Long-term azithromycin for Indigenous children with non-cystic-fibrosis bronchiectasis or chronic suppurative lung disease (Bronchiectasis Intervention Study): a multicentre, double-blind, randomised controlled trial

Patricia C Valery, Peter S Morris, Catherine A Byrnes, Keith Grimwood, Paul J Torzillo, Paul A Bauert, I Brent Masters, Abbey Diaz, Gabrielle B McCallum, Charmaine Mobberley, Irene Tjhung, Kim M Hare, Robert S Ware, Anne B Chang

Lancet Respir Med 2013; 1: 610–20

Published Online September 17, 2013 http://dx.doi.org/10.1016/S2213-2600(13)70185-1

See Comment page 587

Menzies School of Health Research, Charles Darwin University, Darwin, NT, Australia (P C Valery PhD, P S Morris PhD, A Diaz MAppSc, G B McCallum MPH, K M Hare MPH, Prof A B Chang PhD); **Department of Paediatrics, Royal Darwin Hospital, Darwin, NT, Australia** (P S Morris, P A Bauert FRACP); **Department of Paediatrics, University of Auckland, Auckland, New Zealand** (C A Byrnes MD, C Mobberley RN); **Paediatric Respiratory Medicine, Starship Children's Health, Auckland, New Zealand** (C A Byrnes, C Mobberley); **Queensland Children's Medical Research Institute, The University of Queensland, Brisbane, QLD, Australia** (Prof K Grimwood MD, I B Masters PhD, R S Ware PhD); **Queensland Paediatric Infectious Diseases Laboratory, Royal Children's Hospital, Brisbane, QLD, Australia** (Prof K Grimwood); **University of Sydney, Sydney, NSW, Australia** (Prof P J Torzillo FRACP); **Royal Prince Alfred Hospital, Sydney, NSW, Australia** (Prof P J Torzillo); **Queensland Children's Respiratory Centre, Royal Children's Hospital, Brisbane, QLD, Australia** (I B Masters, Prof A B Chang); **Torres Strait-Northern Peninsula Hospital and Health Service, Thursday Island, QLD, Australia** (I Tjhung FRACGP); **School of Population Health, The University of Queensland, Brisbane, QLD, Australia** (R S Ware); **and Queensland Children's Medical Research**

Summary

Background Indigenous children in high-income countries have a heavy burden of bronchiectasis unrelated to cystic fibrosis. We aimed to establish whether long-term azithromycin reduced pulmonary exacerbations in Indigenous children with non-cystic-fibrosis bronchiectasis or chronic suppurative lung disease.

Methods Between Nov 12, 2008, and Dec 23, 2010, we enrolled Indigenous Australian, Maori, and Pacific Island children aged 1–8 years with either bronchiectasis or chronic suppurative lung disease into a multicentre, double-blind, randomised, parallel-group, placebo-controlled trial. Eligible children had had at least one pulmonary exacerbation in the previous 12 months. Children were randomised (1:1 ratio, by computer-generated sequence with permuted block design, stratified by study site and exacerbation frequency [1–2 *vs* ≥3 episodes in the preceding 12 months]) to receive either azithromycin (30 mg/kg) or placebo once a week for up to 24 months. Allocation concealment was achieved by double-sealed, opaque envelopes; participants, caregivers, and study personnel were masked to assignment until after data analysis. The primary outcome was exacerbation (respiratory episodes treated with antibiotics) rate. Analysis of the primary endpoint was by intention to treat. At enrolment and at their final clinic visits, children had deep nasal swabs collected, which we analysed for antibiotic-resistant bacteria. This study is registered with the Australian New Zealand Clinical Trials Registry; ACTRN12610000383066.

Findings 45 children were assigned to azithromycin and 44 to placebo. The study was stopped early for feasibility reasons on Dec 31, 2011, thus children received the intervention for 12–24 months. The mean treatment duration was 20·7 months (SD 5·7), with a total of 902 child-months in the azithromycin group and 875 child-months in the placebo group. Compared with the placebo group, children receiving azithromycin had significantly lower exacerbation rates (incidence rate ratio 0·50; 95% CI 0·35–0·71; p<0·0001). However, children in the azithromycin group developed significantly higher carriage of azithromycin-resistant bacteria (19 of 41, 46%) than those receiving placebo (four of 37, 11%; p=0·002). The most common adverse events were non-pulmonary infections (71 of 112 events in the azithromycin group *vs* 132 of 209 events in the placebo group) and bronchiectasis-related events (episodes or investigations; 22 of 112 events in the azithromycin group *vs* 48 of 209 events in the placebo group); however, study drugs were well tolerated with no serious adverse events being attributed to the intervention.

Interpretation Once-weekly azithromycin for up to 24 months decreased pulmonary exacerbations in Indigenous children with non-cystic-fibrosis bronchiectasis or chronic suppurative lung disease. However, this strategy was also accompanied by increased carriage of azithromycin-resistant bacteria, the clinical consequences of which are uncertain, and will need careful monitoring and further study.

Funding National Health and Medical Research Council (Australia) and Health Research Council (New Zealand).

Introduction

Bronchiectasis and chronic suppurative lung disease, which we collectively term bronchiectasis, unrelated to cystic fibrosis, is characterised by recurrent bacterial infection and airway inflammation.[1,2] Its prevalence is especially high in Indigenous children from high-income countries such as Australia, New Zealand, and the USA, ranging from 63 to 1600 per 100 000 children.[2] Treatment of bronchiectasis aims to resolve acute infection and control infection and inflammation. Treatment improves symptoms (persistent or recurrent wet cough and breathlessness), reduces frequency of acute pulmonary exacerbations, preserves lung function, and improves quality of life.[1] Pulmonary exacerbations (especially those needing admission to hospital) are the only known independent risk factor for long-term pulmonary decline in children with bronchiectasis.[3] The public health importance of bronchiectasis is shown by Indigenous Australians dying from bronchiectasis in the third and fourth decades of life.[4] This poor outcome might be the result of scarce access to medical care and delayed or

inadequate treatment early in life, since lung function is stable when children are managed optimally.[4]

Because bacteria have a central role in pathogenesis,[5] antibiotics are used to reduce bacterial load and accompanying airway inflammation.[1,6] Antibiotics are administered regularly for treatment of exacerbations;[1,6] however, their use as maintenance therapy over prolonged periods is controversial. Although long-term antibiotics might reduce exacerbations, the absence of high-quality evidence in children (and concerns about antibiotic resistance) means they are not recommended as routine treatment.[1] Moreover, evidence is also scarce for Indigenous populations, who are among the most disadvantaged groups in affluent countries and for whom optimum management of disease is often most difficult to achieve.

In children with cystic fibrosis, 6 months of treatment with azithromycin leads to modest improvement in lung function, reduced pulmonary exacerbation rates, and improved weight gain.[7] Its antimicrobial effects, anti-inflammatory actions, and prolonged half-life (allowing once-weekly oral dosing)[8] make azithromycin an attractive option for maintenance treatment. Randomised controlled trials in adults with bronchiectasis showed that 6 months and 12 months of azithromycin reduced rates of pulmonary exacerbation and respiratory symptoms.[9,10] By contrast, there are no reported randomised controlled trials of long-term antibiotics in children with bronchiectasis, even though infective exacerbations in developing lungs could lead to substantial impairment of lung function in adulthood.[11]

Our study (the Bronchiectasis Intervention Study) aimed to establish whether long-term (24 months) antibiotic treatment with azithromycin would reduce the rate of pulmonary exacerbations in Indigenous children with non-cystic-fibrosis bronchiectasis. We also monitored for serious adverse events associated with azithromycin and examined its effect on nasopharyngeal carriage of bacterial pathogens.[12]

Methods

Study design and participants

We did this multicentre, double-blind, randomised, parallel-group, placebo-controlled trial in Australia and New Zealand. Details of this study were described previously.[13] Briefly, between Nov 12, 2008, and Dec 23, 2010, we enrolled Indigenous children from community clinics in central and northern Australia, and urban Maori and Pacific Island children from a tertiary paediatric hospital in Auckland (New Zealand) who were aged 1–8 years, lived within the study area, had either bronchiectasis confirmed radiographically by high-resolution CT (HRCT) scans or chronic suppurative lung disease (bronchiectasis suspected clinically when HRCT scans were unavailable), and had had at least one pulmonary exacerbation in the past 12 months. Children were excluded if they were receiving chemotherapy, immunosuppressive treatment, or long-term antibiotics; had an underlying cause for their bronchiectasis (eg, cystic fibrosis, primary immunodeficiency), other chronic disorders (eg, cardiac, neurological, renal, or hepatic abnormality), or macrolide hypersensitivity. All study participants had been investigated previously in accordance with national guidelines on chronic suppurative lung disease and bronchiectasis (appendix).[14] Human research ethics committees of all participating institutions approved the study. Caregivers provided written informed consent.

Randomisation and masking

An independent statistician used a computer-generated, permuted-block design to provide the randomisation sequences. Children were allocated in a 1:1 ratio (stratified by study site and exacerbation frequency in the preceding 12 months [1–2 *vs* ≥3 episodes]) to azithromycin or placebo. Allocation concealment was achieved by sequentially numbered, double-sealed, opaque envelopes. An independent person at the Queensland Institute of Medical Research (Brisbane, QLD, Australia) prepared the individual envelopes labelled with the randomisation number that contained the treatment code inside. Study drugs (powder for reconstitution to suspension) were in identical packaging and the placebo (Institute of Drug Technology, Melbourne, VIC, Australia) was much the same in appearance, taste, and smell to azithromycin (Pfizer Australia, West Ryde, NSW, Australia). Participants, families, health professionals, and study personnel were unaware of treatment assignment until data analysis was completed.

Procedures

Children entered the study when they were clinically stable (at least 8 weeks after their last exacerbation) as decided by clinic staff; children who were already receiving azithromycin (four in each treatment group) had the antibiotic discontinued and underwent a 3 month washout period before commencing the study. Participants received either oral azithromycin (30 mg/kg; maximum 600 mg) or placebo once weekly for 24 months from study entry. For feasibility reasons (slow recruitment and funding limitations), the intervention was ceased on Dec 31, 2011. Thus the actual intervention period ranged from 12 months to 24 months.

Study drug was administered under direct supervision at the community clinic (Australia) or at the child's home, preschool, or school (New Zealand). New Zealand children also had scheduled hospital-clinic visits. Research nurses contacted the community clinic, child's caregiver, preschool, or school weekly to record drug adherence (children receiving medication and, if any, children who were absent from the community) and any issues with administration, such as the child spitting out the medication. These data were recorded in a participant medication logbook. Study personnel did a medical review every 3–4 months. Because participants received

Institute, Queensland University of Technology, Brisbane, QLD, Australia
(Prof A B Chang)

Correspondence to:
Dr Patricia C Valery, Menzies School of Health Research, Spring Hill, QLD 4000, Australia
patricia.valery@menzies.edu.au

See **Online** for appendix

their clinical care at community or hospital-based clinics, all medically attended exacerbation episodes were captured. Children were withdrawn (treatment failure) if exit criteria occurred (six or more outpatient-managed pulmonary exacerbations or four or more hospital inpatient-managed pulmonary exacerbations, over 12 months). Local clinicians or investigators were also able to withdraw children at any time if they decided that further participation was likely to be harmful.

At enrolment and at their final clinic visits, children had deep nasal swabs collected, which were placed into skim-milk tryptone glucose glycerol broth, and transported to the laboratory for storage at –80°C until testing, as described previously.[12] Batches of swabs were thawed and 10 µL aliquots cultured overnight on selective media at 37°C in 5% CO_2. We did antibiotic susceptibility testing on *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis,* and *Staphylococcus aureus* isolates using methods described previously.[12]

Serious adverse events were any unexpected medical occurrence that resulted in death or was life-threatening, caused significant disability or incapacity or admission to hospital, or prolonged existing hospital stay. All serious adverse events were reported to an independent data safety monitoring board.[13] When serious adverse events were judged to be associated with the study drug, the drug was ceased (although the child continued to be monitored).

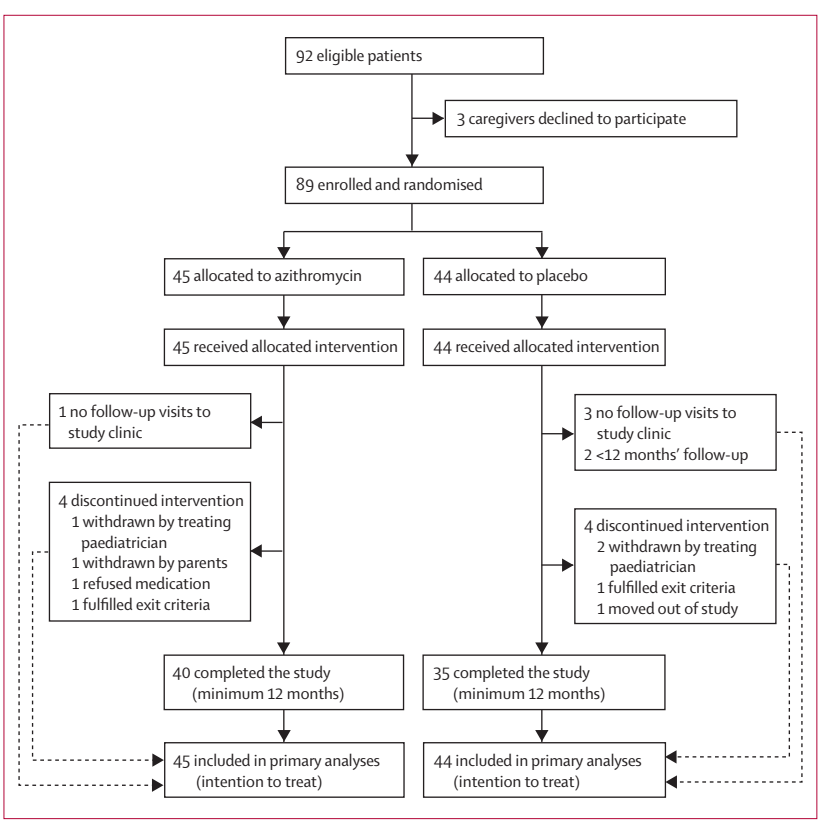

Figure 1: **Trial profile**

The primary outcome was pulmonary exacerbation rate as established by medical record review (number of episodes per child-year over the study period). We defined pulmonary exacerbation as treatment by clinic or hospital staff with antibiotics for any of the following (as recorded in the medical chart): increased cough, dyspnoea, increased sputum volume or colour intensity, new chest examination or radiographic findings, deterioration in predicted forced expiratory volume in 1-second (FEV_1) percentage by more than 10%, or haemoptysis. All treatments of acute exacerbations were with non-macrolide antibiotics and we counted all clinic visits for a respiratory infection within 2 weeks as part of the same exacerbation.

Secondary outcomes were: time to first pulmonary exacerbation, duration of exacerbation episode (discharge date minus admission date plus 1 day), severity (admission to hospital, oxygen supplementation), weight-for-age *Z*-scores (*Z*-score at last study clinic minus its value at baseline), respiratory signs and symptoms (assessed by study personnel on history and physical examination), sputum characteristics (using a validated sputum colour chart, Bronkotest [Bronkotest, Middlesex, UK]),[15] school absenteeism, FEV_1 percentage in those aged 6 years and older, serious adverse events, and antibiotic resistance in bacterial pathogens cultured from deep nasal swabs. All data were recorded on standardised forms.

Statistical analysis

The sample size and power calculations were based on previous data;[16] we anticipated that participants in the placebo group would have four episodes during the 24-month trial period. Guided by results from an earlier randomised trial of azithromycin in patients with cystic fibrosis,[17] we assumed pulmonary exacerbations would be reduced by 50% in the intervention and by 15% in the placebo group. 51 participants per group would give 90% power to detect an average difference of 1·4 respiratory exacerbations per participant over a 2-year period at the 5% level of significance.

Analysis of the primary endpoint was by intention to treat. Analysis of secondary endpoints was by modified intention to treat, excluding patients with missing data, except for the analysis of nasal swabs, which was done only for participants with swabs available from baseline and last clinic visits. Summary statistics are presented as either mean (SD) or median (range) for continuous data, depending on their distribution, and as frequency (percentage) for categorical data. All tests were two-tailed, 95% CIs were reported where appropriate, and statistical significance was set at $\alpha=0\cdot05$. All outcomes with count data, including the primary outcome of number of pulmonary exacerbations, were modelled using negative binomial regression with robust SEs. Main effects included in the model were treatment group and the two stratification variables, study site and exacerbation frequency in 12 months before trial

	Azithromycin (n=45)	Placebo (n=44)
Sociodemographic characteristics		
Age at enrolment (years)	3·99 (2·14)	4·22 (2·30)
Boys	26/45 (58%)	21/44 (48%)
Female caregiver completed high school	14/38 (37%)	12/40 (30%)
Mother used tobacco in pregnancy	14/42 (33%)	12/42 (29%)
HRCT-proven bronchiectasis	34/45 (76%)	39/44 (89%)
Medical history		
Premature at birth	13/45 (29%)	16/41 (39%)
Birthweight (g)	3176 (974; n=44)	2808 (1152; n=39)
Mechanical ventilation needed in the neonatal period	2/43 (5%)	9/41 (22%)
Breastfed as an infant	37/43 (86%)	31/43 (72%)
Number of previous respiratory episodes	12 (1 to 38)	13 (4 to 39)
Age at first respiratory episode (months)	5·5 (0·4 to 51)	4·2 (0·0 to 22)
Number of respiratory episodes needing admission to hospital	3 (0 to 17)	4 (0 to 16)
Age at first respiratory episode needing admission to hospital (months)	6·5 (0·4 to 29)	4·2 (0·0 to 54)
Number of previous pneumonia episodes	2 (0 to 11)	3 (0 to 10)
Age at first pneumonia episode (months)	9·3 (0·37 to 47; n=40)	6·8 (0·0 to 54; n=39)
Number of previous reactive airways disease episodes	1 (0 to 22)	1 (0 to 27)
Wheeze in past 12 months	21/44 (48%)	18/44 (41%)
Age at first wheeze (months)	4·6 (4·57; n=34)	7·3 (2·83; 38)
Antibiotic use in the 2 weeks before enrolment	16/40 (40%)	12/36 (33%)
First clinical examination		
Normal respiratory examination	17/45 (38%)	23/44 (52%)
Respiratory crackles present	11/45 (24%)	10/44 (23%)
Wheeze present	5/45 (11%)	3/44 (7%)
BronkoTest colour chart*	3·5 (2 to 5; n=10)	4 (2 to 4; n=9)
Weight-for-age Z-score	0·35 (–1·98 to 8·66)	–0·15 (–2·60 to 6·40)

Data are mean (SD), n/N (%), or median (range). Information was unavailable for various items in one to 17 children (detailed in appendix). HRCT=high-resolution CT.
*A standardised and validated colour chart used to grade sputum visually in which 1=non-purulent, 5=purulent and dark (worse).[15]

Table 1: **Sociodemographic, medical history, and baseline characteristics of participants by treatment group**

enrolment (1–2 *vs* >3 episodes). To account for the different amounts of study time contributed by each participant we included years in study as an offset. Results are reported as incidence rate ratios (IRRs). Binary outcomes were modelled using logistic regression and are reported as odds ratios (ORs). Main effects included in the model were treatment group and stratification variables. Continuous outcomes were modelled using linear regression and mean differences (MD) are reported. Main effects included in the model were treatment group, stratification variables, and years in study. Time to first exacerbation was assessed using Kaplan-Meier survival curves. The curves were compared with the log-rank test statistic. Cox proportional hazard modelling was used to calculate hazard ratios (HRs), after testing the proportional hazards assumption was justified. Estimates were adjusted for the stratifying factors. The reporting period was for 24 months or until censor time (Dec 31, 2011, or earlier if discontinuing treatment). We used the Statistical Package for Social Science (version 20) and Stata (version 12.0) to do the analysis. We used Epi Info (version 3.5.3) to calculate weight-for-age Z-scores and prevalence rates (with 95% CI).

Post-hoc subgroup analyses were also done, including participants taking 70% or more of their expected doses, those who received the intervention for 23–24 months, children with HRCT-proven bronchiectasis, children who had at least two hospital-managed pulmonary exacerbations before enrolment, children who had at least ten pulmonary exacerbations before enrolment, and those carrying any respiratory bacterial pathogens at baseline. In a post-hoc sensitivity analysis, analyses were rerun after the inclusion of the potential confounders birthweight, children with history of mechanical ventilation as neonates, and breastfeeding as main effects in regression models.[16]

This trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12610000383066.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, or data interpretation, or writing of the report. PSM, ABC, CAB, IT, PCV, RSW,

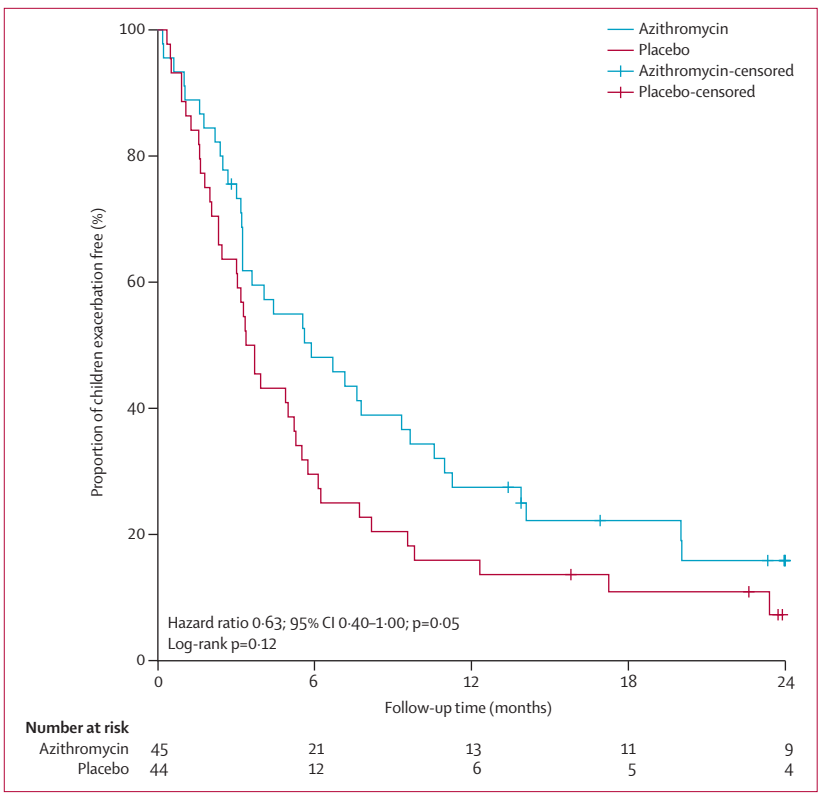

Figure 2: **Kaplan-Meier curves showing the proportion of children remaining exacerbation-free during the intervention period**

	Azithromycin (n=45)	Placebo (n=44)
Any exacerbation		
0	9 (20%)	4 (9%)
1	7 (16%)	7 (16%)
2	9 (20%)	5 (11%)
3	10 (22%)	4 (9%)
4	5 (11%)	5 (11%)
5	4 (9%)	1 (2%)
6	0	3 (7%)
7	0	8 (18%)
8	0	3 (7%)
9	1 (2%)	1 (2%)
10	0	2 (5%)
14	0	1 (2%)
Hospital-managed		
0	42 (93%)	35 (80%)
1	1 (2%)	5 (11%)
2	1 (2%)	3 (7%)
3	0	1 (2%)
5	1 (2%)	0

Table 2: **Distribution of pulmonary exacerbations per participant during the course of the study, by treatment group**

GBM, and CM had access to the raw data. The corresponding author had full access to all the data in the study and the final responsibility for the decision to submit for publication.

Results

Of 92 eligible children, 89 were enrolled, 45 were randomised to receive azithromycin and 44 placebo (figure 1). Of children enrolled, 75 (84%) received the intervention for 12 months or more (52 children [58%] received the intervention for 23–24 months [26 in each group] and 11 children [12%] for 18–22 months [four in the placebo group and seven in the azithromycin group]). Table 1[15] shows baseline characteristics. The most substantial difference was mechanical ventilation with more children in the placebo group needing ventilation as neonates compared with those in the azithromycin group (22% *vs* 5%). However, participants in the azithromycin group were also less likely to be premature (29% *vs* 39%), fewer had proven bronchiectasis (76% *vs* 89%), and their first admission to hospital for respiratory disease occurred later in life (mean of 6·5 *vs* 4·2 months).

The mean duration of intervention in both groups was 20·7 months (SD 5·7), with a total of 902 child-months in the azithromycin group and 875 child-months in the placebo group. All children were included in the primary endpoint analyses, including four children who had primary outcomes measured, but who failed to attend any follow-up study visits. Overall, eight children ceased the intervention early, mainly after being withdrawn by their treating physician or because of treatment failure (two in the azithromycin group, three in the placebo group). Medication logbook recordings showed that adherence was 88% in the azithromycin and 84% in the placebo group (p=0·83).

Compared with those receiving placebo, participants in the azithromycin group were significantly less likely to have pulmonary exacerbations (incidence rate ratio [IRR] 0·50; 95% CI 0·35–0·71; p<0·0001). For hospital-managed exacerbations, the IRR was 1·08 (95% CI 0·19–6·26). Although time to the first pulmonary exacerbation was longer in the azithromycin group compared with the placebo group, the difference was not significant (p=0·12; figure 2). Children receiving azithromycin were less likely to have any exacerbations after study enrolment (HR 0·63; 95% CI 0·40–1·00; p=0·05) and to have an exacerbation needing admission to hospital (HR 0·31; 95% CI 0·08–1·15; p=0·08) than were those receiving placebo, but results were not significant. Table 2 shows the distribution of pulmonary exacerbations by treatment group.

The only significant difference in clinical examination findings (last study clinic visit items) was that weight-for-age *Z*-scores were significantly better in the azithromycin group (table 3). Severity of pulmonary exacerbation episodes was examined by length of hospital stay and need for oxygen supplementation. Median length of stay for hospital-managed exacerbations was 7·2 days (range 3·5–16·0) in the azithromycin group versus 12·0 days

(2·5–17·0) in the placebo group (p=0·58). Of the 22 hospital episodes, only three episodes involving three children in the placebo group needed oxygen. We identified no difference in the number of school-age (≥6 years) children (n=40) reporting reduced school attendance as a result of their cough (three of 18 [17%] in the azithromycin group *vs* six of 22 [27%] in the placebo group, p=0·48).

The nasal swab bacteriological profile of the groups was much the same at baseline (table 4). Substantial differences emerged at study completion with lower carriage of *H influenzae* and *M catarrhalis* in the azithromycin group compared with placebo, but increased carriage of azithromycin-resistant bacteria (table 4). Overall, the odds of carrying azithromycin-resistant bacteria were seven times greater in the azithromycin group than in the control group. None of the children had *Pseudomonas aeruginosa* detected.

Of the 15 children in the azithromycin group colonised with *H influenzae* at baseline, only one was colonised at the last visit, while of the nine placebo recipients carrying *H influenzae* at baseline, five still carried the organism at their last visit. By contrast, of the 12 children with azithromycin-resistant *S pneumoniae* at the last visit, only two had been colonised at baseline (both in the

	Azithromycin	Placebo	OR* or IRR† or MD‡ (95% CI)	p value
Medical chart review items§				
Number of pulmonary exacerbations (median [range])	104 (2 [0–9])	195 (4 [0–14])	IRR 0·50 (0·35 to 0·71)	<0·0001
Number of hospital-managed pulmonary exacerbations (median [range])	8 (0 [0–5])	14 (0 [0–3])	IRR 1·08 (0·19 to 6·26)	0·93
Children exacerbation-free at 24-months	9 (20%)	4 (9%)	OR 0·39 (0·11 to 1·41)	0·15
Children exacerbation-free (hospital-managed) at end of intervention period	42 (93%)	35 (80%)	OR 0·25 (0·06 to 1·07)	0·06
Last study clinic visit items¶				
Mean (SD) weight-for-age *Z* score‖	1·03 (1·91)	0·20 (1·25)	OR 0·93 (0·32 to 1·54)	0·003
Current cough in the past 3 months	13 (30%)	17 (41%)	OR 0·56 (0·22 to 1·39)	0·21
Normal respiratory examination	24 (55%)	19 (46%)	OR 1·32 (0·51 to 3·47)	0·56
Wheeze on auscultation	1 (2%)	2 (5%)	OR 0·50 (0·04 to 5·97)	0·58
Respiratory crackles on auscultation	3 (7%)	8 (20%)	OR 0·31 (0·08 to 1·29)	0·11
Mean (SD) predicted FEV_1 % **	84·7 (12·9)	81·0 (18·3)	MD 4·08 (–5·23 to 13·40)	0·38
Sputum present ††	6 (14%)	11 (27%)	OR 0·44 (0·14 to 1·39)	0·16

Data are n (%), unless otherwise specified. OR=odds ratio. IRR=incidence rate ratio. MD=mean difference. FEV_1%=percentage predicted forced expiratory volume in 1 second. *Multivariable logistic regression model, adjusting for the stratifying factors. †Negative binomial regression model, including treatment group and the stratifying factors (number of years spent in the study was included as an offset). ‡Linear regression, adjusting for the stratifying factors. §n=45 in azithromycin group and 44 in placebo group. ¶n=44 in azithromycin group and 41 in placebo group. ‖Information available for 44 children in the azithromycin group and 38 children in the placebo group. **Test done in 42 children.††Children either produced sputum at the last clinic or parents reported presence of sputum.

Table 3: **Study endpoints by treatment group**

	At enrolment		At end of study		OR (95%CI)*	p value
	Azithromycin (n=41)	Placebo (n=37)	Azithromycin (n=41)	Placebo (n=37)		
Streptococcus pneumoniae carriage	14 (34%)	12 (32%)	14 (34%)	12 (32%)	0·83 (0·24–2·79)	0·76
Azithromycin-resistant *S pneumoniae*	5 (12%)	6 (16%)	11 (27%)	1 (3%)	14·62 (1·70–125·88)	0·015
Penicillin non-susceptible *S pneumoniae*	5 (12%)	7 (19%)	6 (15%)	6 (16%)	0·96 (0·25–3·64)	0·95
Haemophilus influenzae carriage	15 (37%)	9 (24%)	3 (7%)	14 (38%)	0·10 (0·02–0·42)	0·002
Azithromycin-resistant *H influenzae*	1 (2%)	0	0	0	..	..
Ampicillin-resistant *H influenzae*	1 (2%)	3 (8%)	1 (2%)	1 (3%)	..	..
Staphylococcus aureus carriage	8 (20%)	4 (11%)	11 (27%)	4 (11%)	2·96 (0·84–10·48)	0·09
Azithromycin-resistant *S aureus*	5 (12%)	2 (5%)	11 (27%)	3 (8%)	4·11 (1·02–16·46)	0·046
Meticillin-resistant *S aureus*	5 (12%)	2 (5%)	5 (12%)	3 (8%)	1·82 (0·37–9·09)	0·47
Moraxella catarrhalis carriage	7 (17%)	6 (16%)	0	9 (24%)	..	..
Ampicillin-resistant *M catarrhalis*†	7 (17%)	3 (9%)	0	5 (15%)	..	..
Bacterial carriage (any of the above)	27 (66%)	20 (54%)	22 (54%)	22 (60%)	0·60 (0·21–1·65)	0·32
Azithromycin-resistant bacteria (any)	10 (24%)	8 (22%)	19 (46%)	4 (11%)	7·39 (2·15–25·39)	0·002

Data are n (%). Data included 78 children who provided two swabs (baseline and at least one follow-up swab). Resistance was defined using European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints. None of the children had *Pseudomonas aeruginosa* detected. *Multivariable logistic regression model, adjusting for the stratifying factors and preintervention carriage. †Three nasal swabs positive for *M catarrhalis* were not tested from New Zealand children.

Table 4: **Paired deep nasal swab microbiology at enrolment and at the end of the intervention period**

	Needing admission to hospital		All	
	Azithromycin (24 events in 11 children)	Placebo (39 events in 19 children)	Azithromycin (112 events in 26 children)	Placebo (209 events in 28 children)
Bronchiectasis related (episode or investigation)	16 (67%)	25 (64%)	22 (20%)	48 (23%)
Non-pulmonary infection	4 (17%)*	5 (13%)†	71 (63%)	132 (63%)
Surgery	3 (13%)	3 (8%)	3 (3%)	3 (1%)
Dental procedures	0	2 (5%)	0	2 (1%)
Accident, fracture, foreign body	0	1 (3%)	2 (2%)	2 (1%)
Burn	1 (4%)	0	1 (1%)	0
Glomerulonephritis	0	1 (3%)	0	1 (1%)
Investigations unrelated to bronchiectasis	0	2 (5%)	2 (2%)	2 (1%)
Dosage error in administration of trial drug	0	0	3 (3%)	1 (1%)
Eye disease	0	0	0	2 (1%)
Hyperactive at school after medication	0	0	2 (2%)	0
Spat, vomited medication, or had less than full dosage	0	0	6 (5%)	16 (8%)

Data are n (%) of total adverse events. *One child had a gastrointestinal infection. †Two children had a gastrointestinal infection.

Table 5: **Adverse events**

azithromycin group), and the only child with azithromycin-resistant *S pneumoniae* at the last visit in the placebo group was also negative at baseline.

Study drug was generally well tolerated. There were 203 episodes of non-pulmonary infection, 70 bronchiectasis-related episodes (treatment or investigations), and 22 episodes of spitting or vomiting the study drug reported to the data safety monitoring board as adverse events (table 5). There were 63 admissions to hospital because of serious adverse events (11 children in the azithromycin and 19 in the placebo group). Of these, 41 were attributable to either exacerbation or an investigation related to bronchiectasis (eg, bronchoscopy). All children recovered (or were recovering) from these illnesses at the time of study completion.

In addition to clinic visits for respiratory exacerbations, post-hoc analyses of antibiotic use for non-pulmonary infections showed 71 clinically diagnosed bacterial illnesses recorded in the azithromycin group (26 children) and 132 in children receiving placebo (28 children; IRR 0·50; 95% CI 0·31–0·81; p=0·005). All these illnesses were treated with non-macrolide antibiotics, mostly amoxicillin or amoxicillin-clavulanate. The most common diagnoses were otitis media and skin and soft tissue infections. There were 23 visits for otitis media in the azithromycin group, with 30 visits in the placebo group (0·67; 0·32–1·38; p=0·27), and 12 visits for skin and soft tissue infections in the azithromycin, with 26 in the placebo group (0·41; 95% CI 0·17–1·00; p=0·05).

Post-hoc subgroup analyses showed increased efficacy for azithromycin when confined to children who received more than 70% of their study drug (appendix), and when restricted to the 78 children without a history of mechanical ventilation (data not shown). The threshold value of 70% (decided before data analyses, but after protocol development) was based on reported adherence rates in other studies.[18,19] No other differences from the main results were identified with a sensitivity analysis restricted to the 52 children who received the intervention for 23–24 months (appendix). When the analysis was restricted to 73 children with HRCT-proven bronchiectasis (appendix), a difference in favour of azithromycin was still seen, and the effect sizes between treatments were either much the same as for the main analysis, or increasing in favour of azithromycin. Subgroup analyses including children at highest risk, such as those who had two or more hospital-managed pulmonary exacerbations before enrolment (appendix), those who had ten or more pulmonary exacerbations before enrolment (appendix), and children carrying any respiratory bacterial pathogens at baseline (appendix) also showed much the same (or increased) effect sizes as the main results, favouring the azithromycin group. No other differences from the main results were identified with a sensitivity analysis adjusting for potential confounders (data not shown).

Discussion

We showed that once-weekly azithromycin administered for 12–24 months to Indigenous children with non-cystic-fibrosis bronchiectasis or chronic suppurative lung disease significantly reduced pulmonary exacerbations and improved weight-for-age *Z*-scores. Additionally, post-hoc analysis showed that children given azithromycin had significantly fewer non-pulmonary illnesses treated acutely with non-macrolide antibiotics. The study drug was well tolerated with no trial-medication-related differences in serious adverse events between the two groups. However, a significant increase in macrolide resistance in respiratory bacterial pathogens colonising the nasopharynx occurred in the azithromycin-group. Although the few differences between groups at baseline could have biased the results in favour of the azithromycin group, sensitivity analyses and adjustment in multivariable models showed that these imbalances did not affect the overall results.

Antibiotics have a major role in management of bronchiectasis. Our study supports use of maintenance azithromycin for up to 2 years to decrease exacerbations in Indigenous children with non-cystic-fibrosis bronchiectasis. Reduction of exacerbations might also help to preserve future lung function and quality of life. Short-term antibiotic treatments are recommended to reduce the bacterial load and to improve airway and systemic inflammatory profiles.[6] In adults with non-cystic-fibrosis bronchiectasis a cohort study[20] and three randomised controlled trials[9,10,21] (maximum duration 12 months) have shown that macrolide antibiotics resulted in fewer pulmonary exacerbations; in two[10,21] of the three randomised controlled trials (both 12 months duration) lung function was also improved. By contrast,

the sole published placebo-controlled randomised trial assessing antibiotic efficacy in children was small and reported reduced sputum purulence and airway hyperresponsiveness in the 13 children who received 3 months of roxithromycin.[22] As far as we are aware, our trial examined azithromycin efficacy for longer than any previous study in children or adults (panel). Although studies in patients with cystic fibrosis showed beneficial effects for azithromycin, it was important to obtain evidence specific to non-cystic-fibrosis bronchiectasis in children because extrapolation from cystic fibrosis trials might be harmful, and bronchiectasis in children and adults can differ in several ways (eg, in respiratory pathogens, degree of inflammation, effect of lung development, and assessment of clinical outcomes).[2]

Our study design, like other placebo-controlled, randomised trials,[9,10,21] does not allow determination of the most suitable macrolide antibiotic or identify which patients are most likely to benefit from regular macrolide use. However, in our post-hoc analyses, effect sizes for differences between the groups were marginally larger in children who had two or more admissions to hospital for bronchiectasis exacerbations or who were carrying respiratory bacterial pathogens at baseline. Also, during the intervention period (table 3), the azithromycin group had predominantly lower number of exacerbations and the placebo group had a higher number (2% in the azithromycin group had more than five episodes *vs* 20% in the placebo group). Thus, on the basis of our study and those in adults,[9,10,20] we believe that at this stage long-term azithromycin for 12–24 months should be considered for Indigenous children with bronchiectasis who have frequent exacerbations (at least two) needing medical intervention in the previous 12 months, especially if these episodes need admission to hospital.

Nevertheless, widespread use of macrolide antibiotics risks inducing antibiotic resistance in bacterial pathogens in the respiratory tract.[23] The positive aspect of azithromycin—a prolonged half-life, allowing once-weekly dosing—is counterbalanced by extended periods of subinhibitory antibiotic concentrations that increase the risk of antibiotic resistance developing in the child's resident nasopharyngeal flora. Furthermore, clonal expansion of resistant strains increases the risk of their transmission to untreated individuals within the community.[23,24] Consequently, the clinical benefits of long-term azithromycin treatment must be weighed against increased antibiotic resistance in respiratory bacterial pathogens as shown previously in children from Indigenous Australian and African communities after even one dose of azithromycin.[24,25] Although in our study azithromycin reduced both *H influenzae* and *M catarrhalis*, these organisms were replaced by strains of macrolide-resistant *S pneumoniae* and *S aureus*. Indeed, 79% of children carrying *S pneumoniae* in the azithromycin group had macrolide-resistant strains, compared with 8% of those receiving placebo, and 5% in colonised Aboriginal children from the same communities immediately before commencement of this study.[26] The clinical consequences of these observations to the participants and broader community are unknown and are complicated by the absence of a clear association between in-vitro susceptibility results for macrolides and clinical outcomes, especially in *S pneumoniae* isolates.[27] Nevertheless, the potential risk of treatment failures during empirical macrolide therapy remains. Treatment failure has been reported in children and adults receiving macrolide monotherapy for bacteraemic pneumonia caused by *S pneumoniae* isolates resistant to erythromycin.[28] The high rates of skin and soft tissue infection in Indigenous children in Australia and New Zealand also need consideration.[29] Management of these and other more severe staphylococcal infections could be compromised by increasing macrolide resistance in communities where person-to-person transmission is common and where meticillin resistance already limits initial empirical antibiotic choices.[30] Despite these concerns, children in the azithromycin group had significantly less overall acute antibiotic use compared with those receiving placebo. This observation is consistent with the reported short-term, non-respiratory benefits in azithromycin mass distribution programmes for trachoma in African children.[31,32] Furthermore, the higher use of acute antibiotics in the placebo group might have reduced their risk of exacerbations and masked an even greater benefit of azithromycin in study participants.

***Panel:* Research in context**

Systematic review

Before our study's commencement, we did two searches of the scientific literature: one focusing on controlled trials for bronchiectasis and chronic suppurative lung disease and the second focusing on azithromycin. For the first we searched PubMed and Cochrane Central Library databases using the text-words "bronchiectasis" or "suppurative lung disease" and "controlled trials". We indentified few randomised controlled trials of non-cystic-fibrosis bronchiectasis and no long-term studies in either children or adults. For the second strategy, we used keywords "macrolide" or "azithromycin" AND "respiratory" or "chest" in the same databases. Searches were restricted to reports in English. The last searches were done on Feb 12, 2005.

Interpretation

As far as we are aware, this is the first long-term randomised controlled trial assessing the use of a macrolide antibiotic in children with non-cystic-fibrosis bronchiectasis or chronic suppurative lung disease. Our study supports and extends trial data for 6–12 months of macrolides in adults with bronchiectasis.[9,10,21] A treatment strategy of up to 24 months of weekly azithromycin reduced respiratory exacerbations by 50%, but was accompanied by increased carriage of azithromycin-resistant bacteria. However, acute use of antibiotics for other non-pulmonary infections was also reduced. Weekly azithromycin for up to 12–24 months could be considered for Indigenous children with bronchiectasis or chronic suppurative lung disease, who in the past 12 months, have had at least two exacerbations needing medical intervention, especially if these exacerbations resulted in admission to hospital. However, macrolide antibiotic resistance will need close monitoring at an individual and community level, although its clinical significance is still to be established.

Other possible adverse events from prolonged azithromycin use need to be considered. Despite sensorineural hearing loss being described in adults,[33] we did not assess hearing because the very high levels of otitis media (up to 91% of children)[34] would make interpretation difficult. Also, we did not test systematically for non-tuberculous mycobacteria because, at present, these organisms are detected rarely in children with non-cystic-fibrosis bronchiectasis.[5,12] Furthermore, theoretical concerns about azithromycin increasing susceptibility to mycobacteria have not been realised in populations with cystic fibrosis and there is emerging evidence that azithromycin might even protect against such infections.[35,36] A major advantage of azithromycin is its long half-life (see protocol[13] for discussion of choice and dose regimen). Compared with other populations, Indigenous families, particularly those living in remote communities, have lower levels of education and higher socioeconomic disadvantage. This contributes to difficulties with securing medicines and adhering to long-term, frequent treatment regimens. Consequently, simplified and supervised once-weekly regimens have substantial advantages.

Our findings should be considered in the context of the study methods. All post-hoc analyses were not prespecified and should be interpreted with caution. Our high response rate (97%) limits the potential for selection bias. The study was done in two very different settings: one in remote Indigenous communities in Australia with little health-care provision (some children lived in remote communities and needed a plane flight to be seen by the study team) and another in a tertiary hospital in a city in New Zealand. At the time the study commenced, maintenance weekly azithromycin was rarely used in central Australia and the Torres Strait (two regions of recruitment), but common in the top end of the Northern Territory. In New Zealand, government funding of azithromycin was restricted to treatment of chlamydia-associated sexually transmitted infections and used rarely for other indications. The small number of children who were taking long-term azithromycin for bronchiectasis had a 3-month washout period and so a carry-over effect is unlikely in this trial.

We targeted Indigenous children because they are among the most disadvantaged groups in Australia and New Zealand and have a greater disease burden than do others in the community.[37] Our study is likely to have implications for children in developing countries too, since disadvantaged Indigenous children in Australia and New Zealand share a similar burden of respiratory illness with those living in developing countries.[38–40]

The inclusion of local community workers, and use of strict protocols for inclusion and exclusion criteria, monitoring of adherence, collection of data, and measurement of study endpoints reduced the potential limitation of heterogeneity in study settings. Administration of study drugs under direct supervision aided the successful conduct of the study. All medically attended respiratory episodes needing antibiotics were captured. However, episodes that did not result in a presentation to the clinic or hospital, and therefore not recorded in the medical records, were not captured, and nor were adverse events not needing medical attention. We have no reason to suspect that underreporting of episodes, if any, would have been differentially biased because the number of respiratory episodes before enrolment was much the same in both groups. However, the study was underpowered for the detection of small differences between groups, particularly with the subgroup analyses. Nevertheless, even though our final enrolment of 89 participants was less than the original sample size estimate of 102 participants, the trial still detected statistically significant differences between the intervention and placebo groups. This limitation is most relevant when assessing secondary study outcomes for which information was not available for all children. The logistics of collecting and transporting nasal swab samples, for example, were the main reason for missing data. Also, despite thorough review of medical charts, some information was not documented routinely. Study personnel who collected study data were unaware of treatment assignment, therefore bias attributable to missing data, if any, was unlikely to be differential. Nevertheless, it is important to note the difficulties in obtaining good follow-up in our setting, especially in Australia where participants lived in small remote communities (200–1000 people) and study team access was only by air. Larger studies are needed to establish whether site-specific effects exist between: Australia and New Zealand; urban and remote, rural settings; and regions where there has been historically either common or infrequent use of azithromycin in the community and for children with bronchiectasis.

We believe that our inclusion of children with chronic suppurative lung disease (without CT-confirmed bronchiectasis) is valid for several reasons. First, the disorders overlap and children with chronic suppurative lung disease have much the same clinical disease patterns as do children with CT-confirmed bronchiectasis.[1] Second, children with chronic suppurative lung disease receive the same standard of care as those with bronchiectasis.[1] Third, Indigenous children and children in developing countries have limited access to CT scanning to confirm bronchiectasis and defining irreversibility needs two CT scans, which is often not feasible.[14] Fourth, there are limitations in the radiographic definitions of bronchiectasis in children because HRCT definitions are derived from adult studies and are not necessarily equivalent to those in children. In particular, the key diagnostic criterion of bronchiectasis is increased bronchoarterial ratio, which is clearly affected by age (r=0·77, p<0·0001).[41] Also the sensitivity of determining bronchiectasis radiographically is dependent on the methods used because scans obtained on a multidetector CT are more sensitive than those from a HRCT.[42] Thus in children, the term chronic suppurative

lung disease is used to describe a diagnosis in which there are clinical symptoms of bronchiectasis without CT confirmation.[1] Finally, analysis restricted to children with HRCT-proven bronchiectasis showed the robustness of our data because the significant differences between the treatment groups remained.

The routine investigations done for assessment of bronchiectasis in our setting do not include extensive testing for primary ciliary dyskinesia.[1] Also, we did not undertake FEV_1 measurements in every study participant because it is only possible to do spirometry in older children. We also restricted the age limit at enrolment to 8 years so as to reduce heterogeneity, since in our clinical experience children with bronchiectasis undergoing puberty have a different pattern of illness. Furthermore, by contrast with the experience in cyctic fibrosis, reports in children[43] and adults[44] have shown that FEV_1 values do not change significantly during hospital stay for exacerbations. Additionally, in the randomised controlled trials of azithromycin in adults, there was no significant difference in FEV_1 between groups in one study of 6 months duration,[10] and the other reported only a marginally significant improvement after 12 months of treatment.[9]

In conclusion, the novelty of our study is three-fold. First, as far as we are aware, this is the first randomised controlled trial of azithromycin in children with non-cystic-fibrosis bronchiectasis and the first in children and adults exceeding 12 months in duration. Second, we targeted children living among the most disadvantaged groups in Australia and New Zealand for whom provision of treatment is often most difficult. Third, in this setting, other clinically diagnosed bacterial illnesses were reduced in children receiving long-term azithromycin. Overall, once-weekly azithromycin for a 12–24 month period is feasible in our setting and reduced pulmonary exacerbation frequency by 50% in Indigenous children with non-cystic-fibrosis bronchiectasis. However, additional long-term studies are needed to identify children most likely to benefit from maintenance azithromycin, to describe how long these beneficial effects persist, to define the optimum duration of treatment, and establish the clinical significance of acquisition of azithromycin-resistant pathogens.

Contributors

PCV and ABC had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. ABC, PCV, PSM, KG, PJT, CAB, IBM, and PAB contributed to the study design. ABC, PSM, CAB, GBM, CM, and IT actively recruited participants. GBM and CM participated in coordination and data acquisition. PCV participated in coordination and statistical analysis. KMH assisted with processing the deep nasal swabs. AD assisted with data cleaning and statistical analysis. RSW assisted with the statistical analysis. PCV, ABC, and KG drafted the initial report. All authors contributed to editing the report and approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

This work was supported by the National Health and Medical Research Council (NHMRC) of Australia (project grant numbers 389837 [clinical component], 545223 [microbiology component] and CRE for lung health 1040830 [feedback]), Telstra Foundation (seeding grant—Telstra Community Development Grant, 2004), the Health Research Council of New Zealand (grant number 08/158), and the Auckland Medical Research Foundation (grant number 81542). PCV is supported by an Australian Research Council Future Fellowship (number 100100511). ABC is supported by an NHMRC fellowship 545216. KMH is supported by NHMRC Gustav Nossal Postgraduate Scholarship 1038072 and the Australian Academy of Science's Douglas and Lola Douglas Scholarship. This work was produced as part of the In-Kind activities of the Lowitja Institute incorporating the Cooperative Research Centre for Aboriginal and Torres Strait Islander Health. We thank the children and their families for participating in the study. We also thank the research personnel, including Valerie Logan (Menzies School of Health Research) and Hayley Williams (Menzies School of Health Research) for their help with data management and data cleaning, research nurses Clare Mckay (Menzies School of Health Research), Kobi Schutz (Menzies School of Health Research), and Lesley Versteegh (Menzies School of Health Research) for their help with data collection, and Vanya Hampton (Menzies School of Health Research) for processing the specimens. We thank Sara Kake (Pacific Island/Māori whanau worker and support person; University of Auckland) who engaged with the families to ensure robust adherence to protocol. We also thank the Indigenous Reference Group of the Child Health Division in Menzies for overseeing the cultural aspects of the Australian group. Finally, we thank Kerrie Gell, Carmel Hattch, and Cyndi Cole for their valuable help in logistics with the Central Australian children.

References

1 Chang AB, Bell SC, Byrnes CA, et al. Chronic suppurative lung disease and bronchiectasis in children and adults in Australia and New Zealand. *Med J Aust* 2010; **193:** 356–65.

2 Chang AB, Marsh RL, Smith-Vaughan HC, Hoffman LR. Emerging drugs for bronchiectasis. *Expert Opin Emerg Drugs* 2012; **17:** 361–78.

3 Kapur N, Masters IB, Chang AB. Longitudinal growth and lung function in pediatric non-cystic fibrosis bronchiectasis: what influences lung function stability? *Chest* 2010; **138:** 158–64.

4 Steinfort DP, Brady S, Weisinger HS, Einsiedel L. Bronchiectasis in Central Australia: a young face to an old disease. *Respir Med* 2008; **102:** 574–78.

5 Grimwood K. Airway microbiology and host defences in paediatric non-CF bronchiectasis. *Paediatr Respir Rev* 2011; **12:** 111–18.

6 Chalmers JD, Smith MP, McHugh BJ, Doherty C, Govan JR, Hill AT. Short- and long-term antibiotic treatment reduces airway and systemic inflammation in non-cystic fibrosis bronchiectasis. *Am J Respir Crit Care Med* 2012; **186:** 657–65.

7 Southern KW, Barker PM, Solis-Moya A, Patel L. Macrolide antibiotics for cystic fibrosis. *Cochrane Database Syst Rev* 2011; **12:** CD002203.

8 Masekela R, Green RJ. The role of macrolides in childhood non-cystic fibrosis-related bronchiectasis. *Mediators Inflamm* 2012; **2012:** 134605.

9 Altenburg J, de Graaff CS, Stienstra Y, et al. Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial. *JAMA* 2013; **309:** 1251–59.

10 Wong C, Jayaram L, Karalus N, et al. Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. *Lancet* 2012; **380:** 660–67.

11 Shi W, Bellusci S, Warburton D. Lung development and adult lung diseases. *Chest* 2007; **132:** 651–56.

12 Hare KM, Grimwood K, Leach AJ, et al. Respiratory bacterial pathogens in the nasopharynx and lower airways of Australian indigenous children with bronchiectasis. *J Pediatr* 2010; **157:** 1001–05.

13 Valery P, Morris PS, Grimwood K, et al. Azithromycin for Indigenous children with bronchiectasis: study protocol for a multi-centre randomized controlled trial. *BMC Pediatr* 2012; **12:** 122.

14 Chang AB, Grimwood K, Maguire G, King PT, Morris PS, Torzillo PJ. Management of bronchiectasis and chronic suppurative lung disease in indigenous children and adults from rural and remote Australian communities. *Med J Aust* 2008; **189:** 386–93.

15 Stockley RA, Bayley D, Hill SL, Hill AT, Crooks S, Campbell EJ. Assessment of airway neutrophils by sputum colour: correlation with airways inflammation. *Thorax* 2001; **56:** 366–72.

16 Valery PC, Torzillo PJ, Mulholland K, Boyce NC, Purdie DM, Chang AB. Hospital-based case-control study of bronchiectasis in indigenous children in Central Australia. *Pediatr Infect Dis J* 2004; **23:** 902–08.

17 Saiman L, Marshall BC, Mayer-Hamblett N, et al. Azithromycin in patients with cystic fibrosis chronically infected with *Pseudomonas aeruginosa*: a randomized controlled trial. *JAMA* 2003; **290:** 1749–56.

18 DiMatteo MR. Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. *Med Care* 2004; **42:** 200–09.

19 Modi AC, Lim CS, Yu N, Geller D, Wagner MH, Quittner AL. A multi-method assessment of treatment adherence for children with cystic fibrosis. *J Cyst Fibros* 2006; **5:** 177–85.

20 Anwar GA, Bourke SC, Afolabi G, Middleton P, Ward C, Rutherford RM. Effects of long-term low-dose azithromycin in patients with non-CF bronchiectasis. *Respir Med* 2008; **102:** 1494–96.

21 Serisier DJ, Martin ML, McGuckin MA, et al. Effect of long-term, low-dose erythromycin on pulmonary exacerbations among patients with non-cystic fibrosis bronchiectasis: the BLESS randomized controlled trial. *JAMA* 2013; **309:** 1260–67.

22 Koh YY, Lee MH, Sun YH, Sung KW, Chae JH. Effect of roxithromycin on airway responsiveness in children with bronchiectasis: a double-blind, placebo-controlled study. *Eur Respir J* 1997; **10:** 994–99.

23 Serisier DJ. Risks of population antimicrobial resistance associated with chronic macrolide use for inflammatory airway diseases. *Lancet Respir Med* 2013; **1:** 262–74.

24 Coles CL, Mabula K, Seidman JC, et al. Mass distribution of azithromycin for trachoma control is associated with increased risk of azithromycin-resistant *Streptococcus pneumoniae* carriage in young children 6 months after treatment. *Clin Infect Dis* 2013; **56:** 1519–26.

25 Leach AJ, Shelby-James TM, Mayo M, et al. A prospective study of the impact of community-based azithromycin treatment of trachoma on carriage and resistance of *Streptococcus pneumoniae*. *Clin Infect Dis* 1997; **24:** 356–62.

26 Leach AJ, Morris PS, McCallum GB, et al. Emerging pneumococcal carriage serotypes in a high-risk population receiving universal 7-valent pneumococcal conjugate vaccine and 23-valent polysaccharide vaccine since 2001. *BMC Infect Dis* 2009; **9:** 121.

27 Nuermberger E, Bishai WR. The clinical significance of macrolide-resistant *Streptococcus pneumoniae*: it's all relative. *Clin Infect Dis* 2004; **38:** 99–103.

28 Lonks JR, Garau J, Gomez L, et al. Failure of macrolide antibiotic treatment in patients with bacteremia due to erythromycin-resistant *Streptococcus pneumoniae*. *Clin Infect Dis* 2002; **35:** 556–64.

29 Andrews RM, McCarthy J, Carapetis JR, Currie BJ. Skin disorders, including pyoderma, scabies, and tinea infections. *Pediatr Clin North Am* 2009; **56:** 1421–40.

30 Turnidge JD. High burden of staphylococcal disease in indigenous communities. *J Infect Dis* 2009; **199:** 1416–18.

31 Coles CL, Seidman JC, Levens J, Mkocha H, Munoz B, West S. Association of mass treatment with azithromycin in trachoma-endemic communities with short-term reduced risk of diarrhea in young children. *Am J Trop Med Hyg* 2011; **85:** 691–96.

32 Keenan JD, Ayele B, Gebre T, et al. Childhood mortality in a cohort treated with mass azithromycin for trachoma. *Clin Infect Dis* 2011; **52:** 883–88.

33 Mick P, Westerberg BD. Sensorineural hearing loss as a probable serious adverse drug reaction associated with low-dose oral azithromycin. *J Otolaryngol* 2007; **36:** 257–63.

34 Morris PS, Leach AJ, Silberberg P, et al. Otitis media in young Aboriginal children from remote communities in Northern and Central Australia: a cross-sectional survey. *BMC Pediatr* 2005; **5:** 27.

35 Binder AM, Adjemian J, Olivier KN, Prevots DR. Epidemiology of nontuberculous mycobacterial infections and associated chronic macrolide use among persons with cystic fibrosis. *Am J Respir Crit Care Med* 2013; published online Aug 8. DOI:10.1164/rccm.201307-1200OC.

36 Catherinot E, Roux AL, Vibet MA, et al. Inhaled therapies, azithromycin and *Mycobacterium abscessus* in cystic fibrosis patients. *Eur Respir J* 2013; **41:** 1101–06.

37 Anderson I, Crengle S, Kamaka ML, Chen TH, Palafox N, Jackson-Pulver L. Indigenous health in Australia, New Zealand, and the Pacific. *Lancet* 2006; **367:** 1775–85.

38 Chang AB, Byrnes CA, Everard ML. Diagnosing and preventing chronic suppurative lung disease (CSLD) and bronchiectasis. *Paediatr Respir Rev* 2011; **12:** 97–103.

39 Kapur N, Karadag B. Differences and similarities in non-cystic fibrosis bronchiectasis between developing and affluent countries. *Paediatr Respir Rev* 2011; **12:** 91–96.

40 Trenholme AA, Byrnes CA, McBride C, et al. Respiratory health outcomes 1 year after admission with severe lower respiratory tract infection. *Pediatr Pulmonol* 2013; **48:** 772–79.

41 Matsuoka S, Uchiyama K, Shima H, Ueno N, Oish S, Nojiri Y. Bronchoarterial ratio and bronchial wall thickness on high-resolution CT in asymptomatic subjects: correlation with age and smoking. *AJR Am J Roentgenol* 2003; **180:** 513–18.

42 Jung KJ, Lee KS, Kim SY, Kim TS, Pyeun YS, Lee JY. Low-dose, volumetric helical CT: image quality, radiation dose, and usefulness for evaluation of bronchiectasis. *Invest Radiol* 2000; **35:** 557–63.

43 Kapur N, Masters IB, Morris PS, Galligan J, Ware R, Chang AB. Defining pulmonary exacerbation in children with non-cystic fibrosis bronchiectasis. *Pediatr Pulmonol* 2012; **47:** 68–75.

44 Murray MP, Turnbull K, Macquarrie S, Hill AT. Assessing response to treatment of exacerbations of bronchiectasis in adults. *Eur Respir J* 2009; **33:** 312–18.