DANISH MEDICAL JOURNAL

Systematic Review

Dan Med J 2020;67(11):A04200272

Acute otitis media and antibiotics – a systematic review

Niels Højvang Holm[1], Maria Rusan[2] & Therese Ovesen[1]

1) ENT Department, Regional Hospital West Jutland, 2) Department of Oncology, Aarhus University Hospital, Denmark

Dan Med J 2020;67(11):A04200272

ABSTRACT

Introduction: Although acute otitis media (AOM) is a very frequent illness in children, it remains unclear to what extent children with AOM benefit from antibiotics (ABX). This systematic review aimed to clarify this subject by including randomised clinical trials (RCTs) from the pneumococcal vaccine era only.

Methods: We performed a systematic literature search in four databases from 1 January 2000 to 1 January 2019 for RCTs comparing ABX to placebo in patients with AOM. Pain was registered as the main outcome. Adverse events (AE), development of contralateral otitis media, tympanic membrane perforation, late AOM recurrence, abnormal tympanometry and time to resolution of middle ear effusion were registered as secondary outcomes.

Results: Six publications based on five RCTs with 1,862 patients were included. The number needed to treat (NNT) to reduce pain varied from seven (pain at day 7-10) to 28 (pain at day 2-3). The NNT for preventing contralateral otitis was ten. AE were seen in every 13th patient treated with ABX.

Conclusions: ABX appears to have a limited effect on both primary and secondary outcomes compared with placebo. A substantial number of patients experienced AE. New RCTs are needed to further clarify the effect. Ideally, RCTs could be conducted in Danish general practices in collaboration with practicing ear, nose and throat specialists to obtain large unselected populations with high rates of vaccine coverage. Until more evidence is provided, ABX should be considered among children younger than two years of age with severe symptoms of AOM, i.e. fewer and affected well-being.

KEY POINTS

- Based on our inclusion and exclusion criteria, six studies were included.
- Antibiotics appear to have a limited effect on pain and secondary outcomes compared with placebo in AOM patients.
- Adverse events are seen in every 13th patient treated with antibiotics.
- New RCTs are needed to further clarify the effect.

Acute otitis media (AOM) is the infectious disease that most frequently leads to contact with the healthcare system in children [1, 2]. Symptoms include ear pain, otorrhoea, fever and symptoms of upper airway infection. Objective findings encompass a bulging tympanic membrane, opacity/redness/yellowness of the tympanic membrane and abnormal tympanometry. Spontaneous remission of acute symptoms is frequent, especially among children who are older than two years of age, but the acute condition is often followed by a more subtle

course with middle ear effusion for weeks to months, i.e. otitis media with effusion. Infectious complications to AOM include mastoiditis, labyrinthitis, facial nerve palsy, meningitis and cerebral abscesses. Long-term consequences reported include atelectasis of the middle ear, persistent perforation of the tympanic membrane and even cholesteatoma.

The conjugate pneumococcal vaccine (PnV) 7 was added to the childhood immunisation schedule in the United States in 2000 and was replaced by the PnV13 in 2010 [3]. Thereafter, many Western countries have followed suit. Before the introduction of the vaccine, *Streptococcus pneumoniae* was the most common cause of AOM among children [4, 5]. Other pathogens included *Haemophilus influenzae*, *Moraxella catarrhalis* and Group A streptococcus. Recent studies have shown a shift in otopathogens in patients with AOM in countries with nationwide PnV-programmes towards pneumococcus-serotypes not covered by the vaccines as well as non-typeable *H. influenzae* [6, 7].

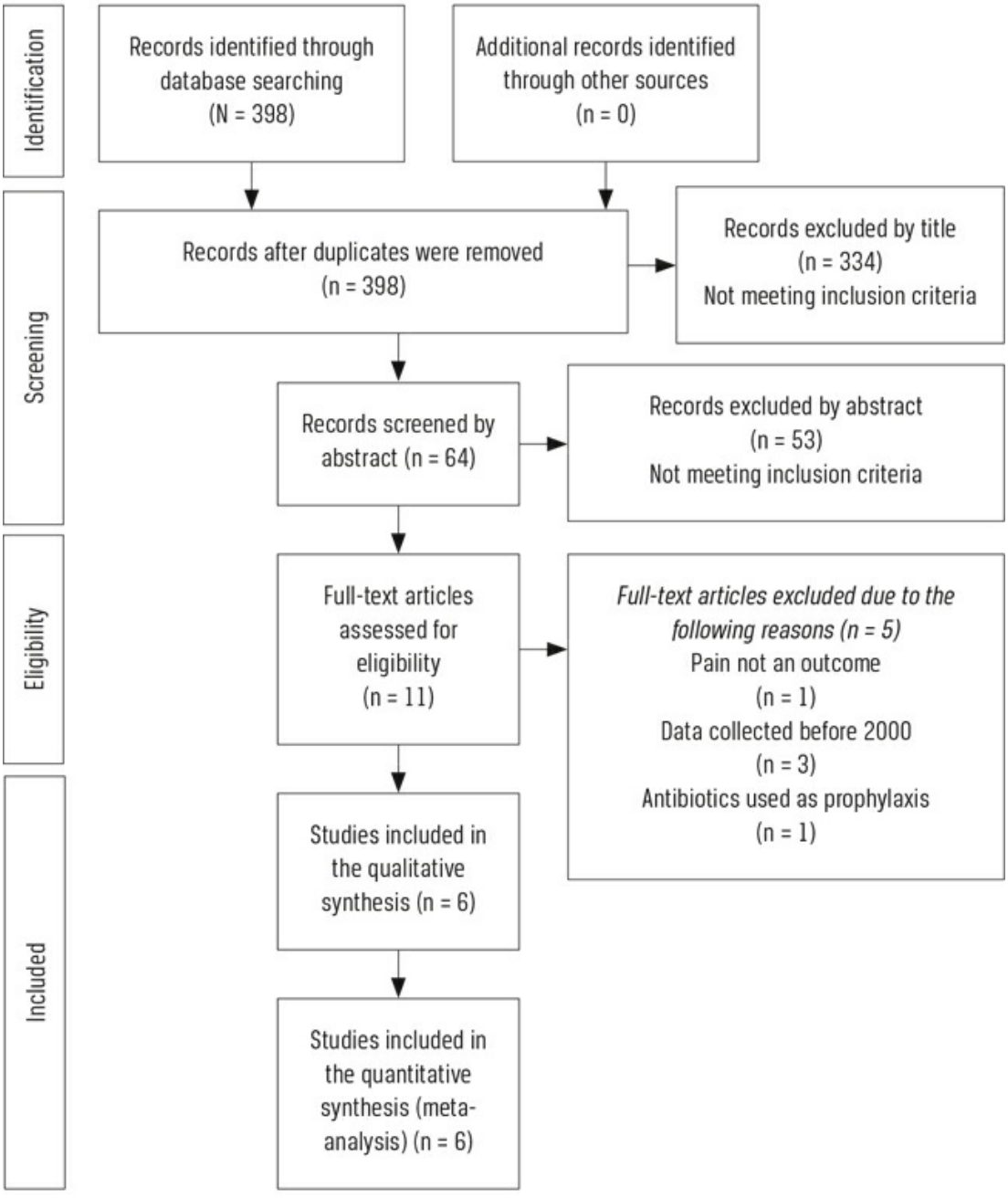
Despite the high incidence of AOM, it remains unclear which patients benefit from ABX. In the US, AOM is the most common reason for prescribing ABX to children [8]. The number of AOM patients treated with ABX ranged from 56% in the Netherlands [9] to 86-91% in the US in a study covering the 2011-2016 period [10]. In light of increasing antibacterial resistance worldwide, it is essential to restrict the use of ABX to the correct patient population and with as narrow-spectrum treatment as is feasible. Several randomised controlled trials (RCTs) have been published comparing antibiotic treatment to placebo or watchful waiting in patients with AOM. In 2015, a Cochrane review was published covering studies from 1968 to 2011 [11]. The authors concluded that ABX had a minor effect on pain after three to seven days and were more beneficial for children under the age of two years with bilateral AOM or with AOM and otorrhoea. They also concluded that every 14th patient treated with ABX experienced a side effect. Therefore, the authors suggested an expectant observation strategy in most AOM cases. As antibiotic resistance has emerged and PnV have been introduced worldwide, especially post-millennium, the conclusions drawn by the Cochrane review may be confounded by the inclusion of rather early studies. The aim of the present systematic review was to include only RCTs from the PnV era in order to provide contemporary, updated information about the effects of ABX in AOM.

METHODS

The first author performed a systematic literature search according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12]. Embase, SCOPUS, PubMed and Cochrane were searched using *"acute otitis media"* OR *"otitis media acuta"* OR *"AOM".* The search was expanded by citations from the included studies. The inclusion criteria were: Patients < 18 years, patients with AOM, RCT, ABX versus placebo or watchful waiting and data collected after 2000.

A total of 398 studies were identified and screened by title and abstract by the first and the last author. Selection of the studies is shown in **Figure 1**. Eleven publications were full-text assessed for eligibility. Five studies were excluded due to: pain not being an outcome (n = 1), data collected before 2000 (n = 3), and ABX used as prophylaxis against AOM in patients with upper respiratory tract infections (n = 1).

FIGURE 1 / Study selection flow chart.

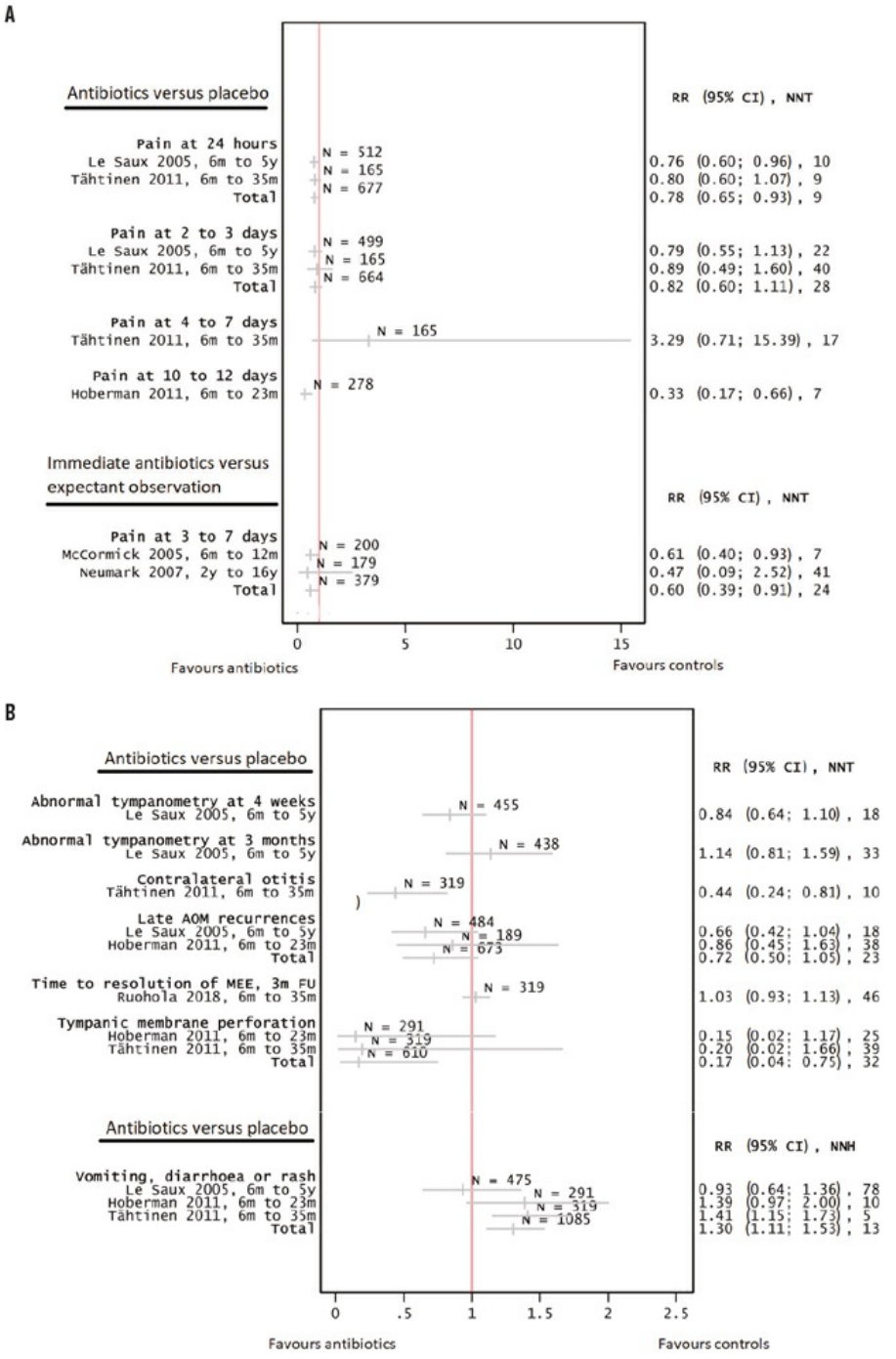


The primary outcome considered was pain reduction. Additionally, the following secondary outcomes were registered: adverse events (AE) (diarrhoea, vomiting, dermatitis, oral thrush and rash), development of contralateral otitis media, tympanic membrane perforation, late AOM recurrence, abnormal tympanometry and time to resolution of middle ear effusion.

The quality of evidence was assessed for each outcome as high, moderate, low or very low using the GRADE framework. In general, RCTs were rated as high quality, but could be downgraded depending on GRADE domains (risk of bias, imprecision of results, inconsistency of results, indirectness of evidence, publication bias).

Confidence intervals and p-values were extracted. Data were analysed [13]. Forest plots were created comparing ABX or watchful waiting and placebo. Relative risk (RR), 95% confidence intervals (CIs) and numbers needed to treat (NNT) are shown in **Figure 2**A + B.

FIGURE 2 / Forest plots comparing antibiotics or watchful waiting (**A**) and placebo (**B**)[a].



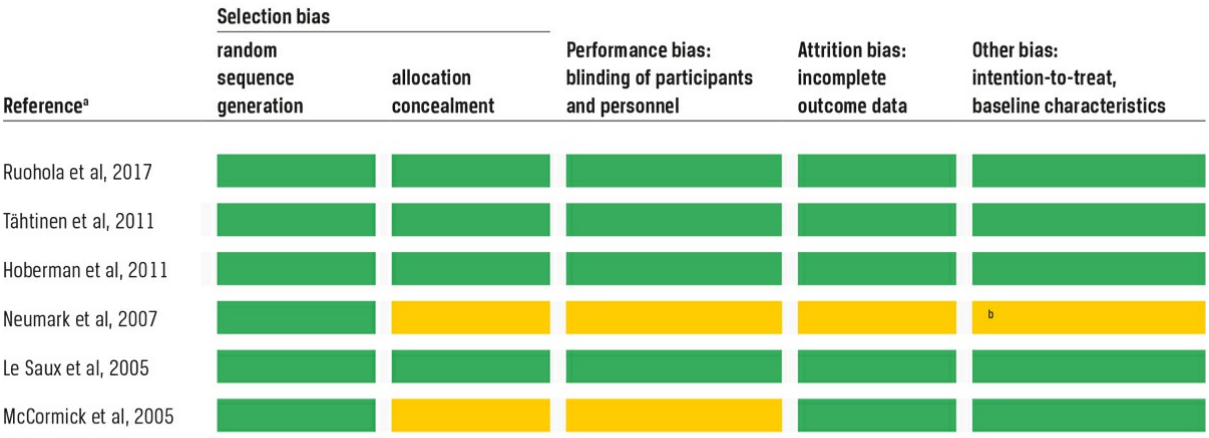
AOM = acute otitis media; CI = confidence interval; FU = follow-up; m = months; MEE = middle ear effusion; NNH = number needed to harm; NNT = number needed to treat; RR = relative risk; y = years.
a) Please contact the authors for further information about the references.

RESULTS

Six publications of five different trials with a total of 1,862 patients were included. The quality of evidence for each outcome was evaluated as high with the exception of: 1) pain at ten to 12 days, as this outcome was not specified in the Methods section; 2) abnormal tympanometry at four weeks due to a higher number of patients lost to follow-up in the expectant observation group than in the immediate ABX group (11% versus 4%).

The overall risk of bias of the included studies is low (**Figure 3**). The risk of bias and the quality of the included studies is in line with Venekamp et al [11] and a modified overview is provided in Figure 2.

FIGURE 3 / Risk of bias summary: review authors judgement about bias for each included study. Modified after [11].



a) Please contact the authors for further information about the references.
b) Unclear intention-to-treat.

An overview of the studies is shown in **Table 1** and Supplementary Material. Primary and secondary outcomes are shown in Supplementary Material. The studies were from the USA (n = 2), Finland (n = 2), Sweden (n = 1) and Canada (n = 1). Patients included were between six months and 16 years of age. The population sizes ranged from 179 to 512 patients. PnV status was provided in four studies, and the number of patients vaccinated with PnV ranged from 1.9% [14, 15] to 100% [16]. Five of the six studies employed amoxicillin and one used penicillin. The duration of treatment varied between seven and ten days for amoxicillin and was five days for penicillin. The studies were from the USA (n = 2), Finland (n = 2), Sweden (n = 1) and Canada (n = 1). Patients included were between six months and 16 years of age. The population sizes ranged from 179 to 512 patients. PnV status was provided in four studies, and the number of patients vaccinated with PnV ranged from 1.9% [14, 15] to 100% [16]. Five of the six studies employed amoxicillin and one used penicillin. The duration of treatment varied between seven and ten days for amoxicillin and was five days for penicillin.

Comparison of primary and secondary outcomes for antibiotic versus placebo treatment or watchful waiting was made using forest plots and is shown in Figure 2A + B. Pain in the placebo-controlled studies was significantly reduced in children treated with ABX at 24 hours (RR = 0.78 (95% CI: 0.65-0.93), NNT = 9) and at 10-12 days (RR = 0.33 (95% CI: 0.17-0.66), NNT = 7). No significant difference was found at 2-3 days and 4-7 days. Immediate ABX versus observation showed significantly reduced pain at 3-7 days (RR = 0.60 (95% CI: 0.39-0.91), NNT = 24).

ABX significantly reduced the risk of contralateral otitis media compared with placebo (RR = 0.44 (95% CI: 0.24-0.81), NNT = 10). Tympanic membrane perforation was also significantly reduced with ABX (RR = 0.17 (95% CI: 0.04-0.71), NNT = 32).

TABLE 1 / Overview of studies.

Reference[a] Study place and time	Population, n	Setting	Age	Follow-up	Inclusion criteria	Exclusion criteria
Ruohola et al, 2017 Finland, 2006-2008	319	Primary care, the health centre of Turku	6 -35 mo.s	Scheduled visits on study days 3, 8, 15, 30[b] and 60 Patients who had persistent MEE were followed up every other wk until study day 90 ± 10 days or until referral to tympanostomy tube placement At each visit, the study physician interviewed the parents about the symptoms of their child and performed a clinical examination	AOM based on 3 criteria: Middle ear fluid detected by pneumatic otoscopic examination showing ≥ 2 of the following tympanic-membrane findings: bulging position, decreased or absent mobility, abnormal colour or opacity not due to scarring, or air-fluid interfaces ≥ 1 of the following acute inflammatory signs in the tympanic membrane: distinct erythematous patches or streaks or increased vascularity over full, bulging or yellow tympanic membrane The child had to have acute symptoms, such as fever, ear pain or respiratory symptoms	Ongoing antimicrobial treatment, AOM with spontaneous perforation of tympanic membrane, systemic or nasal steroid therapy within the 3 preceding days, antihistamine therapy within the 3 preceding days, oseltamivir therapy within the 3 preceding days, allergy to pneumococcal vaccine or amoxicillin, tympanostomy tube present in tympanic membrane, severe infection requiring systemic antimicrobial treatment, documented Epstein-Barr virus infection within the 7 preceding days, Down syndrome or other condition affecting middle ear diseases e.g., cleft palate, known immune-deficiency, severe vomiting or another symptoms to violate per oral dosage, poor parental cooperation due to language or other reasons, use of any investigational drugs during the 4 preceding weeks
Tähtinen et al, 2011 Finland, 2006-2008	319	Primary care, the health centre of Turku	6-35 mo.s	Clinical visits day 3 and 8 Parents recorded symptoms in a diary Used and unused study drug capsules were returned and adherence to the study drug was estimated	As above	As above
Hoberman et al, 2011 USA, 2006-2009	291	Secondary care, Children's Hospital of Pittsburgh and a private paediatric clinic	6-23 mo.s	Structured interview of 1 of the child's parents by telephone every day until the 1st follow-up visit and in person at each visit Clinical visits were scheduled for day 4-5, 10-12 and 21-25 Parents were asked to complete a diary twice a day for 3 days and once a day thereafter	Patients were required to have received ≥ 2 doses of pneumococcal conjugate vaccine and to have AOM that was diagnosed on the basis of 3 criteria: The onset within the preceding 48 h of symptoms that parents rated with a score of ≥ 3 on the AOM-SOS scale The presence of MEE Moderate or marked bulging of the tympanic membrane or slight bulging accompanied by either otalgia or marked erythema of the membrane	Another acute illness e.g., pneumonia, or a chronic illness e.g., cystic fibrosis, allergy to amoxicillin, treatment with ⟩ 1 dose of an antimicrobial drug within the previous 96 h, otalgia for ⟩ 48 h or perforation of the tympanic membrane
Neumark et al, 2007 Sweden, 2002-2003	179	Primary care, 23 health-care centres	2-16 yrs	Participants completed a diary daily for 7 days A nurse telephoned all participants after approx. 14 days to supplement the information in the diary and to register all acute contacts that had occurred during the 1st wk of treatment After 3 mo.s a follow-up was performed and perforations and serous otitis media were registered	AOM diagnosis was based on direct inspection of the eardrum by a pneumatic otoscope or preferably an aural microscope Findings had to include a bulging, red eardrum displaying reduced mobility	Perforation of the eardrum, chronic ear conditions or impaired hearing, previous adverse reactions to penicillin, concurrent disease that should be treated with ABX, recurrent AOM: ≥ 3 episodes of AOM during the past 6 mo.s, children with immune-suppressive conditions, genetic disorders, and mental disease or retardation
Le Saux et al, 2005 Canada, December 1999-2002	512	Children's hospital, urgent care centre and paediatric office	6 mo.s-5 yrs	The parent or guardian was contacted on days 1, 2 and 3 after randomisation and once day 10-day 14 for administration of a standard questionnaire The child was clinically assessed at 1 mo. and 3 mo.s to determine the number of subsequent episodes of acute and to undergo tympanometry	New onset ⟨ 4 days of symptoms referable to the upper respiratory tract and either ear pain or fever: temperature ⟩ 38 °C In addition, evidence of MEE defined as ≥ 2 of the following signs: opacity, impaired mobility on the basis of pneumatic otoscopy, and redness or bulging or both of the tympanic membrane	Allergy to penicillin or amoxicillin or sensitivity to ibuprofen or aspirin, if they had received antimicrobial treatment in the preceding 14 days, if they had any clinical suspicion of sepsis or mastoiditis, and if they had otorrhoea, co-morbid disease such as sinusitis or pneumonia, prior middle ear surgery, placement of a ventilation tube, history of recurrent AOM ⟩ 4 episodes in 12 mo.s, compromised immunity, craniofacial abnormalities, or any chronic or genetic disorder
McCormick et al, 2005 USA, 2000-2003	223	Secondary care, paediatric clinic of University of Texas, Medical Branch (USA)	6 mo.s-12 yrs	Parents were instructed to complete a diary documenting symptoms and ABX doses given on day 1-10 The parents also completed a health status questionnaire on day 12 and day 30	Subjects were required to have: Symptoms of ear infection Otoscopic evidence of AOM, including MEE Non-severe AOM	Co-morbidity requiring ABX, anatomical defect of ear or nasopharynx, allergy to study medication, immunologic deficiency, major medical condition, and/or indwelling tympanostomy tube or draining otitis in the affected ear(s)

ABX = antibiotics; AOM = acute otitis media; AOM-SOS = Acute Otitis Media - Severity of Symptoms; MEE = middle ear effusion.
a) Please contact the authors for further information about the references.
b) 45, if MEE had not resolved earlier.

No significant differences were noted on tympanometry at four weeks and three months in patients treated with ABX versus those not treated [17]. On the other hand, a trend was observed towards ABX reducing late AOM

recurrence and time to resolution of middle ear effusion.

AE were noted in every 13th patient treated with ABX (Figure 2B).

Abnormal tympanometry was noted equally frequently at four weeks and three months in patients treated with ABX versus those not treated. A trend was observed towards ABX reducing late AOM recurrence and time to resolution of middle ear effusion.

Regarding AE, the number needed to harm was 13 as shown in Figure 2B.

DISCUSSION

The introduction of PnV may have changed the pathogens causing AOM. A number of studies have been published on the subject. However, doubts still exist about the effectiveness of ABX. Antibacterial resistance has been increasing over the past couple of decades, which may have changed the response to antibiotic treatment. By only including post-millennium studies, the cohorts are expected to be more suited for comparison with today's patients, thereby providing a better picture of the issue. Our aim to mainly study vaccinated patients was not completely achieved since fewer patients in the included studies were vaccinated than we had assumed.

Inclusion criteria, vaccination coverage, outcomes and definitions of failure differed between the included studies. This heterogeneity complicates comparison of the studies. There is a substantial risk of volunteer bias due to the fact that many parents declined participation. Presumably, the parents with the most heavily affected children would be more likely to decline participation since they would rather obtain the ABX than risk receiving placebo. This might have biased the size of the effect, because the children who needed the ABX most were not included. However, randomisation of the patients who were included in the studies was carried out independently of the investigators, and the randomisation sequences were computer generated, thus minimising the risk of selection bias between the ABX group and the control group.

All of the included studies except for one [16] included children older than 24 months. A meta-analysis concluded that children under the age of two years with bilateral AOM and children with otorrhoea seemed to benefit more from ABX [18]. It has been suggested that AOM rarely requires ABX if the child is over five years of age. Including older children who may spontaneously have cleared the infection would underpower the positive effect of ABX among small children. This was confirmed by the study of Hoberman et al [16].

Heterogeneity in the vaccination status of the included studies further complicates comparison of the studies. In one study, only patients having received two doses of PnV were included [14]. PnV-status was provided in four studies and not mentioned in two [17, 19]. In both of these studies, the vaccine was not yet included in the national immunisation schedule. In Canada, the vaccine was included shortly after the study ended [17]. In Sweden, PnV was included in the national vaccination programme in 2009 [20], seven years after the study by Neumark et al concluded [19].

An important, yet unknown factor in the included studies is the specific pathogens. None of the studies collected samples from middle ear fluid. A recent study showed that the proportion of *S. pneumoniae* and non-typeable *H. influenza* in middle ear fluid in AOM patients < 2 months of age decreased after the introduction of PnV in the national immunisation programme [21]. Another study showed a trend towards a decrease in *S. pneumoniae*; however, the study also found an increase in *H. influenza* after the addition of PnV in the national immunisation programme [22]. This change in pathogens may potentially have had an influence in the studies where PnV was included in the national immunisation programme [14, 16].

In general, a minor effect on pain was seen at 24 hours and 10-12 days, with relatively high NNTs (nine and

seven, respectively). Notably, the NNT for pain at 3-7 days in patients aged 2-16 years was 41. This supports the hypothesis that children above the age of two years have an insignificant effect from ABX.

In the placebo group, there was a risk of placebo effect which might lead to parents reporting a lower pain score. This would weaken the true effect of ABX on pain. In the observation group, on the contrary, there was a risk of parents reporting a higher pain score since they knew that the child was not receiving ABX. This would strengthen the measured effect of ABX.

An additional challenge associated with the included studies is that the primary outcome was pain, which is very difficult to quantify for small children. Therefore, pain was assessed either by the parents or by the amount of analgesics taken as a proxy for pain. In general, pain was divided dichotomously into pain/no pain. This excludes the opportunity of grading pain and makes the studies less nuanced. Furthermore, it is debatable whether pain is an ideal marker of the effect of ABX. In all available studies, various analgesic regimens and pain-scoring systems were used, which, indeed, limits the ability to pool data and to draw a common conclusion. Is existing pain due to insufficient dosage of analgesics, or does it mirror the extent of the physiological/systemic response to the middle ear infection? And how to differentiate between pain and affection of general well-being due to an immunological response?

The ABX used in the included studies possess bactericidal properties aiming to reduce the entire bacterial load. The immediately derived effect hereof is a diminished systemic response, which primarily increases well-being and normalises body temperature. Scoring the child's well-being and temperature therefore may be the best way to assess the effect of ABX. However, the temperature is also affected by the analgesics, leaving scoring of the child's well-being as the only parameter describing the effect of ABX.

Secondary to increasing the well-being, ABXs are also thought to reduce the time to normalisation of the infected tissue. The various trials included in this study have indirectly addressed this by assessing various parameters such as abnormal tympanometry, contralateral AOM, resolution of middle ear effusion, AOM recurrences and tympanic membrane perforations. A trend towards ABX reducing AOM recurrence was noted. However, the result may be underpowered due to the relatively low number of patients included, and they may be weakened by the inclusion of children above the age of five years who would more likely clear the infection spontaneously. Again, this inconsistency in the applied measures makes it difficult to pool the results.

In the placebo group, there is a risk of placebo effect which could lead to parents reporting a lower pain score. This would weaken the true effect of ABX on pain. In the observation group, on the contrary, there is a risk of parents reporting a higher pain score, since they know that the child is not receiving ABX. This would strengthen the effect of ABX.

A significant difference was observed in the analgesics allowed in the included studies. In two studies [15, 16], pain medication was optional and unspecified. In one study [14], only acetaminophen was allowed. One study [17] allowed ibuprofen and codeine, whereas another allowed acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) [19]. This complicates comparison of pain between the studies, since the analgesic effect of acetaminophen, opioids and NSAIDs is different. Furthermore, NSAIDS have an anti-inflammatory effect which may theoretically produce a more rapid recovery.

A trend towards ABX reducing AOM recurrence was noted. However, the result may be underpowered due to the relatively low number of patients included and may be weakened by the inclusion of children over the age of five years of age who would more likely clear the infection spontaneously.

AE were reported in every 13th patient receiving ABX. In some cases, the AE (e.g. diarrhoea, vomiting, oral thrush or skin rash) may cause greater harm to the child than the infection, which would have often improved

spontaneously. Overall, the quality of evidence was high among the included trials and the risk of bias low. However, assessment of AE ought to be questioned with regards to definition and severity, and especially as regards who decides whether there is an adverse effect or not.

CONCLUSIONS

Based on current studies published in the PnV era, the effect of ABX on pain associated with AOM appears to be relatively limited. Some data suggest that children who are younger than two years of age with AOM benefit more from antibiotic treatment than older children. However, possible side effects should be taken into account.

These findings are in line with the conclusions of a Cochrane review covering RCTs outside the PnV era. More RCTs in the PnV era with children below the age of two years are needed in order to further clarify the effect of antibiotic treatment as well as the severity and frequency of adverse effects. Ideally, such RCTs should be conducted in general practices in Denmark in collaboration with practicing ear, nose and throat specialists to obtain unselected populations with a high PnV coverage. In addition, future studies ought to apply uniform grading of symptoms and outcomes as well as a consistent use of analgesics regimens. Until more evidence is provided, ABX should be considered among children younger than two years of age with severe symptoms of AOM, i.e. fewer and affected well-being.

CORRESPONDENCE: *Niels Højvang Holm*. E-mail: NielsHolm@gmail.com

ACCEPTED: 13 August 2020

CONFLICTS OF INTEREST: none. Disclosure forms provided by the authors are available with the full text of this article at Ugeskriftet.dk/dmj

LITERATURE

1. Schilder AG, Chonmaitree T, Cripps AW et al. Otitis media. Nat Rev Dis Primers 2016;2:60-3.
2. Rovers MM, Schilder AGM, Zielhuis GA et al. Otitis media. Lancet 2004;363:465-73.
3. Centers for Disease Control and Prevention. Epidemiology and Prevention of Vaccine-Preventable Diseases. 13th ed. Atkinson W, Wolfe S, Hamborsky J, McIntyre L, eds. Washington DC: Public Health Foundation, 2015. www.cdc.gov/vaccines/pubs/pinkbook/index.html (18 Aug 2020).
4. Bluestone CD, Stephenson JS, Martin LM. Ten&;year review of otitis media pathogens. Pediat Infect Dis J 1992;11(8 suppl):7&;11.
5. Jacobs MR, Dagan R, Appelbaum PC et al. Prevalence of antimicrobial&;resistant pathogens in middle ear fluid: multinational study of 917 children with acute otitis media. Antimicrob Agent Chemother 1998;42:589&;95.
6. Allemann A, Frey PM, Brugger SD et al. Pneumococcal carriage and serotype variation before and after introduction of pneumococcal conjugate vaccines in patients with acute otitis media in Switzerland. Vaccine 2017;35:1946-53.
7. Barenkamp SJ, Chonmaitree T, Hakansson AP et al. Panel 4: report of the Microbiology Panel. Otolaryngol Head Neck Surg 2017;156(suppl 4):S51-S62.
8. Finkelstein JA, Metlay JP, Davis RL et al. Antimicrobial use in defined populations of infants and young children. Arch Pediatr Adolesc Med 2000;154:395-400.
9. Akkerman AE, Kuyvenhoven MM, van der Wouden JC et al. Analysis of under-and overprescribing of antibiotics in acute otitis media in general practice. J Antimicrob Chemother 2005;56:569-74.
10. 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;36:7479-86.
11. Venekamp RP, Sanders SL, Glasziou PP et al. Antibiotics for acute otitis media in children. Cochrane Database Syst Rev

2015;6:CD000219.

12. www.prisma-statement.org/PRISMAStatement/Checklist.aspx (8 Feb 2019).
13. StataCorp. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC, 2017.
14. Ruohola A, Laine MK, Tähtinen PA. Effect of antimicrobial treatment on the resolution of middle-ear effusion after acute otitis media. J Pediatric Infect Dis Soc 2018;7:64-70.
15. Tähtinen PA, Laine MK, Huovinen P et al. A placebo-controlled trial of antimicrobial treatment for acute otitis media. NEJM 2011;364:116-26.
16. Hoberman A, Paradise JL, Rockette HE et al. Treatment of acute otitis media in children under 2 years of age. NEJM 2011;364:105-15.
17. Le Saux N, Gaboury I, Baird M et al. A randomized, double-blind, placebo-controlled noninferiority trial of amoxicillin for clinically diagnosed acute otitis media in children 6 months to 5 years of age. Can Med Ass J 2005;172:335-41.
18. Rovers MM, Glasziou P, Appelman CL et al. Antibiotics for acute otitis media: a meta-analysis with individual patient data. Lancet 2006;368:1429-35.
19. Neumark T, Molstad S, Rosen C et al. Evaluation of phenoxymethylpenicillin treatment of acute otitis media in children aged 2-16. Scand J Prim Health Care 2007;25:166-71.
20. www.folkhalsomyndigheten.se/smittskydd-beredskap/vaccinationer/vacciner-a-o/pneumokocker/ (14 Apr 2020).
21. Ziv O, Kraus M, Holcberg R et al. Acute otitis media in infants younger than two months of age: Epidemiologic and microbiologic characteristics in the era of pneumococcal conjugate vaccines. Int J Pediatr Otorhinolaryngol 2019;119:123-30.
22. Abdelnour A, Arguedas A, Dagan R et al. Etiology and antimicrobial susceptibility of middle ear fluid pathogens in Costa Rican children with otitis media before and after the introduction of the 7-valent pneumococcal conjugate vaccine in the National Immunization Program: acute otitis media microbiology in Costa Rican children. Medicine 2015;94:e320.