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Long-term Azithromycin in Children With Bronchiectasis Unrelated to Cystic Fibrosis

Treatment Effects Over Time

Don Vicendese, PhD; Stephanie Yerkovich, PhD; Keith Grimwood, MD; Patricia C. Valery, PhD; Catherine A. Byrnes, MD; Peter S. Morris, PhD; Shyamali C. Dharmage, PhD; and Anne B. Chang, PhD

BACKGROUND: Following evidence from randomized controlled trials, patients with bronchiectasis unrelated to cystic fibrosis receive long-term azithromycin to reduce acute respiratory exacerbations. However, the period when azithromycin is effective and which patients are likely to most benefit remain unknown.

RESEARCH QUESTIONS: (i) What is the period after its commencement when azithromycin is most effective? and (ii) Which factors may modify azithromycin effects?

STUDY DESIGN AND METHODS: A secondary analysis was conducted of our previous randomized controlled trial involving 89 indigenous children with bronchiectasis unrelated to cystic fibrosis. Semi-parametric Poisson regression identified the azithromycin efficacy period. Multivariable Poisson regression identified factors that modify azithromycin effect.

RESULTS: Azithromycin was associated with fewer exacerbations per child-week during weeks 4 through 96, with the most effective period observed between weeks 17 and 62. Eleven factors were associated with different azithromycin effects; four were significant at the $P < .05$ level. Compared with their counterparts, higher reduction in exacerbations was observed in children with nasopharyngeal carriage of bacterial pathogens (incidence rate ratio [IRR] = 0.81 [95% CI, 0.57-1.14] vs 0.29 [0.20-0.44]; $P < .001$); New Zealand children (IRR = 0.73 [0.51-1.03] vs 0.39 [0.28-0.55]; $P = .012$); and those with higher weight-for-height z scores (interaction IRR = 0.82 [0.67-0.99]; $P = .044$). Compared with their counterparts, lower reduction was observed in those born preterm (IRR = 0.41 [0.30-0.55] vs 0.74 [0.49-1.10]; $P = .012$).

INTERPRETATION: Regular azithromycin is best used for at least 17 weeks and up to 62 weeks, as these periods provide maximum benefit for indigenous children with bronchiectasis unrelated to cystic fibrosis. Several factors modified azithromycin benefits; however, these traits need confirmation in larger studies before being adopted into clinical practice.

CLINICAL TRIALS REGISTRATION: Australian New Zealand Clinical Trials Registry; ACTRN12610000383066.

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KEY WORDS: azithromycin; bronchiectasis; child; effective period; treatment modification

ABBREVIATIONS: IRR = incidence rate ratio; RCT = randomized control trial

AFFILIATIONS: From the Allergy and Lung Health Unit (D. V. and S. C. D.), Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, VIC, Australia; the School of Engineering and Mathematical Sciences (D. V.), La Trobe University, Bundoora, VIC, Australia; the Australian Centre for Health Services Innovation (S. Y. and A. B. C.), Queensland University of Technology, Brisbane, QLD, Australia; the Child Health Division (S. Y. and A. B. C.), Menzies School of Health Research, Darwin, NT, Australia; the NHMRC Centre for Research Excellence in Paediatric Bronchiectasis (AusBREATHE) (S. Y., K. G., P. S. M., and A. B. C.); the School of Medicine and Dentistry (K. G.), and Menzies Health Institute Queensland, Griffith University, Gold Coast, QLD, Australia; the Departments of Infectious Diseases, and Paediatrics (K. G.), Gold Coast Health, Gold Coast, QLD, Australia; the Population Health Department (P. C. V.), QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia; the Department of Paediatrics (C. A. B.), University of Auckland, Auckland, New Zealand; Paediatric Respiratory Medicine (C. A. B.), Starship Children's Health & Kidz First Hospital, Auckland,

Take-home Points

Study Questions: What is the period following its commencement when azithromycin is most effective and what factors may modify azithromycin effects?
Results: Azithromycin is most effective between weeks 17 and 62 after treatment commencement, and its effects may be modified positively by nasopharyngeal carriage of bacterial pathogens, and higher weight-for-height *z* scores, but negatively by preterm birth.
Interpretation: Regular azithromycin is best used for at least 17 weeks and up to 62 weeks, because these periods provide maximum benefit for children with bronchiectasis. Whether azithromycin-response phenotypes exist warrants further evaluation.

As randomized controlled trials (RCTs) of 6 to 24 months duration have demonstrated the efficacy of long-term azithromycin at reducing acute respiratory exacerbations in both children and adults with bronchiectasis unrelated to cystic fibrosis (henceforth referred to as bronchiectasis),[1] this antibiotic is now recommended by all current major guidelines.[2-4] However, many clinical gaps regarding its use remain. The recently published European Respiratory Society clinical practice guideline for managing children and adolescents with bronchiectasis[2] recommends prescribing long-term macrolide antibiotics to reduce exacerbations in those with three or more exacerbation episodes in the preceding 12 months. The guideline also stated research was needed to "identify those who are most likely to benefit as well as to define the optimum duration of azithromycin, describe how long these beneficial effects persist, and establish the clinical significance of acquiring azithromycin-resistant pathogens."[2] Given the lack of high-quality data guiding clinical practice, it is unsurprising that prescribing of long-term azithromycin by Australian and New Zealand respiratory pediatricians varies widely.[5]

The RCTs of long-term azithromycin in children and adults with bronchiectasis employed different entry criteria, and intervention periods varied from 2 to 24 months duration.[1] Our RCT[6] is the only study to examine its efficacy beyond 12 months in people (children or adults) with bronchiectasis, whereas other RCTs were for 2 to 12 months.[1] We found that once-weekly azithromycin, administered for a median of 102 weeks in indigenous children with bronchiectasis, significantly reduced respiratory exacerbations, with an incidence rate ratio (IRR) of 0.50 (95% CI, 0.35-0.71; $P < .0001$), and improved weight-for-age *z* scores, compared with the placebo group.[6] However, long-term azithromycin also significantly increased macrolide-resistant bacteria in the respiratory tract,[6,7] including postintervention *Staphylococcus aureus* strains remaining 100% macrolide-resistant in the azithromycin-treated group.[7] These observations are important because antibiotic resistance, including resistance to macrolide antibiotics, is of global concern.[8]

Thus, the optimal duration of long-term azithromycin treatment, how long its beneficial effects persist, and identifying children with bronchiectasis who are most likely to benefit from maintenance azithromycin need to be defined. Studies to formally evaluate these aspects will inform clinical practice. By conducting a secondary analysis of data from our previous RCT,[6] we aimed to (1) determine the efficacy period of azithromycin, including its peak benefit period; and (2) identify children with bronchiectasis who are most likely to benefit from regular azithromycin use.

Study Design and Methods

This observational study was nested within the Bronchiectasis Intervention Study, a multicenter, double-blind, randomized, 1:1 parallel-group, placebo-RCT that was conducted in Australia and New Zealand.[6,9] Human research ethics committees of all participating institutions approved the original study. Caregivers provided written informed consent.[6,9]

Study Population and Data Collection

Details of our RCT were described previously.[6,9] Briefly, Aboriginal, Torres Strait Islander, Māori, or Pacific Island children aged 1 to 8 years, diagnosed with bronchiectasis with at least one respiratory exacerbation in the previous 12 months, were randomized to receive either azithromycin (30 mg/kg once weekly) or placebo (once weekly) for 12 to 24 months from study entry. Data on respiratory exacerbations, including frequency,

New Zealand; Menzies School of Health Research (P. S. M.), Charles Darwin University, Darwin, NT, Australia; the Department of Paediatrics (P. S. M.), Royal Darwin Hospital, Darwin, NT, Australia; and the Department of Respiratory and Sleep Medicine (A. B. C.), Queensland Children's Hospital, Brisbane, QLD, Australia.

S. C. Dharmage and A. B. Chang are equal co-senior authors for this manuscript.

CORRESPONDENCE TO: Don Vicendese, PhD; email: don.vicendese@unimelb.edu.au

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time to next respiratory exacerbation, and length and severity of respiratory exacerbation episodes, were collected by review of medical records. Antibiotic resistance in bacterial pathogens carried in the nasopharynx was monitored (Additional details are described in the e-Appendix 1).

An exacerbation was defined by clinic or hospital staff prescribing antibiotics for any of the following (as recorded in the medical chart): increased cough, sputum volume or color intensity, increased dyspnea, new chest examination or radiographic findings, deterioration in the predicted FEV_1 percentage by $> 10\%$, or hemoptysis.[6]

Statistical Analysis

Treatment Effect Over Time

The outcome for determining the efficacy period was per child-week incident rate of respiratory exacerbations after each child's enrolment analyzed via a semi-parametric general additive model[10] for the azithromycin and placebo arms separately. Graphic presentation of model results was used to identify a continuous period in which the placebo and azithromycin means were outside one another's 95% CI (indicating a statistical difference at $P \leq .05$).

This continuous period is referred to as the noncrossover period, and we hypothesized that the efficacy period would likely lie here. A computer algorithmic search was conducted within it to find the starting and ending weeks of a window that differed statistically from the adjacent temporal windows. This window was defined as the most effective period.

For the algorithmic search, a statistical difference when comparing a potential most effective period with the pre- and postperiods was defined by a P value $\leq .05$. The comparisons are presented as IRRs, comparing placebo with azithromycin. The analysis was done using freeware R,[11] using the mgcv[12] and ggplot[13] libraries for the general additive model and graphing purposes, respectively.

Treatment Effect Modification

We conducted multivariate Poisson linear regressions with 23 factors considered as potential modifiers based on biological plausibility. Variables adjusted in the multivariate regressions were selected from the remaining 22 based on directed acyclic graphs.[14] Because our sample size was small, in conjunction with biological plausibility, we chose P values $\leq .2$ for the interaction term as being potentially important. In the presence of a potentially important interaction, associations were stratified by the modifying variable. These stratified results for categorical variables were presented in tables as IRRs, whereas for continuous modifying variables, results were presented graphically based on the mean number of exacerbations. The analysis and graphs for continuous modifying variables were done using Stata16.[15]

Additional details for the statistical analyses are described in the online supplementary data.

Results

Of the 89 participants included in the study, 45 had received azithromycin and 44 placebo. Overall, 37% were aged younger than 3 years, 53% were males, and 53% were recruited in Australia (Table 1).

The study period ranged between 13 and 120 weeks, with an overall median of 102 weeks (interquartile range, 74-105), which was very similar across the azithromycin and placebo groups. Most children (69%) received azithromycin for 79 to 105 weeks. Over the study period, participants had a total of 299 exacerbations (Table 2). As reported previously,[6] the crude IRR of the placebo group was almost double that of the azithromycin group, 1.93 (95% CI, 1.52-2.45); $P < .0001$.

Most Effective Period

There was a continuous temporal window between weeks 4 and 96 in which the estimated mean weekly exacerbation rate for each of the treatment arms was outside the other's 95% CI boundaries and in which the placebo mean exceeded the azithromycin mean (Fig 1). This is the noncrossover period. Further analysis of this period identified the window between 17 and 62 weeks as the most effective period (additional detail on the statistical analysis is provided in the online supplementary data, including e-Figs 1-3). Based on the treatment difference (placebo minus azithromycin), compared with weeks 1 to 16 and 63 to 105, weeks 17 through 62 had an IRR of 2.0 (95% CI, 1.1-3.8), $P = .034$, and 1.8 (95% CI, 1.04-3.1), $P = .037$, respectively. This indicated that the treatment difference (placebo minus azithromycin) in mean per child-week exacerbation rate was double and 1.8 times greater between weeks 17 and 62 compared with weeks 1 to 16 and 63 to 105, respectively.

Because the data came from a joint time-series, in which all incident respiratory exacerbations for all children were combined by setting the day of enrollment to 0 for each child, it was not possible to control for seasonality. However, a multinomial regression with month of year of exacerbation occurrence as the outcome, and allowing for repeat measures within each child, showed little statistical evidence of differences between the months and azithromycin groups (Table 3). This indicated it was unlikely that differences in seasonality at time-of-enrollment confounded our identification of the effective period.

Factors Modifying Azithromycin Treatment Effects

Table 1 presents the distribution of the possible modifying factors by intervention group. Table 4

TABLE 1] Participant Characteristics and Description of Sociodemographic, Breastfeeding, Environmental, Medical History, and Bacterial Carriage Factors Considered as Possible Treatment Modifiers

Possible Treatment Modifier	Azithromycin (n = 45)	Placebo (n = 44)
Sociodemographic characteristics		
Age < 3 y	17 (38%)	16 (37%)
Male	26 (58%)	21 (48%)
Enrolled in Australia	24 (53%)	23 (52%)
Adherence < 70%	15 (33%)	16 (35%)
Breastfeeding and environmental factors		
Breastfed as an infant	37 (n = 43, 86%)	31 (n = 43, 72%)
Mother smoked during pregnancy	14 (n = 42, 33%)	12 (n = 41, 29%)
People per household room, median (IQR)	2.3 (1.3-3.0)	2.0 (1.5-2.8)
Medical history		
Preterm at birth	13 (n = 45, 29%)	16 (n = 41, 39%)
Intrauterine growth restriction at birth	11 (n = 44, 25%)	16 (n = 39, 41%)
Weight-for-height *z* scores at baseline, mean (SD)	0.83 (1.4) (n = 44)	0.33 (1.2) (n = 42)
Respiratory medical history		
No. of all previous respiratory episodes, mean (SD)	13.1 (6.8)	15.2 (9.0)
No. of previous medically attended wheezing episodes, median (IQR)	1.0 (0.0-3.0)	1.0 (0.0-3.5)
Parent-reported wheeze in past 12 mo[a]	21 (48%)	18 (41%)
Wheeze at first clinical examination	5 (11%)	3 (7%)
Bacterial carriage and azithromycin resistance at baseline		
Streptococcus pneumoniae[b]	14 (34%)	12 (32%)
Moraxella catarrhalis[b]	7 (17%)	6 (16%)
Haemophilus influenzae[b]	15 (37%)	9 (24%)
Any bacterial carriage[bc]	22 (54%)	17 (46%)
No. of bacterial species[bc]		
0	19 (46%)	20 (54%)
1	13 (32%)	9 (24%)
2 or 3	9 (22%)	8 (22%)
Azithromycin-resistant *S pneumoniae*	5 (n = 14, 36%)	6 (n = 12, 50%)
Azithromycin-resistant *H influenzae*	1 (n = 15, 7%)	0 (n = 9, 0%)
Any azithromycin-resistant bacteria[d]	6 (n = 11, 55%)	6 (n = 10, 60%)
Medication history		
Any previous azithromycin use	8 (18%)	11 (25%)

IQR = interquartile range.
[a]Azithromycin n = 44, placebo n = 44.
[b]Azithromycin n = 41, placebo n =37.
[c]Either of *S pneumoniae, M catarrhalis,* or *H influenzae.*
[d]Either of *S pneumoniae* or *H influenzae.*

displays the modifying factors in which interaction with the azithromycin arm was statistically significant at the 0.2 level in the adjusted Poisson regression, and Table 5 displays the variables that were used for adjusting in the Poisson regression, as indicated by directed acyclic graphs (For an example, see eFig 4 in the online supplementary materials). The IRRs compare azithromycin with placebo within each level of the modifying factor and indicate differences in azithromycin benefit between children conditioned on these factors. New Zealand children's incident rate of respiratory exacerbation was 61% lower (IRR, 0.39) in the azithromycin group compared with placebo, but only 27% (IRR, 0.73) lower for Australian children, indicating that New Zealand children were more likely to benefit. Similarly, wheezing at baseline, nasopharyngeal carriage of respiratory bacterial pathogens at baseline, or no prior exposure to azithromycin were associated with beneficial effects of azithromycin. Children born preterm or who were not breastfed as infants benefited less from long-term azithromycin. Finally, although the mean number of exacerbations decreased with increasing current weight in the azithromycin group, the opposite was observed in the placebo arm (Fig 2. See eFig 5 for this graph with the added data points). Adherence to treatment was similar in the azithromycin and placebo arms (Table 1), but this factor was not found to be a statistically significant modifier of treatment benefit.

Discussion

We observed novel findings by identifying the most beneficial period in which long-term azithromycin reduced respiratory exacerbations. This was achieved by using data from the RCT that evaluated azithromycin efficacy for the longest period[6] (median follow-up, 102 weeks; other major RCTs were of 26-52 weeks duration) in either children or adults with bronchiectasis.[16,17] We found that azithromycin was superior to placebo at reducing respiratory exacerbations between weeks 4 and 96, with the most effective period observed between weeks 17 and 62 following azithromycin initiation. Additionally, we identified factors that modified the efficacy of azithromycin for reducing exacerbations. Compared with their counterparts, children with nasopharyngeal carriage of respiratory bacterial pathogens, wheeze at baseline, no prior azithromycin use, or higher weight-for-height scores benefited more, whereas children born preterm or who had not been breastfed benefited less.

In both children and adults with bronchiectasis, interventions that decrease respiratory exacerbations are both patient and parent priorities.[18] Furthermore,

TABLE 2] Characteristics of the Study by Intervention Arm

Study Characteristic	Azithromycin No. (%)	Placebo No. (%)	Total No. (%)
No. of weeks of intervention in the study			
13-52	4 (8.9%)	4 (9.1%)	8 (9.0%)
53-78	8 (17.8%)	11 (25.0%)	19 (21.3%)
79-105	33 (73.3%)	28 (63.6%)	61 (68.5%)
120	0	1 (2.3%)	1 (1.1%)
Total	45 (100%)	44 (100%)	89 (100%)
Median (IQR)	102 (75-105)	101 (71-105)	102 (74-105)
No. of respiratory exacerbations			
0	9 (20%)	4 (9.1%)	13 (15%)
1	7 (16%)	7 (16%)	14 (16%)
2	9 (20%)	5 (11%)	14 (16%)
3	10 (22%)	4 (9.1%)	14 (16%)
4	5 (11%)	5 (11%)	10 (11%)
5+	5 (11%)	19 (44%)	26 (26%)
Total No.	104	195	299
Median (IQR)	2 (1 to 3)	4 (1.8 to 7)	3 (1 to 5)
Range	0-9	0-14	0-14

IQR = interquartile range.

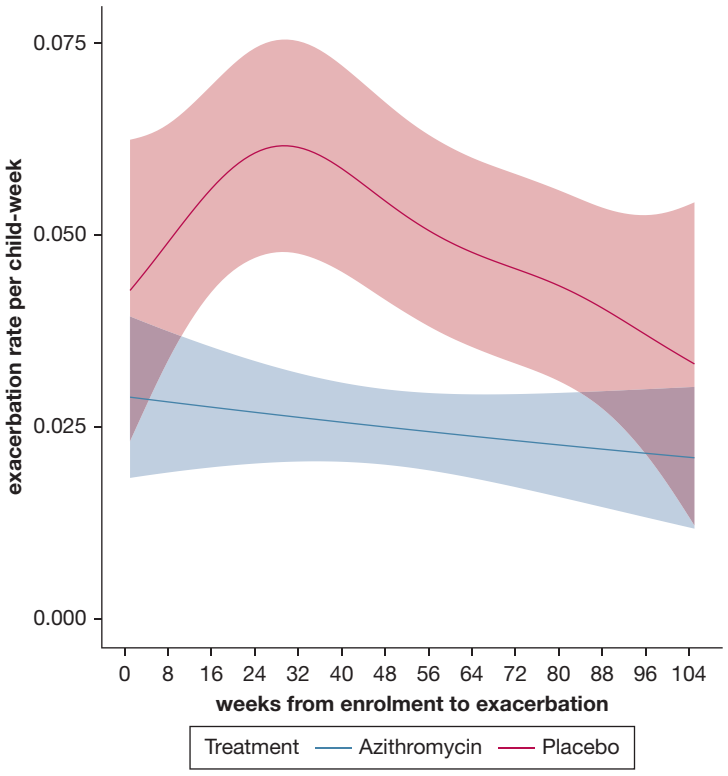

Figure 1 – *Results of the general additive models for the mean per child-week exacerbation rate by treatment arm. See online supplementary data, e-Figure 1, for this graph with the added data points.*

exacerbations cause a substantial burden on patients and their families, resulting from an impaired quality of life and costs from seeking health care and being hospitalized.[19] Given its importance, both pediatric[2] and adult[3,4] bronchiectasis guidelines recommend azithromycin for those with frequent exacerbations. However, azithromycin is also associated with airway and other pathogens acquiring macrolide resistance. Thus, key gaps remain, and the European Respiratory Society clinical practice guideline for managing

TABLE 3] The Association Between Seasonality (Month of the Year) and Risk of Exacerbation

Season (Southern Hemisphere)	Month (n = No. of exacerbations[a])	OR[b] (95% CI)	*P* Value
Summer	December (n = 20)	1.2 (0.35, 4.3)	.75
	January (n = 21)	1.6 (0.46, 5.8)	.45
	February (n = 20)	1 (Reference level)	
Fall	March (n = 31)	1.1 (0.36, 3.5)	.83
	April (n = 19)	2.3 (0.59, 8.8)	.23
	May (n = 30)	1.9 (0.59, 6.2)	.28
Winter	June (n = 29)	0.76 (0.24, 2.4)	.64
	July (n = 21)	1.6 (0.46, 5.8)	.45
	August (n = 33)	2.2 (0.68, 7.0)	.19
Spring	September (n = 24)	1.6 (0.48, 5.6)	.43
	October (n = 27)	2.3 (0.68, 8.0)	.18
	November (n = 24)	2.0 (0.57, 6.9)	.28

[a]Total No. of exacerbations = 299.
[b]OR compares placebo with azithromycin treatment.

TABLE 4] Factors That Were Associated With a Modifying Effect on Azithromycin

Variable	Comparing Azithromycin With Placebo in Each Level of the Modifying Factor: Crude Rate, Azithromycin vs Placebo; Adjusted IRR (95% CI), *P* value[a]			Interaction *P* Value[a]
Country of enrollment	New Zealand (n = 42) 2.2 vs 5.9 0.39 (0.28-0.55), < .0001	Australia (n = 47) 2.4 vs 3.1 0.73 (0.51-1.03), .074		.012
Period of gestation	< 37 weeks (n = 29) 2.9 vs 4.3 0.74 (0.49-1.10), .14	≥ 37 weeks (n = 57) 2.1 vs 4.8 0.41 (0.30-0.55), < .0001		.012
Breastfed	No (n = 18) 3.5 vs 5.0 0.71 (0.43-1.17), .18	Yes (n = 68) 2.1 vs 4.3 0.46 (0.34-0.61), < .0001		.13
Wheeze at first clinical examination	Yes[b] (n = 8) 1.6 vs 7.3 0.18 (0.08 to 0.42), < .0001	No (n = 81) 2.4 vs 4.2 0.58 (0.45 to 0.75), < .0001		.15
Parent-reported wheeze in the past 12 mo	Yes (n = 39) 2.5 vs 4.9 0.69 (0.47-1.02), .061	No (n = 49) 2.1 vs 4.1 0.43 (0.30-0.62), < .0001		.12
Any previous azithromycin use	Yes (n = 19) 2.4 vs 2.9 0.76 (0.42-1.37), .36	No (n = 70) 2.3 vs 4.9 0.49 (0.38-0.64), < .0001		.17
S pneumoniae Baseline	Present (n = 26) 2.1 vs 6.1 0.36 (0.20-0.63), .00040	Not present (n = 59) 2.6 vs 4.1 0.66 (0.48-0.90), .0088		.017
M catarrhalis Baseline	Present (n = 13) 1.9 vs 5.5 0.26 (0.07-0.90), .033	Not present (n = 65) 2.6 vs 4.6 0.59 (0.44-0.77), .00016		.077
Any bacteria[c] Baseline	Present (n = 39) 1.9 vs 5.2 0.29 (0.20-0.44), < .0001	Not present (n = 39) 3.2 vs 4.3 0.81 (0.57-1.14), .22		< .001
No. of bacterial species[c] Baseline	2 or 3 (n = 17) 2.0 vs 4.9 0.44 (0.19-1.03), .059	1 (n = 22) 1.9 vs 5.6 0.24 (0.14-0.42), < .0001	0 (n = 39) 3.2 vs 4.3 0.81 (0.57-1.14), .22	.24 (2 or 3 species) .010 (1 species)
Weight-for-height *z* scores	Continuous variable (n = 86) IRR for the interaction effect, 0.82 (0.67, 0.99)[d] Children with higher weight benefited more from treatment See Figure 2 for a graphical presentation.			.044

Crude rate = unadjusted mean No. of exacerbations per child; Adjusted IRR = incidence rate ratio (No. of exacerbations per child week).
[a]*P* value obtained after adjustment for variables identified by directed acyclic graphs (e-Fig 4).
[b]Crude association only is presented because the small size of this category prevented adjustment for confounders.
[c]Either of *Streptococcus pneumoniae, Moraxella catarrhalis, or Haemophilus influenzae*.
[d]Because weight-for-height *z* score is a continuous variable, categorical comparisons are not possible, and hence the IRR for the interaction effect is displayed instead.

children and adolescents with bronchiectasis[2] recommended research to identify those who are most likely to benefit from azithromycin and defining its optimum treatment duration. This study attempted to address these gaps and has important implications for clinical practice and future bronchiectasis guidelines.

We found that azithromycin was superior to placebo at reducing respiratory exacerbations between weeks 4 and 96, with the most efficacious period being between weeks 17 and 62 after azithromycin initiation. This suggests that, if azithromycin is commenced to reduce exacerbation frequency in a child or adolescent with

TABLE 5] Adjustment Variables, Chosen With Directed Acyclic Graphs, That Were Used in the Multivariable Analysis to Identify the Modifying Variables Shown in Table 4

Modifying Variable	Adjustment Variables
Country of enrollment	The directed acyclic graph indicated no adjustment needed
Period of gestation	Mother smoked during pregnancy
Breastfed	Preterm at birth
Wheeze at first clinical examination[a]	Age, male, enrolled in Australia, breastfed as an infant Mother smoked during pregnancy No. of all previous respiratory episodes No. of previous medically attended wheezing episodes
Parent-reported wheeze in the past 12 mo	Age, male, enrolled in Australia, breastfed as an infant Mother smoked during pregnancy No. of all previous respiratory episodes No. of previous medically attended wheezing episodes
Any previous azithromycin use	Enrolled in Australia Mother smoked during pregnancy
S pneumoniae Baseline	Breastfed as an infant, mother smoked during pregnancy No. of people in the home Any previous azithromycin use
M catarrhalis Baseline	Breastfed as an infant, mother smoked during pregnancy No. of people in the home Any previous azithromycin use
Any bacteria[b] Baseline	Breastfed as an infant, mother smoked during pregnancy No. of people in the home Any previous azithromycin use
No. bacterial species[b] Baseline	Breastfed as an infant, mother smoked during pregnancy No. of people in the home Any previous azithromycin use
Weight-for-height *z* scores	Age, enrolled in Australia, breastfed as an infant Mother smoked during pregnancy, preterm at birth Intrauterine growth restriction at birth

[a]Unable to introduce adjustment variables because of the small size of this category.
[b]Either of *S pneumoniae, M catarrhalis, or H influenzae.*

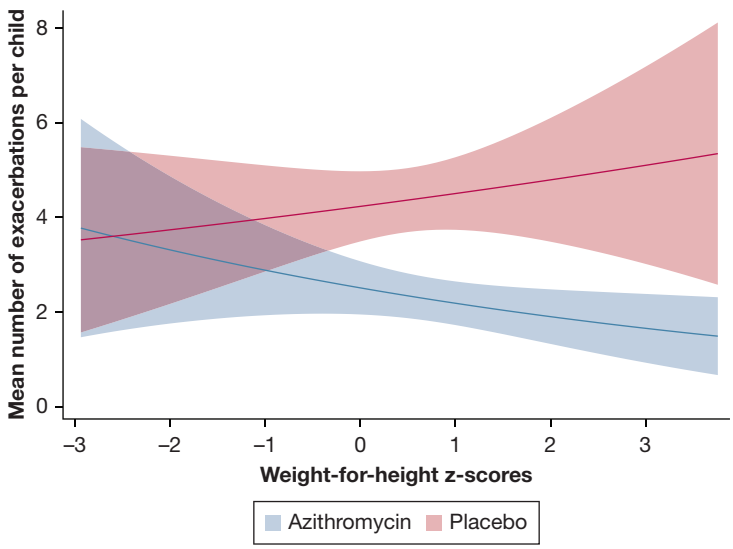

Figure 2 – *The interaction between treatment group and weight-for-height z scores. See online supplementary data, e-Figure 5, for this graph with the added data points.*

bronchiectasis, it should be used for a period of at least 16 weeks before assessing its effectiveness. The data also suggest ceasing azithromycin by week 63, and definitely by week 96. Current pediatric guidelines[2] recommend assessing response to therapy at 6 months and reevaluation with respect to continuing treatment at 12 months. Thus, guidelines may have to take into consideration our study's findings.

Although the duration of azithromycin efficacy has not been studied previously in bronchiectasis, some studies in cystic fibrosis should be highlighted. A retrospective study over 3 years of 68 children with cystic fibrosis (mean age, 9.95 years ± SD 3.61), treated with azithromycin for at least 1 year, found that the significant attenuation in respiratory exacerbations, antibiotic courses, and lung function decline in the first 12 months was not maintained for the next 24 months.[20] In contrast, although two large registry-based studies from France[21] and the United States[22] reported sustained slowing of lung function decline in those receiving azithromycin for 3 to 5 years, only the French study observed a significant attenuation in severe exacerbations, which was confined to children and not adults. These studies made comparisons with the 1 to 2 years before starting azithromycin and not on the in-depth method we used from our RCT data, and thus their findings are not comparable to our own.

We identified significant modifiers that indicate there are subgroups in which azithromycin has better efficacy at reducing respiratory exacerbations, suggesting possible treatable traits. Although this finding requires validation in another cohort, our data are the first to suggest that azithromycin treatment-response phenotypes likely exist in bronchiectasis. The importance of identifying phenotypes of chronic airway disease, including in bronchiectasis, is now being recognized.[23] Currently, the clinical implications are speculative, but an example is that a child born preterm, who is currently underweight or who was not breastfed, is significantly less likely to benefit from long-term azithromycin, and other interventions may have to be studied. Additional therapies are also a consideration for children who have used azithromycin previously. In our study, these children benefited less than those without prior azithromycin usage, suggesting macrolide resistance in airway pathogens or secondary changes in the respiratory microbiota may play a role in determining response to treatment.[24] However, those with nasopharyngeal carriage of respiratory bacterial pathogens or wheeze at baseline were significantly more likely to benefit from long-term azithromycin and could represent an azithromycin-responsive phenotype. In these children, irrespective of challenges with administering regular azithromycin in settings in which adherence is difficult, health professionals should try and persist in its use.

How modifiers of azithromycin efficacy act on exacerbation frequency is unknown in the absence of mechanistic studies from our RCT. The antimicrobial, immunomodulatory, and anti-mucus secretion properties of azithromycin are believed important.[25,26] In those with nasopharyngeal respiratory bacterial pathogen carriage, it is biologically plausible that the antimicrobial effect of azithromycin reduces the bacterial load in both the upper airways[7] and the respiratory secretions aspirated into the lower airways, which likely contribute to the pathobiology of bronchiectasis in children.[27] Interestingly, a post hoc analysis of an RCT evaluating azithromycin in adults with chronic severe asthma found that higher baseline sputum *Haemophilus influenzae* loads predicted superior efficacy of azithromycin for reducing asthma exacerbations.[28]

In children with bronchiectasis, wheeze may relate to airway narrowing from secretions or bronchoconstriction related to airway reactivity. We suspect that the modifying effect of wheeze at baseline is more likely from the immunomodulatory effects of azithromycin and inhibition of mucus hypersecretion with reduction in airway secretions, rather than airway reactivity, which was not found to be a modifying factor.

The factors associated with reduced azithromycin efficacy of preterm birth or being nonbreastfed possibly relate to the different mechanisms contributing to the development of bronchiectasis or exacerbations. Children born preterm are known to have impaired lung function shortly after birth, more frequent respiratory illnesses, and subsequent airway disease.[29-31] Although being nonbreastfed possibly influenced host immune ontogeny or the gut-airway axis and airway microbiome development, these proximal mechanisms are likely less affected by later exposure to macrolides.[32]

We found that, for children with higher weight-for-age *z* scores, those in the intervention arm had fewer exacerbations, suggesting a higher beneficial effect of azithromycin in higher-weight children, which is biologically plausible. Surprisingly, we observed a higher exacerbation rate in those with higher weight in the placebo arm. Compared with indigenous Australian

children, New Zealand Māori and Pacific Island children have more severe[33,34] bronchiectasis and higher weight.[35] Although our models adjusted for country of enrollment (Table 5), there was likely residual confounding related to sociocultural or genetic differences.[36] However, we can only speculate about the potential residual confounding because these factors were not collected in our study.[6] Alternatively, obesity is associated with lung diseases, including severe bronchiectasis.[37] Nevertheless, this could also be just a chance finding and will need to be verified by further studies.

Our study has several limitations. For the analysis of the treatment effect over time, the data were obtained by combining from each child the time-series of all incident respiratory exacerbations counted from enrollment, and so the analysis was unable to control for confounders at the individual level. It also was not possible to control for seasonality, which may be an important confounder in New Zealand participants. However, a multinomial regression with month of year of exacerbation occurrence as the outcome, and allowing for repeat measures within each child, showed little statistical evidence of differences between months and azithromycin groups. This indicated it was unlikely that differences in seasonality at time-of-enrollment confounded our identification of the effective period. Sample size also may have limited the analysis of seasonality impact. Analysis of modifying factors was limited by the sample size of 89, and hence a statistical level of 0.2 was chosen to indicate statistical evidence for interaction in conjunction with biological plausibility. Finally, because our RCT was undertaken in indigenous children with postinfectious or idiopathic bronchiectasis, our findings may not apply to children with bronchiectasis secondary to other causes or to those living in other settings. Postinfection is the most common cause of bronchiectasis among Australian Indigenous children.[38]

Interpretation

Our study attempted to address important clinical gaps related to the long-term use of azithromycin. We found that although regular azithromycin for reducing respiratory exacerbations among indigenous children with bronchiectasis is efficacious between 4 and 96 weeks, the most effective period occurred between 17 and 62 weeks of treatment. Azithromycin-responsive and less-responsive phenotypes likely exist as, compared with their counterparts, children carrying bacterial pathogens in their nasopharynx, having wheeze at baseline, or high current body weight benefited more, whereas children born preterm or not having been breastfed benefited less. Although these azithromycin-related phenotype data are insufficient to change current clinical practice, they deserve further evaluation in future studies.

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