitis media, primarily intracranial infection, and...

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that chronic suppurative otitis is a major cause of hearing loss in many developing countries. WHO’s estimates suggest that worldwide 65 million to 330 million individuals develop chronic suppurative otitis media, 60% of whom will suffer from hearing impairment. Geographical distribution of auditory sequelae is uneven, with 85% in western Pacific and eastern Asian regions and to a lesser extent in Africa. In addition to the socioeconomic conditions (overcrowding, reduced sanitation, limited access to diagnosis and treatment) that might account for a major part of the difference, some genetic or possibly cultural factors are likely to contribute to the unusually high rates of early onset acute otitis media and chronic suppurative otitis media in Indigenous Australian, Native American, or Native Alaskan children.

**Guidelines to reduce antibiotic use in children**

The pathogenesis of acute otitis media in developed countries has changed over the past 50 years to a largely self-limited condition, with 80% of cases resolving spontaneously. A decline noted in supplicative complications in developed countries, together with increased awareness of the link between the prescription of antimicrobial drugs and the resistance of bacteria to antibiotics, has led to a reassessment of the role of treatment with antimicrobial drugs in children with acute otitis media. This recognition resulted, in part, in the development and publication of guidelines for acute otitis media, endorsed by scientific societies in many countries. However, several studies have shown that the adherence of physicians to these guidelines is poor and is likely to reflect of our groups’ inability to reach consensus on whom to treat with antimicrobial drugs.

Guidelines for acute otitis media uniformly stress that adequate management starts with appropriate diagnosis, but changes in practice will be hard to achieve without new focus on diagnostic skills or new technology. Most guidelines emphasise the need for optimum treatment with analgesic drugs (mainly paracetamol and ibuprofen), but present this as an adjunct for pain control and not as an alternative to antibiotics for disease management. Guidelines also recommend using an approach of “watchful waiting” or “observation” as an alternative to treatment with antibiotics in selected children older than 6 months of age with acute otitis media.

Often these guidelines recommend treating severely ill or certain clinical scenarios in children 6–24 months old, but are permissive for initial observation in older children, or those less severely ill. Although such guidelines are described as evidence based, the inevitably vague formulation of criteria to avoid over-precision and over-literature means that they have to rely largely on clinical experience and subjective clinical acumen to establish which child is severely ill. Some clinical severity scores have been developed to help in the decision making, however, they might not be practical outside research settings. Evidence from randomised clinical trials of initial observation in children with acute otitis media is in general subject to different interpretations of whether the differences in outcome between children initially treated with antibiotics or managed with watchful waiting are substantial.

The ability to generalise these findings is often limited because they include few or no children younger than 2 years of age, exclude children that seem ill, lacked standardised or stringent criteria for the diagnosis of acute otitis media or for defining improvement or cure, have inadequate timing of follow-up, use an antimicrobial drug or dose with less than optimum efficacy against common middle-ear pathogens, and have limited sample size and statistical power. Identification of children who will benefit most from treatment with antibiotics seems to be a challenging task for clinicians and epidemiologists. Some factors such as bilateral otitis media in children younger than 2 years of age and otorrhoea presumably increase the likelihood of bacterial otitis media and the benefit of treatment with antimicrobial drugs, but a substantial proportion of acute otitis media in the children with these clinical presentations will resolve without antimicrobial drugs.

By contrast with our consensus on other issues, our group expressed a spectrum of opinions about the use of antibiotics as part of initial management, even in children meeting the guideline definition of acute otitis media. Prompt analgesia and supportive care was unanimously recommended for all children, but indications for antibiotic treatment ranged from very limited to large. This lack of consensus reflects the change in the prescription of antibiotics for acute otitis media in various countries. Dutch physicians, who traditionally had a low rate of prescribing antibiotics for acute otitis media, have increased their prescription rates from about 30% in the 1980s to over 50% for the most recent period (1998–2002), while physicians in the UK have succeeded in reducing their antibiotic prescription rates from about 50% in 1998–2002 to 30% for the most recent period (1998–2002), while physicians in the UK have succeeded in reducing their antibiotic prescription rates from about 50% in 1998–2002 to 38%.

Summary

Suppurative complications have not emerged as a substantial proportion of acute otitis media in the children with these clinical presentations will resolve without antimicrobial drugs. By contrast with our consensus on other issues, our group expressed a spectrum of opinions about the use of antibiotics as part of initial management, even in children meeting the guideline definition of acute otitis media. Prompt analgesia and supportive care was unanimously recommended for all children, but indications for antibiotic treatment ranged from very limited to large. This lack of consensus reflects the change in the prescription of antibiotics for acute otitis media in various countries. Dutch physicians, who traditionally had a low rate of prescribing antibiotics for acute otitis media, have increased their prescription rates from about 30% in the 1980s to over 50% for the most recent period (1998–2002), while physicians in the UK have succeeded in reducing their antibiotic prescription rates from about 50% in 1998–2002 to 38%.

**Accuracy of diagnosis is a major issue**

Clinical diagnosis of acute otitis media is difficult because signs and symptoms might overlap with symptoms of other respiratory infections. Moreover, diagnosis relies on visualisation (otoscopy) and functional testing of the eardrum (pneumatic otoscopy, tympanometry, acoustic reflectometry), which is done inconsistently. Diagnosis needs training, good instruments, removal of cerumen from the external auditory canal (often a difficult task), and cooperation from medical staff, children, and parents. Lack of
accuracy in the diagnosis of acute otitis media is illustrated by the discrepancies in diagnosis between ear, nose, and throat specialists and paediatricians,22,23 by the widely varying incidence rates reported among European countries,28,45 and by the rate of culture-negative disease found by use of tympanocentesis in clinical trials.19 In the era of the internet, useful free training exists that could be used by paediatricians and general practitioners to expand their knowledge and skills in the diagnosis of acute otitis media. The group agrees that imprecision in discriminating acute otitis media from otitis media with effusion or uncomplicated inflammation of the tympanic membrane is a major hurdle in reaching consensus about appropriate management of acute otitis media. This poor specificity will continue to result in unnecessary use of antimicrobial drugs to treat what is presumed to be acute otitis media.

**When detrimental effects outweigh the benefits**

Many clinicians might not have a clear understanding of the benefits and disadvantages of treating a particular child with antibiotics. The use of antibiotics in acute otitis media is supported by biological plausibility because most cases of acute otitis media are caused by bacteria and large studies showing that failure to eradicate the bacteria early increases clinical failure rate in acute otitis media in children younger than 2 years of age.43 Moreover, widespread use of antibiotics in developed countries coincides with a reduction of complications caused by acute otitis media, specifically disease due to group A streptococci. However, in the USA and western Europe, where acute otitis media has become mostly a self-limited disease, antibiotic benefits are now confined to the acute phase of otitis media. Pain and fever subside more rapidly with antibiotics, but in a meta-analysis of ten studies where very young infants and children at high risk for complications were excluded pain resolved within 2–7 days with or without antimicrobial drugs. Antibiotics hastened pain resolution at 2–7 days in 6% (95% CI 0·05–0·07) more children that received antibiotics than in the untreated group (number needed to treat was 16 (95% CI 0·15–0·19)).22 However, no data exist regarding symptomatic treatment alone of children thought at higher risk for complications. Moreover, optimum pain management with non-steroidal anti-inflammatory drugs rather than antibiotics has never been assessed, especially in young children.

Treatment with antimicrobial drugs for acute otitis media has not been shown to speed up resolution of middle-ear fluid. The effect of antimicrobial therapy on complications of acute otitis media in developed countries is difficult to determine, because mastoiditis, meningitis, and other supplicative complications have become exceedingly rare.21,22 Two recent population-based studies in the UK28,45 noted that antibiotic treatment of acute otitis media was associated with a reduced risk of mastoiditis in children. However, the number of children needed to be treated to prevent one case of mastoiditis exceeded 4000,28,45 and when balanced against detrimental effects of increasing antibiotic resistance and considering the benign course of treated mastoiditis in developed countries, there is inadequate evidence to justify routine use of antibiotics to prevent supplicative complications caused by acute otitis media.20,28

Antibiotic consumption has deleterious effects on individuals as well as society. Antibiotics, although usually well tolerated, have classic adverse effects such as rash and hypersensitivity. A recent study suggested that more than 142 000 department visits per year in the USA were attributable to systemic antibiotic adverse events, mainly allergic reactions representing an incidence of 10·5 emergency department visits per 10 000 outpatient prescription visits (note that the rate of visits to an emergency department for high-risk drugs such as warfarin is only two-fold greater).46

Importantly, antibiotics directly disturb the commensal microbial flora causing diarrhoea and an increasing the risk of colonisation by drug-resistant *Staphylococcus aureus* or drug-resistant *Streptococcus pneumoniae*.51–54 From a worldwide perspective, antibiotic consumption is linked to increased antibiotic resistance.
for many clinically relevant pathogens, which results in higher rates of treatment failures and increased costs. Treatment failures for acute otitis media due to multidrug-resistant \textit{S pneumoniae} have been described.\textsuperscript{55} Isolates of \(\beta\)-lactamase-negative ampicillin-resistant (highly resistant to cephalosporins and co-amoxiclav) non-typable \textit{Haemophilus influenzae} are increasingly reported in microbiological studies from some European countries (France, Spain)\textsuperscript{56,57} and specifically from children with acute otitis media in Japan.\textsuperscript{58}

Clinically important antibiotic resistance results in a vicious spiral (figure) where broader antibiotic use selects for more resistant pathogens resulting in additional treatment failures. So far, high-level penicillin resistance (minimum inhibitory concentration of 2 mg/L or greater) among isolates of \textit{S pneumoniae} has been reduced in countries that have implemented routine immunisation of infants with pneumococcal conjugate vaccine, by reducing carriage (and disease) due to historically resistant serotypes 6B, 9V, 14, 19F, and 23F.\textsuperscript{59,60} However, increase in intermediate resistance among both vaccine serotypes and non-vaccine serotypes and emergence of multidrug-resistant serotypes such as 19A have been noted and probably result from continuous selective pressure due to the use of antibiotics. Evidence of whether more prudent use of antibiotics can reduce resistance is incomplete; however, it is clear that in the presence of high prescribing benefits; however, the use of xylitol might be challenging and new antimicrobial drugs effective against resistant respiratory pathogens are not on the horizon.\textsuperscript{59}

\textbf{Prevention is better than cure, but is not easy}

Factors that increase colonisation with otopathogens, as well as viral respiratory infection, contribute to the development of acute otitis media.\textsuperscript{61} Exposure to smoke, attendance of day-care centres, and viral infection of the respiratory tract all increase the frequency or burden of colonisation, whereas breast feeding reduces the likelihood of colonisation. Importantly, the integrity of the nasopharyngeal microbiome (where bacteria such as \(\alpha\)-haemolytic streptococci, \textit{Peptostreptococcus} spp, and \textit{Prevotella} spp predominate) is protective against colonisation by otopathogens in healthy children as opposed to children prone to otitis (panel).\textsuperscript{62} Additional factors that correlate with increased risk of acute otitis media include young age (probably reflecting a naive and immature immune system and impaired function of the eustachian tube), family history (genetic predisposition)\textsuperscript{63} of recurrent otitis media, and the use of a pacifier.\textsuperscript{64} Intervention studies evaluating changes in attendance at day-care centres have not been reported, although decrease in continuous use of pacifiers was associated with a reduction of acute otitis media in one randomised controlled trial.\textsuperscript{65} One randomised controlled trial reported a protective effect of a nasally sprayed solution of \(\alpha\)-haemolytic streptococci on recurrences of acute otitis media in children prone to otitis.\textsuperscript{66} Additionally, increased hand washing, disinfection in day-care centres,\textsuperscript{67} and use of xylitol syrup or chewing gum\textsuperscript{68,69} might result in small benefits; however, the use of xylitol might be challenging if multiple doses every day are needed for it to be effective in young children.\textsuperscript{69}

\textbf{Can vaccines contribute to solving the problem?}

Vaccination has proven highly efficacious as a strategy to prevent many infectious diseases in circumstances where other preventive measures had no or limited effect, such as for hepatitis A and B\textsuperscript{70,71} and rotavirus infections.\textsuperscript{72} However, acute otitis media poses a challenge to prevention by vaccination because it is caused by many pathogens, is primarily a disease of the respiratory tract mucosa, and is most frequent in infants with immature host defences. Further understanding of the pathogenesis of acute otitis media has clarified the role of coinfection with viral and bacterial pathogens providing a rationale for vaccines that target both. \textit{S pneumoniae} and \textit{H influenzae} are the main otopathogens, responsible for nearly 80\% of bacterial otitis media worldwide. \textit{Moraxella catarrhalis} is usually the third most common.\textsuperscript{73} \textit{Streptococcus pyogenes}, less frequent and found in older age groups, can be associated with severe disease and complications.\textsuperscript{74}

Two meta-analyses\textsuperscript{75,76} and a large randomised placebo-controlled trial\textsuperscript{77} have evaluated the efficacy of influenza vaccine for prevention of acute otitis media and suggest that targeting single viruses might be insufficient to affect the disease burden. By contrast, clinical trials with seven-valent and nine-valent pneumococcal conjugate vaccines have shown substantial serotype specific efficacy against culture-proven pneumococcal acute otitis media.\textsuperscript{78–80} Although the efficacy on overall clinical cases
has been very modest (6% [95% CI –4 to 16] to 7% [95% CI 4 to 10] decrease).77,79 greater reductions in recurrent episodes and tympanostomy tube placement were noted.77,79 Furthermore, these studies support the potential reduction in pneumococcal resistance and the use of antimicrobial drugs, for acute otitis media in particular, but also in general as a result of vaccination.77,78

As population-wide immunisation decreases carriage of vaccine serotypes, greater affect against acute otitis media and its consequences has been reported from observational postlicensure studies presumably as a result of herd protection (ie, indirect effect).84–86 A substantial decrease of up to 42% in ambulatory visits for all visits relating to otitis media and antibiotic prescriptions for acute otitis media has been noted in one study analysing data from a large population of privately insured children in the USA.86 However, results are potentially confounded by study design (before and after the introduction of the seven-valent pneumococcal conjugate vaccine), changing diagnostic criteria, and therapeutic approaches.

Recently, de Wals and colleagues87 reported on the decline in the number of cases of acute otitis media in Quebec before (2000–04) and after introduction of the seven-valent pneumococcal conjugate vaccine. The investigators found a declining linear trend starting before introduction of the vaccine, presumably reflecting secular changes in diagnostic criteria or viral respiratory tract infection in the community. The noted reduction in claims for otitis media in children younger than 5 years was 25–2%, 13–2% of which was attributed to the vaccine by use of a time-series model. These studies suggest that vaccines effective against bacterial otopathogens have the potential to reduce cases of acute otitis media and antimicrobial usage and warrant further research to define their affect on disease morbidity. However, once recurrent otitis media has been established it has an unhealthy role of pneumococcal serotypes included in the vaccine was shown, and no reduction in cases of otitis media was shown after vaccination.88,89 These studies in children with established recurrent otitis media suggest that efficacy of pneumococcal conjugate vaccines is dependent upon immunisation in early infancy, ideally before developing acute otitis media for the first time.

Preliminary studies in high-risk indigenous populations are ongoing to establish the effect on disease burden and complications such as chronic supplicative otitis media. The success of the first-generation pneumococcal conjugate vaccine encourages the development of second-generation vaccines that extend serotype-specific protection and target additional bacterial otopathogens. So far, replacement of *S pneumoniae* by other pathogens that cause acute otitis media has not been an important issue in children that have been vaccinated,88–95 but disease due to non-vaccine serotypes of *S pneumoniae* seems to have increased, requiring careful monitoring of the microbial causes of acute otitis media. Ultimately, new viral vaccines might also contribute to prevention of the disease.

**Will second-generation vaccines help?**

Two second-generation pneumococcal conjugated vaccines are in development. One is a 13-valent vaccine including six additional serotypes among which serotypes 3 and 6A are found relatively commonly in acute otitis media,89,94 and type 19A, a commonly multidrug-resistant serotype, which has been reported as an otopathogen.95–97 The other conjugated vaccine is a pneumococcal ten-valent vaccine in which eight of the ten serotypes are conjugated to protein D from *H influenzae*; it has just been licensed in European Union, Australia, Canada, and Chile. Efficacy data for acute otitis media from a study using a prototype of the ten-valent vaccine (an 11-valent formulation with slightly different composition) done in the Czech Republic and Slovakia show serotype-specific pneumococcal efficacy similar to the seven-valent vaccine.14 However, a 35% (95% CI 2–57) reduction (63 of 2452 cases of acute otitis media in the control group vs 41 of 2455 in the pneumococcal vaccine group) in disease due to non-typable *H influenzae* was noted in the per-protocol analysis and overall cases of acute otitis media were reduced by 34% (95% CI 21–44): 499 of 2452 cases of acute otitis media in the control group versus 333 of 2455 in the pneumococcal vaccine group. Protective effect on non-typable *H influenzae* barely reached statistical significance possibly because of the relatively small number of non-typable *H influenzae* cases of otitis media. Recurrent otitis media and the placement of tympanostomy tubes were reduced, although for these endpoints results did not reach statistical significance.96 Therefore, both the ten-valent and 13-valent vaccines have the potential to expand protection against otopathogens that cause acute otitis media in healthy children. The potential of a reduction of about one-third in overall cases of acute otitis media, although less than traditional vaccine effectiveness against other diseases, such as invasive pneumococcal or meningococcal disease, nevertheless would be a highly valuable strategy to reduce the incidence of otitis media and its resultant burden. Data from the USA96 suggest the medical and non-medical costs associated with these cases and their sequela are about US$3·5 billion dollars ($1·6 billion medical [direct] costs with $1·9 billion in non-medical costs, primarily parental work-loss). Lost time from work is especially important because it might cause a disproportionate burden for those with lower income, who are more likely to be hourly wage earners with inflexible work schedules.

**Developing countries need prevention**

Most of the burden of acute otitis media in terms of supplicative complications, deaths, and deafness lies in...
developing countries where antibiotic resistance is also becoming a public health issue.104 It is difficult to promote recommendations to limit antibiotic treatment for acute otitis media in these countries where access to medical care and diagnosis is much more limited than in developed countries and supplicative complications likely to result from lack of care are prevalent. In these circumstances, prevention should be a high priority. It has already been shown that improvement in sanitation and access to care has an important effect on chronic supplicative otitis media in Thailand102 and that basic hand-washing has a substantial effect in reducing upper respiratory tract infections in developing countries.103 Pneumococcal conjugate vaccines have the potential to affect acute otitis media in these populations where colonisation with otopathogens happens at a much earlier age and in much higher proportions than in developed countries.104 Studies of pneumococcal conjugate vaccines in developing countries have shown efficacy against invasive pneumococcal disease and radiographically proven pneumonia,105–108 and reduction of serotype specific carriage and pneumococcal resistance.109 Early studies to establish the potential to prevent chronic supplicative otitis media in populations at high risk are ongoing and those published so far seem underpowered to definitively answer the question.109

### Responsible stewardship facing new challenges

In developed countries, treatment with antimicrobial drugs—although not proven to reduce overall burden of acute otitis media in children—increases antimicrobial resistance at a rate that outpaces the development of new drugs. We can no longer remain silent observers of these events. By contrast, prevention of acute otitis media with vaccines and other preventive measures reduces the burden of both overall disease and that caused by some antibiotic-resistant pathogens in children. Additionally, this prevention benefits the community by decreasing antimicrobial use and the resulting selective pressure on bacteria. Accordingly, prevention of acute otitis media and responsible prescribing of antimicrobial drugs represent crucially important and synergistic worldwide public health strategies to combat bacterial resistance to antimicrobial drugs.

### Contributors

All authors contributed to the evaluations and discussions from which this paper arose. The paper was written primarily by AV and SP, with all authors contributing to discussions regarding the paper and reviewing several drafts, including the final version. Richard B Weisskopf from LMS-Group (Paris, France) supported AV and SP in the writing and contributed to editing of the first submitted version.

### Conflicts of interest

AV has been a speaker for GlaxoSmithKline (GSK), Wyeth, and Sanofi, and has been a consultant for GSK and Wyeth. AA has received honoraria from GSK and Wyeth for research grants, advisory boards, and conferences. RC has served as consultant to or has received research grants from GSK, Sanofi-Aventis, and Wyeth. RD has received research support from Berna/Cruecell, Wyeth, and Sanofi Pasteur MSD (MSD); has been a scientific consultant for Berna/Cruecell, GSK, Novartis, Wyeth, Protea, and MSD; has received speaker fees from Berna/Cruecell, GSK, and Wyeth; and owns stock of Protea. JL has been a speaker for GSK, Wyeth, MSD; has received research support from GSK, Novartis, and Sanofi Pasteur MSD; and scientific consultancy fees from GSK and Abbott. PM has received an honorarium for serving on an advisory board for vaccines for GSK. AAP has done research projects for which his employer has received funding from GSK and Solvay, has received honoraria from GSK to attend expert group meetings, and a travel grant from Sanofi-Pasteur. GTR has received research support from Wyeth. LS has received unrestricted grants from Wyeth and Baxter for research, consulting fees from Wyeth and GSK, lecturing fees from Wyeth, and grant support from Wyeth and GSK for vaccine studies. MU has received travel grants and acted as a consultant for GSK and MSD. SIP has received investigator-initiated grants from Wyeth and GSK, has served on advisory boards for pneumococcal vaccines for GSK and Wyeth, and has received honoraria for time and efforts as consultant to Wyeth, Novartis, GSK, and Sanofi Pasteur. JB, IDH, AH, EAFS, and JvE declare that they have no conflicts of interest. GSK is the manufacturer of the ten-valent pneumococcal vaccine referred to in this paper.

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