Australian Aboriginal children are prone to frequent and severe episodes of acute otitis media (AOM). In a 2003 survey of over 600 children living in 29 Aboriginal communities throughout the Northern Territory, 20% had tympanic membrane perforation, despite 87% uptake of pneumococcal conjugate vaccine. Such high rates of AOM with perforation (AOMwp) and chronic supplicative otitis media (CSOM) are seldom reported in the medical literature. A contributing factor to disease progression may be failed detection of AOM due to the absence of acute symptoms (pain, irritability or fever) in the presence of a bulging tympanic membrane. Thus, a diagnosis of AOM without perforation (AOMwoP) is recommended if a bulging tympanic membrane is present, whether symptoms are present or not. There are few studies assessing antibiotic treatment in such high-risk populations.

We have found that, compared with placebo, long-term antibiotic treatment resolves middle ear effusion and reduces perforation. However, these regimens are difficult to deliver effectively, particularly to poor families in remote settings. Previous studies have shown that short-course azithromycin (for 3–5 days), 6-9 weekly single-dose azithromycin prophylaxis for 12 weeks, or a single dose of azithromycin is likely than amoxicillin clavulanate to be associated with gastrointestinal side effects. The primary aim of our study was to determine the clinical effectiveness of a single dose of azithromycin compared with a standard 7-day treatment course of amoxicillin in a population at high risk of tympanic membrane perforation and CSOM.

**Methods**

**Study design**

We conducted a participant-blinded, care provider-blinded, assessor-blinded, randomised controlled trial — the Azithromycin versus Amoxicillin for Treatment of Acute Otitis Media in Aboriginal Children (AATAAC) study — comparing single-dose azithromycin with 7 days of twice-daily amoxicillin treatment. Treatment allocation was stratified by health centre, body weight and diagnosis (AOMwoP or AOMwp), using randomly varying block sizes.

**Participants**

Our study commenced on 24 March 2003 and was completed on 20 July 2005. We screened Aboriginal children from 14 remote communities and two Aboriginal medical services in northern and central Australia. Our inclusion criteria were (a) age between 6 months and 6 years; (b) new diagnosis of AOMwoP or AOMwp; and (c) willingness of parents to bring their child for a follow-up visit. Children were excluded if they had (a) previously been allocated to an intervention group in the same study; (b) received antibiotics in the previous 7 days; (c) had another ear disease; or (d) had a tympanostomy tube.
(c) current severe illness requiring intravenous or intramuscular antibiotic treatment to be given within the following 7 days; (d) a known allergy to penicillin or azithromycin; or (e) perforation covering more than 2% of the tympanic membrane.

**Interventions**

Children with AOM were randomly allocated to receive either azithromycin (30 mg/kg as a single dose) and amoxycillin placebo, or amoxycillin (50 mg/kg/day in two divided doses for a minimum of 7 days) and azithromycin placebo. All children were scheduled to be examined on Day 0 and at the end of therapy (between Day 6 and Day 11). Children diagnosed with AOMwiP at the end of therapy received a second course of treatment and were also examined between Day 12 and Day 21.

**Outcomes**

**Primary outcomes**

In our clinical trial protocol, we pre-specified two primary outcomes:

- **Clinical failure:** the proportion of children with persistent ear pain, a bulging tympanic membrane or middle ear discharge at the end of therapy (children lost to follow-up were assumed not to have improved); and
- **Failure to improve:** the proportion of examined children with no improvement in clinical signs at the end of therapy. Improvement in clinical signs was determined by healing of a tympanic membrane perforation or substantial reduction in tympanic membrane bulging. Improvement could occur despite clinical failure at end of therapy.

**Secondary outcomes**

We also compared the azithromycin and amoxycillin groups with regard to the following secondary outcomes:

- **Clinical outcomes:** the proportion of children with clinical failure or failure to improve when seen before Day 11 after commencement of therapy (per-protocol analysis); clinical failure according to baseline diagnosis (AOMwoP or AOMwiP); clinical failure according to age (<2 years or ≥2 years); clinical failure according to nasal carriage of otitis media pathogens (*Streptococcus pneumoniae* or non-capsular *Haemophilus influenzae* [NCHi]) at the end of therapy; and additional clinical observations (runny nose and skin sores). We also recorded new episodes of AOMwiP or pain.
- **Microbiological outcomes:** nasal carriage of *S. pneumoniae*, NCHi, resistant *S. pneumoniae* or β-lactamase-positive NCHi; and the proportion of ear discharge cultures positive for *S. pneumoniae* or NCHi.

**Clinical assessment**

All clinical assessments were made by ear health research officers. Otoscopic findings were recorded on a standardised form. Assessments were made using a GSI 38 tympanometer (Grason-Stadler, Eden Prairie, Minn, USA), a LumiView portable binocular microscope (Welch Allyn, Skaneateles Falls, NY, USA), a Siegle speculum for pneumatic otoscopy, and a videotoscope (Welch Allyn, Skaneateles Falls, NY, USA). Video recordings of the tympanic membranes were reviewed by an independent unblinded observer.

We categorised middle ear states into one of six diagnostic categories, using criteria based on recommendations for clinical practice in this population.3

- Normal
- Otitis media with effusion (intact and non-bulging tympanic membrane and type B tympanogram);
- AOMwoP (any bulging of the tympanic membrane and type B tympanogram);
- AOMwiP (middle ear discharge observed and perforation recently healed or present for less than 6 weeks or covering less than 2% of the pars tensa of the tympanic membrane [CSOM is nearly always associated with larger perforations]);
- Dry perforation (tympanic membrane perforation without any discharge observed); or
- CSOM (middle ear discharge observed and perforation present for longer than 6 weeks and covering at least 2% of the pars tensa of the tympanic membrane).

The final middle ear diagnosis reflected the child’s more severely affected ear (highest category).

The presence of nasal discharge was recorded if nasal discharge was visible from 1 metre away at any time during the clinical examination. Skin sores (raised crust or pus visible) were recorded if visible on the arms, legs or head.

**Microbiology**

Nasal swabs were taken at baseline and at follow-up examinations. Swabs of ear discharge were also collected on the days when nasal swabs were taken. All swabs were collected, transported, stored and cultured as previously described.13 Azithromycin resistance was defined as a minimum inhibitory concentration (MIC) of ≥ 2 μg/mL. High-level resistance was defined as MIC > 32 μg/mL.

**Sample size**

We estimated that in at least 50% of children receiving standard therapy for AOM the condition would fail to resolve within 8 days. With 150 children in each intervention arm, the study would have a power of 95% to detect an improved outcome in an additional 20% of children (α = 0.05). This difference was chosen as the minimum improvement that would potentially result in a change in recommended therapy for AOM from amoxycillin to azithromycin.

All statistical analyses were conducted using Stata software, version 10 (StataCorp, College Station, Tex, USA). Assessment of statistical significance was based on the Fisher exact test.

**Ethics approval and registration**

Our study was approved by the human research ethics committees of the Menzies School of Health Research and the Royal Darwin Hospital and by the Central Australian Human Research Ethics Committee, and was registered with the Australian Clinical Trials Registry (ACTRN 12609000691246). An independent Data and Safety Monitoring Board chaired by Professor David Brewster and Associate Professor Alan Ruben of the NT Clinical School, Flinders University, reviewed the data.

**RESULTS**

**Clinical observations, nasal carriage and ear discharge at baseline (Box 1)**

**Clinical observations.** Of 320 children taking part in the trial, 165 were randomly allocated to the azithromycin treatment group and 155 to the amoxycillin treatment group. As seven children were lost to follow-up in each group, analysis was carried out on the remaining 306 children (Box 2). Most were less than 2 years of age, and about half were male. For each group at baseline, 85% had AOMwoP and 15% had AOMwiP, and 5% of mothers reported that they thought their child had ear pain. Nasal discharge was seen in 69% of children and skin sores in 6%–7%.

**Nasal carriage.** For both treatment groups, nasal carriage of *S. pneumoniae* and NCHi was 83% or more. About 14% of children were colonised by *S. pneumoniae* with intermediate or full resistance to penicillin (MIC ≥ 0.12 μg/mL), and about 5% carried azithromycin-resistant *S. pneumoniae* (MIC ≥ 2 μg/mL). Less than 10% of children swabbed carried β-lactamase-producing NCHi.
Clinical outcomes, nasal carriage and ear discharge cultures at the end of therapy (Box 3). At the end of therapy, 50% of the azithromycin group and 54% of the amoxycillin group were clinical failures. Similar proportions (45% and 49%) failed to improve, and about 5% were worse in both groups (nine children developed new perforations). Differences between the azithromycin and amoxycillin groups in clinical failure rates were not significant.

No differences in clinical failure or failure to improve were indicated in a per-protocol analysis (children seen before Day 11 after commencement of treatment). Only four parents reported that their child had ear pain (three of the children were in the amoxycillin group). Fewer children in the azithromycin group than the amoxycillin group had runny nose (35% v 46%), but the difference was not significant, and about 4% of children in both groups had skin sores.

Clinical failure rates in children who had AOMwP at baseline were higher in the azithromycin group, children in the azithromycin group had significantly lower carriage of S. pneumoniae and H. influenzae, lower carriage of S. pneumoniae with intermediate or full resistance to penicillin (RD, –0% [but this difference was non-significant]), and significantly higher carriage of azithromycin-resistant S. pneumoniae (RD, 7%) (Box 5). Ear discharge. The proportion of ear discharge cultures that were positive for S. pneumoniae and NCHi was about 25 percentage points lower in the azithromycin group (Box 5).

Comparison between baseline and end of therapy (Box 1 and Box 5). Compared with baseline, nasal carriage of S. pneumoniae was significantly lower in both groups at follow-up (azithromycin group RD, –56% [95% CI, –65% to –47%]; and carriage of NCHi was also significantly reduced (azithromycin group RD, –31% [95% CI, –40% to –21%]). In the azithromycin group, compared with baseline, car-

Ear discharge. In the azithromycin and amoxycillin groups, respectively, S. pneumoniae was cultured from 22% and 32% of ear discharge swabs, and NCHi from 36% and 41% of ear discharge swabs.

No differences in clinical failure or failure to improve were indicated in a per-protocol analysis (children seen before Day 11 after commencement of treatment). Only four parents reported that their child had ear pain (three of the children were in the amoxycillin group). Fewer children in the azithromycin group than the amoxycillin group had runny nose (35% v 46%), but the difference was not significant, and about 4% of children in both groups had skin sores.

Clinical failure rates in children who had AOMwP at baseline were 40% in the azithromycin group and 46% in the amoxycillin group. For children who had AOMwP at baseline, clinical failure rates were 92% and 83%, respectively. (Clinical failure rates were 84% and 63%, respectively, at Day 12–21.) There was no significant association between age group (<2 years or ≥2 years) and clinical failure.

No significant difference in clinical failure was detected between azithromycin and amoxycillin groups for carriers or non-carriers of S. pneumoniae or NCHi at the end of therapy. Carriage of resistant S. pneumoniae or NCHi at baseline did not predict greater clinical failure. The risk difference (RD) in clinical failure between children carrying susceptible organisms (S. pneumoniae or NCHi) at baseline and those carrying resistant organisms at baseline was –9%.

Complications and side effects. There were three serious adverse events that resulted in admission to hospital during the treatment period. The independent Data and Safety Monitoring Board found that these were not associated with the study interventions. No side effects (eg, allergic, gastrointestinal) led to cessation of treatment or withdrawal from the study.

New episodes of disease. In both groups, new perforations were detected in 3%–4% of children who had AOMwP at baseline. Pain resolved in all children who had had pain at baseline, but four children developed “new” pain (Box 4).

Nasal carriage. Compared with children in the amoxycillin group, children in the azithromycin group had significantly lower carriage of S. pneumoniae and H. influenzae, lower carriage of S. pneumoniae with intermediate or full resistance to penicillin (RD, –0% [but this difference was non-significant]), and significantly higher carriage of azithromycin-resistant S. pneumoniae (RD, 7%) (Box 5).
DISCUSSION

To our knowledge, this is the first randomised controlled trial of antibiotic treatment of AOM in a population with high rates of acute and chronic tympanic membrane perforation. Although our study was not designed or powered to show equivalence, our findings suggest that the two antibiotic regimens are likely to have similar efficacy in this population. However, in view of the substantial problems of adherence to twice-daily regimens in such populations, single-dose azithromycin treatment may be a more appropriate standard treatment option than a 7-day course of amoxicillin.

Azithromycin treatment reduced nasal carriage of both S. pneumoniae and NCHi. Although overall rates of antibiotic resistance were unchanged, azithromycin treatment was associated with an increase in carriage of azithromycin-resistant S. pneumoniae.

In other published trials, an evidence summary and a meta-analysis that included azithromycin treatment of AOM, clinical response rates in groups receiving azithromycin have generally been 70% or higher.6-8,11,12,15-18 In a Cochrane review of short-course antibiotic treatment for AOM, outcomes of short courses of agents such as cefixime or azithromycin were comparable with outcomes of longer courses of other antibiotics.8 Clinical trials assessing outcomes of single-dose azithromycin treatment11,12 have reported similarly high success rates. The Cochrane meta-analysis summary odds ratio for primary outcomes after 3–5 days’ treatment with azithromycin (n = 1347) compared with 10 days’ treatment with another antibiotic (n = 1246) was 1.09 (95% CI, 0.86 to 1.38). Success rates were about 86% in both azithromycin groups and comparison groups.8 In a single trial that reported outcome data for perforated or non-perforated eardrums of 28 evaluable patients with spontaneous perforation, there were more failures after 5 days of therapy than after 10 days of therapy.19

In our study, clinical success rates among Aboriginal children receiving azithromycin therapy for AOM were much lower than the rates reported in previous published studi-
ies. Reduced likelihood of cure is reported for patients with azithromycin-resistant *S. pneumoniae* (67%) compared with those with susceptible *S. pneumoniae* (90%). The rates of antimicrobial resistance found in our study (about 21%) do not explain the high proportion of clinical failures observed. Poor adherence to recommended treatment regimens could explain poor clinical outcomes in the amoxycillin group. However, as the single dose of azithromycin was given under supervision, compliance with azithromycin treatment was close to 100%. In another of our studies in which compliance with twice-daily amoxycillin therapy was monitored, we estimated that 17/30 participants took less than half their recommended treatment. In that study, we found that AOM persisted in about three-quarters of participants and could not be explained by nasopharyngeal carriage of penicillin-resistant *S. pneumoniae* strains.

The poor clinical outcomes associated with failure to eradicate NCHi in our study are consistent with clinical and bacteriological studies by Dagan et al showing clinical failure rates of 65% and 53% in patients with NCHi infections receiving azithromycin treatment.

We believe that persistent ear disease is related to high bacterial load in the nasopharynx. Antibiotics that eradicate otitis media pathogens and reduce bacterial load are needed for clinical success. While azithromycin was more effective at eradicating AOM pathogens than amoxycillin, nasal carriage of any *S. pneumoniae* or NCHi remained high at the end of therapy (65% in the azithromycin group and 92% in the amoxycillin group). For children with AOMwIP, ear discharge cultures were less likely to be positive after treatment with azithromycin. The observed association of better clinical outcomes with pathogen clearance and the greater impact of azithromycin on carriage (particularly for NCHi) led us to believe that clinical trials of longer courses of azithromycin treatment are required. The potential benefits for other important child health problems (eg, skin sores, runny nose and trachoma) should also be evaluated.

In the AATAAC study, most children with AOM at enrolment had an intact bulging tympanic membrane. However, as few had ear pain, it is likely that many children in this population will have undiagnosed AOM. This may explain the high rate of tympanic membrane perforation in this population. Further research is needed to determine the benefits of early detection of at-risk children as well as predictors of which children will progress to perforation.

### ACKNOWLEDGEMENTS
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### COMPETING INTERESTS
None identified.

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### REFERENCES

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**5 Microbiological outcomes at the end of therapy (between Day 6 and Day 11)**

<table>
<thead>
<tr>
<th>Nasal carriage of pathogens*</th>
<th>Azithromycin group (n=157)</th>
<th>Amoxycillin group (n=146)</th>
<th>RD (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. pneumoniae</em></td>
<td>42/157 (27%)</td>
<td>92/146 (63%)</td>
<td>-36% (-47% to -26%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>NCHi</td>
<td>86/157 (55%)</td>
<td>124/146 (85%)</td>
<td>-30% (-40% to -21%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><em>S. pneumoniae</em> and NCHi</td>
<td>26/157 (17%)</td>
<td>82/146 (56%)</td>
<td>-40% (-50% to -30%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Any <em>S. pneumoniae</em> or NCHi</td>
<td>102/157 (65%)</td>
<td>134/146 (92%)</td>
<td>-27% (-36% to -18%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Resistant <em>S. pneumoniae</em></td>
<td>Penicillin (MIC &gt; 0.12 μg/ml)</td>
<td>16/157 (10%)</td>
<td>23/146 (16%)</td>
<td>-6% (-13% to 2%)</td>
</tr>
<tr>
<td>Azithromycin (MIC &gt; 2 μg/mL)</td>
<td>15/157 (10%)</td>
<td>5/146 (3%)</td>
<td>7% (0.1% to 12%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Azithromycin (MIC &gt; 32 μg/mL)</td>
<td>9/157 (6%)</td>
<td>3/146 (2%)</td>
<td>4% (-1% to 8%)</td>
<td>0.140</td>
</tr>
<tr>
<td>Any resistant <em>S. pneumoniae</em></td>
<td>25/157 (16%)</td>
<td>26/146 (18%)</td>
<td>-2% (-10% to 7%)</td>
<td>0.749</td>
</tr>
<tr>
<td>β-lactamase-producing NCHi</td>
<td>8/157 (5%)</td>
<td>7/146 (5%)</td>
<td>0.3% (-4% to 5%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Any resistant <em>S. pneumoniae</em> or NCHi</td>
<td>33/157 (21%)</td>
<td>32/146 (22%)</td>
<td>-1% (-10% to 8%)</td>
<td>0.889</td>
</tr>
</tbody>
</table>

| Culture of ear discharge from children with AOMwIP† | *S. pneumoniae* | 0/27 | 6/24 (25%) | -25% (-40% to -3%) | 0.040 |
| NCHi | 6/27 (22%) | 12/24 (50%) | -28% (-53% to -2%) | 0.046 |

AOMwIP = acute otitis media with (tympanic membrane) perforation. NCHi = non-capsular *Haemophilus influenzae*. RD = risk difference. * Figures are proportion (%) of children swabbed. † Figures are proportion (%) of ears swabbed.
media with effusion (OME) and prevent acute otitis media with perforation (AOMwiP) in a high-risk population: a randomized controlled trial. *BMC Pediatrics* 2008; 8: 23.


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