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Prevention of Acute Otitis Media

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Introduction

Acute otitis media (AOM) is the most common disease occurring in infants and children: almost all children experience at least one episode and about a third have two or more episodes in the first three years of life [1,2].

The burden of the disease has important medical, social and economic effects. AOM always requires considerable financial assistance, as it implies at least one visit with the doctor, prescription of antipyretics, and in a proportion which varies from one country to another, of antibiotics [3-6] . Alongside the direct costs, the disease is associated with high indirect costs that are equivalent and often higher than the direct ones, mostly related to working day loss of one of the parents [7] . Moreover, due to its acute symptoms and frequent recurrences, AOM has considerable impact on the quality of life of both the child and the family. Finally, although rarely, AOM can cause important complications like mastoiditis.

In recent years the occurrence of new data has deeply modified the way in which AOM should be considered: the availability of new instruments for a more precise diagnosis and the role of prevention thanks to vaccines able to exert an undeniable preventive action.

AOM prevention today represents a primary goal of the pediatric practice [8,9]. This is mostly true for recurrent forms, but it can also be applied to the first episode of the disease, in otherwise healthy children. Considering that AOM onset is favored by a wide range of predisposing factors, and that it usually follows a viral infection of the upper respiratory tract, AOM prevention attempts mostly rely on the reduction of risk factor contribution, of the viral respiratory infection and of the bacterial colonization of the upper respiratory mucosa.

Reduction of risk factors

The onset of AOM is much more frequent when certain risk factors are present. Among these, some are modifiable and, then, at least theoretically, likely to be reduced. Such risk factors include day- care attendance, bottle-feeding, exposure to passive smoking and the use of pacifiers [10-11]. Few studies have evaluated the impact of the elimination of one or more risk factors on the incidence of AOM. As regards day care attendance, Alho et al [12] have calculated, on a sample of 825 children followed for up to 2 years, that staying at home instead of day care attendance could avoid one AOM episode out of 5 in the pediatric population in general and 2 out of 5 in children with recurrences. Subsequently, Uhari et al [13], in a case-control study in day-care centers, evaluated the impact of using hygiene measures (hand washing, use of alcoholic solutions) on the prevalence of respiratory infections, including AOM: in a follow-up of 15 months a reduction of 27% of episodes of AOM was demonstrated.

As regards breastfeeding, most of the studies, but not all, have shown a protective effect of prolonged breast-feeding: a meta-analysis of observational studies[10] found that breastfeeding prolonged for at least 3 months reduces the risk of AOM by 13% (RR 0.87, CI 95% 0.79 - 0.95). Saarinen et al [14], in a cohort of 256 children followed from birth to 3 years, showed that no child who was breastfed until 6 months of age had AOM. Duffy et al [15], in a cohort study carried out in the USA, observed that between 6 and 12 months of age, the cumulative incidence of first OM episodes increased from 25% to 51% in infants exclusively breastfed and from 54% to 76% in infants formula-fed from birth. Peak incidence of AOM and otitis media with effusion (OME) episodes was inversely related to rates of breastfeeding beyond 3 months of age. A twofold elevated risk of first episodes of AOM or OME was observed in exclusively formula-fed infants compared with infants exclusively breast-fed for 6 months. More recent research raises the issues of how long this increased risk persists, and whether lack of breastfeeding is associated with diagnosis of OME. In fact, measures of the association between breastfeeding history and otitis media risk are sensitive to the definition of breastfeeding used and further studies are needed with more precise and consistent definitions of feeding, with attention to distinctions between direct breastfeeding and human milk feeding by bottle [16].

Regarding the use of the pacifier, the meta-analysis of Uhari et al [10] showed a 24% increase in the risk of AOM in children who routinely use pacifiers (RR 1.24, CI 95% 1.06 - 1.46) and a cohort study of 495 Dutch children aged 0-4 years (mean 2 years) followed for 5 years has shown that the use of pacifier often or sometimes represents a factor risk for acute otitis media (RR = 1.3, CI95% 0.9-1.9) [17]. The effects of reducing the use of pacifiers were studied by Niemelä et al [18] in 14 pediatric centers, divided into seven paired- groups, to standardize the sample size and the socioeconomic status of families. The intervention consisted in the distribution to parents of a document in which they listed the negative effects of continuous pacifier and some helpful tips to limit its use only to the moment of going to sleep. Children younger than 18 months of age were enrolled, 272 in the intervention group and 212 as controls. The results indicate that the availability of adequate information on the use of the pacifier can be extremely useful because, in the period after the intervention, there was an overall reduction in the use of the pacifier in 21% of the children and a 29% decrease of AOM episodes in the intervention group.

In conclusion, although the removal of risk factors is undoubtedly useful, the precise quantification of benefits is only possible with regard to limiting the use of the pacifier and the choice of exclusive breastfeeding during the first months of life.

Influenza vaccine

The greater part of studies on the impact of measures on prevention of viral infections on the incidence of AOM concerns the use of influenza vaccines. In fact, influenza is the only viral respiratory illness for which there are currently specific prevention measures [19].

Influenza vaccinations can be administered in the form of trivalent inacti-

vated influenza virus (TIV) or live attenuated influenza virus (LAIV) vaccines, and the viral content in both vaccinations is modified every year on the basis of antigenic changes in the circulating viruses. TIV vaccines are injected intramuscularly and have been approved throughout the world for their use in children aged more than 6 months [20]. The marketed TIV preparations are different, because some of them contain the whole virus, others contain only virus particles disrupted by detergents, and others only the hemagglutinin and neuraminidase antigens. Moreover some TIVs include adjuvants that increase immune response, and this type of vaccine is usually preferred in children because it is able to increase immunogenicity without giving rise to safety problems [21]. LAIV is a frozen, cold-adapted, temperature-sensitive, trivalent influenza vaccine registered in the United States only for use in healthy children aged 2 years or more. LAIV has been demonstrated to reduce the rate of culture-confirmed influenza by 94% and to reduce episodes of AOM by 30% compared with placebo [22].

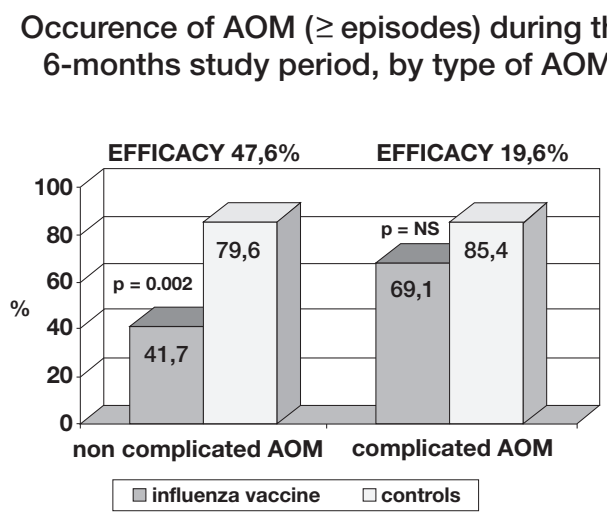
The systematic review by Manzoli et al. [23] includes 11 trials that assessed the efficacy of the vaccine against AOM without having major methodological limitations: in 6 was administered the TIV vaccine and in 5 LAIV. In 8 out of 11 studies influenza vaccine was effective whereas in 3 studies the data showed negative results. In many cases, there were substantial differences in the type of population enrolled, in the methods of diagnosis and in the follow-up of the patients. In particular, Clements et al demonstrated, in 186 healthy children attending the nursery, aged between 6 and 36 months, a 32% reduction of AOM during the influenza season in children vaccinated with inactivated vaccine compared to controls [24]. The study by Hoberman gave conflicting results: in 786 children aged between 6 and 24 months, the inactivated influenza vaccine, during two successive seasons, did not reduce the frequency of AOM compared with unvaccinated children [25]. The study is hindered by a limited circulation in both periods of influenza virus, which may have influenced the overall incidence of AOM and consequently the frequency in the 2 groups.

The systematic review indicates that administration of influenza vaccine reduces by 51% (CI95% 21-71%) the incidence of AOM in the period of circulation of influenza viruses in healthy children without a history of recurrent AOM [23]. Several are, however, the evaluations that emerge from the analysis of results according to the type of vaccine used and the age of the patients. The vaccine based on live attenuated virus has, in fact, significantly better than those obtained with inactivated virus vaccines: Vesikari reported, in 951 healthy children of 6-26 months who received a LAIV intranasally, an effectiveness of over 90% versus AOM associated with laboratory confirmed influenza compared with control group, with a maximum of effectiveness in children over 18 months [26].

As regards the use of influenza vaccine in children with a documented history of recurrent AOM, our group showed that an intranasal inactivated influenza vaccine (not actually marketed) was effective in preventing 43.7% of AOM episodes [27]. In addition, another study, which focused not only on the impact of influenza vaccination on the total number of AOM episodes, but also on the characteristics of the enrolled patients or the nature of the episodes, we showed that

intramuscular administration of TIV virosomal-adjuvanted in children with a history of recurrent AOM significantly reduces AOM-related morbidity, in terms of a significantly smaller number of vaccinated children who experienced at least one AOM episode, the mean number of AOM episodes, the mean number of episodes without perforation, the mean duration of bilateral OME, and the mean number of antibiotic courses [28] . However, the efficacy of this preventive measure seems to be reduced in children with recurrent complicated AOM, associated with repeated tympanic membrane perforation (**Figure 1**).

Figure 1. Occurrence of AOM during 6-months study period, by type of AOM



A recent review compared the efficacy of LAIV against influenza- associated AOM compared with placebo and TIV: LAIV efficacy was 85% (CI95% 78.3%-89.8%) compared with placebo and 54% (95% CI, 27.0%-71.1%) compared with TIV [29].

In conclusion, the use of influenza vaccine appears to be effective in the prevention of AOM. Available data favor children older than 2 years of age, those with a lower risk of AOM. However, if the purpose of vaccination was only to prevent AOM, the vaccine would not currently justify the use except in patients with very frequent recurrences. Since, however, the prevention of influenza aims to reduce complications and indirect cost, doubts about the limited effectiveness in preventing the first episode of AOM in younger children are outweighed by other advantages medical, social and economic information supplied by the vaccine.

Pneumococcal vaccine

Among all bacterial infections involved in causing AOM, the ones with a documented possibility of prevention are those supported by *S. pneumoniae*. Contrary to what is true for *H. influenzae* non typeable (NTHi), *M. catarrhalis* and *S. pyogenes*, for which only scarce data or no effective vaccines are available, against *S. pneumoniae* there are conjugate vaccines able to induce an immune response even in the youngest subjects, those more likely to develop AOM [30-32].

Pneumococcal conjugated vaccines (PCV) are globally available for prevention of potentially life-threatening pneumococcal diseases, such as pneumonia and meningitis, as well as non invasive but extremely common, expensive and distressing diseases as acute middle ear infections.

The pneumococcal vaccines for which there are data of efficacy in preventing AOM are 3, different for the transport proteins used for conjugation with the capsular polysaccharides of individual bacterial strains and / or by the number of serotypes:

- 7-valent vaccine (PCV-7) (4,6 B, 9V, C 14.18, 19F, 23F)
- 10-valent vaccine (7-valent serotypes + serotypes 1,5,7)
- 13-valent vaccine (10-valent serotypes + serotypes 3, 6 A, 19A)

When dealing with these vaccines and AOM, one must distinguish between the efficacy, that is data derived from randomised clinical trials, and effectiveness, that is data derived from the real-world setting after implementation.

As regards PCV7, the two more important controlled clinical trials, randomized, double-blind (Northern California Kaiser Permanente study and Fin OM study) indicated that the efficacy against OM episodes was a whole was less than 10%, ranging from 8 to 9% in the United States and 6 to 8% in Finland [33]. However, PCV7 was able to prevent over 30% of culture-confirmed pneumococcal AOM and up to 57% of AOM causes by pneumoccoccal serotypes included in the vaccine [34]. The preventive efficacy improves if one consider the rate of recurrences, as demonstrated by a reduction of 28% of recurrent AOM and of 18% of insertion of tympanostomy tubes [33,35,36]. The efficacy of PCV-7 , even if limited, in the prevention AOM is, however, present only when the vaccine is administered in the first year of life. When, instead, PCV-7 is administered in older children, who have already suffered from OM, the vaccine is not able to reduce the risk of appearance of new episodes, probably because the late administration has little influence on the nasopharyngeal colonization of the pneumococcus [37].

An experimental 11-valent pneumococcal vaccine, including protein D as carrier protein, which does not interfere with other vaccines and may give protection against NTHi, has shown an efficacy of 33.6% in reducing overall AOM episodes, and of 57.6% in reducing AOM episodes due to pneumococcal serotypes [38]. In addition it showed an efficacy of 35.3% for AOM due to NTHi. The 11-valent pneumococcal vaccine has not been marketed, but was replaced by a commercially prepared 10 components (except serotype 3 and some variations in transport proteins) [39]. The European Medicines Agency, in 2009, authorized the 10 valent vaccine for the prevention of infections caused by *S. pneumoniae* and predicted on the basis of comparison data between the immunogenicity of 10 valent vaccine used in the study and that the 10 valent can provide similar protection against AOM caused by *S. pneumoniae* [40].

Interestingly, the efficacy against AOM due vaccine serotypes was remarkably similar between PCV7 and 11-valent pneumococcal vaccine trials, and ranged between 56 to 58 %. The discrepancy between overall and vaccine-type AOM impact suggests that the net-all-cause AOM result is multifactorial (differ-

ences in study background; design; local epidemiology; impact, if any, on disease caused by non-vaccine serotypes/other pathogens). In fact, the data of FinOM study were further analysed by applying the stricter definition used in the study varied out with the 11-valent pneumococcal vaccine: no major differences were seen between the vaccine efficacy estimates using different case definition for vaccine serotype AOM. Other factors, including the additional efficacy of the 11-valent vaccine against NTHi otitis may play a role [41].

In the observational database studies analysing post-marketing data, largely from the Unites States and Canada, effectiveness estimates against overall AOM varied widely, ranging between 3 and 43%, with an average of 19% (**Figure 2**) [42].

Figure 2. Evolution of AOM visits post-PCV-7

Evolution of AOM visits post - PCV7		
	Decrease (%)	Age (yrs)
- US (Poehling 2004) outpatients[1]	4 or 19	<2
- US (Poehling 2007) outpatients[2]	-7 to 18	<2
- US (Grijalva 2006)[3]	12	<2
- USA (Sox 2008)[4]	37	≤12
- US (Zhou 2008)[4]	48*	<2
- Italy (Durando 2009, inpatients)[6]	36	<2
- Quebec (de Wals 2009, 2+1)[7]	13	<5
- US (Grijalva 2009)[8]	33	<5
- US (Singleton, 2009)[9]	29	<5
- Review (Taylor 2012)[10]	-7 to +48	<2 to ≤12

Average decrease of 19%[10]

*Recalculation from yearly estimates[10].
Zhou et al. originally presented a 43% decrease between 1997-1999 and 2004

[1]Poehling et al. Pediatrics 2004; 114:755-61; [2]Poehling et al. Pediatrics 2007; 119:707-15 [3] Grijalva et al. Pediatrics 2006; 118:365-73;
[4]Sox et al. Pediatrics 2008; 121:674-9; [5]Zhou et al. Pediatrics 2008; 121:253-60; [6]Durando et al. Vaccine 2009; 27:3459-62;
[7]de Wals et al. Pediatr Infect Dis J 2009; 28:e271-5; [8]Grijalva et al. Jama 2009; 302:758-66;
[9]Singleton et al. Pediatr Infect Dis J 2009; 28:102-107; [10]Taylor et al. Clinical Infectious Diseases 2012; E pub May

In most cases, AOM visits rates were declining already in the 3-5 years before PCV7 introduction (mean change – 15%) and continued to decline afterwards [42]. This warrants caution when interpreting the data of effectiveness. In other words, real-life data show greater effectiveness against OM than expected from clinical efficacy studies. Several are the possible explanations (**Figure 3**).

The 13- valent pneumoccoccal vaccine is identical to PCV-7 for what concerns the transport protein of the capsular polysaccharides, but it contains six additional serotypes. This vaccine should be considered an extension of PCV-7 and the addition of 6 new serotypes does not reduce the immune response to 7 common serotypes [43,44]. No studies have yet investigated the capacity of PCV13 to prevent AOM. However, some calculations 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 strains should decline from 53% to 19% in a few years, and that the global reduction in pneumococcal AOM could reach 2.7% and that of all-cause AOM more than 10% [45]. These calculations were based on data collected in a specific area and thus they cannot be considered representative of serotype distribution in all countries: however the impact of PCV-13 is potentially greater than that of PCV7 [32].

Figure 3. Real-life impact of PCV on AOM

Real- Life impact of PCV on AOM

- Real - life data show greater effectiveness against OM than expected from clinical efficacy studies
- Possible explanations:
  - AOM consultations and reporting rates
  - Patient and physician perception
  - Availability of antibiotics without prescription
  - Frequency and type of antibiotic used
  - Diagnostic criteria
  - Awareness of vaccination
  - 'Lifestyle' factors such as exposure to smokers, use of day-care centres, number of siblings
  - Prevention of viral infection (influenza vaccination)
  - Diagnostic codes used in databases
  - Insurance reimbursement practices

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How will we have better answer to solve the problem of the discrepancy between pneumococcal conjugate vaccine efficacy versus effectiveness? What is the future going to bring us? As double-blinded parallel controlled trials are the gold standard for demonstrating vaccine effects, the currently on-going trial in Finland (FinIP), a community-randomised double-blind trial with 10-valent pneumococcal vaccine, will likely and soon provide more accurate estimates of both the direct and indirect effects of the introduction of PCV mass vaccination programs on AOM related endpoints.

As stated by a recent expert consensus:

"Prevention of AOM 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" [9].

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