Abstract and Introduction

Abstract

Acute otitis media (AOM) is common in infants and children. Although approximately two-thirds of cases are due to bacteria, almost all of the episodes are preceded by upper respiratory viral infection. Several viruses, among which respiratory syncytial virus is the most common, are involved in the determination of AOM. However, a significant number of AOM cases are associated with influenza infection, and influenza viruses are among the most frequently found respiratory viruses in the middle ear fluid during an acute episode of AOM. Consequently, influenza vaccination may have a favorable impact on the incidence and course of AOM. Moreover, as *Streptococcus pneumoniae* is one of the leading AOM bacterial pathogens and it is well known that influenza virus infection predisposes to pneumococcal infection, there is a further reason to suggest the use of influenza vaccine to reduce the risk of AOM. On the other hand, the administration of pneumococcal conjugate vaccine is considered per se a possible means of reducing the incidence of the disease. However, although a number of studies have measured the impact of both vaccines on AOM, it is still not known whether (and to what extent) they are really effective, nor what impact the more recently licensed vaccines may have. The aim of this review is to examine the clinical impact of vaccinations on AOM.

Introduction

Acute otitis media (AOM) is common in infants and children: a number of studies have shown that almost all children experience at least one episode of the disease in the first years of life, and that up to 50% suffer from recurrent episodes.\(^1\) In most cases, AOM spontaneously disappears or evolves favorably when treated with antibiotics, but it can occasionally give rise to troublesome problems, such as tympanic membrane perforation, or serious complications, such as mastoiditis, meningitis or brain abscesses.\(^3\) Because of its very high absolute frequency and risk of complications, AOM has substantial medical, social and economic consequences.\(^4\) Moreover, as most cases are treated with antibiotics, AOM is considered one of the most important causes of the emergence of microbial resistance. For all of these reasons, the prevention of AOM is widely advocated.\(^2\)

Together with other preventive measures, the use of vaccines could lead to a significant reduction in the incidence of the disease.\(^2\) This assumption is based on an evaluation of the etiology of AOM, which includes some infectious agents for which effective and safe vaccines are available. Although approximately two-thirds of the cases of AOM are caused by bacteria, almost all of the episodes are preceded by an upper respiratory viral infection that plays a fundamental role in the pathogenesis of the disease.\(^8\) Moreover, respiratory viruses can be cultured from the middle ear fluid of up to 30% of children with AOM.\(^9\) Although several respiratory viruses, including respiratory syncytial virus, are more frequently associated with AOM, a relevant number of influenza cases every year are complicated by the development of this disease.\(^9,11\) and in most of them, influenza viruses are identified in the middle ear fluid.\(^12\) It has therefore been suggested that the vaccine prevention of influenza may have a favorable effect on the incidence and course of AOM, and various experts have supported its use as a means of reducing the risk of AOM, particularly in otitis-prone children.\(^13,14\) Moreover, as *Streptococcus pneumoniae* is one of the leading AOM bacterial pathogens,\(^15\) and it has been repeatedly demonstrated that the influenza virus alters the respiratory mucosa in a way that predisposes to adherence, invasion and induction of disease by pneumococcus,\(^18\) this has been considered a further reason for the administration of influenza vaccine to prevent AOM. Finally, independently from a previous influenza infection, because the administration of pneumococcal conjugate vaccine (PCV) is capable of inducing a
significant immune response even in younger children (i.e., those with the highest incidence of AOM), it has been supposed that its use could be *per se* a possible means of reducing the incidence of AOM and its related problems.\cite{19} However, although a number of studies have measured the impact of both vaccines on AOM, it is still not known whether (and to what extent) they are really effective, nor what impact the more recently licensed vaccines may have. The aim of this review is to examine the clinical impact of vaccinations on AOM.

**Influenza Vaccines**

### Problems in Evaluating Studies of the Impact of Influenza Vaccines on AOM

Attempts to reduce the incidence of AOM using influenza vaccines go back approximately 20 years, when only the traditional injectable trivalent influenza vaccine (TIV) was available. Despite its only relative immunogenicity in younger patients, TIV was found to have a positive effect on AOM by Heikkinen *et al.*\cite{20} and Clements *et al.*\cite{21} The former found that TIV had 83% efficacy against influenza-associated AOM and 36% efficacy against all-cause AOM in subjects aged 7–50 months\cite{20} and the latter found a 30% reduction in all-cause AOM in subjects aged 6–30 months.\cite{21} However, despite these and other favorable findings, a randomized, double-blind, placebo-controlled study of a very large sample of children failed to demonstrate any significant effect: TIV did not reduce the proportion of children experiencing at least one episode of AOM during the winter season or any other AOM-related problem, such as the estimated proportion of time with otitis media with effusion or the use of selected healthcare and related resources.\cite{22} Although a re-evaluation of the data collected with this study found in the first year of the trial that with the highest incidence of influenza, the effectiveness of the vaccine against influenza-associated AOM was good and higher than 60%,\cite{23} many experts remained doubtful of the real efficacy of influenza vaccine in AOM prevention. It was pointed out that some of the positive studies were affected by methodological limitations, such as a small sample size, the absence of randomization, single or incomplete blinding, dependence on parental reporting rather than active surveillance and the lack of standardized criteria for diagnosing AOM.\cite{22}

Since then, other studies have used TIV and live-attenuated influenza vaccine (LAIV), but an exact evaluation of the role of influenza vaccination in preventing AOM was hampered by other factors, including: the enrollment of children at different degrees of risk for AOM, the use of the reduction in all-cause AOM instead in influenza-associated AOM as reference for efficacy testing the administration of vaccines with various degrees of immunogenicity against influenza viruses. It is well known that children attending daycare centers or who are clearly prone to otitis are at higher risk of developing AOM,\cite{24,25} and their enrollment can lead to results that are quite different from those found in studies of children without these characteristics. Furthermore, evaluation of reduction of all-cause AOM can underestimate efficacy because it cannot be expected that influenza vaccines are effective against AOM induced by other viruses. On the other hand, most of the studies that have considered influenza-associated AOM have shown a clear benefit of vaccination. Finally, adjuvanted TIVs and LAIVs are more immunogenic\cite{26,27} and more effective,\cite{28} respectively, than conventional TIV, and so the data collected in studies using the more effective vaccines cannot be pooled with those in which conventional TIV is administered.

All of these factors may explain why the impact of influenza vaccines on AOM is still not clear, and why three recently published systematic reviews have come to quite different conclusions.\cite{29–31} Jefferson *et al.* did not find that administering influenza vaccine led to any advantage in terms of AOM,\cite{29} whereas Manzoli *et al.* found a significant reduction in the number of cases of AOM in vaccinated children, with an overall efficacy of 51%.\cite{31}

### Subjects & Vaccines That Can have the Best Preventive Effect

Despite these limitations, a detailed analysis of all of the studies into the impact of influenza vaccines on AOM allows some provisional conclusions to be drawn concerning what can be expected: a favorable response is more likely in children aged more than 24 months, those with recurrent AOM without complications and those administered a LAIV.

The importance of age has been highlighted by various studies, including the previously cited study by...
Hoberman et al., which found that TIV was ineffective.[22] These authors evaluated the vaccine in a group of children aged 6–24 months (mean age 14 months) and noted that, although there was no difference in the number of AOM episodes between the vaccine and placebo group, the proportion of children aged 19–24 months who experienced at least one episode of AOM during the subsequent influenza and winter seasons was lower in the vaccine group.[22] Furthermore, most of the studies finding that TIV had a positive effect involved groups of children whose mean age ranged from 20 to 43 months,[20,21–32] significantly higher than that of the patients in the study by Hoberman et al.[22] A trend towards the greater efficacy of vaccination in children aged ≥24 months was also found by Block et al., who analyzed pooled data regarding the AOM-preventing effect of LAIV.[33]

Otitis-prone children seem to benefit from the administration of influenza vaccines, particularly when the individual episodes of AOM are not complicated by perforation of the tympanic membrane. We randomized 133 children with recurrent AOM aged 1–5 years to receive an intranasal, inactivated, virosomal-adjuvanted subunit vaccine or no vaccination and found that only 35.8% of the treated children experienced new episodes of AOM during the 6-month follow-up period compared with 63.6% of controls, representing an overall vaccination efficacy of 43.7%.[34] The efficacy of influenza vaccination in preventing AOM in otitis-prone children was confirmed by another of our studies in which the injectable virosomal-adjuvanted TIV was used; in this case, overall vaccine efficacy was 33.8%, but was significantly greater in the children without a history of recurrent perforation (p = 0.006), who also showed a significant reduction in the mean duration of unilateral otitis media with effusion (p = 0.02).[35]

Block et al. have recently made a detailed analysis of the effect of LAIV in preventing AOM[33] by considering separately the studies in which LAIV was compared with placebo[32,36–40] and those in which it was compared with TIV.[28,41] The impact of LAIV on AOM was always very favorable. In particular, the placebo-controlled studies enrolled a total of 14,109 children, 8353 of whom received LAIV; AOM associated with culture-confirmed influenza was diagnosed in 0.4% of the LAIV recipients and 2.9% of those receiving placebo, giving an overall vaccine efficacy of 85%. Moreover, the data collected in the two studies comparing LAIV with TIV clearly showed the superiority of the former. These studies involved a total of 9937 children, 4966 of whom received LAIV and 4971 received TIV. AOM occurred in 0.56% of the children in the LAIV group and 1.23% of those in the TIV group, thus indicating a 54.0% superiority of the nasal vaccine. However, given the efficacy of LAIV against influenza, it was perhaps not surprising that it also offered greater protection against influenza-associated AOM.

Belshe et al. administered LAIV or TIV to 7852 children aged 6–59 months in a prospective, randomized, comparative trial and found 54.9% fewer cases of cultured-confirmed influenza in the group who received LAIV (153 vs 338 cases; p < 0.001).[32] The superior efficacy of LAIV concerned both antigenically well-matched viruses and drifted ones.[32]

In conclusion, although no definitive data are available, an analysis of what has so far been published suggests that influenza vaccination can be useful in preventing AOM and that appropriate selection of both children and vaccine can increase the probability of a satisfactory response.

Pneumococcal Vaccination

Polysaccharide 23-valent Vaccine & PCV7

The polysaccharide 23-valent vaccine is poorly immunogenic in young children because of the characteristics of its antigens, which are T-cell-independent and unable to stimulate the immature immune system. It was therefore not expected that its administration would have an impact on the epidemiology of AOM. Furthermore, it has not been demonstrated to be efficacious for use in children against recurrent AOM when used to boost pneumococcal conjugate vaccination.[42,43]

By contrast, because it is highly immunogenic in children in the first months of life and includes most of the serotypes associated with AOM (4, 6B, 9V, 14, 19F, 18C and 23F),[44,45] it was supposed that PCV7 would be
able to reduce the incidence of AOM significantly. However, the first randomized controlled trials planned to evaluate the efficacy of PCV7 and reported poorer results than expected. Although the efficacy against AOM due to serotypes included in PCV7 was 57%, the effect on overall AOM was far less impressive (6–8%), despite a significant reduction of nasopharyngeal carriage of pneumococcal serotypes included in the vaccine.\[46,47\]

Although in these studies efficacy in children with recurrent AOM was a little higher, and a reduction of 6–8% could be considered substantial for society because of the very high incidence of the disease, these results were considered disappointing. As S. pneumoniae is the cause of 25–50% of the cases of AOM\[17–19\] and PCV7 prevented more than 90% of the cases of invasive pneumococcal disease (IPD),\[48\] it was thought that a significantly greater reduction in the incidence of AOM might follow the implementation of programs for its universal use in younger children. Explanations for these results were found in the demonstration that a relevant number of AOM cases were due, even before PCV7 extensive use, to serotypes not included in the vaccine\[49\] in the finding that the use of PCV7 was accompanied by an immediate and complete replacement at the nasopharyngeal level of vaccine serotypes by serotypes not included in the vaccine, so favoring a reduction in vaccination efficacy\[42,47,48\] and in the evidence that pneumococcal antibody levels higher than those useful to prevent IPD were probably needed to prevent AOM.\[50\] Moreover, further doubts on the real importance of PCV7 in the prevention of AOM have been arisen from some studies that have assessed, instead of the general pediatric population, children at greater risk, such as those with recurrent episodes of this disease who have clearly demonstrated no effect of the vaccine, mainly because the replacement phenomenon reduces the effect of PCV7.\[42,43\] However, new enthusiasm for the PCV7 prevention of AOM arose with the evaluation of the data collected in postlicensing studies of the effect of widespread immunization on AOM.\[51,52\] Comparisons of the rates of AOM outpatient visits before and after the introduction of PCV7 have demonstrated a 13–43% decrease in the number of AOM or AOM-related visits in children aged less than 2 years.\[51,52\] Moreover, it was reported that after the introduction of PCV7, the rates of otorrhea visits per 10,000 emergency department visits decreased by 38% (p < 0.001), mainly as a result of the decrease in the incidence of pneumococcal disease.\[53\] As these values were significantly higher than those found in clinical trials, it was concluded that PCV7 may have had a significantly greater effect than previously thought. It has been suggested that these differences may be attributable to indirect effects, such as unvaccinated and partially vaccinated children maybe being protected as a result of the reduced carriage and the transmission of vaccine serotypes by vaccinated children.\[54\] In other words, as in the case of IPD,\[55\] the reduction in nasopharyngeal colonization by the serotypes included in the vaccine may have limited the spread of the pathogens in the community, and thus reduced the risk of developing AOM in both vaccinated and unvaccinated children. This hypothesis was considered valid by most experts,\[56\] who still remain convinced that the impact of PCV7 on AOM was significantly greater than that observed during the clinical trials.

However, some doubts arise when consideration is given to the estimated capacity of each pneumococcal serotype to cause AOM and the changes in nasopharyngeal pneumococcal serotype distribution before and after the introduction of PCV7. Shea et al. developed a model based on these variables and found that the expected decrease in the number of AOM episodes attributable to S. pneumoniae in children aged less than 3 years between 2000 and 2007 due to the combined effects of PCV7 vaccine efficacy and vaccine-induced serotype replacement was approximately 12%.\[57\] This corresponds to a 4–5% decrease in the number of all-cause AOM episodes, which is even lower than that found in clinical trials.

Furthermore, other hypotheses suggest that the greater effect on AOM found in postlicensing studies could be at least partially independent of PCV7, including natural variations in the incidence of AOM, a concomitant increase in the use of influenza vaccine and the efforts of pediatricians to apply more stringent criteria for a correct diagnosis of AOM.\[52,58\] Decreases in the number of AOM clinic visits were repeatedly reported in various countries before PCV7 became widely used.\[59,60\] Furthermore, influenza vaccination may have had a positive effect on the occurrence of AOM, particularly in countries where it is also recommended for healthy children,\[61\] which includes the USA, where most of the PCV7 efficacy data have been collected. Finally, educational programs aimed at reducing misdiagnoses of AOM have been introduced in order to promote the judicious use of antibiotics, and this per se may have reduced the total number of AOM episodes recorded in the studies.\[62\]
In conclusion, although the real extent of the effect of PCV7 on the incidence of AOM cannot be precisely defined, it exists and has been found in all pre-registration and postmarketing studies. This is particularly important if we remember that PCV7 has been mainly used to prevent IPD and the prevention of AOM is an additive effect.

**Theoretical Impact of PCV10 & PCV13**

The use of PCV7 has significantly modified the characteristics of pneumococcal carriage and the role of *S. pneumoniae* as a cause of AOM. It has been shown that the pneumococcal serotypes contained in PCV7 are almost completely replaced by nonvaccine serotypes in the nasopharynx, and similar variations in the pneumococci isolated from middle ear fluid were found in children diagnosed as having AOM some years after the introduction of PCV7. In particular, the proportion of pneumococcal AOM episodes due to PCV7 serotypes decreased from 62% in 2000 to 5.5% in 2007, whereas the cases due to non-PCV7 serotypes increased from 38 to 95% in the same period. As the two variations did not occur simultaneously, the proportion of bacterial AOM cases due to pneumococci initially significantly decreased, and nontypable *Haemophilus influenzae* became the most frequent cause of AOM. However, this proportion has since returned to very near its original levels and is now not substantially different from that of cases due to nontypeable *H. influenzae*. Although there are considerable national differences, the most frequently isolated pneumococcal serotypes in children with AOM living in countries where PCV7 has been extensively used are currently serotypes 3, 6A, 7F and 19A.

Two new vaccines containing ten and 13 pneumococcal serotypes, respectively, have recently become available. As both contain all of the serotypes included in PCV7 and others that have emerged as common causes of pneumococcal disease, it is reasonable to think that both may be more efficacious than PCV7 in preventing AOM. The serotypes added to PCV10 are 1, 5 and 7F, and eight of the ten serotypes are conjugated to a recombinant nonlipidated form of protein D, a 42-kDa cell surface lipoprotein of *H. influenzae* that acts as a carrier protein for pneumococcal antigens and simultaneously elicits a significant immune response against *H. influenzae*. It was therefore thought that this PCV would not only extend protection against pneumococcal AOM, but also induce protection against AOM due to nontypeable *H. influenzae*, the second most important bacterial cause of this disease. A study of an investigational 11-valent PCV, a precursor of the presently available decavalent vaccine, which also contained serotype 3 and in which all of the serotypes were conjugated with protein D, found that it could avoid 33.6% of all-cause AOM, with a reduction of 57.6% in pneumococcal cases and 35.3% in the episodes due to nontypeable *H. influenzae*.

Although the higher efficacy of this vaccine in comparison with PCV7 could not be ascribed to differences in case definition, the findings of this study have, however, been questioned, mainly because its design apparently led to considerable case selection, as the incidence of AOM in the control group was only approximately a tenth that observed in most American and European studies. It is therefore not possible to evaluate the real advantages of this vaccine, particularly its real efficacy in preventing AOM due to *H. influenzae*. Only the large-scale efficacy trials that are currently ongoing with the decavalent vaccine can definitively state the real importance of this new product in AOM prevention. On the other hand, the absence of serotypes 3 and 19A suggests that the decavalent vaccine cannot be more effective than PCV7, at least against *S. pneumoniae* AOM.

No studies have yet investigated the capacity of PCV13 to prevent AOM. However, some suppositions of its theoretical efficacy have been made on the basis of the change in nasopharyngeal colonization induced by PCV7, the risk of AOM in colonized children and the potential impact of PCV13 on carriage. It has been calculated that the total number of AOM cases caused by PCV13 should decline from 53% in 2007 to 19% in 2013, and that the global reduction in pneumococcal AOM could reach 2.7%, and that of all-cause AOM could reach more than 10%. Although these calculation were based on data collected in a specific area (and so they cannot be considered representative of serotype distribution in all countries) and the capacity of each serotype to cause AOM was evaluated using a simple method (i.e., by dividing serotype-specific disease prevalence by serotype-specific carriage prevalence), they clearly suggest that the impact of PCV13 may be...
significantly greater than that of PCV7. However, because replacement phenomena could also take place after PCV13 use, only investigations into the field can definitively ascertain the efficacy of this vaccine against AOM.

**Conclusion**

Influenza vaccines and PCVs can have a substantial effect on the incidence of AOM, although it is not possible to quantify the reduction exactly. Further studies are needed in order to identify the subjects who benefit most from vaccination and the vaccines that offer the best preventive effect. This seems to be particularly important in the case of influenza vaccines because they are not systematically recommended for healthy children in all countries. Understanding whether, by how much and which influenza vaccines can reduce the incidence of AOM may be important in order to allow the health authorities of countries in which influenza vaccination is not included in the immunization schedule of young healthy children to decide whether they should change their policy. On the other hand, clarifying the effect of pneumococcal vaccines seems to be less urgent because they are currently recommended in all industrialized countries (mainly for the prevention of invasive diseases) and their effects on AOM would not modify their universal use.

**Future Perspective**

Over the next 5 years, it should be possible to identify the subjects who would benefit most from influenza and pneumococcal vaccinations, establish which influenza vaccines have the best preventive effect in the first years of life and quantify the real impact of PCV10 and PCV13 on the natural history of AOM. It will be particularly important to understand whether adjuvanted influenza vaccines or the intradermal administration of conventional TIV significantly increase the immune response of younger children to influenza vaccine. The data concerning their immunogenicity in younger children are still limited, and there is little information about their efficacy in preventing AOM,[73] but it does seem that more younger subjects (precisely those in whom preventing influenza and its related complications is most important) develop more of a protective immune response than those given conventional TIV. Confirmation of these data in a greater number of subjects, however, is needed before these vaccines could be recommended for use in children. When available, these data would remove most of the doubts of some experts about the use of influenza vaccines to prevent AOM. Furthermore, the ability of an influenza vaccine to prevent AOM could itself be considered sufficient to justify its universal use in healthy children.

Over the next 10 years, new influenza and pneumococcal vaccines produced by means of alternative vaccine manufacturing technologies will become available. These will have wide strain specificity and may increase the reduction in the incidence of AOM. The most recent studies of the prevention of both influenza and pneumococcal disease have been based on identifying antigens common to all influenza subtypes and pneumococcal serotypes.[74] It is well known that influenza viruses are highly unstable and, every year, undergo more or less important genetic modifications that lead to changes in the exposed regions of viral surface proteins. These make the viruses less susceptible to immediate neutralization by the immune system in subjects who have received an influenza vaccination in previous years.

Vaccination failure can occur with conventional TIV when there is a mismatch between the circulating influenza viruses that cause disease and those included in the vaccine. In order to overcome this, influenza vaccines containing conserved proteins are being prepared. These contain antigens common to all of the influenza viruses that remain unmodified over time and should therefore be able to evoke an immune response to influenza viruses regardless of antigenic drifts and the presence of mismatched strains. They should also be able to offer significantly more protection against AOM.

A similar approach is being used to prepare pneumococcal vaccines but, in this case, the problem is that the vaccines containing the most serotypes still only contain 13 of the approximately 90 known serotypes, and so a number of pneumococcal AOM cases cannot be prevented. If a vaccine containing conserved proteins (i.e., antigens common to all pneumococcal serotypes) becomes available, the prevention of pneumococcal AOM could be easier and more effective. However, despite being attractive, this hypothesis needs to be accurately
evaluated because the disappearance of human microbiota may not be entirely beneficial. Moreover, from a practical point of view, difficulties in setting benchmarks for licensure of these new vaccines could arise.

Sidebar

Executive Summary

Background

- The use of vaccines can significantly reduce the incidence of acute otitis media (AOM).

Influenza Vaccines

- Influenza vaccination can be useful in preventing AOM, and a favorable response is more likely in children aged more than 24 months, those with recurrent AOM without complications and those administered live-attenuated influenza vaccine.

Pneumococcal Vaccinations

- Although the effect of heptavalent pneumococcal conjugate vaccine (PCV7) has been demonstrated in all pre-registration and postmarketing studies, its real effect on the incidence of AOM cannot be precisely defined.
- The impact of PCV10 and PCV13 may be significantly greater than that of PCV7.

References

   - International multidisciplinary group of experts in middle ear and pediatric infections explore the consensus concerning the management of acute otitis media (AOM).
   - Estimates the use of medical resources and the direct and indirect costs (lost productivity) of episodes of AOM in young children.
12. Wiertsema SP, Chidlow GR, Kirkham LA et al. High detection rates of nucleic acids of a wide range of


   • Shows that children receiving live-attenuated influenza vaccine have a higher level of protection against influenza-associated AOM than those receiving placebo or trivalent influenza vaccine, and that this was most evident in children aged more than 2 years.
50. Jódar L, Butler J, Carlone G et al. Serological criteria for evaluation and licensure of new pneumococcal


57. Shea KM, Weycker D, Stevenson AE, Strutton DR, Pelton SI. Modeling the decline in pneumococcal acute otitis media following the introduction of pneumococcal conjugate vaccines in the US. *Vaccine* 29(45),8042–8048 (2011).

- Shows that in children less than 3 years of age, a 12% decline in the number of AOM episodes attributable to *Streptococcus pneumoniae* due to the combined effects of heptavalent pneumococcal conjugate vaccine efficacy and vaccine-induced serotype replacement occurred between 2000 and 2007. Moreover, it predicts that 13-valent pneumococcal conjugate vaccine will decrease pneumococcal AOM an additional 27% from 2007 to 2013.


67. McEllistrem MC, Adams JM, Patel K et al. Acute otitis media due to penicillin-nonsusceptible *Streptococcus pneumoniae* before and after the introduction of the pneumococcal conjugate vaccine.

Papers of special note have been highlighted as:
• of interest
•• of considerable interest

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