Recurrence up to 3.5 years after antibiotic treatment of acute otitis media in very young Dutch children: survey of trial participants

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ABSTRACT
Objective To determine the long term effects of antibiotic treatment for acute otitis media in young children.
Design Prospective three year follow-up study within the framework of a primary care based, double blind, randomised, placebo controlled trial.
Setting 53 general practices in the Netherlands.
Participants 168 children aged 6 months to 2 years with acute otitis media.
Interventions Amoxicillin 40 mg/kg/day in three doses compared with placebo.
Main outcome measures Recurrence of acute otitis media; referral to secondary care; ear, nose, and throat surgery.

RESULTS
Acute otitis media recurred in 63% (47/75) of children in the amoxicillin group and in 43% (37/86) of the placebo group (risk difference 20%, 95% confidence interval 5% to 35%); 30% (24/78 amoxicillin; 27/89 placebo) of children in both groups were referred to secondary care, and 21% (16/78 of the amoxicillin group compared with 30% (27/90) of the placebo group had ear, nose, and throat surgery (risk difference −9%, −23% to 4%).

Conclusion Recurrent acute otitis media occurred more often in the children originally treated with amoxicillin. This is another argument for judicious use of antibiotics in children with acute otitis media.

TRIAL REGISTRATION Netherlands Trial Register NTR1426.

INTRODUCTION
Acute otitis media, one of the most common infections in childhood, remains the leading cause of doctors’ consultations by children and the most common reason for children to take antibiotics. Current guidelines recommend prescription of antibiotics in children with severe illness and in those younger than 2 years of age with bilateral acute otitis media or acute otorrhoea. For most other children with acute otitis media, initial observation is recommended.

So far, little is known about the long term effects of antibiotics in acute otitis media. On the other hand, it may encourage doctors’ attendance in future episodes, increase pressure on doctors to prescribe, increase future use of antibiotics, and therefore increase antibiotic resistance. In addition, antibiotic treatment may cause an unfavourable shift towards colonisation with resistant pathogens, which are likely to promote recurrence of the infection.

We aimed to study the long term effects of antibiotics on recurrence of acute otitis media; referrals to secondary care; and ear, nose, and throat surgery.

METHODS
We did the study within the framework of a primary care based, double blind, randomised, placebo controlled, double blind trial on the effects of amoxicillin compared with placebo in children with acute otitis media aged between 6 and 24 months. The diagnosis of acute otitis media was based on the presence of acute signs of infection and otoscopy. The original study took place in the Netherlands between February 1996 and May 1998 and included 240 children, who were followed actively for six months. At trial entry, parents were informed that treatment allocation would be revealed only after the final follow-up, including the post-trial period of about three years. Only in case of severe complications or side effects would the treatment code be broken during the trial. The results at days four and 11 and at six months were reported in 2000 and 2006.

In 2000—that is, approximately three and half years after the start of the trial—we sent a questionnaire to parents of the participating children, asking them about episodes of recurrent acute otitis media; referral to secondary care; and ear, nose, and throat surgery. We defined the primary outcome measure, reported recurrent acute otitis media, as at least one episode of acute otitis media that occurred between the last study appointment at six months and the current survey. In addition, we compared the proportion of children referred to secondary care (paediatrician or ear, nose, and throat surgeon) and the rate of ear, nose, and throat surgery.
In the first instance, we looked only at risk difference and did not adjust for potential confounders, as we were reporting on the long term effects of a randomised placebo controlled trial. To be sure that confounding was not a problem in the post-randomisation period, we also studied the following potential confounders by using logistic regression analysis: mean age at inclusion, sex, breast feeding, number of siblings, season of inclusion, attendance at day care centre, family history of recurrent upper respiratory tract infections, (duration of) symptoms at presentation, subsequent use of antibiotics within six months, and the clinical outcome at days four and 11 and six months.

Finally, we did a sensitivity analysis on the primary outcome restricted to the children in each group who did not receive antibiotics within the first six months of the post-trial follow-up period. We did all analyses with SPSS 14.0 on an intention to treat basis.

RESULTS

Of the 240 participants originally randomised, 168 (70%) returned the questionnaire. At this stage, about 95% of these parents were still blinded to the original treatment. The baseline characteristics of these 168 children were similar to those initially randomised (table 1).

Three years after randomisation, acute otitis media had recurred in 47/75 (63%) children in the amoxicillin group compared with 37/86 (43%) children in the placebo group (risk difference 20%, 95% confidence interval 5% to 35%) (table 2). Logistic regression analysis showed that sex, allergy, and history of recurrent acute otitis media might be relevant confounding factors. Adjustment for these factors resulted in an adjusted odds ratio of 2.5 (95% confidence interval 1.2 to 5.0)—that is, children who were assigned to the amoxicillin group had a 2.5 times higher risk of recurrent acute otitis media than children in the placebo group.

Twenty four out of 78 (31%) children in the amoxicillin group and 27/89 (30%) in the placebo were referred to secondary care (risk difference 0%, −14% to 14%) (table 2). Finally, 16/78 (21%) children in the amoxicillin group compared with 27/90 (30%) children in the placebo group had ear, nose, and throat surgery (risk difference −9%, −23% to 4%).

Sensitivity analysis for the primary outcome measure, comparing only those children in each group who did not receive antibiotics in the first six months of the post-trial follow-up period, showed a risk difference of 32% (13% to 51%) and an adjusted odds ratio of 4.4 (1.7 to 11.5).

### Table 1 | Baseline characteristics. Values are numbers (percentages) unless stated otherwise

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Trial (n=240)</th>
<th>Long term survey (n=168)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Amoxicillin</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>(n=117)</td>
<td>(n=123)</td>
</tr>
<tr>
<td>Mean age at inclusion (months)</td>
<td>13.3</td>
<td>13.4</td>
</tr>
<tr>
<td>Male</td>
<td>64 (55)</td>
<td>66 (54)</td>
</tr>
<tr>
<td>Breast fed for ≥6 months</td>
<td>21 (18)</td>
<td>22 (18)</td>
</tr>
<tr>
<td>≥2 children in family</td>
<td>30 (26)</td>
<td>25 (20)</td>
</tr>
<tr>
<td>Season of inclusion (Oct-March)</td>
<td>76 (65)</td>
<td>79 (64)</td>
</tr>
<tr>
<td>Smoking in household</td>
<td>46 (39)</td>
<td>39 (32)</td>
</tr>
<tr>
<td>Attendance at day care centre</td>
<td>28 (24)</td>
<td>19 (15)</td>
</tr>
</tbody>
</table>

### Table 2 | Clinical outcomes between six months and three years after randomised controlled trial. Values are numbers (percentages) unless stated otherwise

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Amoxicillin (n=78)</th>
<th>Placebo (n=90)</th>
<th>Risk difference (95% CI)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent acute otitis media</td>
<td>47/75 (63)</td>
<td>37/86 (43)</td>
<td>20% (5% to 35%)</td>
<td>1.5 (1.1 to 2.0)</td>
</tr>
<tr>
<td>Referral rate</td>
<td>24 (31)</td>
<td>27/89 (30)</td>
<td>0% (~14% to 14%)</td>
<td>1.0 (0.6 to 1.6)</td>
</tr>
<tr>
<td>Surgery rate</td>
<td>16 (21)</td>
<td>27 (30)</td>
<td>~9% (~23% to 4%)</td>
<td>0.7 (0.4 to 1.2)</td>
</tr>
</tbody>
</table>
This is another argument for judicious use of antibiotics in children with acute otitis media.

Antibiotics shorten the course of acute otitis media but encourage doctors to prescribe them more often than is necessary. Evidence on the long term effects of antibiotics in children with acute otitis media is lacking.

**DISCUSSION**

Using a questionnaire about recurrent episodes of acute otitis media, we found a 20% higher recurrence rate in the amoxicillin group compared with the placebo group in the post-trial period between six months and three years after randomisation. The corresponding confidence intervals, however, are wide, so this rate must be interpreted with some caution.

To our knowledge, we are the first group to study the long term effects of antibiotics in children with acute otitis media. Others have studied the effects up to one year and found no differences between the groups. This seems to be in agreement with our results for the first six months of follow-up, in which we found similar recurrence rates in the amoxicillin and placebo group (51% ± 50%; risk difference 1%, 95% confidence interval –12% to 15%).

Our findings might be explained by unfavourable changes in the colonisation of the nasopharynx as a result of the use of antibiotics, as reported in this survey, changes in practice since then may have reduced the applicability of our results. As antibiotics are still widely prescribed in young children with acute otitis media, however, we believe that the results of our study are still applicable to current day to day practice.

In conclusion, recurrent acute otitis media occurred more often in the children originally treated with amoxicillin. This is another argument for judicious use of antibiotics in children with acute otitis media.

We thank the participating children and all the general practitioners who included patients in this trial.

**Contributors:** NB analysed and interpreted the data. RAMJD was responsible for the design, planning, and data collection of the original trial and contributed to the initial concept and data interpretation of the study. MMR supervised the study and interpreted the data. AWH and AGMS contributed to the data interpretation. NB and MMR prepared the manuscript, and all authors commented on it. MMR is the guarantor.

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**Ethical approval:** The ethics committee of the University Medical Center Utrecht approved the protocol.

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