

# Updated Guidelines for the Management of Acute Otitis Media in Children by the Italian Society of Pediatrics

## Prevention

Paola Marchisio, MD,\* Barbara Bortone, MD,† Martina Ciarcià, MD,† Marco Antonio Motisi, MD,† Sara Torretta, MD,\* Guido Castelli Gattinara, MD,‡ Marina Picca, MD,§ Giuseppe Di Mauro, MD,¶ Marisa Bonino, Nurse D,|| Nicola Mansi, MD,# Alfonso Varricchio, MD,# Gian Luigi Marseglia, MD,\*\* Fabio Cardinale, MD,†† Alberto Villani, MD,‡ Elena Chiappini, MD, PhD,† and the Italian Panel for the Management of Acute Otitis Media in Children

**Background:** In recent years, new information has been acquired regarding the diagnosis, treatment and prevention of acute otitis media (AOM). The Italian Pediatric Society, therefore, decided to issue an update to the Italian Pediatric Society guidelines published in 2010.

**Methods:** The search was conducted on Pubmed, and only those studies regarding the pediatric age alone, in English or Italian, published between January 1, 2010 and December 31, 2018, were included. Each study included in the review was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology. The quality of the systematic reviews was evaluated using the A MeaSurement Tool to Assess systematic Reviews (AMSTAR) 2 appraisal tool. The guidelines were formulated using the GRADE methodology by a multidisciplinary panel of experts.

**Results:** The importance of eliminating risk factors (passive smoking, environmental pollution, use of pacifier, obesity, limitation of day-care center attendance) and the promotion of breastfeeding and hygiene practices (nasal lavages) was confirmed. The importance of pneumococcal vaccination in the prevention of AOM was reiterated with regard to the prevention of both the first episode of AOM and recurrences. Grommets can be inserted in selected cases of recurrent AOM that did not respond to all other prevention strategies. Antibiotic prophylaxis is not recommended for the prevention of recurrent AOM, except in certain carefully selected cases. The use of complementary therapies, probiotics, xylitol and vitamin D is not recommended.

**Conclusions:** The prevention of episodes of AOM requires the elimination of risk factors and pneumococcal and influenza vaccination. The use of other products such as probiotics and vitamin D is not supported by adequate evidence.

**Key Words:** prevention, risk factors, vaccines, acute otitis media, guidelines

(*Pediatr Infect Dis J* 2019;38:S22–S36)

Accepted for publication June 24, 2019.

From the \*Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Pediatric highly intensive care unit, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy, †Department of Human Health Sciences, University of Florence, AOU Firenze, Italy, ‡Department of Pediatrics, Bambino Gesù Children's Hospital (IRCCS), Rome, Italy, Primary care paediatrician, Florence, Italy, §Primary care paediatrician, Milan, Italy, ¶Primary care paediatrician, Caserta, Italy, ||Nurse, Novara, Italy, #Associazione Italiana Vie Aeree (AIVAS): Study Group on Respiratory Infections, Genoa, Italy, \*\*Pediatric Clinic, Department of Pediatrics, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy, and ††Division of Pulmonology, Allergy, and Immunology, Pediatric Unit, AOU "Policlinico-Giovanni XXIII", Bari, Italy.

The authors have no funding or conflicts of interest to disclose.

All authors approved the final version of this document.

Address for correspondence: Elena Chiappini, Department of Pediatrics, Anna Meyer Children's University Hospital, Viale Pieraccini, 24, Florence, 50100 Italy. E-mail: elena.chiappini@unifi.it

Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.

ISSN: 0891-3668/19/3812-0S22

DOI: 10.1097/INF.0000000000002430

Acute otitis media (AOM) is a very common condition with significant medical, social and economic negative impact.<sup>1–4</sup> At the age of 1 year, 25%–36% of children have already had at least 1 episode of AOM and approximately 20% of children develop recurrent otitis.<sup>5,6</sup>

AOM has a considerable impact on the quality of life of both the children and their families. It also has considerable costs, which, given its very high frequency, make it one of the pediatric illnesses that most affects global spending on health.<sup>5,6</sup> Consequently, the prevention of AOM currently represents a primary objective of pediatric care.

## METHODS

For the drafting of the update of the previous guideline,<sup>7</sup> the Italian Pediatric Society appointed a commission including experts in general pediatrics, research methodology, pneumology, clinical immunology, emergency medicine, epidemiology, pharmacology and microbiology. These aspects and outcomes were identified by the methodology group and then shared and discussed with the rest of the panel by adopting the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology.<sup>8</sup> The search was conducted on Pubmed, and only those studies regarding the pediatric age alone, in English or Italian, published between January 1, 2010 and December 31, 2018, were included. For each question, the keywords used for the search strategy (annex 1) were identified by the members of a subcommission. Relevant articles retrieved from the reference lists of the selected studies were also considered. The references were regularly updated during the drafting of the guidelines. The abstracts and articles were analyzed by a subcommission that selected those that were relevant, especially double-blind, randomized clinical studies, cohort studies, systematic reviews and all general position papers.

Each study included in the review was summarized in summary of findings tables and assessed in terms of methodology and contents using the GRADE criteria.<sup>8</sup> The quality of the systematic reviews was evaluated using the A MeaSurement Tool to Assess systematic Reviews (AMSTAR 2) appraisal tool.<sup>9</sup>

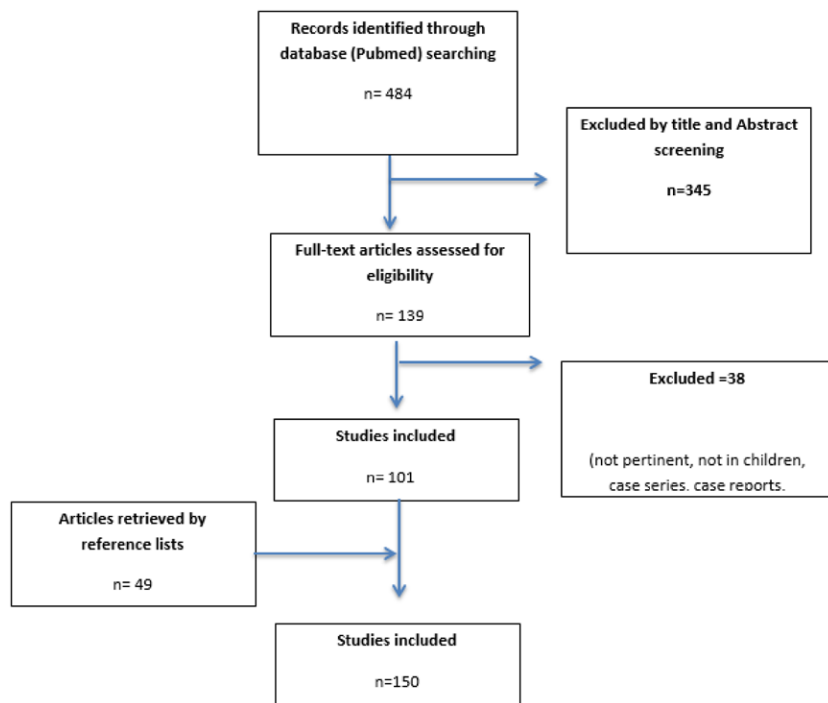
The results of the analysis were then discussed and approved by the whole panel involved in the drafting of the guidelines, using the Consensus Conference method.

## RESULTS

One hundred fifty articles were selected as shown in Figure 1. The recommendations set forth below were formulated on the basis of the evidence obtained for each question.

### Question No. 1 What Role Does Risk Factor Limitation Play in the Prevention of AOM?

The unmodifiable predisposing factors are age, male gender, ethnic origin (Caucasian),<sup>6</sup> having siblings in day care,<sup>10,11</sup>



**FIGURE 1.** PREVENTION search strategy and result flow chart.

premature birth, immunodeficiencies, atopy, anatomical factors such as Eustachian tube dysfunction or craniofacial abnormalities<sup>6,12–15</sup> and genetic factors.<sup>2,16–20</sup>

The modifiable risk factors, on the other hand, are attendance of day-care centers, type of feeding, exposure to passive smoking and pollutants, use of pacifiers and obesity.<sup>5,21–23</sup>

By summarizing the evidence provided in literature, it is clearly demonstrated in large, good-quality studies<sup>24</sup> that a reduction in the use of pacifiers is associated with a reduction in the risk of recurrence, whereas the data available regarding the other factors are less conclusive.

### Use of Pacifiers and Other Similar Devices

The use of devices such as pacifiers and push-and-pull cap bottles can cause a reduction in nasopharyngeal pressure able to increase the reflux of nasopharyngeal secretions in the Eustachian tube, which consequently increases the risk of AOM.

The 4 observational studies selected showed conflicting results.<sup>21,25–27</sup> Two good-quality studies clearly show a relationship between pacifier use and the risk of AOM.<sup>21,25</sup>

Furthermore, one interventional study, despite presenting methodologic limitations, showed that a benefit was obtained when pacifier use was reduced by limiting it to the phase in which the baby falls asleep.<sup>24</sup>

The meta-analysis conducted by Uhari et al showed a 24% increase in the risk of developing AOM in babies who used a pacifier after the age of 6 months [Relative Risk (RR): 1.24; 95% confidence interval (CI): 1.06–1.46].<sup>20</sup> One more recent cohort study conducted in Holland including 495 children under 4 years of age showed pacifier use to be a risk factor for recurrent AOM (RR = 1.3; 95% CI: 0.9–1.9). One significant limitation of this study in terms of result interpretation is the fact that pacifier use was only analyzed at the time of enrollment, and it was not possible to establish a relationship between the child's age, period of use and effective risk of AOM.<sup>24</sup>

Conversely, Labout et al conducted a prospective observational study on a population of 5323 children to study the

relationship between the frequency of AOM in the second year of life and the presence of certain factors such as attendance of day-care centers, parental smoking, pacifier use, breastfeeding and nasopharyngeal *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* colonization. The only factors that correlated significantly with AOM in the second year of life were seen to be the presence of siblings and having an episode of AOM during the first year of life. No other associations were observed between pacifier use and the frequency of AOM (adjusted OR (OR):1.01; 95% CI: 0.88–1.16).<sup>26</sup> The significant limitations of this study are the fact that the diagnosis of AOM was based on parental reports not confirmed by a physician and the fact that the time of pacifier use was not specified.

In one retrospective study conducted in Italy by telephone interviews with the parents of 59 children, regular use of bottles with push-and-pull caps was more common in children with recurrent AOM (50.0%) than in the control group (24.2%;  $P = 0.047$ ), regardless of age. Pacifier use, on the other hand, was not associated with an increased risk of recurrent AOM.<sup>25</sup> This study presented methodologic limitations, because it was based on information provided by parents, and the time of pacifier use was not specified.

The effects of reducing pacifier use were studied by Niemelä et al in 14 Finnish community pediatric centers,<sup>23</sup> split into 2 groups adjusted according to the number of children and the families' social and economic status. The study included 484 babies under 18 months of age. In one group, the parents were given an information sheet listing the negative effects of continuous pacifier use and providing helpful hints on how to limit use to the phase in which the baby falls asleep, whereas the control group did not receive any specific educational intervention. During the monitoring period following the intervention, there was a 21% reduction in continuous pacifier use and a 29% reduction in the episodes of AOM in the group that received the educational intervention and a 33% reduction amongst the babies who had not made continuous use of a pacifier. However, this study presents a number of limitations, as it was an open-label study, and the diagnosis of AOM was not formulated by expert otoscope users.<sup>27</sup>

## Type of Feeding

Most studies showed prolonged breastfeeding to have a protective effect: one meta-analysis of observational studies (22 studies; 14,069 children)<sup>21</sup> showed that breastfeeding for at least 3 months is associated with a 13% reduction in the risk of AOM (RR: 0.87; 95% CI: 0.79–0.95). Saarinen et al, in a cohort of 256 children monitored from birth to the age of 3 years, state that at the end of the first year, the incidence of  $\geq 2$  episodes of AOM was 6% in the group of children who were exclusively breastfed up to 6 months and was 19% in the group of children who were bottle-fed under 2 months of age ( $P < 0.05$ ).<sup>28</sup> Duffy et al, in one cohort study conducted in the United States on 306 children, observed that the risk of developing AOM was twice as high in babies who were exclusively bottle-fed for 6 months than in babies who were exclusively breastfed for 6 months.<sup>29</sup>

By administering a cross-sectional questionnaire to the parents of 221 Finnish children between 1 and 3 years of age attending day care, Hatakka et al reported that partial breastfeeding for more than 6 months of age is associated with a lower risk of recurrent AOM (aOR: 0.20;  $P = 0.002$ ).<sup>30</sup>

One large prospective observational study conducted on 5000 children in the Netherlands showed that breastfeeding probably has a protective effect [odds ratio (OR) 0.76; 95% CI: 0.61–0.95]. This result, however, was not confirmed by the multivariate analysis (OR: 0.86; 95% CI: 0.63–1.16).<sup>26</sup>

One recent meta-analysis included 24 observational studies to assess the correlation between the duration and exclusivity of breastfeeding and the risk of AOM. The cohort studies monitored the children with an average follow-up until the age of 6–24 months, whereas the cross-sectional analyzes studied the outcomes from 12 months to 8 years. Exclusive breastfeeding for the first 6 months was associated with a lower frequency of AOM before the age of 2 years (OR: 0.57; 95% CI: 0.44–0.57) than in children who were not exclusively breastfed up to 6 months of age. Breastfeeding of any type for longer than 3–4 months was found to be associated with a lower risk than breastfeeding with a shorter duration (OR: 0.85, 95% CI: 0.70–1.02). Breastfeeding of any type or duration was associated with a lower risk of AOM than no breastfeeding (OR: 0.67; 95% CI: 0.56–0.80). However, no association was reported between a longer duration of breastfeeding and a lower frequency of AOM, after 24 months of life (OR: 1.03; 95% CI: 0.59–1.79). It is possible that this result may have been influenced by the low number of studies assessing the incidence of AOM after 2 years of age.<sup>31</sup>

In one more recent prospective observational study, including 615 children of 6–36 months of age, breastfeeding was significantly associated with a reduction in the risk of AOM ( $P = 0.024$ ); partial breastfeeding (for 50% of the time) up to 6 months was also seen to be associated with a lower risk of AOM.<sup>2</sup>

On the contrary, in one prospective observational study conducted by Prins-van Ginkel et al in the Netherlands on 1056 infants over the age of 6 months, the population was split into 3 groups: never breastfed, breastfed in the current month, breastfed in the past. No significant difference between the 3 groups was described in terms of the frequency of AOM.<sup>2</sup>

To conclude, the data of the observational studies and the 2 meta-analyses selected are concordant, with a single exception, in indicating that breastfeeding has a protective role with regard to the occurrence of AOM. However, the nonhomogeneity of the studies does not make it possible to precisely define the importance of the exclusivity and duration of breastfeeding.

## Day-Care Attendance

The committee identified a number of observational studies of day-care attendance that were concordant regarding the presence of a strong association with an incremental risk of AOM, most

likely due to the increased exposure to the main colonizing otopathogens and upper respiratory tract viral agents.

In one large Dutch observational study, Labout et al did not observe a significant risk of AOM in children going to day care (OR: 0.86; 95% CI: 0.66–1.13).<sup>26</sup>

The prospective study conducted in the Netherlands by de Hoog et al observed 2217 children in follow-up until the age of 6 years. Children who attended day care from their first year of life had a frequency of AOM that was similar to that of children who did not attend day care; a higher frequency of AOM was reported in the first year of life, whereas cases of AOM were less frequent after 4 years of age ( $P < 0.001$ ). The subgroup of children who went to day care at 6–12 months of age had the highest frequency of AOM, antibiotic prescription and doctor's and specialist appointments.<sup>32</sup>

Prins-van Ginkel et al conducted a prospective observational study on 1056 children over 6 months, by interviewing their parents at monthly intervals regarding the occurrence of AOM and days of day care, antenatal and postnatal exposure to passive smoking and exclusive breastfeeding. This study showed that day care attendance was the main risk for AOM (OR: 5.0; 95% CI: 2.6–9.6); the authors reported that the OR increased in an inversely proportionate manner to age: for each month of life less the OR was 22% higher, in the first year of life.<sup>2</sup>

Csákányi et al conducted an observational study in Hungary on 412 babies between 6 and 18 months of age, by interviewing their parents. This study reported a higher number of episodes of AOM amongst children going to day care (OR: 2.74; 95% CI: 1.59–4.74).<sup>33</sup>

Kaur et al conducted a prospective observational study in the United States between 2006 and 2016 on 615 children between 6 and 36 months of age who had received 4 doses of pneumococcal conjugate vaccine (PCV)7 or PCV13. Day care was the strongest predictive factor for both AOM and recurrent AOM (OR 2.78; 95% CI: 2.19–3.52;  $P < 0.0001$ ).<sup>5</sup>

On the basis of a cross-sectional questionnaire on 594 Finnish children between 1 and 6 years of age going to day care, Hatakka et al reported that the risk of recurrent AOM in children between 1 and 3 years was higher with an intermediate duration of day-care attendance (13–23 month) than with short-term attendance (0–12 months) (OR: 3.34;  $P = 0.044$ ).<sup>30</sup> On the other hand, longer-term attendance (24 months) was not associated with a greater risk of AOM; indeed, no child with recurrent AOM belonged to the longer attendance group.<sup>31</sup>

The meta-analysis conducted by Zhang et al analyzed studies on the risk factors for chronic and recurrent otitis media, including a total of 24 observational studies. The analysis of 7 studies, on a total population of 2454 children, showed that day-care attendance did not have a significant impact on the risk of recurrent or chronic otitis media, with an OR of 1.70 (95% CI: 0.95–3.05) and  $P = 0.07$ .<sup>11</sup>

Uhari et al,<sup>21</sup> in one case-control study in nursery schools, studied the impact of using hygiene measures (careful hand washing, use of alcohol hand rubs) on the prevalence of upper respiratory tract infections, including AOM: over a 15-month follow-up period, there was a 27% reduction in the episodes of AOM.<sup>20</sup>

Appropriate caregiver education regarding the management of respiratory infections was associated with a reduction in the prevalence of AOM compared with the control group (AOM: 9.5% vs. 27.0%;  $P = 0.03$ ).<sup>35</sup> Alexandrino et al compared the prevalence of AOM in 3 groups: one group in which the caregivers performed nasal irrigation, one group in which caregivers received education and were able to perform nasal irrigation and a control group. The combination of adequate caregiver education and performance of nasal irrigations was associated with a lower prevalence of AOM than in the control group (AOM 7.7% vs. 32.4%;  $P = 0.042$ ).<sup>35</sup>



Alexandrino et al also conducted a cross-sectional analysis on 6 days care centers, for a total of 152 children  $\leq 3$  years of age. The possible association between the frequency of AOM and risk factors deriving from day-care attendance (nasal cleansing method, number of children and size of shared facilities) and individual risk factors, such as age, weight and body mass index (BMI) at birth were analyzed. Of the factors associated with day-care attendance, a greater frequency of AOM was observed in children who were subject to nasal cleansing using a suction device. This could be because of the fact that the day-care staff had not received adequate education regarding the correct nose cleansing technique to be used or that they performed nasal irrigation using a suction device more frequently on children with AOM.<sup>36</sup>

### Passive Smoking

Passive smoking favors nasopharyngeal colonization by otopathogens and is, therefore, a predisposing factor for the development of AOM.<sup>37</sup>

Seven observational studies were selected that evaluated the association between exposure to antenatal and postnatal passive smoking and the risk of AOM. A clear association was reported in 3 studies,<sup>34,39,40</sup> whereas the correlation between the 2 factors did not reach statistically significant levels in 4 studies and 1 meta-analysis.<sup>5,11,27,41,42</sup> However, generally speaking, most of the studies selected have significant methodologic limitations. For example, in some of the studies, data were obtained through telephone interviews;<sup>39,41</sup> in others, such as the meta-analysis conducted by Zhang et al,<sup>11</sup> the definition of recurrent AOM (RAOM) is not clearly specified and the outcome pools RAOM and chronic exudative otitis media (CEOM).

More specifically, in one large Norwegian study, the incidence of AOM in the first 6 months of life was seen to be 4.7% in babies who were not exposed, compared with 6% in those exposed to smoking both during pregnancy and after birth (RR: 1.24; 95% CI: 1.01–1.52).<sup>38</sup> Similarly, one Hungarian study reports an association between passive smoking and the occurrence of more than 2 episodes of AOM (aOR: 2.19; 95% CI: 1.17–4.07).<sup>33</sup> In one Iranian study, the incidence of recurrent AOM in children exposed to passive smoking reached 70.3% versus 27% in unexposed children ( $P = 0.001$ ).<sup>39</sup>

However, this association was not observed in a study conducted in Poland by interviewing 201 parents<sup>40</sup> or in the studies conducted by Prins-van Ginkel et al, Labout et al and Mc Cormick et al. Lastly, the meta-analysis conducted by Zhang et al analyzed literature on the risk factors for chronic and recurrent otitis media, including a total of 24 observational studies. The analysis of just 2 studies (422 children) showed that exposure to the mother's smoke during pregnancy did not have a significant impact (OR: 2.34; 95% CI: 0.64–8.54).<sup>11</sup> Conversely, in one analysis of 6 studies ( $n = 18,876$ ), exposure to passive smoking was seen to be significantly associated with a higher risk (OR: 1.39; 95% CI: 1.02–1.89;  $P = 0.04$ ).<sup>11</sup>

### Exposure to Outdoor and Indoor Pollutants

Some literature data suggest an association between exposure to outdoor and indoor pollutants and AOM. These studies explored the effects of pollutants with regard to cytotoxicity, inflammation and increased mucin expression.<sup>42</sup>

One observational study conducted in the Czech Republic on the distribution of respiratory diseases in 2 cities with different levels of environmental pollution showed that in the first 2 years of life, children living in an industrial or urban area had a significantly higher incidence of AOM than the group living in a rural area (RR: 2.3; 95% CI: 1.7–4.1;  $P < 0.001$ ).<sup>43</sup> However, this cannot be explained exclusively by the exposure to environmental

pollutants and may in part be influenced by greater crowding that promotes the spread of viral diseases of the upper airways.<sup>43</sup> One case-crossover study in Georgia analyzed pediatric Accident and Emergency Department admissions for a number of upper and lower respiratory tract infections, including AOM ( $n = 422,268$ ). A weak association was reported between the concentration of  $O_3$ , PM 2.5,  $SO_4^{2-}$ ,  $NO_3^-$ , and  $NH_4^+$  and the risk of AOM (OR: 1.059; 95% CI: 1.042–1.077).<sup>44</sup> The retrospective study by Deng et al, conducted in China, recruited 1617 children between 3 and 4 years of age. A parental questionnaire was used to record the prevalence of AOM and the degree of exposure to outdoor and indoor pollutants. Antenatal and postnatal exposure to nitric oxide, sulfur dioxide and Particulate Matter (PM)<sub>10</sub> particulate was estimated using municipal environmental data. The prevalence of AOM was seen to be associated with prenatal exposure to industrial environmental pollutants (aOR: 1.44; 95% CI: 1.09–1.88 for each  $27 \mu\text{g}/\text{m}^3$  increment in  $SO_2$ ) and with postnatal exposure to pollutants during domestic refurbishment work and wall painting (aOR: 1.62; 95% CI: 1.05–2.49 and aOR: 1.81; 95% CI: 1.12–2.91), especially in little girls.<sup>45</sup>

Girguis et al conducted an observational study in the United States to analyze the impact of an increase in the concentration of PM 2.5 on the incidence of AOM. An association was reported in between an increase in the concentration of PM 2.5 in the air 4 and 7 days before the diagnosis of AOM in premature subjects alone (OR: 1.09; 95% CI: 1.02–1.16 and OR: 1.08; 95% CI: 1.02–1.15, respectively).<sup>46</sup>

Park et al studied the association between the incidence of AOM in children up to 15 years of age in South Korea and the airborne concentration of 5 pollutants including PM<sub>10</sub> ( $\leq 10 \mu\text{m}$  diameter), nitric oxide ( $NO_2$ ), ozone ( $O_3$ ), sulfur dioxide and carbon monoxide. An association was reported with the incidence of otitis media at higher concentrations of these 5 pollutants than at reference values. PM<sub>10</sub> was associated with a higher risk of OM at time 0 (OR: 1.34; 99.9% CI: 1.17–1.54), whereas the higher concentrations of  $NO_2$  and  $O_3$  are associated with a higher incidence of OM at an interval of 1 [OR: 1.15, 99.9% (1.09–1.22)] and 4 weeks [OR: 1.16, 99.9% (1.07–1.25)], respectively.<sup>47</sup>

The systematic review conducted by Bowatte et al included 24 observational studies conducted before the end of 2017 on the association between exposure to different types of outdoor and indoor pollutants and the incidence of AOM. The studies analyzed include 9 cohorts studies, 2 case-control studies, 4 crossover studies, 8 cross-sectional studies and 1 time series. Significant nonhomogeneity was observed in terms of the pollutant measurement strategies, time and stage of exposure, outcome and the duration of follow-up between the various studies. The authors, therefore, conclude that the evidence of a causal relationship between pollutants and otitis media is still limited (very low quality according to AMSTAR 2 criteria).<sup>42</sup>

### Obesity

Another possible risk factor for AOM could be obesity. Indeed, recent studies have reported a relationship between high BMI and Eustachian tube dysfunction that could favor the development of AOM.<sup>48,49</sup> Certain experts also suggest that in children with recurrent AOM repeated exposure to antibiotic therapy could cause changes in the gut microbiome that, in turn, could correlate with an increased risk of obesity.<sup>50</sup>

However, the clinical data available in literature is limited, and only 3 observational studies were included.

Alexandrino et al conducted a cross-sectional analysis on 6 day-care centers, for a total of 152 children  $\leq 3$  years of age. The possible association between the frequency of AOM and risk factors deriving from day-care attendance (nasal cleansing method,

number of children and size of shared facilities) and individual risk factors, such as age, current weight and BMI at birth were analyzed. A significant association was observed between cases of AOM and BMI at birth (OR: 2.247; 95% CI: 1.011–4.992) and weight at the time of the study (OR: 1.607; 95% CI: 1.014–2.545).<sup>36</sup>

Sydell et al conducted an observational study in the United States on the clinical data of over 42 million children over 6 years of age, to study the possible association between obesity and AOM, allergic rhinitis and chronic nasal sinusitis. One multivariate analysis showed a significant association between obesity and the risk of AOM (OR: 1.44; 95% CI: 1.08–1.93;  $P=0.033$ ).<sup>51</sup>

Seaberg et al recruited 152 children (5–18 years of age), recorded the number of previous episodes of AOM and BMI and studied chorda tympani function. No significant relationship was identified between chorda tympani function and history of AOM or between history of otitis media and BMI.<sup>52</sup>

The studies analyzing the risk of AOM in children exposed to the various risk factors are observational and therefore produce low-quality evidence, with corresponding weak recommendations. On the basis of the evidence available, the recommendations to avoid exposure to passive smoking and to favor breastfeeding are also weak positives; however, given the many beneficial effects of eliminating passive smoking and promoting breastfeeding, the panel expressed strong positive recommendations.

### Recommendation 1

To reduce the risk of AOM, it is recommended

1. to avoid exposure to passive smoking (strong positive recommendation);
2. to limit the use of pacifiers, especially after 6 months of age (weak positive recommendation);
3. to practice exclusive breastfeeding for at least 6 months (strong positive recommendation);
4. to restrict day-care attendance, especially in large groups and/or full-time attendance (weak positive recommendation);
5. to perform nasal irrigations and adopt suitable hygiene measures at home and in day-care centers (especially frequent hand washing) (weak positive recommendation);
6. to limit exposure to indoor and outdoor pollutants (weak positive recommendation);
7. to monitor BMI due to a possible association between obesity and risk of AOM (weak positive recommendation).

An example of an educational tool that is easy for family members/caregivers to use is provided in Figure 2.

### Question No. 2. What Role Do Influenza Vaccines Play in the Prevention of AOM?

The systematic review by Manzoli et al includes 11 studies, for a total of 11,349 children, and analyzes the efficacy of influenza vaccination on AOM, in terms of the incidence in the vaccinated group compared with the control group: in 6 studies, the inactivated vaccine was administered by injection, and in 5 the live-attenuated vaccine was administered by nebulizer.<sup>53</sup>

In 8 out of 11 studies, a relationship was reported between influenza vaccination and a lower incidence of AOM, whereas the data in the other studies indicate negative results. Overall, the administration of the influenza vaccine is associated with a 51% (95% CI: 21%–71%) reduction in the incidence of AOM in the influenza virus circulation period in healthy children without a history of recurrent AOM.<sup>53</sup>

Vesikari et al reported, in 951 healthy children 6–36 months of age attending day care, who had been administered live-attenuated influenza vaccine via the intranasal route, an efficacy of over

90% for AOM associated with laboratory-confirmed influenza compared with the group receiving placebo (665 children), with a maximum efficacy in children over 18 months.<sup>54</sup>

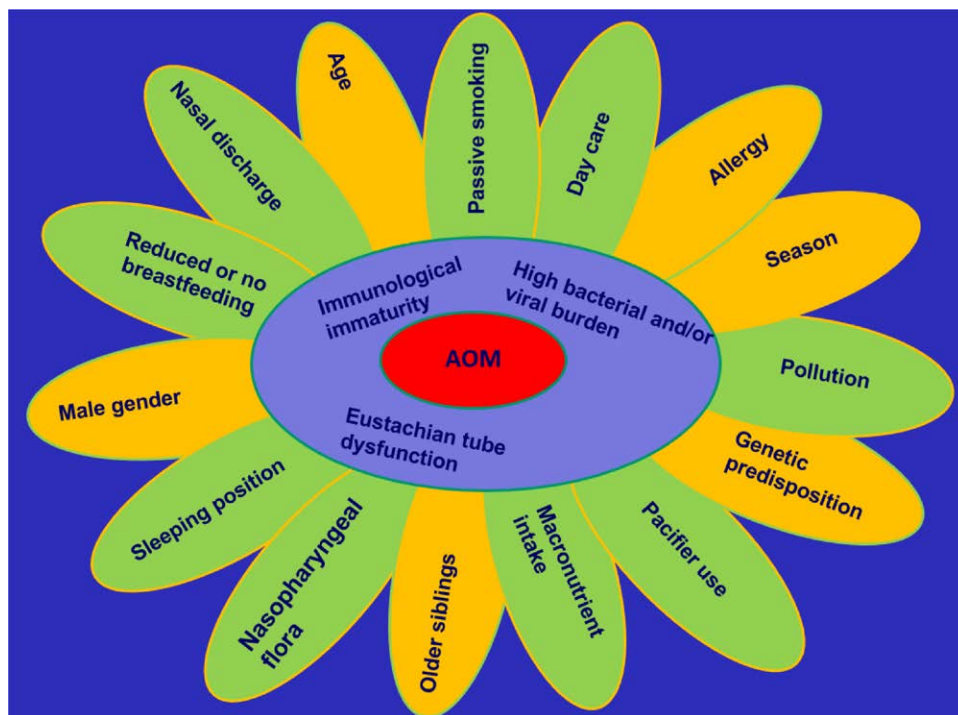
One study conducted in Italy reported that a significantly lower number of children with a history of recurrent AOM vaccinated with trivalent inactivated vaccine had at least 1 episode of AOM in the follow-up period than in the group of unvaccinated children (49/90, 54.4% vs. 74/90, 82.2%;  $P < 0.001$ ). The average number of episodes of AOM, the duration of bilateral exudative forms and the duration of antibiotic therapy were also lower in the vaccinated group.<sup>55</sup>

A good-quality Cochrane systematic review conducted in 2017 analyzed 11 trials on the efficacy of influenza vaccination in the prevention of AOM (6 trials in high-income countries and 5 multicenter trials in high-, intermediate- and low-income countries) on a total of 17,123 children, between 6 months and 6 years of age. Vaccination was associated with at least 1 less episode of AOM in a 6-month follow-up period (4 trials, 3134 children; RR: 0.84; 95% CI: 0.69–1.02). The analysis per subgroup of children (number of doses and type of vaccine administered) did not show significant differences. In vaccinated children, less use of antibiotics was observed (2 studies, 1223 children; RR: 0.70; 95% CI: 0.59–0.83; RR –0.11; 95% CI: –0.16 to –0.06; medium-low quality) (Norhayati et al; high quality according to AMSTAR 2 criteria).<sup>56</sup>

In the randomized, placebo-controlled, double-blind study conducted by Hoberman et al in 786 children between 6 and 24 months of age, the use of inactivated vaccine in 2 consecutive influenza seasons was not seen to be associated with a reduced frequency of AOM in the epidemic period and in the subsequent year's follow-up or in children presenting at least 1 episode of AOM.<sup>57</sup> However, a limited circulation of influenza viruses in the 2 periods studied could have influenced the results.

Cuhaci Çakir et al conducted a single-blind, randomized, prospective study in which they recruited, between December 2009 and April 2010, 46 children between 6 and 60 months of age, who were vaccinated with H1N1 pandemic vaccine and 46 unvaccinated children. A significant association was observed between vaccination and a lower frequency of exudative otitis media but not of cases of AOM.<sup>58</sup>

Heikkinen et al studied the frequency of all-cause AOM in children between 6 and 83 months of age vaccinated with live-attenuated vaccine in 6 randomized, placebo-controlled studies and in 2 randomized studies with a control group receiving the inactivated vaccine. During the influenza season, the efficacy of vaccination with the live-attenuated vaccine compared with placebo in patients between 6 and 71 months of age ( $N = 9497$ ) was 12.4% (95% CI: 2.0%–21.6%) in the first year, and in children between 18 and 83 months of age ( $N = 4142$ ) it was 6.2% in the second year (95% CI: –12.4% to 21.7%). When compared with the inactivated vaccine, the efficacy of the live-attenuated vaccine in children between 6 and 71 months ( $N = 9901$ ) was 9.7% (95% CI: –2.1% to 20.1%).<sup>59</sup> The same data were used to analyze the efficacy of the live-attenuated vaccine in the prevention of cases of influenza-associated AOM. The live-attenuated vaccine has 85% efficacy (95% CI: 78.3%–89.8%) compared with placebo and 54.0% efficacy (95% CI: 27.0%–71.7%) compared with the inactivated vaccine. In the placebo-controlled trials, the frequency of AOM in children who developed influenza despite vaccination with the live-attenuated vaccine was 10% versus 17% amongst those receiving placebo, causing a 38% reduction in AOM (95% CI: 11.0%–58.2%). In the trivalent influenza vaccine-controlled trials, the frequency of AOM in the cases of influenza developed despite vaccination was similar for the 2 groups.<sup>60</sup>



**FIGURE 2.** Risk factors daisy: the yellow petals represent the unmodifiable risk factors, and the green petals the modifiable risk factors.

One cost-effectiveness study conducted in Germany regarding the introduction of universal vaccination for children and adolescents with intranasal live-attenuated vaccine showed a significant economic advantage due also to the reduction in cases of AOM.<sup>61</sup>

### Recommendation 2

Influenza vaccination is recommended for the prevention of episodes of AOM (weak positive recommendation)

### Question No. 3. What Role Do Antibacterial Vaccines Play in the Prevention of AOM?

The study by Fortunato et al reported that the universal pneumococcal vaccination programme introduced in Italy in 2006 caused a significant (40%) reduction in the frequency of hospitalizations for AOM in children under 5 years of age, both nationwide and in those regions of Italy with a longer-standing vaccination history.<sup>62</sup>

Kaur et al conducted a prospective observational study in United States on 615 children between 6 and 36 months of age who had received 4 doses of PCV7 or PCV13.<sup>5</sup> Whereas before pneumococcal vaccination, it was reported that 80% of children presented an episode of AOM within the third year of life, with a 40% recurrence rate of  $\geq 3$  episodes, in the postvaccination era 26% of children presented an episode within the first year of life and 60% in the first 3 years with a  $\geq 3$  episode recurrence rate of 24%. However, it must be noted that these data are undoubtedly influenced also by the adoption of diagnostic criteria that have become more stringent over time and that may have in part contributed to the reduction of diagnoses.<sup>5</sup>

One study conducted in Japan compared the frequency of outpatient appointments and myringotomy in the pre-PCV7 and post-PCV7 and pre-PCV13 and post-PCV13 period and reported a significant reduction in the use of myringotomy but not in outpatient appointments for AOM. This study, therefore, concluded that the vaccine had been efficacious in reducing the clinical severity of episodes in children 1 to 5 years of age.<sup>63</sup> A similar finding is

reported in one large epidemiologic study conducted in Sweden, in which, following the introduction of pneumococcal vaccination on a vast scale, the incidence of all-cause AOM underwent a significant 41.5% and 20.9% reduction in children under and over 4 years of age, respectively.<sup>64</sup>

Similarly, a number of other epidemiologic studies conducted in various other countries reported a reduction in the incidence of AOM, the use of antibiotics and/or insertion of grommets in the postpneumococcal vaccination era [PCV7, protein D-conjugate vaccine (PHiD-CV) 10 or PCV13].<sup>65–73</sup>

According to the systematic review by Taylor et al, the efficacy of vaccination with PCV7 on cases of all-cause AOM was 0%–9% in randomized clinical trials and 7%–23% in observational studies. However, the number of doctor's appointments for AOM had started to drop in the 3–5 years prior to the introduction of PCV7. Therefore, in addition to pneumococcal vaccination, other factors could have contributed to the reduction in the incidence of AOM (very low quality according to AMSTAR 2 criteria).<sup>74</sup>

The Cochrane review by Fortanier et al included 9 randomized, controlled, blinded studies of which 5 studied vaccination within the first year of life in healthy children and 4 in children 1–7 years of age who were healthy or had a history of respiratory disease with or without a history of AOM, for a total of 48,426 children. The vaccines studied were *H. influenzae* protein D-conjugate PCV7, PCV9 and PCV11. The primary outcome studied was the frequency of all-cause AOM. PCV7 had a modest effect with a relative risk reduction (RRR) of 7% when administered during the first year of life to children with a low risk of AOM. The RRR with PCV7 and PCV11 was lower for AOM caused specifically by *S. pneumoniae* (RRR: 20%–52%). A greater efficacy was reported for the PCV11 vaccine for cases caused by nontypeable *H. influenzae* (NTHi). The administration of the PCV7 vaccine to children over 1 year was not associated with a reduction in risk, whereas the administration of the PCV9 vaccine was associated with a reduction in the risk of all-cause AOM in the group of older children. Some studies also evaluated the effect on cases of RAOM. The administration of



PCV7 was associated with a significant reduction (RRR: 9%–10%) in the cases of RAOM for the group of children under 1 year of age only (high quality according to AMSTAR 2 criteria).<sup>75</sup>

The meta-analysis by Ewald et al assessed 21 randomized controlled trials published before the end of 2014, of which 12 included children under 2 years of age, 2 included children between 2 and 15 years of age, 2 studies were conducted in subjects between 16 and 59 years and 5 studies involved subjects over 60 years of age, for a total population of 361,612 subjects. Vaccination with PCV was associated with a reduction in the risk of all-cause AOM (RR: 0.93; 95% CI: 0.86–1.00;  $P = 0.038$ ). PCV was also seen to be associated with a reduction in the episodes of AOM determined by the serotypes included in the vaccine (RR: 0.51; 95% CI: 0.43–0.60,  $P < 0.001$ ). No significant effect was reported regarding the cases of RAOM (RR: 0.87; 95% CI: 0.72–1.05) (low quality according to AMSTAR 2 criteria).<sup>76</sup>

Gisselsson-Solén et al conducted a controlled, randomized, open-label study on 96 children with a history of a first episode of AOM within the first 6 months of life and, therefore, a high risk of RAOM; 46 had been vaccinated with PCV7, 50 had not been vaccinated. The authors reported a reduction in the number of episodes of AOM of 26% ( $P = 0.03$ ), in the number of outpatient appointments of 36% ( $P = 0.01$ ) and in the insertion of grommets of 50% ( $P = 0.02$ ) in the vaccinated group.<sup>77</sup> The same authors subsequently conducted a single-blind randomized study (vaccine vs. placebo) in children with a history of a first episode of AOM in the first 6 months of life and, therefore, a high risk of RAOM, for a total of 109 children, of whom 52 vaccinated and 57 not vaccinated. Healthy condition nasopharyngeal swabs were taken for cases of AOM, and no significant difference was reported between the colonization of the 2 groups or in terms of the resistant strains.<sup>78</sup>

When PCV7 was administered to children who already had RAOM, the vaccine was not seen to reduce the risk of new episodes, probably because the late administration had little influence on nasopharyngeal pneumococcal colonization.<sup>75–80</sup>

The PHiD-CV pneumococcal vaccine, in which *H. influenzae* protein D is the transport protein, demonstrated efficacy in the reduction of all-cause AOM of 33.6%, a 57.6% reduction in those forms caused by pneumococcal serotypes and a 35.3% reduction for AOM caused by NTHi.<sup>81</sup>

Tregnaghi et al conducted a large-scale trial in Latin America including 7359 children to establish the efficacy of the PCV10 *H. influenzae* PHiD-CV in terms of the reduction in cases with a clinical diagnosis of AOM. The efficacy of the vaccine in reducing the number of first episode of AOM was 16% for all-cause AOM and 67% for cases of AOM caused by the pneumococcal serotypes included in the vaccine.<sup>82</sup> Similar results were reported in Chile.<sup>83</sup>

The randomized double-blind study conducted by Palmu et al in Finland studied the efficacy of vaccination with PHiD-CV 2+1 and 3+1 in terms of a reduction in severe pneumococcal infections, including cases of AOM. This study recruited 47,000 children and showed that vaccination with PHiD-CV, started within the first 12 months of life was efficacious with both the 3+1 and the 2+1 regimens.<sup>84</sup> In the same population, an albeit not statistically significant reduction in the insertion of grommets compared with the control group was also observed.<sup>85,86</sup> This reduction was backed up by the statistically significant values of the study subsequently published by the same authors.<sup>87</sup>

The prospective observational study by Oliveira et al conducted in Brazil on 422 children analyzed the association between the frequency of AOM and PHiD-CV vaccination. Vaccination with PHiD-CV was seen to be inversely proportionate to the frequency of AOM [OR (95%CI): 0.16 (0.05–0.52)] (low quality).<sup>88</sup>

Sáez-Llorens et al conducted a randomized double-blind study in which 7359 children were randomized to receive PHiD-CV or the control vaccine at an age of 2 or 4 or 6 and 15–18 months. For an average follow-up period of 32 months, samples of intratympanic fluid were collected in the case of a clinical diagnosis of AOM. The administration of PHiD-CV–conjugate vaccine was associated with efficacy against the first episode of AOM (clinical diagnosis) (24.0%; 95% CI: 8.7–36.7) and microbiologic diagnosis (B-AOM) [48.0% (20.3–66.1)] in children under 24 months of age, with a reduction in efficacy with an increase in age. Efficacy was greater in the prevention of the severe forms compared with the moderate forms [vaccine efficacy for moderate AOM 7.7% (–6.1 to 36.2) and for severe AOM 32.7% (–20.5 to 62.4) 7.7% (–6.1 to 36.2); severe VE: 32.7% (–20.5 to 62.4)]. Efficacy was significant in the prevention of episodes of AOM caused by the pneumococcal strains included in the vaccine, but not for NTHi.<sup>89</sup>

The review by Clarke et al analyzed 5 randomized controlled trials on the efficacy of the PHiD-CV vaccine in preventing NTHi infections of the upper airways and in modifying nasopharyngeal colonization.<sup>90–92</sup> Overall, protein D appears to be able to stimulate immune response and reduce the incidence of NTHi AOM. A reduction in NTHi colonization was observed, albeit short-lived. Therefore, this vaccination does not seem to induce herd immunity to this agent.<sup>91</sup>

The retrospective observational study conducted by Eythorsson et al in Iceland on data regarding appointments for AOM between 2008 and 2015 reported a reduction in the number of appointments for AOM [from 47.5 to 33.9 visits per 1000 person-years; incidence rate ratio (IRR): 0.86; 95% CI: 0.81–0.91;  $P < 0.001$ ] and a reduction in the use of ceftriaxone (6.49 to 2.96 therapies per 1000 person-years; IRR: 0.45; 95% CI: 0.37–0.54,  $P < 0.001$ ) after the introduction of the PHiD-CV vaccine. The reduction in the use of ceftriaxone was used as an indirect indicator of the therapeutic failure attributable to the diffusion of resistant strains.<sup>92</sup> The same group conducted a retrospective study on appointments for AOM conducted between 2005 and 2015 and reported a reduction in the number of appointments for AOM after the introduction of PHiD-CV, with an effect on the first episode (hazard ratio: 0.84; 95% CI: 0.82–0.86) and on the second episode (hazard ratio: 0.95, 95% CI: 0.93–0.98) of AOM, but not on subsequent episodes.<sup>93</sup> Similar results were published previously in 2015.<sup>94</sup> The same group also monitored in follow-up from birth 53,510 children and recorded the incidence of AOM in the cohort of children vaccinated and not vaccinated with PHiD-CV. In the group of vaccinated subjects, the frequency of antibiotics prescriptions for AOM was significantly lower, with an impact of 21.8% (95% CI: 11.5%–30.9%).<sup>95</sup> Cost-effectiveness studies conducted in a number of countries are available and demonstrate the advantage of using the PHiD-CV vaccine in terms of a reduction in the costs generated by cases of AOM.<sup>96,97</sup>

The 13-valent pneumococcal–conjugate vaccine is composed of the capsular polysaccharide transport protein of PCV7 but contains 6 additional serotypes. It is the only one to include serotype 19 A, identified as the most important cause of invasive pneumococcal disease, including mastoiditis.<sup>98</sup> Furthermore, whereas the PCV10–conjugate vaccine is able to modify the nasopharyngeal colonization to the same extent as PCV7, PCV13 significantly reduces the colonization of the 1, 6A, 7F, 6C, 10A, and 19F serotypes.<sup>99</sup> One study conducted in Italy on 177 children in an area with high PCV13 vaccine coverage presenting otorrhea during AOM required a culture test to be performed on the exudate. *S. pneumoniae* was isolated in 27% of children. In 77% of cases, these were serotypes not included in the PCV13 vaccine.<sup>100</sup> Lau et al, in a large observational study conducted in the United Kingdom,

showed that the introduction of vaccination with PCV7 was associated with a significant 22% reduction in cases of otitis media in children under 10 years of age. A further 19% reduction occurred following the introduction of vaccination with PCV13.<sup>101</sup>

Ben-Shimol et al conducted a prospective observational study in Israel by recruiting all the cases of AOM for which an intratympanic fluid test had been requested in children under 3 years of age, from 2004 to 2015. Three periods were established: pre-PCV, PCV7, and PCV13 and the incidence of cases of AOM caused by *S. pneumoniae*, NTHi, *Moraxella catarrhalis* and *Streptococcus pyogenes* and cases of AOM with a negative culture were analyzed. This study reported a reduction in cases of AOM, both those caused by pneumococcus and with a different bacterial etiology. The authors hypothesized that protection towards cases of early AOM may result in the prevention of subsequent forms caused by other agents.<sup>102</sup>

The retrospective observational study by Marom et al compared the frequency and characteristics of hospitalizations associated with a diagnosis of AOM and acute mastoiditis in children under 1 year of age in the pre-PCV13 period (2010–2011) with the frequency in the post-PCV13 period (2012–2015), reporting a reduction in the duration of hospitalization and the frequency of acute mastoiditis after the introduction of PCV13 compared with the previous period.<sup>103</sup> The same authors reported a greater prevalence of penicillin-sensitive pneumococcal strains in the exudate samples of children vaccinated with PCV7 or PCV13 compared with those not vaccinated.<sup>104</sup>

Kawai et al conducted a retrospective observational study in the United States to analyze the impact of pneumococcal vaccination on the number of outpatient appointments for suspected AOM. Compared with the pre-PCV7 period, in the post-PCV13 period, the frequency of outpatient appointments for AOM was 51% (95% CI: 42%–58%) lower in children under 2 years and 37% (95% CI: 23%–48%) lower in children between 2 and 4 years. This finding is probably influenced by the greater diagnostic accuracy developed gradually over the years.<sup>105</sup>

Conflicting results were reported in the United States by Talathi et al. Unlike the role of PCV13 in reducing invasive pneumococcal disease, the effect in reducing the incidence of AOM (26.4%) was minimal compared with that determined by PCV7 (26%) (OR:1.02; 95% CI: 0.65–1.60).<sup>106</sup> However, this study uses the presence of otorrhea and bulging as the only diagnostic criteria for AOM, and in the absence of these parameters, exudative OM was diagnosed. Therefore, the results could be affected by the definition of AOM and should be interpreted with caution.<sup>106</sup>

Rybak et al conducted a cross-sectional study for the period 2001–2016 on nasopharyngeal *S. pneumoniae*, *H. influenzae* and *Moraxella catarrhalis* colonization comparing the frequency of colonization in the pre-PCV13 period and that of the post-PCV 13 period (from 2013). This study reported a significant reduction in the penicillin-resistant strains of *S. pneumoniae* and, on the other hand, an increase in colonization by beta-lactamase-producing *H. influenzae* strains.<sup>99</sup>

Pichichero et al conducted a prospective observational study in the United States by recruiting, between 2010 and 2013, healthy children vaccinated with PCV 13 and examined as outpatients for a suspicion of AOM. Tests were performed on the serotypes present in the intratympanic fluid and compared with those of a group of children vaccinated with PCV7 and recruited between 2007 and 2009. PCV13-specific serotypes were isolated in 8% of the samples of the group vaccinated with PVC13 compared with 52% of the samples collected in the group vaccinated with PCV7, with an 86% reduction (95% CI: 61–94;  $P = 0.0010$ ). The most significant reduction was that in serotype 19A, of 91% (58–97;  $P = 0.0010$ ).<sup>107</sup>

A number of cost-effectiveness studies are also available for different countries and show an advantage of using PCV13 in terms of a reduction in the costs generated by cases of AOM in vaccinated and non-vaccinated children.<sup>109–112</sup> In a number of countries such as Canada, Peru, Colombia, Sweden, Italy and Denmark, vaccination with PCV13 has a cost-effectiveness that is greater than that of PHiD-CV.<sup>113–118</sup>

In other countries such as New Zealand and Japan, on the other hand, the cost-effectiveness of PHiD-CV has been reported as being greater than that of PCV13.<sup>119,120</sup> On the basis of this result, in 2017, in New Zealand PCV13 was replaced by PHiD-CV.<sup>119</sup> In Croatia, the cost-effectiveness analysis did not show any advantage in the use of pneumococcal vaccination, PHiD-CV or PCV13.<sup>120</sup>

To conclude, the overall analysis of the evidence shows that pneumococcal vaccination is efficacious for prevention in the first year of life, on the basis of the Cochrane review by Fortanier et al and a subsequent good-quality RCT.<sup>83</sup> As far as the prevention of recurrences is concerned, the Cochrane review and a good-quality RCT<sup>87</sup> do not show a certain advantage in terms of significance with the use of conjugate vaccination, whereas 1 RCT of an intermediate quality not included in the Cochrane review<sup>77</sup> and a number of observational studies show consistent results in terms of a reduction in the incidence of AOM.

### Recommendation 3

It is recommended to perform pneumococcal vaccination to prevent the first episode of AOM (strong positive recommendation) and recurrences (weak positive recommendation)

### Question No. 4 What Is the Role of Tympanostomy?

The insertion of grommets for the surgical prophylaxis of recurrent AOM is a controversial subject. Tympanostomy has been extensively studied for the prevention of exudative otitis media in the presence or absence of AOM.<sup>80,121</sup>

The placement of grommets is extensively used for both exudative OM and RAOM.<sup>122–124</sup>

Randomized studies have compared the number of episodes of AOM after tympanostomy and in the absence of surgery. Two RCTs showed a reduction in the number of episodes of AOM following tympanostomy with a 6-month follow-up.<sup>124,125</sup> One randomized study compared the frequency of AOM in 3 groups: the first receiving placebo, the second receiving prophylaxis with amoxicillin and the third undergoing tympanostomy. This trial showed, on the one hand, a lower frequency of AOM in the children receiving antibiotic prophylaxis and, on the other, no significant difference between those receiving tympanostomy and the placebo.<sup>126</sup>

One nonrandomized multicenter study showed an improvement in the quality of life in terms of an improvement in hearing, emotional stress and caregiver concerns.

The insertion of grommets was seen to be associated with complications such as anatomical changes in the tympanic membrane, focal atrophy, tympanosclerosis (32%) and chronic perforation in 2.2 % of cases of short-term grommets and 16% of cases of long-term grommets.<sup>127</sup>

The systematic review by Lous et al included 5 RCTs, of which 3 were antibiotic therapy-controlled, 2 were placebo-controlled and 2 had control groups that did not receive treatment, for a total of 519 children. Tympanostomy was able to prevent an episode of AOM or prevent one child in every 2–5 treated children from having another episode of AOM. Similar results were reported after 6 months of antibiotic prophylaxis (moderate quality according to AMSTAR 2 criteria).<sup>128</sup> The systematic review by Hellström et al analyzed 63 randomized and nonrandomized studies, to evaluate



the efficacy of tympanostomy in terms of a reduction in episodes of AOM and improvement in quality of life. The authors concluded that the evidence available was inadequate for supporting the efficacy of tympanostomy for RAOM (very low quality according to AMSTAR 2 criteria).<sup>129</sup>

Kujala et al conducted a randomized study in Finland on 300 children between 10 months and 2 years of age, with recurrent AOM without chronic exudate. The population was randomized to 3 groups: the first receiving grommets and adenoidectomy, the second receiving grommets alone and the third acting as a control group. The children were followed up for 12 months. The primary outcome was therapeutic failure, defined by at least 2 episodes of AOM in 2 months, 3 episodes in 6 months or persistent middle ear effusion for 2 months. Failure was significantly less frequent for cases treated with grommets and adenoidectomy (−18%; 95% CI: −30 to −6%;  $P < 0.004$ ) and the placement of grommets alone (−13%; 95% CI: from −25% to −1%;  $P < 0.04$ ) compared with the control group. The number of episodes of AOM in the 3 groups was also analyzed. A significant reduction in the number of cases of AOM was observed following the insertion of grommets with or without adenoidectomy of 46% and 32% respectively, compared with the control group, as well as a significant increase in the time to occurrence of a new episode of AOM amongst those who received grommets alone and the control group ( $P = 0.01$ ) and the group treated with grommets and adenoidectomy ( $P = 0.002$ ) compared with the control group.<sup>120</sup> However, this study was characterized by a number of limitations: the presence of spontaneous perforation and adenoid hypertrophy observed by endoscopy was not analyzed and, therefore, the groups could not be compared. Furthermore, the time for which the grommets remained in place, and the presence of otorrhea from the tube were not considered. The same group compared the improvement in quality of life after the placement of grommets with or without adenoidectomy. The overall score and caregiver concern parameters improved over time but without a significant difference between the 2 groups.<sup>131</sup>

The meta-analysis by Steele et al included studies analyzing the efficacy of grommet placement in children with CEOM (54 studies) and RAOM (8 studies). It was reported that the children with CEOM treated by tympanostomy, when compared with those who were followed by watchful waiting, presented a clear reduction in auditory threshold at a follow-up of 1–3 months but not of 12–24 months. In the population of children with recurrent AOM, those who received grommets presented fewer episodes of AOM, than observed with watchful waiting and placebo; however, this evidence is based on limited sample sizes.<sup>132</sup>

The meta-analysis by Mikals evaluated the efficacy of combining the adenoidectomy procedure with the placement of grommets. The primary outcome was the number of repeat tympanostomy procedures; the secondary outcomes were the number of episodes of RAOM, exudative otitis media and otorrhea. The combination with adenoidectomy was seen to be associated with fewer repeat tympanostomy procedures in children over 4 years of age. However, there were no differences in terms of episodes of RAOM.<sup>133</sup>

The Cochrane review by Venekamp et al analyzed 5 RCTs (805 children) comparing bilateral grommet insertion with and without adenoidectomy with watchful waiting, antibiotic prophylaxis or placebo, in children up to 16 years of age. The outcomes assessed were the proportion of children without episodes of AOM at 3–6 months' follow-up and the absence of persistent tympanic membrane perforation. The secondary outcome analyzed the frequency of children with recurrence after more than 12 months, the total number of episodes of AOM, quality of life, the presence of tympanic exudate and other adverse events. The authors concluded

in favor of a slight reduction in the recurrence of AOM in children who received grommets compared with watchful waiting and placebo, with a 1.5 reduction in the episodes of AOM in the 6 months following surgery, compared with watchful waiting (high quality according to AMSTAR 2 criteria).<sup>130–134</sup>

#### Recommendation 4

Grommets can be inserted in selected cases of recurrent AOM that did not respond to all other prevention strategies (weak positive recommendation).

#### Question No. 5 What Is the Role of Antibiotic Prophylaxis?

For years, antibiotic prophylaxis was considered a primary option for the prevention of AOM, with the rationale of reducing nasopharyngeal bacterial colonization and consequently reducing the frequency of AOM. However, it has now been extensively demonstrated that upper airway viral infections are the main cause of AOM.<sup>135</sup> Therefore, the efficacy of the use of antibiotics for treatment and prophylaxis was questioned and has been extensively studied.

In older studies, antibiotic prophylaxis (penicillin V, amoxicillin or azithromycin) was administered intermittently, whereas more recent studies have analyzed the efficacy of continuous prophylaxis for the entire duration of the winter period or for 1 year.<sup>136–141</sup>

The Cochrane review by Leach et al included 16 randomized controlled trials of which 14 were blinded, for a total of 1461 children, on the use of continuous antibiotic prophylaxis for at least 6 weeks compared with placebo or no treatment for the prevention of AO and CEOM. All the children were at risk of AOM or had a history of RAOM. The antibiotics used were sulfisoxazole (25–50 or 75 mg/kg/day), trimethoprim-sulfamethoxazole (12 mg/kg/day), amoxicillin (20 or 50 mg/kg/day), penicillin V (25 mg/kg/day) usually for 3–6 months, administered as 1 or 2 daily doses. Two hundred ninety-three out of 800 children (37%) in the treated group and 368/661 (56%) in the control group experienced at least 1 episode of AOM during the intervention period, with an RR of 0.65 (95% CI: 0.53–0.79). A 21% reduction was estimated, meaning that 5 children would have to be treated (95% CI: 4–6) to prevent 1 child from experiencing an episode of AOM during prophylaxis. It was also reported that antibiotic prophylaxis was associated with an average of 1.5 fewer episodes of AOM per year of prophylaxis, during the treatment (high quality according to AMSTAR 2 criteria).<sup>142</sup> However, the results of this meta-analysis must be interpreted with caution because the studies included had different inclusion criteria, used different types of antibiotics and had variable follow-up periods. Furthermore, most of the studies were conducted prior to the introduction of pneumococcal vaccination.

The systematic review by Cheong et al included 4 studies comparing the use of antibiotic prophylaxis and placebo in the prevention of AOM in terms of the reduction in recurrence, the frequency of cases of AOM and the total time with AOM. Although it was not possible to conduct a pooled-analysis, it was reported that antibiotic prophylaxis is an efficacious method for preventing recurrences (3 studies), the frequency of cases of AOM (2 studies) and the total time with AOM (2 studies) and a better efficacy than the placement of grommets and adenoidectomy (very low quality according to AMSTAR 2 criteria).<sup>143</sup>

To conclude, a number of studies show a statistically significant reduction in the number of episodes of AOM compared with placebo. However, the clinical relevance of these results is controversial in literature, considering also the limited number of events of AOM prevented over a long period of time, the risk of adverse events and the possibility of selecting resistant bacteria.

Furthermore, most of the studies were conducted prior to the introduction of pneumococcal vaccination.

### Recommendation 5

Antibiotic prophylaxis is not recommended for the prevention of recurrent AOM, except in certain carefully selected cases (weak negative recommendation).

### Question No. 6. What Is the Role of Xylitol?

Xylitol is a pentitol that occurs naturally in fruits such as plums, strawberries and raspberries. It is a noncaries-producing sweetener that is extensively used in the manufacture of chewing gum, toothpaste and medicinal products. Some data present in literature suggest that the addition of 1% to 5% of xylitol to culture medium is associated with a reduction in *in vitro* growth and that exposure to 5% xylitol is associated with a reduction in the cell adhesion of *S. pneumoniae*.<sup>144,145</sup> The meta-analysis by Danhauer et al, which included 4 RCTs, concluded in favor of a significant efficacy of xylitol in the prevention of cases of AOM (RR: 0.68; CI: 0.57–0.83) (low quality).<sup>146</sup>

The more recent Cochrane review conducted in 2016, identified 3 RCTs for a total of 1826 healthy Finnish children attending day care. The group treated with xylitol (in any formulation) for 2–3 months presented a lower incidence of AOM than the control group (RR: 0.75; 95% CI: 0.65–0.88). It was also reported that in children under 2 years of age, and who were not therefore able to use chewing gum, the use of a solution containing xylitol was seen to be associated with a 30% reduction in the risk of AOM. In studies including older children, who were able to chew gum, the reduction in the risk of AOM was 41%. The use of xylitol for a short period, only during an acute respiratory tract infection or in children with a high risk of AOM alone, on the other hand, was not associated with a reduction in the frequency of AOM (high quality according to AMSTAR 2 criteria).<sup>147</sup> This meta-analysis has a number of limitations: the average age of the children included was higher than that of the children who usually experience AOM, as children under 2 years of age were not included; furthermore, the administration regimen applied in the included studies is not practical in daily life (eg, administration 5 times a day after meals for 5 minutes).

The randomized controlled trial conducted by Vernacchio et al analyzed the efficacy of the administration of a xylitol 5 g solution 3 times a day, in terms of the reduction in the incidence of AOM in children 6 months to 5 years of age with risk factors for AOM. In all 326 children were recruited, 160 treated with xylitol and 166 with placebo. No differences were observed in the 2 groups in the incidence of AOM or in terms of the use of antibiotic therapy after 90 days of therapy.<sup>148</sup>

To conclude, the data available suggest that the use of xylitol could prevent the onset of AOM and that the chewing gum/ tablet formulation is more efficacious than the syrup formulation. However, there are certain practical aspects to be considered: children under 2 years of age, who are those at the greatest risk of AOM, cannot use these formulations safely. Furthermore, to be efficacious, xylitol should be administered frequently, 3 to 5 times a day.<sup>80,147</sup>

### Recommendation 6

The use of xylitol, in any formulation, is not recommended for the prevention of AOM (weak negative recommendation).

### Question No. 7. What Is the Role of Probiotic Administration?

There are few available studies analyzing the efficacy of probiotics in the prevention of respiratory tract infections, in particular AOM, and those available are often contradictory.<sup>149–152</sup>

In some randomized, double-blind, placebo-controlled studies, the reduction observed in the incidence of AOM was nonsignificant or only marginal.<sup>152–155</sup>

One randomized, double-blind, placebo-controlled study reported that the recurrence of AOM in children administered one capsule of probiotics a day (*Lactobacillus rhamnosus* GG and LC705, *Bifidobacterium breve* 99 and *Propionibacterium freudenreichii* JS) was similar to that amongst children receiving placebo.<sup>152</sup>

In one randomized, double-blind, placebo-controlled study conducted in Finland, 72 children were randomized to daily probiotic administration (*L. rhamnosus* GG and *Bifidobacterium lactis* Bb-12) or placebo for 12 months. The group treated with probiotics was associated with a lower incidence of AOM (RR: 0.44; 95% CI: 0.21–0.90)  $P = 0.014$  and with a significantly lesser use of antibiotics (RR: 0.52; 95% CI: 0.29–0.92;  $P = 0.015$ ). On the other hand, no change was reported in pharyngeal *S. pneumoniae* or *H. influenzae* colonization, whereas there was an increase in *M. catarrhalis* colonization (OR: 1.79).<sup>153</sup>

In one randomized, double-blind, placebo-controlled trial, 224 children (7–13 months of age) at a high risk of AOM were randomized to receive formula supplemented with probiotics (*Streptococcus thermophilus* CC 2496, *Streptococcus salivarius* DSM 13084 and *L. rhamnosus* LPR CGMCC 1.3724) and prebiotics (Raftilose/Raftiline) or to receive normal formula alone. During the follow-up period, the 2 groups did not show significant differences in terms of incidence in AOM (IRR: 1.0; 95% CI: 0.8–1.2), respiratory tract infections (IRR: 0.9; 95% CI: 0.7–1.2) or frequency of antibiotic therapy (IRR: 1.0; 95% CI: 0.8–1.2), which was prescribed above all for cases of AOM. Neither was there evidence of a difference in the composition of nasopharyngeal colonization in the 2 groups.<sup>154</sup>

The meta-analysis of 4 RCTs by Liu et al, on the other hand, reported a reduction in the risk (RR: 0.76; 95% CI 0.64–0.91) of AOM in 1805 children 0 to 18 years of age taking probiotics containing *L. rhamnosus* GG versus placebo.<sup>155</sup>

Some studies have analyzed the efficacy of topical probiotics administered by nasal spray. The most extensively studied organism is *Streptococcus α-haemolyticus* (AHS), an infectious agent with a low pathogenic power able to interfere with the replication of the nasopharyngeal pathogens commonly associated with AOM.<sup>156</sup> The administration of this probiotic has yielded promising preliminary results. In one randomized study, 43 children were administered 4 months' treatment with a nasal spray containing 5 strains of AHS versus nasal spray with placebo (158). The proportion of children with RAOM was similar in the 2 groups (AHS: 44%; placebo: 40%), and no difference in terms of nasopharyngeal colonization was observed.<sup>157</sup>

Prophylaxis with certain strains of AHS was abandoned due to the possibility of causing infections.<sup>158</sup>

More recently, literature has focused on *S. salivarius*, an AHS isolated from healthy subjects and never associated with infection. *S. salivarius* is a potential nasopharyngeal probiotic due to its immunomodulatory, anti-inflammatory and bactericidal properties and its good safety profile.<sup>159</sup>

Studies on the efficacy of *S. salivarius* 24 SMB have yielded promising results.<sup>160,161</sup> In one randomized controlled study, 100 bambini with a history of RAOM were randomized to receive nasal spray with *S. Salivarius* 24 SMB or with placebo in each nostril twice a day for 5 consecutive days for 3 consecutive months and were monitored through monthly visits and in the case of fever or symptoms compatible with AOM for 6 months. No significant difference was observed in terms of the number of children who developed at least 1 episode of AOM between the 2 groups. However, considering the children with *S. salivarius* 24 SMB colonization alone, the number of episodes of AOM was significantly lower than in uncolonized children (42.8% vs. 13.6%;  $P = 0.03$ ); similarly, the

use of antibiotic therapy was lower amongst colonized children than uncolonized ones (67.8% vs. 95.5%;  $P = 0.029$ ). In a low-quality retrospective observational study by La Mantia et al, children with a history of RAOM were randomized to receive, in the case of an episode of AOM, antibiotic therapy alone (group A) or antibiotic therapy followed by administration of a nasal spray containing *S. salivarius* 24 SMB for 3 months (group B). The primary outcome was to evaluate the number of episodes of AOM the following winter. Seventy-four children (68.5%) in group A versus 15 (9.4%) in group B showed the same number of episodes of AOM as observed in the same period of the previous year,  $P < 0.0001$ . Furthermore, the intergroup analysis showed a significant difference in terms of the number of episodes of AOM ( $P < 0.0001$ ).<sup>160</sup> Arbitrary, open-label randomization and the absence of a true control group reduce the quality of this evidence. One retrospective Italian study including 133 children (3–14 years) treated with *S. salivarius* K12 for 3 months reported a 70% reduction in episodes of otitis compared with the previous season.<sup>162</sup> However, the retrospective design and the absence of a control group are limitations to this study.

### Recommendation 7

The use of oral probiotics for the prevention of AOM is not recommended (weak negative recommendation).

The use of topical probiotics for the prevention of AOM is not recommended on the basis of the limited evidence available (weak negative recommendation).

### Question No. 8. What Is the Role of Vitamin D Supplementation?

Various studies have analyzed the effects of vitamin D supplementation on a number of recurrent respiratory tract infections.<sup>163,164</sup> Data regarding the prevention of AOM is still limited.

Cayir et al conducted a randomized, single-blind, case-control study, including children with AOM and a control group of healthy children. A total of 169 children were recruited, 88 cases and 81 controls, split into 2 groups according to the baseline serum level of 25 OH vitamin D. The number of children with a deficiency ( $<15$  ng/dL) was significantly higher in the group of children with AOM than in the control group ( $P < 0.004$ ).<sup>165</sup>

The meta-analysis by Li et al analyzed 5 studies (4 in pediatric populations and 1 in an adult population), for a total of 16,689 subjects who underwent vitamin D testing. The participants with AOM had lower 25 OH vitamin D levels than those without AOM. More specifically, the group of participants with AOM but not CEOM was associated with lower 25 OH vitamin D levels.<sup>166</sup>

In one Italian randomized, double-blind, placebo-controlled trial, in children with a history of AOM 1–5 years of age, the number of children with AOM was significantly lower in the group receiving 1000 IU/day of vitamin D<sub>3</sub> from November to March, compared with the control group ( $P = 0.03$ ). Furthermore, the difference was seen to be significant for children with prior uncomplicated AOM ( $P < 0.001$ ), but not for children with a history of episodes associated with spontaneous otorrhea.<sup>167</sup>

### Recommendation 8

The use of vitamin D for the prevention of AOM is not recommended on the basis of the limited evidence available (weak negative recommendation).

### Question No. 9. What Is the Role of Other Complementary Therapies?

The use of complementary and alternative medicine has been proposed as an alternative option or supplement to conventional antibiotic prophylaxis.<sup>168–169</sup>

One randomized, controlled, open-label study studied the efficacy of a traditional Japanese product, *juzen-taiho-to*, for the prevention of AOM in children at risk. The episodes of AOM were 57% lower than amongst the children who received conventional prophylaxis alone ( $0.61 \pm 0.54$  vs.  $1.07 \pm 0.72$  AOM episodes/month  $P = 0.005$ ).<sup>170</sup>

One Cochrane review on the use of Zinc supplementation included 10 studies conducted in intermediate- and low-income countries, for a total of 6820 children under 5 years of age, to whom Zinc was administered to prevent pneumonia. The evidence of the efficacy of Zinc in reducing the incidence of AOM is ambiguous. Supplementation appeared to be efficacious in a group of children treated for severe malnutrition; however, this finding is based on a small trial (39 children) and should, therefore, be interpreted with caution (high quality according to AMSTAR 2 criteria).<sup>171</sup>

Although some trials have analyzed the use of complementary therapies for the prevention of AOM, the studies available are burdened by significant methodologic limitations, and it is not possible to reach definitive conclusions regarding their safety and efficacy.

### Recommendation 9

The use of complementary therapies for the prevention of AOM is not recommended on the basis of the limited evidence available (weak negative recommendation).

## DISCUSSION AND CONCLUSIONS

In this version of our guidelines, there is no change in the recommendation regarding pneumococcal vaccination.

As indicated in the previous version, we recommend limiting/eliminating exposure to a number of risk factors, such as day-care attendance in the first year of life, passive smoking and pacifier use. The recommendation to limit exposure to environmental pollutants has been added. The promotion of breastfeeding and hygiene measures at day care are once again proposed.

In this update, specific questions were added regarding the efficacy of grommets and antibiotic prophylaxis, vitamin D, xylitol and probiotic supplementation and complementary therapies. Grommets can be inserted in selected cases of recurrent AOM that did not respond to all other prevention strategies. Antibiotic prophylaxis is not recommended for the prevention of recurrent AOM, except in certain selected cases. The use of probiotics, vitamin D, xylitol and complementary therapies are not recommended on the basis of the limited evidence available.

Good-quality studies on interventions to prevent AOM are required to develop future updates to this document, especially with regard to the use of probiotics, vitamin D and xylitol.

The prevention of AOM requires an integrated, multidisciplinary approach and close cooperation with the family and consequently the diffusion of easily accessible educational tools should be encouraged.

## ACKNOWLEDGMENTS

*Other members of the panel: Sergio Bottero (Roma), Grazia Fenu (Firenze), Giorgio Piacentini (Verona), Renato Cutrera (Roma), Lorenzo Pignataro (Milano); Attilio Varricchio (Napoli); Bottero Sergio (Roma), Paolo Biasci (Livorno), Maria Carmen Verga (Salerno), Roberto Mattina (Milano), Andrea Novelli (Firenze), Luciano Pinto (Napoli), Maria Enrica Bettinelli (Milano), Mattia Doria (Chioggia), Paolo Becherucci (Firenze), Maurizio de Martino (Firenze), Luisa Galli (Firenze), Amelia Licari (Pavia), Salvatore De Masi (Firenze), Riccardo Lubrano (Roma), Maria Bettinelli (Milano), Claudio Vicini (Forlì), Giovanni Felisati (Milano).*



## REFERENCES

- Paradise JL, Rockette HE, Colborn DK, *et al.* Otitis media in 2253 Pittsburgh-area infants: prevalence and risk factors during the first two years of life. *Pediatrics*. 1997;99:318–333.
- Prins-van Ginkel AC, Bruijning-Verhagen PC, Uiterwaal CS, *et al.* Acute otitis media during infancy: parent-reported incidence and modifiable risk factors. *Pediatr Infect Dis J*. 2017;36:245–249.
- Daly KA, Hoffman HJ, Kvaerner KJ, *et al.* Epidemiology, natural history, and risk factors: panel report from the ninth international research conference on otitis media. *Int J Pediatr Otorhinolaryngol*. 2010;74:231–240.
- Hoffman HJ, Daly KA, Bainbridge KE, *et al.* Panel 1: epidemiology, natural history, and risk factors. *Otolaryngol Head Neck Surg*. 2013;148(4 Suppl):E1–E25.
- Kaur R, Morris M, Pichichero ME. Epidemiology of acute otitis media in the postpneumococcal conjugate vaccine era. *Pediatrics*. 2017;140:p11:e20170181.
- Holl K, Rosenlund M, Giaquinto C, *et al.* The impact of childhood acute otitis media on parental quality of life in a prospective observational cohort study. *Clin Drug Investig*. 2015;35:613–624.
- Marchisio P, Bellussi L, Di Mauro G, *et al.* Acute otitis media: from diagnosis to prevention. Summary of the Italian guideline. *Int J Pediatr Otorhinolaryngol*. 2010;74:1209–1216.
- Brouwers MC, Kho ME, Browman GP, *et al.*; AGREE Next Steps Consortium. AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ*. 2010;182:E839–E842.
- Shea BJ, Reeves BC, Wells G, *et al.* AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*. 2017;358:j4008.
- Gisselsson-Solén M, Henriksson G, Hermansson A, *et al.* Risk factors for carriage of AOM pathogens during the first 3 years of life in children with early onset of acute otitis media. *Acta Otolaryngol*. 2014;134:684–690.
- Zhang Y, Xu M, Zhang J, *et al.* Risk factors for chronic and recurrent otitis media—a meta-analysis. *PLoS One*. 2014;9:e86397.
- Pichichero ME. Ten-year study of the stringently defined otitis-prone child in Rochester, NY. *Pediatr Infect Dis J*. 2016;35:1033–1039.
- Casselbrant ML, Mandel EM, Doyle WJ. Information on co-morbidities collected by history is useful for assigning otitis media risk to children. *Int J Pediatr Otorhinolaryngol*. 2016;85:136–140.
- Marchisio P, Nazzari E, Torretta S, *et al.* Medical prevention of recurrent acute otitis media: an updated overview. *Expert Rev Anti Infect Ther*. 2014;12:611–620.
- Rämet M, Löfgren J, Alho OP, *et al.* Surfactant protein-A gene locus associated with recurrent otitis media. *J Pediatr*. 2001;138:266–268.
- Wiertsema SP, Herpers BL, Veenhoven RH, *et al.* Functional polymorphisms in the mannin-binding lectin 2 gene: effect on MBL levels and otitis media. *J Allergy Clin Immunol*. 2006;117:1344–1350.
- Rye MS, Blackwell JM, Jamieson SE. Genetic susceptibility to otitis media in childhood. *Laryngoscope*. 2012;122:665–675.
- Rye MS, Warrington NM, Scaman ES, *et al.* Genome-wide association study to identify the genetic determinants of otitis media susceptibility in childhood. *PLoS One*. 2012;7:e48215.
- van Ingen G, Li J, Goedegeure A, *et al.* Genome-wide association study for acute otitis media in children identifies FNDC1 as disease contributing gene. *Nat Commun*. 2016;7:12792.
- Uhari M, Mäntysaari K, Niemelä M. A meta-analytic review of the risk factors for acute otitis media. *Clin Infect Dis*. 1996;22:1079–1083.
- Lubianca Neto JF, Hemb L, Silva DB. Systematic literature review of modifiable risk factors for recurrent acute otitis media in childhood. *J Pediatr (Rio J)*. 2006;82:87–96.
- Bluestone CD. Epidemiology. In: Bluestone CD, Klein JO, eds. *Otitis Media in Infants and Children*. Hamilton: BC Decker Inc; 2007:73–100.
- Niemelä M, Pihakari O, Pokka T, *et al.* Pacifier as a risk factor for acute otitis media: a randomized, controlled trial of parental counseling. *Pediatrics*. 2000;106:483–488.
- Rovers MM, Numans ME, Langenbach E, *et al.* Is pacifier use a risk factor for acute otitis media? A dynamic cohort study. *Fam Pract*. 2008;25:233–236.
- Torretta S, Marchisio P, Cappadona M, *et al.* Habitual use of push and pull plastic bottle caps is more prevalent among children with recurrent acute otitis media. *Int J Pediatr Otorhinolaryngol*. 2013;77:1179–1182.
- Labout JA, Duijts L, Lebon A, *et al.* Risk factors for otitis media in children with special emphasis on the role of colonization with bacterial airway pathogens: the generation R study. *Eur J Epidemiol*. 2011;26:61–66.
- Nowak AJ, Niemelä M, Uhari M, *et al.* Pacifier as a risk factor for acute otitis media. *Pediatrics*. 2002;109:351–353.
- Saariinen UM. Prolonged breast feeding as prophylaxis for recurrent otitis media. *Acta Paediatr Scand*. 1982;71:567–571.
- Duffy LC, Faden H, Wasielewski R, *et al.* Exclusive breastfeeding protects against bacterial colonization and day care exposure to otitis media. *Pediatrics*. 1997;100:E7.
- Hatakka K, Piirainen L, Pohjavuori S, *et al.* Factors associated with acute respiratory illness in day care children. *Scand J Infect Dis*. 2010;42:704–711.
- Bowatte G, Tham R, Allen KJ, *et al.* Breastfeeding and childhood acute otitis media: a systematic review and meta-analysis. *Acta Paediatr*. 2015;104:85–95.
- de Hoog ML, Venekamp RP, van der Ent CK, *et al.* Impact of early day-care on healthcare resource use related to upper respiratory tract infections during childhood: prospective WHISTLER cohort study. *BMC Med*. 2014;12:107.
- Csákányi Z, Czinner A, Spangler J, *et al.* Relationship of environmental tobacco smoke to otitis media (OM) in children. *Int J Pediatr Otorhinolaryngol*. 2012;76:989–993.
- Alexandrino AS, Santos R, Melo C, *et al.* Impact of caregivers' education regarding respiratory infections on the health status of day-care children: a randomized trial. *Fam Pract*. 2016;33:476–481.
- Alexandrino AS, Santos R, Melo C, *et al.* Caregivers' education vs rhinopharyngeal clearance in children with upper respiratory infections: impact on children's health outcomes. *Eur J Pediatr*. 2017;176:1375–1383.
- Alexandrino AS, Santos R, Melo C, *et al.* Risk factors for respiratory infections among children attending day care centres. *Fam Pract*. 2016;33:161–166.
- Greenberg D, Givon-Lavi N, Broides A, *et al.* The contribution of smoking and exposure to tobacco smoke to *Streptococcus pneumoniae* and *Haemophilus influenzae* carriage in children and their mothers. *Clin Infect Dis*. 2006;42:897–903.
- Häberg SE, Bental YE, London SJ, *et al.* Prenatal and postnatal parental smoking and acute otitis media in early childhood. *Acta Paediatr*. 2010;99:99–105.
- Amani S, Yarmohammadi P. Study of effect of household parental smoking on development of acute otitis media in children under 12 years. *Glob J Health Sci*. 2015;8:81–88.
- Bielska DE, Kurpas D, Nitsch-Osuch A, *et al.* Exposure to environmental tobacco smoke and respiratory tract infections in pre-school children - a cross-sectional study in Poland. *Ann Agric Environ Med*. 2015;22:524–529.
- McCormick DP, Jennings K, Ede LC, *et al.* Use of symptoms and risk factors to predict acute otitis media in infants. *Int J Pediatr Otorhinolaryngol*. 2016;81:55–59.
- Bowatte G, Tham R, Perret JL, *et al.* Air pollution and otitis media in children: a systematic review of literature. *Int J Environ Res Public Health*. 2018;15:p11:E257.
- Dostál M, Průcha M, Rychlíková E, *et al.* Differences between the spectra of respiratory illnesses in children living in urban and rural environments. *Cent Eur J Public Health*. 2014;22:3–11.
- Xiao Q, Liu Y, Mulholland JA, *et al.* Pediatric emergency department visits and ambient air pollution in the U.S. State of Georgia: a case-crossover study. *Environ Health*. 2016;15:115.
- Deng Q, Lu C, Jiang W, *et al.* Association of outdoor air pollution and indoor renovation with early childhood ear infection in China. *Chemosphere*. 2017;169:288–296.
- Girguis MS, Strickland MJ, Hu X, *et al.* Exposure to acute air pollution and risk of bronchiolitis and otitis media for preterm and term infants. *J Expo Sci Environ Epidemiol*. 2018;28:348–357.
- Park M, Han J, Jang MJ, *et al.* Air pollution influences the incidence of otitis media in children: a national population-based study. *PLoS One*. 2018;13:e0199296.
- Kim JB, Park DC, Cha CI, *et al.* Relationship between pediatric obesity and otitis media with effusion. *Arch Otolaryngol Head Neck Surg*. 2007;133:379–382.
- Lee SK, Yeo SG. Relationship between pediatric obesity and otitis media with effusion. *Curr Allergy Asthma Rep*. 2009;9:465–472.

50. Pelton S. Personal presentation. 2018.
51. Sidell D, Shapiro NL, Bhattacharyya N. Obesity and the risk of chronic rhinosinusitis, allergic rhinitis, and acute otitis media in school-age children. *Laryngoscope*. 2013;123:2360–2363.
52. Seaberg RM, Chadha NK, Hubbard BJ, et al. Chorda tympani nerve function in children: relationship to otitis media and body mass index. *Int J Pediatr Otorhinolaryngol*. 2010;74:1393–1396.
53. Manzoli L, Schioppa F, Boccia A, et al. The efficacy of influenza vaccine for healthy children: a meta-analysis evaluating potential sources of variation in efficacy estimates including study quality. *Pediatr Infect Dis J*. 2007;26:97–106.
54. Vesikari T, Fleming DM, Aristegui JF, et al; CAIV-T Pediatric Day Care Clinical Trial Network. Safety, efficacy, and effectiveness of cold-adapted influenza vaccine-trivalent against community-acquired, culture-confirmed influenza in young children attending day care. *Pediatrics*. 2006;118:2298–2312.
55. Marchisio P, Esposito S, Bianchini S, et al. Efficacy of injectable trivalent virosomal-adjuvanted inactivated influenza vaccine in preventing acute otitis media in children with recurrent complicated or noncomplicated acute otitis media. *Pediatr Infect Dis J*. 2009;28:855–859.
56. Norhayati MN, Ho JJ, Azman MY. Influenza vaccines for preventing acute otitis media in infants and children. *Cochrane Database Syst Rev*. 2017;10:CD010089.
57. Hoberman A, Greenberg DP, Paradise JL, et al. Effectiveness of inactivated influenza vaccine in preventing acute otitis media in young children: a randomized controlled trial. *JAMA*. 2003;290:1608–1616.
58. Cuhaci Çakir B, Beyazova U, Kemalolu YK, et al. Effectiveness of pandemic influenza A/H1N1 vaccine for prevention of otitis media in children. *Eur J Pediatr*. 2012;171:1667–1671.
59. Heikkinen T, Block SL, Toback SL, et al. Effectiveness of intranasal live attenuated influenza vaccine against all-cause acute otitis media in children. *Pediatr Infect Dis J*. 2013;32:669–674.
60. Block SL, Heikkinen T, Toback SL, et al. The efficacy of live attenuated influenza vaccine against influenza-associated acute otitis media in children. *Pediatr Infect Dis J*. 2011;30:203–207.
61. Damm O, Eichner M, Rose MA, et al. Public health impact and cost-effectiveness of intranasal live attenuated influenza vaccination of children in Germany. *Eur J Health Econ*. 2015;16:471–488.
62. Fortunato F, Martinelli D, Cappelli MG, et al. Impact of Pneumococcal conjugate universal routine vaccination on Pneumococcal disease in Italian children. *J Immunol Res*. 2015;2015:206757.
63. Sasaki A, Kunimoto M, Takeno S, et al. Influence of Pneumococcal conjugate vaccines on acute otitis media in Japan. *Auris Nasus Larynx*. 2018;45:718–721.
64. Johansson Kostenniemi U, Palm J, Silfverdal SA. Reductions in otitis and other respiratory tract infections following childhood Pneumococcal vaccination. *Acta Paediatr*. 2018 Mar 30. doi: 10.1111/apa.14345.
65. Stamboulidis K, Chatzaki D, Poulakou G, et al. The impact of the heptavalent Pneumococcal conjugate vaccine on the epidemiology of acute otitis media complicated by otorrhea. *Pediatr Infect Dis J*. 2011;30:551–555.
66. Magnus MC, Vestrheim DF, Nystad W, et al. Decline in early childhood respiratory tract infections in the Norwegian mother and child cohort study after introduction of Pneumococcal conjugate vaccination. *Pediatr Infect Dis J*. 2012;31:951–955.
67. Sugino H, Tsumura S, Kunimoto M, et al. Influence of pneumococcal conjugate vaccine on acute otitis media with severe middle ear inflammation: a retrospective multicenter study. *PLoS One*. 2015;10:e0137546.
68. Ochoa-Gondar O, Figuerola-Massana E, Vila-Corcoles A, et al.; EPIVAC Study Group. Epidemiology of streptococcus pneumoniae causing acute otitis media among children in southern catalonia throughout 2007-2013: incidence, serotype distribution and vaccine's effectiveness. *Int J Pediatr Otorhinolaryngol*. 2015;79:2104–2108.
69. Suarez V, Michel F, Toscano CM, et al. Impact of pneumococcal conjugate vaccine in children morbidity and mortality in peru: time series analyses. *Vaccine*. 2016;34:4738–4743.
70. Littorin N, Ahl J, Uddén F, et al. Reduction of streptococcus pneumoniae in upper respiratory tract cultures and a decreased incidence of related acute otitis media following introduction of childhood pneumococcal conjugate vaccines in a Swedish county. *BMC Infect Dis*. 2016;16:407.
71. Gisselsson-Solen M. Trends in otitis media incidence after conjugate pneumococcal vaccination: a national observational study. *Pediatr Infect Dis J*. 2017;36:1027–1031.
72. Marom T, Israel O, Gavriel H, et al. Comparison of first year of life acute otitis media admissions before and after the 13-valent pneumococcal conjugate vaccine. *Int J Pediatr Otorhinolaryngol*. 2017;97:251–256.
73. Suaya JA, Gessner BD, Fung S, et al. Acute otitis media, antimicrobial prescriptions, and medical expenses among children in the United States during 2011-2016. *Vaccine*. 2018;36:7479–7486.
74. Taylor S, Marchisio P, Vergison A, et al. Impact of pneumococcal conjugate vaccination on otitis media: a systematic review. *Clin Infect Dis*. 2012;54:1765–1773.
75. Fortanier AC, Venekamp RP, Boonacker CW, et al. Pneumococcal conjugate vaccines for pre-venting otitis media. *Cochrane Database Syst Rev*. 2014;4:CD001480.
76. Ewald H, Briel M, Vuichard D, et al. The clinical effectiveness of pneumococcal conjugate vaccines: a systematic review and meta-analysis of randomized controlled trials. *Dtsch Arztebl Int*. 2016;113:139–146.
77. Gisselsson-Solén M, Melhus A, Hermansson A. Pneumococcal vaccination in children at risk of developing recurrent acute otitis media - a randomized study. *Acta Paediatr*. 2011;100:1354–1358.
78. Gisselsson-Solén M, Henriksson G, Hermansson A, et al. Effect of pneumococcal conjugate vaccination on nasopharyngeal carriage in children with early onset of acute otitis media - a randomized controlled trial. *Acta Otolaryngol*. 2015;135:7–13.
79. Veenhoven R, Bogaert D, Uiterwaal C, et al. Effect of conjugate pneumococcal vaccine followed by polysaccharide pneumococcal vaccine on recurrent acute otitis media: a randomised study. *Lancet*. 2003;361:2189–2195.
80. Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. *Pediatrics*. 2013;131:e964–e999.
81. Prymula R, Peeters P, Chrobok V, et al. Pneumococcal capsular polysaccharides conjugated to protein D for prevention of acute otitis media caused by both *Streptococcus pneumoniae* and non-typable *Haemophilus influenzae*: a randomized double-blind efficacy study. *Lancet*. 2006;367:740–748.
82. Tregnaghi MW, Sáez-Llorens X, López P, et al.; COMPAS Group. Efficacy of pneumococcal nontypable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV) in young Latin American children: a double-blind randomized controlled trial. *PLoS Med*. 2014;11:e1001657.
83. Rosenblut A, Rosenblut M, García K, et al. Frequency of acute otitis media in children under 24 months of age before and after the introduction of the 10-valent pneumococcal conjugate vaccine into the national immunization program in Chile. *Pediatr Infect Dis J*. 2018;37:132–134.
84. Palmu AA, Jokinen J, Borys D, et al. Effectiveness of the ten-valent pneumococcal *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV10) against invasive pneumococcal disease: a cluster randomised trial. *Lancet*. 2013;381:214–222.
85. Palmu AA, Jokinen J, Nieminen H, et al. Effect of pneumococcal *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV10) on outpatient antimicrobial purchases: a double-blind, cluster randomised phase 3-4 trial. *Lancet Infect Dis*. 2014;14:205–212.
86. Palmu AA, Jokinen J, Nieminen H, et al. Effectiveness of the Ten-valent pneumococcal conjugate vaccine against tympanostomy tube placements in a cluster-randomized Trial. *Pediatr Infect Dis J*. 2015;34:1230–1235.
87. Palmu AA, Rinta-Kokko H, Nohynek H, et al. Impact of national Ten-valent pneumococcal conjugate vaccine program on reducing antimicrobial use and tympanostomy tube placements in Finland. *Pediatr Infect Dis J*. 2018;37:97–102.
88. Oliveira JR, Bouzas ML, Cardoso MR, et al.; Acute Respiratory Infection and Wheeze Study Group Phase I and II. Frequency of complications and the effects of pneumococcal vaccination in young children with acute respiratory tract infection. *Vaccine*. 2016;34:2556–2561.
89. Sáez-Llorens X, Rowley S, Wong D, et al. Efficacy of 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine against acute otitis media and nasopharyngeal carriage in Panamanian children - A randomized controlled trial. *Hum Vaccin Immunother*. 2017;13:1–16.
90. Clarke C, Bakaletz LO, Ruiz-Guiñazú J, et al. Impact of protein D-containing pneumococcal conjugate vaccines on non-typeable *Haemophilus influenzae* acute otitis media and carriage. *Expert Rev Vaccines*. 2017;16:1–14.
91. Vesikari T, Forsten A, Seppä I, et al. Effectiveness of the 10-Valent pneumococcal nontypeable *Haemophilus influenzae* Protein D-Conjugated Vaccine (PHiD-CV) against carriage and acute otitis media-A double-blind randomized Clinical Trial in Finland. *J Pediatric Infect Dis Soc*. 2016;5:237–248.
92. Eythorsson E, Sigurdsson S, Hrafnkelsson B, et al. Impact of the 10-valent pneumococcal conjugate vaccine on antimicrobial prescriptions in young children: a whole population study. *BMC Infect Dis*. 2018;18:505.

93. Sigurdsson S, Eythorsson E, Hrafnkelsson B, *et al.* Reduction in all-cause acute otitis media in children <3 years of age in primary care following vaccination with 10-valent pneumococcal haemophilus influenzae protein-D conjugate vaccine: a whole-population study. *Clin Infect Dis*. 2018;67:1213–1219.
94. Sigurdsson S, Kristinsson KG, Erlendsdóttir H, *et al.* Decreased incidence of respiratory infections in children after vaccination with Ten-valent pneumococcal vaccine. *Pediatr Infect Dis J*. 2015;34:1385–1390.
95. Eythorsson E, Hrafnkelsson B, Erlendsdóttir H, *et al.* Decreased acute otitis media with treatment failure after introduction of the Ten-valent pneumococcal haemophilus influenzae protein D conjugate vaccine. *Pediatr Infect Dis J*. 2018;37:361–366.
96. Komakhidze T, Hoestlandt C, Dolakidze T, *et al.* Cost-effectiveness of pneumococcal conjugate vaccination in Georgia. *Vaccine*. 2015;33(Suppl 1):A219–A226.
97. Martí SG, Colantonio L, Bardach A, *et al.* A cost-effectiveness analysis of a 10-valent pneumococcal conjugate vaccine in children in six Latin American countries. *Cost Eff Resour Alloc*. 2013;11:21.
98. Giannakopoulos P, Chrysovergis A, Xirogianni A, *et al.* Microbiology of acute mastoiditis and complicated or refractory acute otitis media among hospitalized children in the postvaccination era. *Pediatr Infect Dis J*. 2014;33:111–113.
99. Rybak A, Levy C, Bonacorci S, *et al.* Antibiotic resistance of potential otopathogens isolated from nasopharyngeal flora of children with acute otitis media before, during and after pneumococcal conjugate vaccines implementation. *Pediatr Infect Dis J*. 2018;37:e72–e78.
100. Marchisio P, Esposito S, Picca M, *et al.*; Milan AOM Study Group. Serotypes not included in 13-valent pneumococcal vaccine as causes of acute otitis media with spontaneous tympanic membrane perforation in a geographic area with high vaccination coverage. *Pediatr Infect Dis J*. 2017;36:521–523.
101. Lau WC, Murray M, El-Turki A, *et al.* Impact of pneumococcal conjugate vaccines on childhood otitis media in the United Kingdom. *Vaccine*. 2015;33:5072–5079.
102. Ben-Shimol S, Givon-Lavi N, Leibovitz E, *et al.* Impact of widespread introduction of pneumococcal conjugate vaccines on pneumococcal and nonpneumococcal otitis media. *Clin Infect Dis*. 2016;63:611–618.
103. Marom T, Bookstein Peretz S, Schwartz O, *et al.* Impact of pneumococcal conjugate vaccines on selected head and neck infections in hospitalized Israeli children. *Pediatr Infect Dis J*. 2017;36:314–318.
104. Marom T, Avraham E, Cinamon U, *et al.* The effect of immunization with pneumococcal conjugated vaccines on streptococcus pneumoniae resistance patterns in acute otitis media. *J Microbiol Immunol Infect*. 2017;50:714–717.
105. Kawai K, Adil EA, Barrett D, *et al.* Ambulatory visits for otitis media before and after the introduction of pneumococcal conjugate vaccination. *J Pediatr*. 2018;201:122–127.e1.
106. Talathi S, Gupta N, Sethuram S, *et al.* Otitis media in fully vaccinated preschool children in the pneumococcal conjugate vaccine era. *Glob Pediatr Health*. 2017;4:2333794X17749668.
107. Pichichero M, Kaur R, Scott DA, *et al.* Effectiveness of 13-valent pneumococcal conjugate vaccination for protection against acute otitis media caused by Streptococcus pneumoniae in healthy young children: a prospective observational study. *Lancet Child Adolesc Health*. 2018;2:561–568.
108. Shen K, Wasserman M, Liu D, *et al.* Estimating the cost-effectiveness of an infant 13-valent pneumococcal conjugate vaccine national immunization program in China. *PLoS One*. 2018;13:e0201245.
109. Maurer KA, Chen HF, Wagner AL, *et al.* Cost-effectiveness analysis of pneumococcal vaccination for infants in China. *Vaccine*. 2016;34:6343–6349.
110. Gouveia M, Fiorentino F, Jesus G, *et al.* Cost-effectiveness of the 13-valent pneumococcal conjugate vaccine in children in Portugal. *Pediatr Infect Dis J*. 2017;36:782–787.
111. Tyo KR, Rosen MM, Zeng W, *et al.* Cost-effectiveness of conjugate pneumococcal vaccination in Singapore: comparing estimates for 7-valent, 10-valent, and 13-valent vaccines. *Vaccine*. 2011;29:6686–6694.
112. Earnshaw SR, McDade CL, Zanotti G, *et al.* Cost-effectiveness of 2 + 1 dosing of 13-valent and 10-valent pneumococcal conjugate vaccines in Canada. *BMC Infect Dis*. 2012;12:101.
113. Gomez JA, Tirado JC, Navarro Rojas AA, *et al.* Cost-effectiveness and cost utility analysis of three pneumococcal conjugate vaccines in children of Peru. *BMC Public Health*. 2013;13:1025.
114. Klok RM, Lindkvist RM, Ekelund M, *et al.* Cost-effectiveness of a 10- versus 13-valent pneumococcal conjugate vaccine in Denmark and Sweden. *Clin Ther*. 2013;35:119–134.
115. Mezones-Holguin E, Canelo-Aybar C, Clark AD, *et al.* Cost-effectiveness analysis of 10- and 13-valent pneumococcal conjugate vaccines in Peru. *Vaccine*. 2015;33(suppl 1):A154–A166.
116. Ordóñez JE, Orozco JJ. Cost-effectiveness analysis of the available pneumococcal conjugated vaccines for children under five years in Colombia. *Cost Eff Resour Alloc*. 2015;13:6.
117. Castiglia P, Pradelli L, Castagna S, *et al.* Overall effectiveness of pneumococcal conjugate vaccines: an economic analysis of PHiD-CV and PCV-13 in the immunization of infants in Italy. *Hum Vaccin Immunother*. 2017;13:2307–2315.
118. Shiragami M, Mizukami A, Leeuwenkamp O, *et al.* Cost-Effectiveness evaluation of the 10-valent pneumococcal non-typeable haemophilus influenzae protein D conjugate vaccine and 13-valent pneumococcal vaccine in Japanese children. *Infect Dis Ther*. 2014. [Epub ahead of print]
119. Varghese L, Talbot L, Govender A, *et al.* A Cost-Effectiveness analysis of the 10-valent pneumococcal non-typeable haemophilus influenzae protein D conjugate vaccine (PHiD-CV) compared to the 13-valent pneumococcal conjugate vaccine (PCV13) for universal mass vaccination implementation in New Zealand. *Appl Health Econ Health Policy*. 2018;16:331–345.
120. Vučina VV, Filipović SK, Kožnjak N, *et al.* Cost-effectiveness of pneumococcal conjugate vaccination in Croatia. *Vaccine*. 2015;33(suppl 1):A209–A218.
121. McIsaac WJ, Coyte PC, Croxford R, *et al.* Otolaryngologists' perceptions of the indications for tympanostomy tube insertion in children. *CMAJ*. 2000;162:1285–1288.
122. Florentzon R, Finizia C. Transmyringeal ventilation tube treatment: a 10-year cohort study. *Int J Pediatr Otorhinolaryngol*. 2012;76:1117–1122.
123. Rosenfeld RM, Schwartz SR, Pynnonen MA, *et al.* Clinical practice guideline: tympanostomy tubes in children. *Otolaryngol Head Neck Surg*. 2013;149(1 suppl):S1–35.
124. Gonzalez C, Arnold JE, Woody EA, *et al.* Prevention of recurrent acute otitis media: chemoprophylaxis versus tympanostomy tubes. *Laryngoscope*. 1986;96:1330–1334.
125. Shin JJ, Stinnett SS, Hartnick CJ. Pediatric recurrent acute otitis media. In: Shin JJ, Hartnick CJ, Randolph GW, eds. *Evidence-Based Otolaryngology*. New York, NY: Springer; 2008:91–95.
126. Casselbrant ML, Kaleida PH, Rockette HE, *et al.* Efficacy of antimicrobial prophylaxis and of tympanostomy tube insertion for prevention of recurrent acute otitis media: results of a randomized clinical trial. *Pediatr Infect Dis J*. 1992;11:278–286.
127. Kay DJ, Nelson M, Rosenfeld RM. Meta-analysis of tympanostomy tube sequelae. *Otolaryngol Head Neck Surg*. 2001;124:374–380.
128. Lous J, Ryborg CT, Thomsen JL. A systematic review of the effect of tympanostomy tubes in children with recurrent acute otitis media. *Int J Pediatr Otorhinolaryngol*. 2011;75:1058–1061.
129. Hellström S, Groth A, Jörgensen F, *et al.* Ventilation tube treatment: a systematic review of the literature. *Otolaryngol Head Neck Surg*. 2011;145:383–395.
130. Kujala T, Alho OP, Luotonen J, *et al.* Tympanostomy with and without adenoidectomy for the prevention of recurrences of acute otitis media: a randomized controlled trial. *Pediatr Infect Dis J*. 2012;31:565–569.
131. Kujala T, Alho OP, Kristo A, *et al.* Quality of life after surgery for recurrent otitis media in a randomized controlled trial. *Pediatr Infect Dis J*. 2014;33:715–719.
132. Steele DW, Adam GP, Di M, *et al.* Effectiveness of tympanostomy tubes for otitis media: a meta-analysis. *Pediatrics*. 2017;139:pii:e20170125.
133. Mikals SJ, Brügger MT. Adenoidectomy as an adjuvant to primary tympanostomy tube placement: a systematic review and meta-analysis. *JAMA Otolaryngol Head Neck Surg*. 2014;140:95–101.
134. Venekamp RP, Mick P, Schilder AG, *et al.* Grommets (ventilation tubes) for recurrent acute otitis media in children. *Cochrane Database Syst Rev*. 2018;5:CD012017.
135. Nokso-Koivisto J, Marom T, Chonmaitee T. Importance of viruses in acute otitis media. *Curr Opin Pediatr*. 2015;27:110–115.
136. Prellner K, Foglè-Hansson M, Jörgensen F, *et al.* Prevention of recurrent acute otitis media in otitis-prone children by intermittent prophylaxis with penicillin. *Acta Otolaryngol*. 1994;114:182–187.
137. Foglè-Hansson M, White P, Hermansson A. Pathogens in acute otitis media—impact of intermittent penicillin V prophylaxis on infant nasopharyngeal flora. *Int J Pediatr Otorhinolaryngol*. 2003;67:511–516.



138. Berman S, Nuss R, Roark R, et al. Effectiveness of continuous vs. intermittent amoxicillin to prevent episodes of otitis media. *Pediatr Infect Dis J*. 1992;11:63–67.
139. Peterson L, Peterson KE, Peterson LR. Intermittent antimicrobial prophylaxis for recurrent acute otitis media. *J Infect Dis*. 1990;161:806–807.
140. Marchisio P, Principi N, Sala E, et al. Comparative study of once-weekly azithromycin and once-daily amoxicillin treatments in prevention of recurrent acute otitis media in children. *Antimicrob Agents Chemother*. 1996;40:2732–2736.
141. Rosenfeld RM. Clinical pathway for acute otitis media. In: Rosenfeld RM, Bluestone CD, eds. *Evidence-Based Otitis Media*. 2nd ed. Hamilton, Canada: BC Decker; 2003:280–302.
142. Leach AJ, Morris PS. Antibiotics for the prevention of acute and chronic suppurative otitis media in children. *Cochrane Database Syst Rev*. 2006;4:CD004401.
143. Cheong KH, Hussain SS. Management of recurrent acute otitis media in children: systematic review of the effect of different interventions on otitis media recurrence, recurrence frequency and total recurrence time. *J Laryngol Otol*. 2012;126:874–885.
144. Kontiokari T, Uhari M, Koskela M. Antiadhesive effects of xylitol on otopathogenic bacteria. *J Antimicrob Chemother*. 1998;41:563–565.
145. Kontiokari T, Uhari M, Koskela M. Effect of xylitol on growth of nasopharyngeal bacteria *in vitro*. *Antimicrob Agents Chemother*. 1995;39:1820–1823.
146. Danhauer JL, Johnson CE, Corbin NE, et al. Xylitol as a prophylaxis for acute otitis media: systematic review. *Int J Audiol*. 2010;49:754–761.
147. Azarpazhooh A, Lawrence HP, Shah PS. Xylitol for preventing acute otitis media in children up to 12 years of age. *Cochrane Database Syst Rev*. 2016:CD007095.
148. Vernacchio L, Corwin MJ, Vezina RM, et al. Xylitol syrup for the prevention of acute otitis media. *Pediatrics*. 2014;133:289–295.
149. Niittynen L, Pitkäranta A, Korpela R. Probiotics and otitis media in children. *Int J Pediatr Otorhinolaryngol*. 2012;76:465–470.
150. Iannitti T, Palmieri B. Therapeutical use of probiotic formulations in clinical practice. *Clin Nutr*. 2010;29:701–725.
151. Principi N, Tagliabue C, Tenconi R, et al. Probiotics and prevention of pediatric upper respiratory tract infections. *Eur J Inflam*. 2013;11:581–589.
152. Hatakka K, Blomgren K, Pohjavuori S, et al. Treatment of acute otitis media with probiotics in otitis-prone children—a double-blind, placebo-controlled randomised study. *Clin Nutr*. 2007;26:314–321.
153. Rautava S, Salminen S, Isolauri E. Specific probiotics in reducing the risk of acute infections in infancy—a randomised, double-blind, placebo-controlled study. *Br J Nutr*. 2009;101:1722–1726.
154. Cohen R, Martin E, de La Rocque F, et al. Probiotics and prebiotics in preventing episodes of acute otitis media in high-risk children: a randomized, double-blind, placebo-controlled study. *Pediatr Infect Dis J*. 2013;32:810–814.
155. Liu S, Hu P, Du X, et al. Lactobacillus rhamnosus GG supplementation for preventing respiratory infections in children: a meta-analysis of randomized, placebo-controlled trials. *Indian Pediatr*. 2013;50:377–381.
156. Santagati M, Scillato M, Patané F, et al. Bacteriocin-producing oral streptococci and inhibition of respiratory pathogens. *FEMS Immunol Med Microbiol*. 2012;65:23–31.
157. Tano K, Grahn Håkansson E, Holm SE, et al. A nasal spray with alpha-haemolytic streptococci as long term prophylaxis against recurrent otitis media. *Int J Pediatr Otorhinolaryngol*. 2002;62:17–23.
158. Roos K, Håkansson EG, Holm S. Effect of recolonisation with “interfering” alpha streptococci on recurrences of acute and secretory otitis media in children: randomised placebo controlled trial. *BMJ*. 2001;322:210–212.
159. Power DA, Burton JP, Chilcott CN, et al. Preliminary investigations of the colonisation of upper respiratory tract tissues of infants using a paediatric formulation of the oral probiotic *Streptococcus salivarius* K12. *Eur J Clin Microbiol Infect Dis*. 2008;27:1261–1263.
160. La Mantia I, Varricchio A, Ciprandi G. Bacteriotherapy with *Streptococcus salivarius* 24SMB and streptococcus oralis 89a nasal spray for preventing recurrent acute otitis media in children: a real-life clinical experience. *Int J Gen Med*. 2017;10:171–175.
161. Marchisio P, Santagati M, Scillato M, et al. *Streptococcus salivarius* 24SMB administered by nasal spray for the prevention of acute otitis media in otitis-prone children. *Eur J Clin Microbiol Infect Dis*. 2015;34:2377–2383.
162. Di Piero F, Rizzo P, Poggi E, et al. Use of *Streptococcus salivarius* K12 to reduce the incidence of pharyngo-tonsillitis and acute otitis media in children: a retrospective analysis in not-recurrent pediatric subjects. *Minerva Pediatr*. 2018;70:240–245.
163. Principi N, Marchisio P, Terranova L, et al. Impact of vitamin D administration on immunogenicity of trivalent inactivated influenza vaccine in previously unvaccinated children. *Hum Vaccin Immunother*. 2013;9:969–974.
164. Esposito S, Baggi E, Bianchini S, et al. Role of vitamin D in children with respiratory tract infection. *Int J Immunopathol Pharmacol*. 2013;26:1–13.
165. Cayir A, Turan MI, Ozkan O, et al. Vitamin D levels in children diagnosed with acute otitis media. *J Pak Med Assoc*. 2014;64:1274–1277.
166. Li HB, Tai XH, Sang YH, et al. Association between vitamin D and development of otitis media: a PRISMA-compliant meta-analysis and systematic review. *Medicine (Baltimore)*. 2016;95:e4739.
167. Marchisio P, Consonni D, Baggi E, et al. Vitamin D supplementation reduces the risk of acute otitis media in otitis-prone children. *Pediatr Infect Dis J*. 2013;32:1055–1060.
168. Marchisio P, Bianchini S, Galeone C, et al. Use of complementary and alternative medicine in children with recurrent acute otitis media in Italy. *Int J Immunopathol Pharmacol*. 2011;24:441–449.
169. Bukutu C, Deol J, Vohra S. Complementary, holistic, and integrative medicine: therapies for acute otitis media. *Pediatr Rev*. 2008;29:193–199.
170. Ito M, Maruyama Y, Kitamura K, et al. Randomized controlled trial of *juzen-taiho-to* in children with recurrent acute otitis media. *Auris Nasus Larynx*. 2017;44:390–397.
171. Gulani A, Sachdev HS. Zinc supplements for preventing otitis media. *Cochrane Database Syst Rev*. 2014;29:CD006639.