Early Administration of Azithromycin and Prevention of Severe Lower Respiratory Tract Illnesses in Preschool Children With a History of Such Illnesses

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Citation

- Bacharier LB, Guilbert TW, Mauger DT, et al.
- *JAMA*. 2015;314(19):2034-2044. doi:10.1001/jama.2015.13896.
- **APRIL**- **A**zithro for **P**reventing the development of upper **R**espiratory tract **I**llness into **L**ower respiratory tract symptoms in children

Introduction

- Episodes of lower respiratory tract illness (LRTI) are common among preschoolers
  - Up to 14% to 26% of preschoolers present with recurrent wheezing during the first 6 years of life[1,2]
- Substantial morbidity
  - Many are diagnosed with asthma[3]
    - 20.9% seek emergency department care
    - 6.5% are hospitalized each year

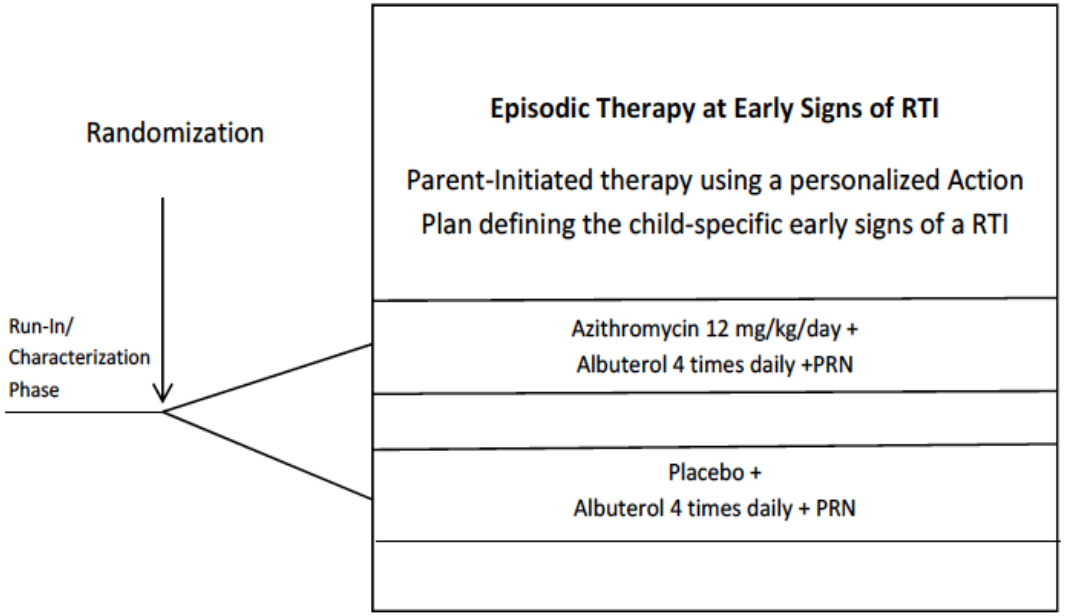
Introduction

- **The etiology of these LRTI has not been completely elucidated**
  - **Initial reports showed detection of respiratory viruses[4,5]**
  - **Bacteria have more recently been detected.[6,7]**
    - Antibiotics have been shown to improve:
      - symptom scores[8]
      - neutrophilic airway inflammation[9]

Methods- Participants

- **Eligible participants:**
  - **12-71 month olds** with **recurrent severe wheezing** in the context of clinically significant LRTIs that required systemic steroids and unscheduled medical care.
- **Exclusion criteria:**
  - > 4 courses of systemic corticosteroids in the past 12 months
  - > 1 hospitalization in the past 12 months
  - use of long-term controllers for asthma for more than 8 months in the past 12 months
  - Receive systemic corticosteroids within the last 2 weeks
  - Received antibiotics for any indication in the last 4 weeks
  - ≥ 2 nocturnal awakenings in the last 2 weeks
  - Higher than NAEPP/EPR3 Step 2 therapy

Methods- Study Design



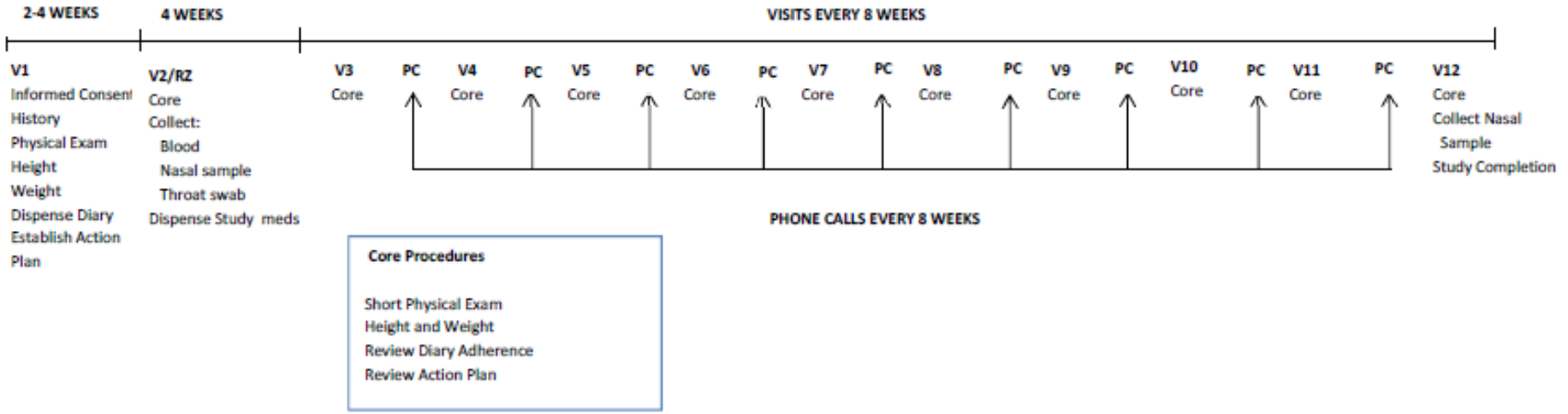
RTI Progresses to Severe Lower Respiratory Tract Illness when ANY of the following criteria are achieved:

a. Having symptoms that are more than mild after 3 albuterol treatments in 1 hour, OR
b. Requiring albuterol treatment more than once every 4 hours, OR
c. Requiring more than 6 albuterol treatments over a 24 hour period, OR
d. Having moderate-severe cough or wheeze for ≥ 5 days during which therapy was used.

Methods- Study Design

- The trial began in April 2011 with a follow-up period of 52 weeks
  - Study treatment used during a maximum of 3 treated RTIs not progressing to severe LRTI.
- In June 2012 the follow-up period was extended to 78 weeks for those participating in the study at that time (n = 164) or enrolled thereafter (n = 292)
  - Increased number of treated RTIs not progressing to a severe LRTI from 3 to 4.

Methods- Study Design



Methods

Treated Respiratory Tract Illness (RTI)	Respiratory Tract Illness (RTI) for which the participant had opportunity to take more than one dose of study medication before meeting Study Failure criteria. Illnesses that progressed to Study Failure on the same day were not counted as Treated RTI. Note: Inclusion in the primary analysis was not dependent on actually taking any study medication, only on having the opportunity to take more than one dose.
Severe Lower Respiratory Tract Illness (SLRTI)	Clinically significant lower respiratory tract symptoms (also called APRIL Treatment Failure) occurring within 14 days of the start of a treated RTI.
Early termination	Study Failure occurring more than 14 days after the start of a treated RTI or on the same day that study medication was initiated.
End of follow-up	The end of the study follow-up period (either 52 or 78 weeks depending on whether it occurred prior to the protocol revision) or the occurrence of a 4th Treated RTI that did not progress to SLRTI.
Drop out	Lost to follow-up or withdrew consent (voluntarily or by study physician discretion) prior to the occurrence of Study Failure, 4th Treated RTI or reaching the end of the follow-up period.

Methods- Outcome Measures

- **Primary outcome measure:** the number of treated RTIs not progressing to severe LRTI
  - If the study physician concurred that the patient was experiencing LRTI the primary end point was reached.
- **Secondary pre-specified outcome measures:**
  - Number of urgent medical visits
  - Measures of disease impairment reflected by symptom severity and albuterol use during treated.
  - Rate of study failures during APRIL
  - Rate of drug side effects
  - Determine if demographic and patient characteristics will be associated with Azithromycin responsiveness.
    - Including IL-8 genotyping
  - Pharmoeconomic impacts of APRIL therapy

Methods- Microbial Data

- Cultures were performed on participants at randomization (n = 86) and at study completion (n = 81).
- Samples were inoculated onto sheep's blood agar containing Azithromycin
  - The absence or presence of normal flora was assessed, and pathogenic organisms were isolated and identified.

	Regimen		All
	Azithromycin	Placebo	
No Virus Present	163 (54.5%)	164 (56.7%)	327 (55.6%)
Adenovirus B	1 (0.3%)	1 (0.3%)	2 (0.3%)
Adenovirus C	3 (1.0%)	6 (2.1%)	9 (1.5%)
Bocavirus		1 (0.3%)	1 (0.2%)
Coronavirus NL63	4 (1.3%)	2 (0.7%)	6 (1.0%)
Coronavirsu OC43	3 (1.0%)	5 (1.7%)	8 (1.4%)
Enterovirus	8 (2.7%)	9 (3.1%)	17 (2.9%)
Enterovirus/Human Rhinovirus	10 (3.3%)	8 (2.8%)	18 (3.1%)
InfluenzaA	1 (0.3%)		1 (0.2%)
Influenza B	1 (0.3%)		1 (0.2%)
Human Rhinovirus	95 (31.8%)	86 (29.8%)	181 (30.8%)
Metapneumovirus	1 (0.3%)	3 (1.0%)	4 (0.7%)
Parainfluenza Virus 1	2 (0.7%)	1 (0.3%)	3 (0.5%)
Parainfluenza Virus 2	4 (1.3%)		4 (0.7%)
Parainfluenza Virus 3		2 (0.7%)	2 (0.3%)
Parainfluenza Virus 4b	3 (1.0%)		3 (0.5%)
Respiratory Syncytial Virus A		1 (0.3%)	1 (0.2%)
All	299 (100.0%)	289 (100.0%)	588 (100.0%)

Methods- *IL-8* rs4073 Genotyping

- *A allele* for a variant at position -251 in the **promoter region of the IL-8 gene** (IL-8/-251) has been associated with increased transcription rates for IL-8 gene
- Participants were genotyped for the *IL-8* rs4073 single-nucleotide polymorphism by PCR

Methods- API

- Patients were classified for having a positive modified asthma predictive index (API)[12]:
  - at least 4 wheezing episodes in the past year **and** 1 major criterion **or** 2 minor criteria
  - **Major criteria**
    - physician-diagnosed atopic dermatitis
    - parental history of asthma
    - allergic sensitization to ≥1 aeroallergen
  - **Minor Criteria**
    - wheezing unrelated to colds
    - blood eosinophils ≥4%
    - allergic sensitization to milk, eggs, or peanuts

Methods- Statistical Analysis

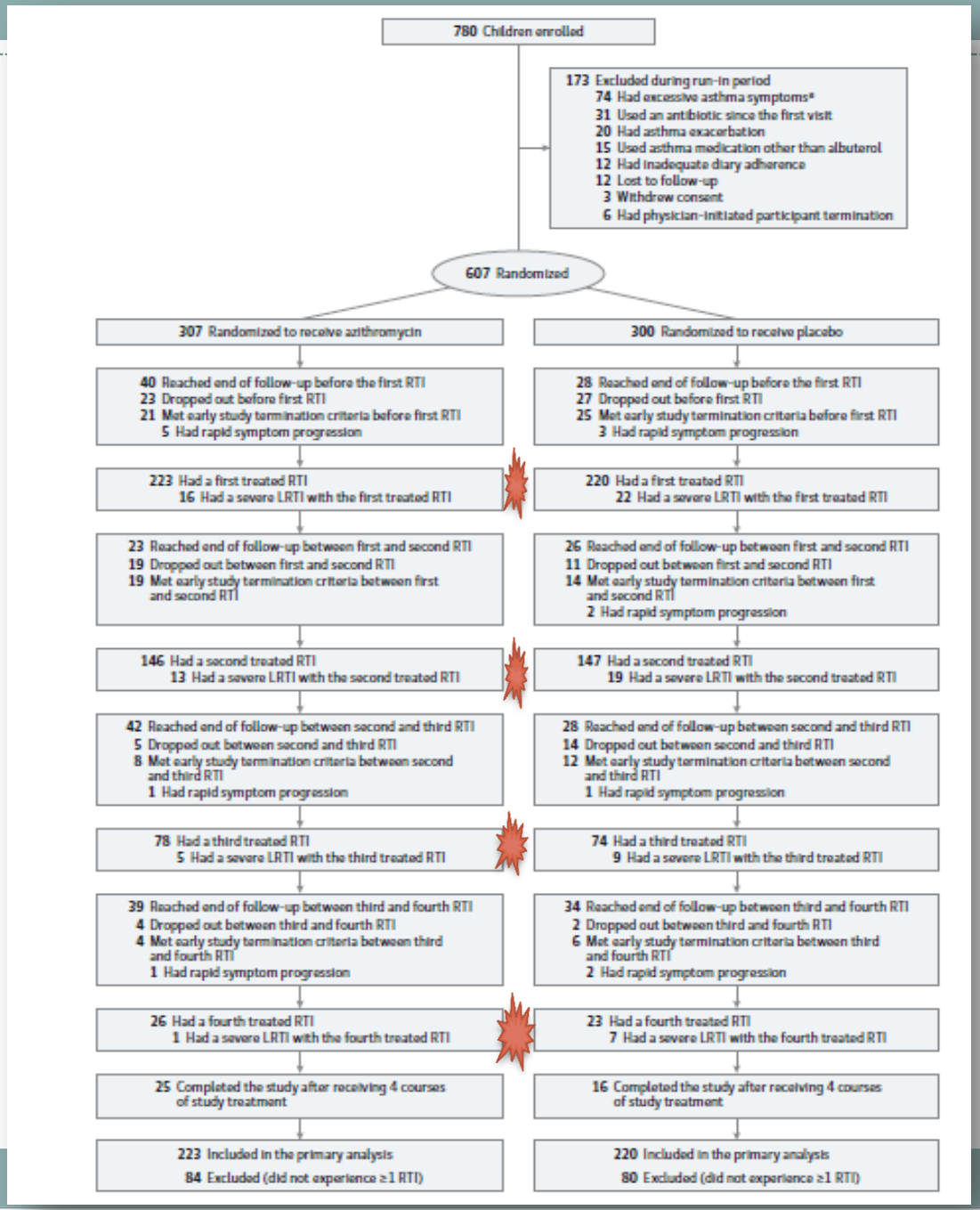
- **Primary outcome:** similar to familiar "time to event" outcomes
- **Null hypothesis:** azithromycin and placebo do not differ using the following covariates:
  - study site
  - age at randomization (12-42 months vs 43-71 months)
  - modified API18 status
  - season during which the RTI occurred (a time-dependent covariate)
  - whether the child enrolled before or after the study was extended to 78 weeks.

Methods- Statistical Analysis

- **Secondary outcomes:** used repeated measures analysis of variance with compound symmetry to account for multiple treated RTIs in the same individual.
- Treatment-effect modification was explored in pre-specified subgroups:
  - defined by age at randomization
  - sex
  - modified API status
  - presence of viral infection during RTI
  - season during which the RTI occurred
  - *IL-8* rs4073 genotype.

Results-

Particpant's Study Enrollment and Outcomes



Results

- 708 enrolled→ 607 were randomized
  - 140 excluded due to severity of symptoms
    - 12 had poor dairy adherence
    - 12 lost to follow up
    - 3 withdrew consent
    - 6 had physician initiated termination
- 164 did not experience a treated RTI
  - 84 Azithromycin group versus 80 Placebo group
- 109 met termination criteria
- 105 patients withdrew from the study
  - 51 in Azithromycin group versus 54 in Placebo group

Results- Participants

At Least 1 RTI versus No RTI

Table 1. Demographic Characteristics of Study Participants

	All Randomized Participants (N = 607)	Participants With at Least 1 Treated RTI (n = 443)	Participants With No RTI (n = 164)	Participants With at Least 1 Treated RTI	
				Azithromycin (n = 223)	Placebo (n = 220)
Demographics, No. (%)					
Age at enrollment, mean (SD), mo	41.5 (16.5)	41.4 (16.5)	41.81 (16.27)	42.5 (16.4)	40.2 (16.6)
12-42	327 (53.9)	241 (54.4)	86 (52.4)	115 (51.6)	126 (57.3)
43-71	280 (46.1)	202 (45.6)	78 (47.6)	108 (48.4)	94 (42.7)
Boys	365 (60.1)	274 (61.9)	91 (55.)5	139 (62.3)	135 (61.4)
Entered study on controller medication	48 (7.9)	41 (9.3)	7 (4.3)	25 (11.2)	16 (7.3)
Race					
American Indian or Alaskan Native	8 (1.3)	7 (1.6)	1 (0.6)	3 (1.3)	4 (1.8)
Asian	10 (1.6)	7 (1.6)	3 (1.8)	4 (1.8)	3 (1.4)
Black or African American	157 (25.9)	89 (20.1)	68 (41.5)	47 (21.1)	42 (19.1)
White	362 (59.6)	290 (65.5)	72 (43.9)	141 (62.3)	149 (67.7)
More than 1 race specified	70 (11.5)	50 (11.3)	20 (12.2)	28 (12.6)	22 (10.0)
Ethnicity					
Hispanic or Latino	183 (30.1)	130 (29.3)	53 (32.3)	63 (28.3)	67 (30.5)
Not Hispanic or Latino	424 (69.9)	313 (70.7)	111 (67.7)	160 (71.7)	153 (69.5)
Height, mean (SD), cm	98.5 (11.7)	98.3 (11.7)	98.87 (11.67)	99.2 (11.4)	97.4 (12.1)
Weight, mean (SD), kg	16.8 (4.6)	16.8 (4.6)	17.0 (4.6)	17.1 (4.5)	16.4 (4.6)

- Patients who experienced ≥1 RTI were more likely to be
  - White
  - Lower rates of tobacco exposure
  - Higher rates of ICS, oral steroid and/or Monteleukast use in the last year
- Otherwise characteristics were comparable between the two groups

Results- Participants

Azithromycin Group versus Placebo Group

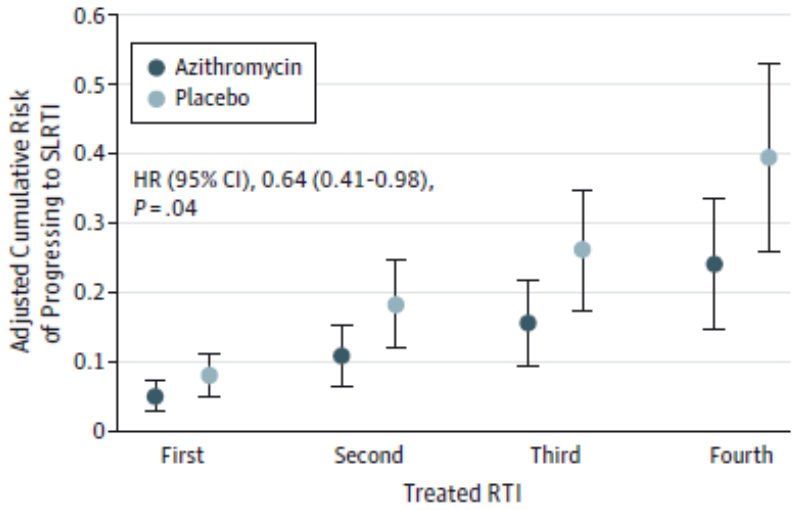
Table 2. Characteristics of Study Participants

	All Randomized Participants (N = 607)	Participants With at Least 1 Treated RTI (n = 443)	Participants With No RTI (n = 164)	Participants With at Least 1 Treated RTI	
				Azithromycin (n = 223)	Placebo (n = 220)
Exposures, No. (%)					
Day-care attendance	307 (50.6)	220 (49.7)	87 (53.1)	123 (55.2)	97 (44.1)
Tobacco smoke exposure, No./total (%)	240/601 (39.9)	164/439 (37.4)	76/162 (46.9)	89/221 (40.3)	75/218 (34.4)
Pet in home	280 (46.1)	228 (51.5)	52 (31.7)	117 (52.5)	111 (50.5)
Feature of Previous Wheezing					
No. of wheezing episodes in the past year, mean (SD)	4.45 (3.15)	4.45 (3.14)	4.45 (3.19)	4.49 (3.41)	4.41 (2.86)
No. of urgent and/or ED visits in the past year, mean (SD)	2.48 (1.64)	2.53 (1.71)	2.34 (1.41)	2.52 (1.72)	2.54 (1.71)
Hospitalized in the past year, No. (%)	87 (14.3)	58 (13.1)	29 (17.7)	34 (15.2)	24 (10.9)
No. of hospitalizations in the past year, median (IQR)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)
At least 1 course of OCS in past year, No. (%)	361 (59.5)	276 (62.3)	85 (51.8)	143 (64.1)	133 (60.5)
No. of OCS courses in the past year, median (range)	1 (0-4)	1 (0-4)	1 (0-4)	1 (0-4)	1 (0-4)
ICS use in past year, No./total (%)	150/605 (24.8)	126/441 (28.6)	24/164 (14.6)	70/223 (31.3)	56/218 (25.7)
Montelukast use in the past year, No. (%)	54 (8.9)	48 (10.8)	6 (3.7)	25 (11.2)	23 (10.5)
Symptom Burden During 14-d Run-in Period					
No. of days in run-in period, median (IQR)	15 (14-19)	15 (14-19)	15 (14-19)	15 (14-19)	14 (14-19)
Percentage of asthma control days, mean (SD)[a]	77.4 (24.1)	76.6 (23.6)	79.6 (25.3)	76.3 (24.5)	77.0 (22.6)
No. of asthma control days per week, mean (SD)[a]	5.4 (1.7)	5.4 (1.7)	5.6 (1.8)	5.3 (1.7)	5.4 (1.6)
Percentage of nights with albuterol use, median (range)	0 (0-43)	0 (0-43)	0 (0-36)	0 (0-24)	0 (0-43)
Percentage of days with albuterol use, median (range)	0 (0-57)	0 (0-57)	0 (0-59)	0 (0-57)	0 (0-54)

- Higher rate of daycare attendance in Azithromycin group.
- Otherwise comparable distribution
- Overall high level of atopy
  - 52.7% sensitized to any allergen
  - 46.8% positive modified API

Results- Primary Outcome

Figure 2. Cumulative Risk of Experiencing an Episode of Severe LRTI Across Treated RTIs for Preschool Children With a History of Severe LRTI



No. of treated RTIs	223	220	146	147	78	74	26	23
No. of SLRTIs	16	22	13	19	5	9	1	7

RTI indicates respiratory tract illness; SLRTI, severe lower RTI. Shown are risks and 95% CIs based on the discrete-time proportional hazards model of treatment effect adjusted for clinical site, age, modified Asthma Predictive Index status, season during which the treated RTI occurred, and whether the child enrolled before or after the study was extended to 78 weeks.

- Azithromycin (AZ) group had significantly lower risk of progressing to severe LRTI
- Absolute risk for first RTI:
  - AZ group: 0.05
  - Placebo group: 0.08
- Cumulative risk for severe LRTI over a max of 4 LRT:
  - AZ group: 0.24
  - Placebo group: 0.4

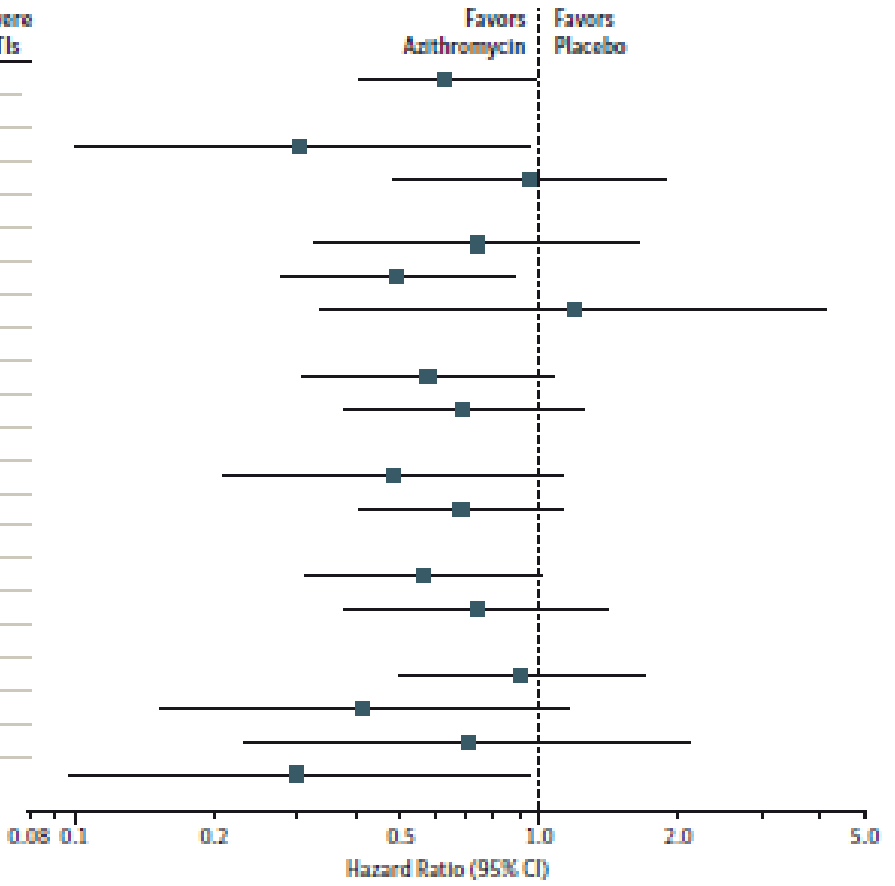
Results- Viral Detection

	All RTIs		RTIs that Did Not Progress to Severe Lower Respiratory Tract Illness		RTIs that Did Progress to Severe Lower Respiratory Tract Illness	
	Azithromycin	Placebo	Azithromycin	Placebo	Azithromycin	Placebo
No Virus Present	77 (17.4%)	87 (19.9%)	72 (17.6%)	82 (21.5%)	5 (14.7%)	5 (8.9%)
Adenovirus B		1 (0.2%)		1 (0.3%)		
Adenovirus C		1 (0.2%)				1 (1.8%)
Bocavirus	2 (0.5%)	1 (0.2%)	1 (0.2%)	1 (0.3%)	1 (2.9%)	
Coronavirus HK	1 (0.2%)		1 (0.2%)	. .		
Coronavirus NL63	12 (2.7%)	5 (1.1%)	12 (2.9%)	5 (1.3%)		
Coronavirus OC43	10 (2.3%)	8 (1.8%)	10 (2.4%)	6 (1.6%)		2 (3.6%)
Enterovirus	12 (2.7%)	19 (4.3%)	9 (2.2%)	17 (4.5%)	3 (8.8%)	2 (3.6%)
Enterovirus/ Human Rhinovirus	66 (14.9%)	51 (11.7%)	64 (15.6%)	39 (10.2%)	2 (5.9%)	12 (21.4%)
Influenza A	8 (1.8%)	6 (1.4%)	8 (2.0%)	5 (1.3%)		1 (1.8%)
Influenza B	2 (0.5%)	5 (1.1%)	2 (0.5%)	5 (1.3%)		
Human Rhinovirus	181 (40.9%)	186 (42.6%)	165 (40.3%)	161 (42.3%)	16 (47.1%)	25 (44.6%)
Metapneumovirus	17 (3.8%)	20 (4.6%)	14 (3.4%)	18 (4.7%)	3 (8.8%)	2 (3.6%)
Parainfluenza 1	13 (2.9%)	12 (2.7%)	10 (2.4%)	10 (2.6%)	3 (8.8%)	2 (3.6%)
Parainfluenza 2	7 (1.6%)	7 (1.6%)	7 (1.7%)	5 (1.3%)		2 (3.6%)
Parainfluenza 3	11 (2.5%)	9 (2.1%)	11 (2.7%)	9 (2.4%)		. .
Parainfluenza 4	5 (1.1%)	3 (0.7%)	5 (1.2%)	2 (0.5%)		1 (1.8%)
Parainfluenza 4b	3 (0.7%)	2 (0.5%)	3 (0.7%)	2 (0.5%)		
Respiratory Syncytial Virus A	10 (2.3%)	12 (2.7%)	9 (2.2%)	12 (3.1%)	1 (2.9%)	
Respiratory Syncytial Virus B	6 (1.4%)	2 (0.5%)	6 (1.5%)	1 (0.3%)	. .	1 (1.8%)
All	443 (100.0%)	437 (100.0%)	409 (100.0%)	381 (100.0%)	34 (100.0%)	56 (100.0%)

Results- Subgroup Analysis

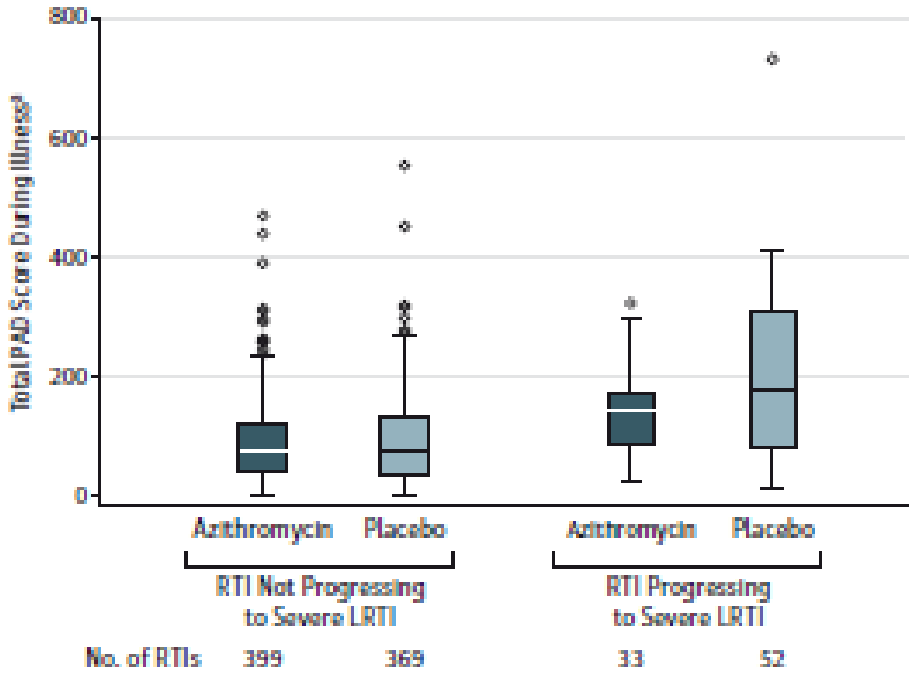
Figure 3. Potential Treatment-Effect Differences In Prespecified Subgroups for Risk of an Episode of Severe LRTI Among Preschool Children With a History of Severe LRTI

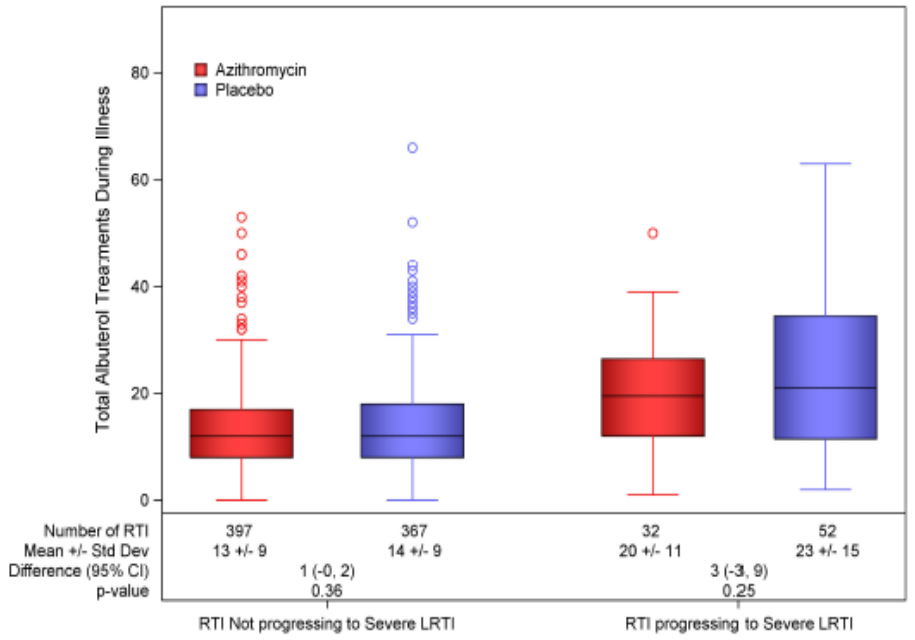
	Azithromycin			Placebo		
	No. of Patients	No. of RTIs	No. of Severe LRTIs	No. of Patients	No. of RTIs	No. of Severe LRTIs
Overall	223	473	35	220	464	57
IL-8 genotype (rs4073)[a]						
TT	41	80	4	46	91	16
AA/AT	82	178	17	81	186	20
Nasal virus						
Other virus[b]	46	119	11	55	113	14
Rhinovirus or enterovirus	123	247	18	105	237	37
No virus	39	77	5	51	87	5
Age group, mo						
43-71	108	213	16	94	200	28
12-42	115	260	19	126	264	29
Sex						
Girls	84	172	8	85	185	20
Boys	139	301	27	135	279	37
mAPI status						
Positive[c]	104	221	19	104	219	33
Negative	119	252	16	116	245	24
Season						
Sept-Nov	77	163	20	75	164	24
Dec-Feb	62	145	6	53	114	11
Mar-May	31	81	5	43	101	10
June-Aug	53	84	4	49	85	12



Results- Secondary Outcomes

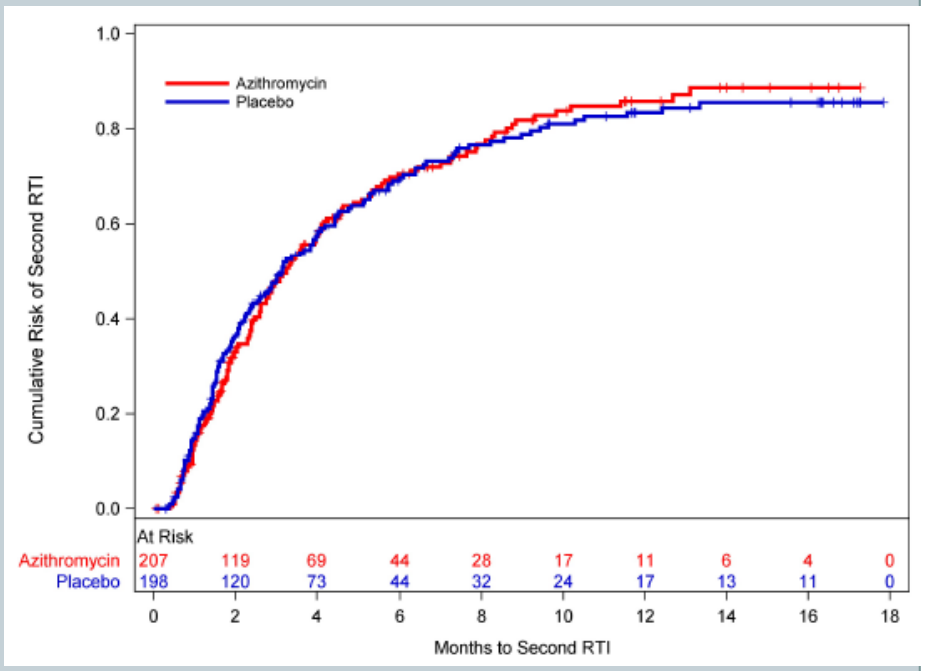
Figure 4. Symptom Scores Over the Duration of Treated RTIs Among Preschool Children With a History of Severe LRTI





Results- Secondary Outcomes

- **Healthcare Utilization**
  - **ED visits:**
    - 3.6% in Azithromycin group
    - 5.4% in placebo group
  - **Hospitalizations: 28**
    - 13 in Azithromycin group
    - 15 in placebo group
- **Microbial Resistance**
  - **At Randomization:**
    - 5 of 41 (12.2%) in Azithromycin group
    - 4 of 45 (8.9%) placebo group
  - **At Study completion:**
    - 8 of 40 (20%) in Azithromycin group
    - 7 of 41 (17%) in placebo group
- **Adverse Events:**
  - Mild GI symptoms



Conclusion

- In preschool children with severe intermittent wheezing in the context of RTIs-
  - Azithromycin at first sign of RTI:
    - Reduces risk of progression to LRTI
    - Reduces symptoms severity of episodes of severe LRTI
  - Effects were detectable regardless of modified API status

Conclusion

- Possible mechanisms:
  - Antibacterial effects[7]
  - Reduction of rhinovirus replication & increase INF gene expression???[22]
  - Reduction of IL-8 levels in nasal secretions
    - Reducing neutrophilic inflammation caused by viruses

Strengths and Limitations

- Strengths
  - Age of Participants
  - Assessed for antimicrobial resistance
  - Allowed for multiple treated RTIs per patient
  - Treatment effect was present regardless of API status
- Limitations
  - Extension of study
  - Study end point
  - Inclusion criteria
  - Parental reporting of symptoms
  - Resistance patterns only done in one site
  - Limited sputum studies

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