Comparative effectiveness of ceftriaxone in combination with a macrolide relative to ceftriaxone alone for pediatric patients hospitalized with community acquired pneumonia

A thesis submitted by

JoAnna K. Leyenaar, MD, MPH

In partial fulfillment of the requirements

for the degree of

Master of Science

in

Clinical and Translational Research

TUFTS UNIVERSITY

Sackler School of Graduate Biomedical Sciences

Date

May 2013

Thesis Chair/Project Mentor: Peter K. Lindenauer

Program Mentor: Laurel K. Leslie

Statistical Mentor: Penelope S. Pekow

External Advisor: John R. Schreiber

Manuscript authors: JoAnna K. Leyenaar, Meng-Shiou Shieh, Tara Lagu, Penelope S. Pekow, Peter K. Lindenauer

Program Director: David M. Kent

Clinical Research Education Coordinator: Nina M. Bonnoyer

Dean of Tufts University Clinical and Translational Science Institute:

Harry P. Selker

Dean of Sackler School of Graduate Biomedical Sciences:

Naomi Rosenberg

Abstract

Community acquired pneumonia is the leading cause of pediatric hospitalization in the United States, with *Mycoplasma pneumonaie* thought to be a causative organism in up to one third of cases. National guidelines recommend empiric combination therapy with a macrolide and beta-lactam antibiotic for patients in whom infection with *M. pneumoniae* is a significant consideration. However, evidence to support this recommendation is limited. The objectives of this study were to: (i) determine the effectiveness of ceftriaxone alone compared to ceftriaxone with a macrolide for the treatment of pneumonia among hospitalized children as measured by length of hospital stay, and; (ii) explore differences in total costs of hospitalization. We conducted a retrospective cohort study of children 1-17 years of age with pneumonia. Poisson regression was used to assess for associations between antibiotic regimen and length of stay, adjusting for patient and hospital characteristics and initial tests and therapies. Multivariable linear regression models were used to assess the log-treatment costs associated with each antibiotic regimen. A propensity score model to predict initial antibiotic therapy was constructed. A total of 13,493 children were included in the analysis, including 4701 who received ceftriaxone in combination with a macrolide and 8892 who received ceftriaxone alone. Among children 1-4 years of age, adjusted models revealed no significant difference in length of hospital stay, with total hospital costs significantly higher among those receiving combination therapy (cost ratio 1.04 (95% CI, 1.01-1.07)). Among children 5-17 years of age, children receiving combination therapy had a shorter adjusted length of stay (RR 0.95 (95% CI,0.92-0.98)), with no significant difference in total hospital costs (cost ratio 1.01 (95% CI, 0.98-1.04)). The addition of a macrolide does not appear to offer an advantage over ceftriaxone alone among preschool aged children with respect to length of hospital stay. Among children 5-17 years of age, empiric treatment of pneumonia with ceftriaxone in combination with a macrolide

was associated with shorter length of hospital stay, equivalent to a need to treat seven children with combination therapy to result in one child staying in hospital for one less day.

Acknowledgements

This study was supported by the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant UL1 RR025752. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. We would like to express our sincere gratitude to Drs. Laurel K. Leslie and John R. Schreiber for their thoughtful review of this manuscript.

Table of Contents

List of Tables

List of Figures

Abbreviations

CAP: Community acquired pneumonia

ICD-9-CM: International Classification of Disease, 9th Edition, Clinical Modification

NHDS: National Hospital Discharge Survey

PDW: Perspective Data Warehouse

PSM: Propensity score matched

USD: United States dollars

A. Introduction

Background

Community acquired pneumonia (CAP) is a common illness in the pediatric population with an annual incidence of 34-40 cases per 1000 in children less than five years of age and 7 cases per 1000 in adolescents in Europe and North America.[1,2] It is the leading cause of pediatric hospitalization in the United States, with more than 160,000 hospital admissions annually.[3]

Despite significant disease burden and healthcare costs, little research has been carried out to compare the effectiveness of different antibiotic regimens in the management of CAP among hospitalized children. Prior to publication of national clinical treatment guidelines for pneumonia in 2011,[4] parenteral ceftriaxone was the most common beta-lactam antibiotic used for CAP management in the inpatient setting in the US.[5] Ceftriaxone provides broad antimicrobial coverage against *Streptococcus pneumonaie*, the most common cause of bacterial pneumonia in children, as well as several other bacterial etiologies. However, like other beta-lactam antibiotics, it does not treat *Mycoplasma pneumonaie*, an atypical organism believed to play a causative role in CAP in up to one third of children.[6–9] While traditionally thought to predominantly affect school-aged children, recent studies suggest that this organism also plays an important role in children less than five years of age.[6,8–10]

Current national recommendations for pneumonia management advise that empiric therapy with an oral or parenteral macrolide be added to a beta-lactam for hospitalized children for whom infection with *M. pneumoniae* is a significant concern.[4] However, in summarizing the research influencing this recommendation, the authors acknowledge a paucity of evidence. A recent systematic review conducted as part of the Cochrane initiative concluded that there is

insufficient evidence that antibiotics are effective in children with CAP caused by *M. pneumoniae*,[10] further highlighting the uncertainty about whether the addition of a macrolide provides a treatment advantage over beta-lactam antibiotics alone among hospitalized children.

The objectives of this study were to determine the comparative effectiveness of ceftriaxone alone relative to ceftriaxone in combination with a macrolide for the treatment of CAP in both preschool and school aged hospitalized children with respect to length of hospital stay, and to explore differences in total hospital costs.

Specific Aims and Hypotheses

Specific Aim 1: To determine patient, provider and hospital characteristics associated with treatment of CAP using parenteral ceftriaxone alone relative to parenteral ceftriaxone plus a macrolide (azithromycin, erythromycin or claryithromycin).

Hypothesis 1: While variation in antibiotic treatment in CAP will be partially driven by patient characteristics, hospital and provider characteristics will be associated with a greater degree of the variance.

Specific Aim 2: To determine the effectiveness of parenteral ceftriaxone alone compared to parenteral ceftriaxone plus a macrolide for the treatment of CAP in hospitalized children.

Hypothesis 2: We hypothesize that the treatment regimens will not be significantly different with respect to our primary outcome, length of hospital stay, as well as secondary outcomes.

Specific Aim 3: To analyze the costs of treatment with parenteral ceftriaxone alone compared to parenteral ceftriaxone plus a macrolide for the treatment of CAP in hospitalized children.

Hypothesis 3: Addition of a macrolide for treatment will be associated with minimal increased treatment costs related only to the cost of the antibiotic.

B. Methods

Study Design & Eligibility Criteria

We conducted a retrospective cohort study of children and adolescents (hereafter referred to as children) one to 17 years of age admitted between 2007 and 2010 to hospitals that contribute data to the Perspective Data Warehouse (PDW) (Premier Healthcare Informatics, Charlotte, NC), a voluntary fee-supported database that measures healthcare utilization. This data warehouse represents geographically and structurally diverse hospitals across the United States with hospitals closely representing the composition of acute care hospitals nationwide, and incorporates approximately 15% of all hospitalizations in the United States. PDW has been previously described[11–13] and has been used in several studies of pediatric populations.[14–16] The database contains fully de-identified information including patient demographic characteristics, length of stay, all International Classification of Disease, 9th Edition, Clinical Modification (ICD-9-CM) discharge diagnoses, as well as a date-specific record of all billed items, including diagnostic tests, medications and their associated costs.

We included children with a principal diagnosis (ICD-9-CM) of pneumonia (480-483 or 485-487.0), applying a previously validated algorithm used in several published studies.[17] All patients received either ceftriaxone alone, or ceftriaxone with the addition of a macrolide (oral or parenteral azithromycin, erythromycin or claryithromycin) beginning on the first day of hospitalization. Because we were interested in understanding the role of macrolides for pneumonia management among previously well children, the target population of the recently published national clinical practice guidelines, we excluded children with complex chronic conditions, defined as "medical conditions that can be reasonably expected to last at least 12 months (unless death intervenes) and to involve either several different organ systems or one system severely enough to require specialty pediatric care and probably some period of

hospitalization in a tertiary care center," using a previously developed classification scheme (Table 1).[18] Infants less than one year of age were excluded, given the high prevalence of bronchiolitis in this age group and increased likelihood of misclassifying lower respiratory tract disease. Patients transferred to or from outside facilities or who left hospital against medical advice were excluded as we were unable to accurately assess length of hospital stay or full course of hospital treatments. Table 2 illustrates all eligibility criteria.

Treatment and Outcome Variables

Our primary independent variable was antibiotic regimen prescribed on the first day of hospitalization - parenteral ceftriaxone alone or in combination with an oral or parenteral macrolide (hereafter referred to as combination therapy). The primary outcome measures were length of hospital stay, reported in days, and total costs of the hospitalization, reported in United States dollars (USD). For approximately 75% of hospitals contributing data to PDW, these reflected actual hospital costs taken from internal cost accounting systems, whereas the remaining hospitals provided cost estimates based on Medicare cost-to-charge ratios. Secondary outcomes included: (i) transfer to the intensive care unit on or after the second day of hospitalization, a measure of clinical deterioration; (ii) inpatient mortality; and (iii) readmission to hospital within 30 days of hospital discharge. Readmission outcomes included all-cause readmission, defined as any hospital readmission within 30 days of discharge, and pneumonia-related readmission, defined as an ICD-9-CM code of 480-483 or 485-487.0 in any diagnostic field for readmissions within 30 days of the index hospitalization.

Patient, hospital, and pneumonia management variables

Study participants in each treatment arm were characterized on the basis of age, gender, race/ethnicity, insurance status, and presence of comorbid conditions that commonly present

concurrently with pneumonia including asthma, influenza, and disorders of fluids and electrolytes. Asthma was defined as (i) an ICD-9-CM code for asthma (493.0–493.9), or (ii) provision of long term asthma control medications (long-acting beta agonists, inhaled corticosteroids, leukotriene antagonists or mast cell stabilizers) on the first day of hospitalization, presumed to represent continuation of home therapies. Characteristics of the admitting hospitals were described, including geographic region, bed size, urban/rural location, children's hospital versus general community hospital, and teaching status. Children's hospitals included both freestanding children's hospitals and children's hospitals within larger adult centers, defined as institutions that had at least ten pediatric subspecialties recorded in the database. The proportions of children admitted to hospital with pneumonia during peak respiratory season was identified, with respiratory season defined as October to March.

We examined detailed billing and ICD-9-CM procedure codes to identify the use of diagnostic tests and adjunctive therapies for patients with pneumonia, including blood tests, chest imaging, and medications, with variables detailed in Table 4. Initial investigations and adjunctive therapies were defined as those provided on the first day of hospitalization.

Statistical analysis

We calculated patient-level summary statistics using frequencies and percents for categorical variables and medians and interquartile ranges for continuous variables. Unadjusted associations between antibiotic treatment group and patient and hospital characteristics, initial therapies, and outcomes were assessed using chi-square tests for categorical variables and Wilcoxon rank-sum tests for continuous variables.

Poisson regression was used to assess for associations between antibiotic treatment regimen and length of stay, adjusting for observable patient and hospital characteristics and initial

investigations and adjunctive therapies. Multivariable linear regression models were used to assess the log-treatment costs associated with each antibiotic regimen, again adjusting for patient and hospital characteristics and initial investigations and adjunctive therapies provided. All models were adjusted for the effects of within-hospital correlation using generalized estimating equations. Costs were trimmed at 3 standard deviations above the mean and log-transformed due to extreme positive skew. Our initial models were adjusted for age group but, due to age-treatment interactions, we evaluated and report age stratified models for preschool children less than five years of age, and school aged children, ages 5-17 years. Given the potential interaction between treatment regimen and having a concurrent diagnosis of asthma, we also explored this interaction, examining the Wald p-value for interaction terms. Variables entered into the multivariate models, determined *a priori,* included all patient and hospital characteristics shown in Table 4, and initial investigations and adjunctive therapies with p-values $\leq$ 0.1 observed in our initial bivariate analyses.

Application of propensity scores

A limitation of observational studies, often described as "confounding by indication" is the fact that treatment allocation is not random, such that differences in outcomes between groups may be related to pre-treatment differences between the groups. Application of propensity scores is one methodology developed to address this limitation. A propensity score is defined as the probability that an individual received a particular treatment or intervention based on that individual's observable pre-treatment characteristics. Traditionally propensity score models are non-parsimonious, with inclusion of all covariates of statistical or clinical significance. Individuals with a given propensity score have, on average, the same distribution of observable characteristics incorporated into the propensity score.

Propensity scores may be applied in a variety of ways, including propensity score matching or regression adjustment. We used both of these applications in our analysis. A propensity score model to predict initial antibiotic therapy was constructed, incorporating all patient and hospital characteristics, comorbid conditions, and initial investigations and adjunctive therapies listed in Table 4. We applied the propensity score in two ways: first, as a covariate in the multivariable models described above, and second, by matching patients who received ceftriaxone alone with those who had a similar propensity score but received combination therapy using a greedy matching algorithm in which we attempted to match subjects first on five digits of the propensity score. For remaining unmatched cases matching was attempted on the first four digits, with a similar process followed, if necessary, to achieve a match up to the first digit of the propensity score. Outcomes in the matched cohorts were adjusted for unbalanced covariates. All statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC). Hypothesis testing was two sided with a type I error rate of α=0.05.

Human Subjects Protection

Because the data do not contain identifiable information, the Institutional Review Board at Baystate Medical Center determined that this study did not constitute human subjects research.

Power calculation

Power was calculated *a priori* to ensure that our sample size was adequate to address our research questions. A decision was made to combine the 5-11 and 12-17 years of age groups, given the relatively small number of adolescents in the sample, and the shared risk for *M. pneumonaie* infection based on literature review.

Preliminary data analysis using a dataset from Premier spanning three years, 2007 to 2010, shows that approximately 32,000 subjects one to 17 years of age were discharged with a principal ICD-9-CM diagnosis of pneumonia. After applying the inclusion and exclusion criteria, we initially identified 11688 patients from 266 hospitals treated with ceftriaxone alone or in combination with a macrolide on the first day of hospitalization, with a mean (SD) hospital length of stay of 2.4 (1.5) days. Power for an equivalency test for length of stay comparing those treated with and without a macrolide in strata defined by age (Table 3) was evaluated. To account for clustering of patients within hospitals, an effective sample size, or adjusted $n`=n/[1+(m-1)\rho]$ is used, adjusting for correlation of responses within a hospital, and the mean number of patients per hospital (m). Assuming a low within hospital correlation (ρ=.001), a Type I error rate of 0.05, power of an equivalency test within 0.25 days is 97% or above for the younger age groups; power for an equivalency test within 0.35 days is 75% or above for 12-17 year olds, based upon the smaller n. Power was computed using NCSS PASS software.

C. Results

Study population

A total of 32,845 children aged 1 to 17 years of age with a diagnosis of pneumonia were admitted to 268 hospitals contributing data to PDW during the study period. As illustrated in Figure 1, 13,493 met our eligibility criteria and were included in our analyses. Approximately one third of children (n=4701) received combination therapy, while two-thirds (n=8892) received ceftriaxone alone beginning on the first day of hospitalization. Approximately one quarter of preschool children ages 1-4 years were treated with combination therapy while approximately half of school aged children (5-17 years) received this antibiotic combination.

As shown in Table 4, children receiving combination therapy were, on average, older, having a median age of 5 relative to the median age of 3 years observed in the ceftriaxone alone group. Children receiving combination therapy were also more likely to have private insurance and were less frequently admitted during respiratory season than those receiving ceftriaxone alone. More than 40% of all children in our sample had asthma in addition to a principal diagnosis of pneumonia (n=5873), and children with asthma were more likely to receive combination therapy (n=2268, 48.2%) than ceftriaxone alone (n=3605, 40.5%). Hospital characteristics also differed between the treatment groups, with children receiving combination treatment less frequently admitted to teaching hospitals (n=1517, 32.3% compared to n=3289, 37.0% of children receiving ceftriaxone alone). There were also small but statistically significant differences between the groups in terms of geographic region of admission and hospital size as well as proportions of patients admitted to children's hospitals.

The majority of children in both treatment groups received chest x-rays and blood cultures during their hospitalization, while less than half of children received tests for viral pathogens. A

small proportion of children in both treatment groups received additional tests on the first day of hospitalization (Table 4). Children who received combination therapy were more likely to have received adjunctive therapies (e.g., steroids, beta-agonists) in the emergency department or on the first day of hospitalization. Approximately one third of children in our sample received oral or intravenous steroids early in their treatment course, with 40.3% (n=1892) children in the combination therapy group receiving this intervention compared to 29.4% (n=2610) in the ceftriaxone group. More than half of children in both groups also received beta-agonists, including almost two-thirds of children in the combination therapy group (n= 3047, 64.8%) compared to 55.9% (n=4966) in the ceftriaxone group. Less than 5% of children in both treatment groups were admitted to the intensive care unit on the first day of hospitalization.

Unadjusted analyses

In our unadjusted analysis, the length of hospital stay was not significantly different between the treatment groups, with both displaying a mean length of stay of 2.4 days and a median of 2 days (IQR 1-3 days). However, unadjusted total hospital costs were significantly higher in the combination therapy group, with a mean total cost of 4317 USD (median 3362 USD, IQR 2304-5099) in the macrolide group relative to a mean cost of 3831 USD for children who received ceftriaxone alone (median 3023 USD, IQR 2083-4512). When we assessed these outcomes stratified by age group, there was no significant difference in the length of hospital stay among preschool aged children in the two treatment groups but total hospital costs were approximately 20% higher among children who received combination therapy (Table 5). Among school-aged children, the combination treatment group had a length of hospital stay approximately 5% shorter than that observed in the ceftriaxone alone group with higher total hospital costs, differences that were statistically significantly. Among both preschool and

school-aged children, there were no significant differences between the treatment groups in our secondary outcomes, including transfer to the intensive care unit, inpatient mortality, or readmission. Among the 126 readmissions observed, two-thirds of these (n=83) were pneumonia-related, with no significant differences in pneumonia-related readmissions observed between the treatment groups.

Multivariable analyses

The interaction between antibiotic regimen and age group was statistically significant ($p < 0.0001$), so all multivariable analyses are stratified by age. In contrast, the interaction between antibiotic regimen and asthma was highly non-significant (p=0.98 for preschool aged children and p=0.52 for school aged children) and therefore excluded from further analyses. Among preschool aged children, there were no significant differences in the length of stay between the treatment groups, controlling for patient and hospital characteristics and adjusting for potential clustering within hospitals (Table 8). Both covariate adjusted and propensity score adjusted models resulted in similar relative risk estimates. Total hospital costs were significantly higher among preschool aged children who received a macrolide in combination with ceftriaxone, with total costs 4-8% greater in the combination therapy group.

Among our cohort of school-aged children, the significantly decreased length of stay observed in our unadjusted analysis remained when we adjusted for patient and hospital characteristics (Table 8). In our standard multivariable model, the average length of stay for patients who received ceftriaxone in combination with a macrolide was 5% less than those who received ceftriaxone alone (RR 0.95; 95% CI, 0.92- 0.98). This result persisted and was almost identical in our propensity score matched (PSM) analysis, controlling for unbalanced covariates. In our

adjusted model of total hospital costs, there were no significant differences between the treatment groups.

Expanded Propensity Score Results

Figure 3 illustrates the distribution of propensity scores among children in our cohort, stratified by age, with the distribution of demographic hospital characteristics in the age-stratified, matched samples illustrated in Tables 6 and 7. In the strata of 1-4 years of age children, 99.9% of children in the combination treatment group were matched with an individual in the ceftriaxone alone group on the basis of the propensity score. The majority of covariates were balanced between the groups, and those that were statistically significantly different showed relatively small differences in clinical terms. The model C-statistic was 0.64. Although the C-statistic is frequently reported as an indicator of the propensity score to control confounding, recent research suggests that it actually provides little information about whether all important confounders have been included in the propensity score.[32–34]

In the strata of children and adolescents aged 5-17 years, 91.9% of children in the combination treatment group were matched with an individual in the ceftriaxone alone group. As illustrated in Figure 3, the unmatched cases were among the most likely to receive macrolides in combination with ceftriaxone. Unbalanced covariates in this strata again showed relatively small differences in absolute terms (Table 7). The model C-statistic was 0.59.

D. Discussion

National clinical practice guidelines for pneumonia management among hospitalized children recommend empiric combination therapy with a macrolide and beta-lactam antibiotic for patients in whom infection with *M. pneumoniae* is a significant consideration.[4] Our study, exploring the comparative effectiveness of ceftriaxone alone relative to ceftriaxone in combination with an oral or parental macrolide, suggests that addition of a macrolide does not have a treatment advantage among preschool children with respect to length of hospital stay, transfer to the intensive care unit, or rate of hospital readmission, but is associated with a significantly increased cost. Among children five to seventeen years of age, combination therapy was associated with a shorter length of hospital stay with no significant difference in total hospital costs or in other secondary outcomes including ICU transfer, mortality or readmission.

Ambroggio et al. explored the comparative effectiveness of empiric beta-lactam therapy and beta-lactam-macrolide combination therapy for pneumonia among patients admitted to freestanding children's hospitals and found that combination therapy decreased length of stay among school-aged children with no benefit to preschool children.[19] Our study confirms and extends their study findings to a larger sample inclusive of both children's hospitals and general community hospitals, where almost three quarters of children admitted to hospitals in the United States for pneumonia receive their care.[20] Taken together, these studies call into question the utility of empiric combination therapy with a macrolide and beta-lactam antibiotic among preschool aged children, perhaps reflecting a lower rate of infection with *M. pneumonaie* or spontaneous clinical resolution of infection hypothesized to occur in this age group.[4,21,22]

The magnitude of difference in length of hospital stay observed among school aged in our combination therapy cohort is less than that observed by Ambroggio et al., which may reflect

differences in the characteristics of patients admitted to general community hospitals. Our adjusted odds ratio for length of stay translates into a need to treat seven school-aged children with combination therapy to result in one child staying in hospital for one less day. Given that approximately 56,000 school-aged children were admitted to hospital with pneumonia in the United States in 2009,[20] on a national level this is equivalent to 8000 children and adolescents discharged from hospital one day sooner, which has clear implications for hospital resource utilization. However, this must be balanced against potential adverse effects associated with broad provision of macrolides, both from the perspective of individual patients' potential side effects, as well as the development of antibiotic resistance. A recent Cochrane review concluded that *M. pneumonaie* cannot be reliably diagnosed on the basis of symptoms and signs,[23] while the utility of diagnostic testing is limited given difficulties interpreting serological results, lag time to culture results, and limited availability of rapid diagnostic technologies in many centers. Development of clinical prediction rules to identify children at highest risk of *M. pneumoniae* infection may allow for more focused prescription of macrolides while creating opportunities for comparative effectiveness studies of targeted provision of combination therapy.

Approximately forty percent of children in our cohort were admitted with concurrent diagnoses of pneumonia and asthma, highlighting the importance of future studies of pneumonia management among children with asthma. Frequent co-occurrence of asthma and pneumonia among hospitalized children has been previously reported in an analysis of the National Hospital Discharge Survey (NHDS), with 24% of children with a primary or secondary discharge diagnosis of asthma having a concurrent primary or secondary discharge diagnoses of pneumonia. [24] The higher rate of asthma seen in our cohort may reflect that, unlike the NHDS analysis, our asthma definition included an ICD-9-CM code for asthma in any secondary discharge diagnosis field and

we excluded infants less than one year of age. The high rates of beta-agonist and steroid use on the first day of hospitalization further suggest that a large fraction of children presented to hospital with wheezing or signs of airway inflammation. Macrolides have both antimicrobial and anti-inflammatory properties,[25–27] and their use for chronic asthma management has been the subject of several studies and a Cochrane systematic review.[28–31] Despite the biologic plausibility that addition of a macrolide to ceftriaxone could reduce airway inflammation and result in decreased length of stay among children with concurrent diagnoses of asthma and pneumonia, we did not find a significant interaction between asthma and macrolide use. However, forty percent of children in our cohort received oral or intravenous steroids in addition to a macrolide, which may have attenuated the anti-inflammatory effects of macrolides.

Our results should be interpreted in light of a number of limitations. First, we used ICD-9-CM codes to retrospectively identify patients with pneumonia, which may have resulted in some potential misclassification. We attempted to minimize misclassification by using a previously validated ICD-9-CM algorithm[17] and by limiting our analysis to children who received either ceftriaxone alone or ceftriaxone in combination with a macrolide on the first day of hospitalization. Second, because our analysis is limited to the data available from PDW, there may be additional factors associated with providers' decisions to provide combination therapy, such as chest x-ray findings, which we were unable to ascertain. Related to this, the outcomes available in the data set, such as length of stay and readmission rates, may be insensitive to differences in patients' functional status and quality of life, both of which would be beneficial to assess in determining the comparative effectiveness of antibiotics for pneumonia. By applying a propensity-score matched analysis, we used a rigorous methodology to account for potential confounding by indication. However, there may be unmeasured confounders that influenced

our observed outcomes. The differences in total hospital costs observed between the groups may be related, in part, to unmeasured confounding. Third, we were very interested in understanding the potential interaction between asthma and antibiotic treatment and elected to incorporate use of long term asthma control medications to supplement ICD-9-CM codes to identify cases with asthma. If these long term control medications were used inappropriately, our definition may have overestimated the prevalence of asthma in our cohort. Further study is needed to explore optimal management of patients presenting with concurrent asthma and pneumonia, both in the pre-hospital setting and during hospitalization.

This study applied a retrospective observational study design to understand the comparative effectiveness of addition of a macrolide to ceftriaxone for the pneumonia management in routine clinical practice. Clinical trials assessing the efficacy of combining a macrolide with a beta-lactam for the in-hospital management of pediatric pneumonia have not been previously conducted and would provide further information about the magnitude of benefit of adding a macrolide for school-aged children. Given our findings regarding the number of children needed to be treated with combination therapy to achieve a clinically meaningful difference in outcomes, a decision analysis would be helpful to inform guidelines and clinical practice, with models determining the costs and benefits of early initiation of a macrolide as well as delayed addition of a macrolide until the second or third day of hospitalization. Future studies exploring potential benefits of combination therapy that also ascertain the incidence of adverse effects associated with empiric macrolide treatment would further inform treatment decisions.

References

1. McIntosh K. Community-acquired pneumonia in children. *New England Journal of Medicine* **346**, 429–437 (2002).

2. Eslamy, H. K. & Newman, B. Pneumonia in normal and immunocompromised children: an overview and update. *Radiologic clinics of North America* **49**, 895–920 (2011).

3. Elixhauser, A. HCUP Statistical Brief #56. July 2008. Agency for Healthcare Research and Quality, Rockville, MD. *AHRQ Hospital Stays for Children.* http://www.hcup–us.ahrq.gov/reports/statbriefs/sb5 (2006).

4. Bradley, J. S. *et al.* The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* **53**, e25–76 (2011).

5. Newman, R. E. *et al.* Impact of a guideline on management of children hospitalized with community-acquired pneumonia. *Pediatrics* **129**, e597–604 (2012).

6. Michelow, I. C. *et al.* Epidemiology and clinical characteristics of community-acquired pneumonia in hospitalized children. *Pediatrics* **113**, 701–707 (2004).

7. Kogan, R. *et al.* Comparative randomized trial of azithromycin versus erythromycin and amoxicillin for treatment of community-acquired pneumonia in children. *Pediatric pulmonology* **35**, 91–8 (2003).

8. Principi, N. & Esposito, S. Emerging role of Mycoplasma pneumoniae and Chlamydia pneumoniae in paediatric respiratory-tract infections. *The Lancet infectious diseases* **1**, 334–44 (2001).

9. Principi, N., Esposito, S., Blasi, F. & Allegra, L. Role of Mycoplasma pneumoniae and Chlamydia pneumoniae in children with community-acquired lower respiratory tract infections. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* **32**, 1281–9 (2001).

10. Mullholland, S., Gavranich, J. & Chang, A. B. Antibiotics for community-acquired lower respiratory tract infections secondary to Mycoplasma pneumoniae in children. *Cochrane Database Syst Review* **7**, (2010).

11. Lindenauer, P. K. *et al.* Association of Corticosteroid Dose and Route of Administration With Risk of Treatment Failure in Acute Exacerbation. *JAMA* **303**, 2359–2367 (2010).

12. Lindenauer, P. K. *et al.* Outcomes of care by hospitalists, general internists, and family physicians. *The New England journal of medicine* **357**, 2589–600 (2007).

13. Rothberg, M. B. *et al.* Antibiotic therapy and treatment failure in patients hospitalized for acute exacerbations of chronic obstructive pulmonary disease. *JAMA : the journal of the American Medical Association* **303**, 2035–42 (2010).

14. Feudtner, C., Dai, D., Hexem, K. R., Luan, X. & Metjian, T. a Prevalence of polypharmacy exposure among hospitalized children in the United States. *Archives of pediatrics & adolescent medicine* **166**, 9–16 (2012).

15. McLeod, L., French, B., Dai, D., Localio, R. & Keren, R. Patient volume and quality of care for young children hospitalized with acute gastroenteritis. *Archives of pediatrics & adolescent medicine* **165**, 857–63 (2011).

16. Lasky, T., Greenspan, J., Ernst, F. & Gonzalez, L. Pediatric vancomycin use in 421 hospitals in the United States, 2008. *PloS one* **7**, e43258 (2012).

17. Aronsky, D., Haug, P. J., Lagor, C. & Dean, N. C. Accuracy of administrative data for identifying patients with pneumonia. *American journal of medical quality : the official journal of the American College of Medical Quality* **20**, 319–28 (2005).

18. Feudtner, C., Christakis, D. A. & Connell, F. A. Pediatric Deaths Attributable to Complex Chronic Conditions: A population based study of Washington State: 1980-1997. *Pediatrics* **106**, (2000).

19. Ambroggio, L. *et al.* Comparative effectiveness of empiric β-lactam monotherapy and β-lactam-macrolide combination therapy in children hospitalized with community-acquired pneumonia. *The Journal of pediatrics* **161**, 1097–103 (2012).

20. Agency for Healthcare Research and Quality HCUPnet. *http://hcupnet.ahrq.gov/HCUPnet.jsp*

21. Bradley JS, Arguedas A, Blumer JL, Sáez-Llorens X, Melkote R, N. G. Comparative study of levofloxacin in the treatment of children with community-acquired pneumonia. *Pediatr Infect Dis Journal* **26**, 868–878 (2007).

22. Esposito, S. *et al.* Antibiotic therapy for pediatric community-acquired pneumonia: do we know when, what and for how long to treat? *The Pediatric infectious disease journal* **31**, e78–85 (2012).

23. Wang K, Gill P, Perera R, Thomson A, Mant D, H. A. Clinical symptoms and signs for the diagnosis of Mycoplasma pneumoniae in children and adolescents with community-acquired pneumonia. *Cochrane Database Syst Review* **10**, CD009175 (2012).

24. Bundy, D. G. Hospitalizations with primary versus secondary discharge diagnoses of asthma: implications for pediatric asthma surveillance. *The Journal of pediatrics* **150**, 446–9, 449.e1 (2007).

25. Cameron, E. J., McSharry, C., Chaudhuri, R., Farrow, S. & Thomson, N. C. Long-term macrolide treatment of chronic inflammatory airway diseases: risks, benefits and future developments. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology* **42**, 1302–12 (2012).

26. Steel, H. C., Theron, A. J., Cockeran, R., Anderson, R. & Feldman, C. Pathogen- and host-directed anti-inflammatory activities of macrolide antibiotics. *Mediators of inflammation* **2012**, 584262 (2012).

27. Kovaleva, A. *et al.* Immunomodulatory effects of macrolides during community-acquired pneumonia: a literature review. *The Journal of antimicrobial chemotherapy* **67**, 530–40 (2012).

28. Richeldi L, Ferrara G, Fabbri LM, Lasserson TJ, G. P. Macrolides for chronic asthma. *Cochrane Database Syst Review* **4**, CD002997 (2005).

29. Brusselle, G. G. *et al.* Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial. *Thorax* 1–8 (2013).doi:10.1136/thoraxjnl-2012-202698

30. Mikailov, A., Kane, I., Aronoff, S. C., Luck, R. & Delvecchio, M. T. Utility of adjunctive macrolide therapy in treatment of children with asthma: a systematic review and meta-analysis. *Journal of asthma and allergy* **6**, 23–9 (2013).

31. Koutsoubari, I. *et al.* Effect of clarithromycin on acute asthma exacerbations in children: an open randomized study. *Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology* **23**, 385–90 (2012).

32. Austin, P. C. & Mamdani, M. M. A comparison of propensity score methods: a case-study estimating the effectiveness of post-AMI statin use. *Statistics in medicine* **25**, 2084–106 (2006).

33. Austin, P. C. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate behavioral research* **46**, 399–424 (2011).

34. Westreich, D., Cole, S. R., Funk, M. J., Brookhart, M. A. & Stu, T. The role of the c-statistic in variable selection for propensity score models. 317–320 (2011).doi:10.1002/pds

Tables and Figures

Table 1: Pediatric Complex Chronic Conditions ICD-9 Diagnostic Scheme as developed by Feudtner et al. (2000).

Condition	ICD9-CM Codes
Neuromuscular malformation	
Brain and spinal cord	740.0–742.9
Mental retardation	318.0–318.2
Central nervous system degeneration and disease	330.0–330.9, 334.0–334.2, 335.0–335.9
Infantile CP	343.0–343.9
Muscular dystrophies and myopathies	359.0–359.3
Cardiovascular malformation	745.0–747.4
Heart and great vessel	425.0–425.5, 429.1
Cardiomyopathies	426.0–427.4
Conduction disorders	427.6–427.9
Dysrhythmias	
Respiratory	748.0–748.9
Respiratory malformations	770.7
Chronic respiratory disease	277.0
Cystic fibrosis	
Renal	753.0–753.9
Congenital anomalies	585

Chronic renal failure	
Gastrointestinal	750.3, 751.1–751.3 751.6–751.9
Congenital anomalies	571.4–571.9
Chronic liver disease and cirrhosis	555.0–556.9
Inflammatory bowel disease	
Hematologic or immunologic	282.5–282.6
Sickle cell disease	282.0–282.4
Hereditary anemias	279.00–279.9, 288.1–288.2, 466.1
Hereditary immunodeficiency	042
Acquired immunodeficiency	
Metabolic	270.0–270.9
Amino acid metabolism	271.0–271.9
Carbohydrate metabolism	272.0–272.9
Lipid metabolism	277.3–277.5
Storage disorders	275.0–275.3, 277.2, 277.4, 277.6, 277.8–277.9
Other metabolic disorders	
Other congenital or genetic defect	
Chromosomal anomalies	758.0–758.9
Bone and joint anomalies	259.4, 737.3, 756.0–756.5
Diaphragm and abdominal wall	553.3, 756.6–756.7
Other congenital anomalies	759.7–759.9

Malignancy	
Malignant neoplasms	140.0–208.9, 235.0–239.9

Table 2: Eligibility criteria for subjects included in the study data set.

Inclusion Criteria	Exclusion Criteria
Children ages: 1-17 years ICD-9-CM diagnosis of pneumonia (480-483; 485-487.0) Antibiotic prescribed on day one of hospitalization: parenteral ceftriaxone +/- oral or parenteral macrolide (erythromycin, azithromycin or clarythromycin)	Parenteral antibiotics other than those listed in the inclusion criteria provided on day one of hospitalization Presence of one or more complex chronic condition, per algorithm (including neuromuscular, cardiovascular, respiratory, renal, gastrointestinal, hematologic, immunologic, or metabolic diseases, malignancies and other congenital or genetic defects) < 1day admissions Transfer from another healthcare facility Transfer to another healthcare facility following admission Left hospital against medical advice Diagnosis-related-group code of "extensive operating room procedure unrelated to principal

	diagnosis”

Table 3: *A priori* sample size calculation: age distribution of patients meeting eligibility criteria.

	Ceftriaxone alone (n)	%	Ceftriaxone + macrolide (n)	%
Ages 1-4 yrs	5213	73	2188	48
Ages 5-11 yrs	1684	23	1710	38
Ages 12-17 yrs	258	4	635	14

Figure 1. Study cohort illustrating application of inclusion and exclusion criteria and treatment groups.

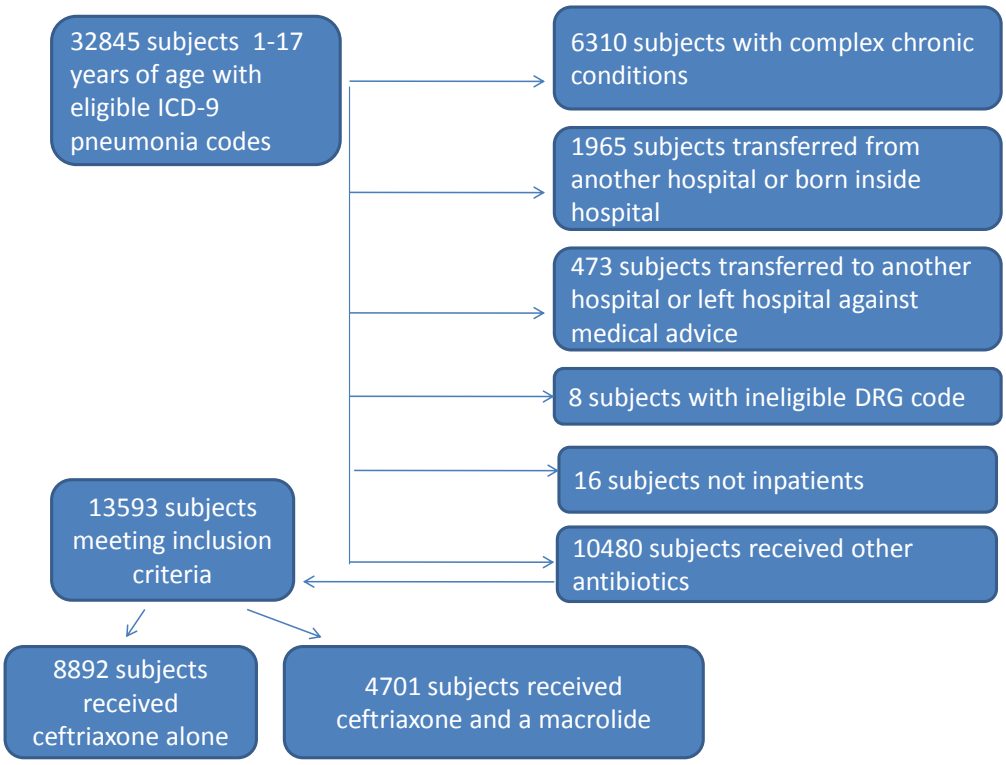

Table 4. Patient and hospital characteristics and initial management among children with pneumonia treated with ceftriaxone alone relative to those treated with ceftriaxone in combination with a macrolide.

	Ceftriaxone alone (n=8892)		Ceftriaxone + macrolide (n=4701)		p-value
Patient Characteristics	n	%	N	%	
Gender (% male)	4814	54.1	2574	54.8	0.49
Age, yrs (median,IQR)	3 (1-5)		5 (2-8)		<0.0001
1-4 yrs	6308	70.9	2282	48.5	<0.0001
5-17 yrs	2584	29.1	2419	51.5	
Race/ethnicity					
White	4414	49.6	2325	49.5	0.0001
Black	1644	18.5	751	16.0	
Hispanic	1178	13.2	723	15.4	
Other	1656	18.6	902	19.2	
Insurance status					
Public payer	4605	51.8	2238	47.6	0.0001
Private payer	3839	43.2	2210	47.0	
Uninsured	327	3.7	191	4.1	
Unknown	121	1.4	62	1.3	
Admission during respiratory season	5877	66.09	2972	63.22	0.0008
Comorbid conditions					
Asthma	3605	40.5	2268	48.2	<0.0001
Influenza	455	5.1	210	4.5	0.09
Fluid and electrolyte disorders	2649	29.8	1149	24.4	<0.0001
Hospital Characteristics					
Urban (vs rural)	6993	78.6	3711	78.9	0.69
Teaching status (vs non-teaching)	3289	37.0	1517	32.3	<0.0001
Bedsize					
<=200 beds	1656	18.6	1001	21.3	<0.0001
201-400 beds	3781	42.5	1708	36.3	
400+ beds	3455	38.9	1992	42.4	
Region					
Northeast	1206	13.6	538	11.4	<0.0001
Midwest	1703	19.2	888	18.9	
West	1092	12.3	754	16.0	
South	4891	55.0	2521	53.6	
Children's hospital (vs general community hospital)	1996	22.4	1135	24.1	0.03
Initial Investigations					
Blood culture	6881	77.4	3629	77.2	0.80
Chest x-ray	7363	82.8	3928	83.6	0.27
Chest ultrasound	13	0.1	7	0.1	0.97
Chest CT	48	0.5	46	1.0	0.003
Arterial blood gas	226	2.5	166	3.5	0.001

Acute phase reactants (ESR or CRP)	1493	16.8	872	18.5	0.01
Urine culture	1404	15.8	570	12.1	<0.0001
Lumbar puncture	43	0.5	5	0.1	0.0004
Test for viral pathogens	3177	35.7	1706	36.3	0.52
Initial Adjunctive Therapies					
IV or oral steroids	2610	29.4	1892	40.3	<0.0001
Short-acting beta-agonists	4966	55.9	3047	64.8	<0.0001
Intravenous fluids	5533	62.2	3225	68.6	<0.0001
Chronic asthma medications	1184	13.3	960	20.4	<0.0001
Intensive care unit admission	245	2.8	199	4.2	<0.0001
Non-invasive ventilation	46	0.52	23	0.49	0.83
Intubation and ventilation	11	0.12	6	0.13	0.95

Table 5. Primary and secondary outcomes among patients receiving pneumonia treatment with ceftriaxone alone compared to cefriaxone with addition of a macrolide, stratified by age group.

Outcome	Ceftriaxone alone (n=8892)	Ceftriaxone + macrolide (n=4701)	p-value
Ages 1- 4 years			
Length of stay, days (mean, SD) Median (IQR)	2.37 (1.51) 2 (1-3)	2.43 (1.61) 2 (1-3)	0.19
Total hospital costs, USD (mean, SD) Median (IQR)	$3691 (3354) $2949 (2051-4355)	$4328 (3689) $3356 (2263-5210)	<.0001
Transfer to intensive care unit >= day 2 (n, %)	35 (0.8%)	7 (0.4%)	0.14
Inpatient mortality (n, %)	1 (0.01%)	0 (0%)	0.57
All cause < 30 d readmission (n, %)	58 (0.9%)	24 (1.1%)	0.58
Pneumonia-related <30 d readmission (n, %)	41 (0.7%)	19 (0.8%)	0.37
Ages 5-17 years			
Length of stay, days (mean, SD) Median (IQR)	2.60 (1.72) 2 (2-3)	2.48 (1.56) 2 (1-3)	0.02
Total hospital costs, USD (mean, SD) Median (IQR)	$4173 (3874) 3258 (2191-4896)	$4306 (5330) 3366 (2328-4979)	0.03
Transfer to intensive care unit >= day 2 (n, %)	26 (1.3%)	13 (0.7%)	0.71
Inpatient mortality (n, %)	0 (0%)	1 (0.04%)	0.30
All cause < 30 d readmission (n, %)	28 (1.1%)	16 (.7%)	0.10
Pneumonia-related <30 d readmission (n, %)	12 (0.5%)	11 (0.6%)	0.96

Table 6. Characteristics of children 1-4 years of age included in the propensity-score matched cohort.

Patient Characteristics	Ceftriaxone alone (n=2281) n	%	Ceftriaxone + macrolide (n=2281) N	%	p-value
Gender (% male)	1250	54.8	1232	54.0	0.59
Race/ethnicity					
White	1140	50.0	1031	45.2	<0.001
Black	396	17.4	378	16.6	
Hispanic	336	14.7	420	18.4	
Other	409	17.9	452	19.8	
Insurance status					
Public payer	1235	54.1	1263	55.4	0.37
Private payer	943	41.3	902	39.5	
Uninsured/unknown	103	4.5	116	5.1	
Admission during respiratory season	1525	66.9	1479	64.8	0.15
Comorbid conditions					
Asthma	1142	50.1	1161	50.9	0.57
Influenza	107	4.7	100	4.4	0.62
Fluid and electrolyte disorders	561	24.6	529	23.2	0.27
Hospital Characteristics					
Urban (vs rural)	1732	48.9	1808	51.1	<0.001
Teaching status (vs non-teaching)	759	33.3	646	28.3	<0.001
Bedsize					
<=200 beds	522	22.9	465	20.4	0.04
201-400 beds	808	35.4	789	34.6	
400+ beds	951	41.7	1027	45.0	
Region					
Northeast	199	8.7	212	9.3	0.18
Midwest	468	20.5	422	18.5	
West	398	17.4	374	16.4	
South	1216	53.3	1273	55.8	
Children's hospital (vs general community hospital)	515	22.6	598	26.2	<0.01
Initial Investigations					
Blood culture	1739	76.2	1794	78.7	0.05
Chest x-ray	1913	83.9	1958	85.8	0.06
chest image	10	0.4	11	0.5	0.83
Chest ultrasound	3	0.1	5	0.2	0.48
Chest CT	7	0.3	6	0.3	0.78
Arterial blood gas	74	3.2	72	3.2	0.87

Acute phase reactants (ESR or CRP)	374	16.4	408	17.9	0.18
Urine culture	302	13.2	288	12.6	0.54
Lumbar puncture	1	0.0	2	0.1	0.56
Test for viral pathogens	970	42.5	1057	46.3	<0.001
Initial Adjunctive Therapies					
IV or oral steroids	983	43.1	1026	45.0	0.20
Short-acting beta-agonists	1587	69.6	1576	69.1	0.72
Intravenous fluids	1625	71.2	1652	72.4	0.37
Chronic asthma medications	494	21.7	546	23.9	0.07
Intensive care unit admission	89	3.9	105	4.6	0.24
Non-invasive ventilation	9	0.4	11	0.5	0.65
Intubation and ventilation	4	0.2	4	0.2	1

Table 7. Characteristics of children and adolescents 5-17 years of age included in the propensity-score matched cohort.

Patient Characteristics	Ceftriaxone alone (n=2224) n	%	Ceftriaxone + macrolide (n=2224) N	%	p-value
Gender (% male)	1199	53.912	1238	55.665	0.24
Age, yrs					
5-11 yrs	1906	85.7	1635	73.5	<0.0001
12-17 yrs	318	14.3	589	26.5	
Race/ethnicity					
White	1193	53.6	1187	53.4	0.07
Black	407	18.3	351	15.8	
Hispanic	248	11.2	279	12.5	
Other	376	16.9	407	18.3	
Insurance status					
Public payer	985	44.3	884	39.7	<0.001
Private payer	1117	50.2	1213	54.5	
Uninsured/unknown	122	5.5	127	5.7	
Admission during respiratory season	1426	64.1	1377	61.9	0.13
Comorbid conditions					
Asthma	985	44.3	1011	45.5	0.43
Influenza	118	5.3	110	4.9	0.59
Fluid and electrolyte disorders	653	29.4	572	25.7	<0.01
Hospital Characteristics					
Urban (vs rural)	1738	49.5	1775	50.5	0.17
Teaching status (vs non-teaching)	816	36.7	819	36.8	0.93
Bedsize					
<=200 beds	449	20.2	419	18.8	0.45
201-400 beds	905	40.7	904	40.6	
400+ beds	870	39.1	901	40.5	
Region					
Northeast	279	12.5	309	13.9	<0.0001
Midwest	391	17.6	430	19.3	
West	265	11.9	353	15.9	
South	1289	58.0	1132	50.9	
Children's hospital (vs general community hospital)	492	22.1	508	22.8	0.57
Initial Investigations					
Blood culture	1637	73.6	1652	74.3	0.61
Chest x-ray	1786	80.3	1803	81.1	0.52

chest image	33	1.5	38	1.7	0.55
Chest ultrasound	6	0.3	1	0.0	0.06
Chest CT	27	1.2	37	1.7	0.21
Arterial blood gas	64	2.9	57	2.6	0.52
Acute phase reactants (ESR or CRP)	426	19.2	419	18.8	0.79
Urine culture	290	13.0	277	12.5	0.56
Lumbar puncture	3	0.1	3	0.1	1
Test for viral pathogens	528	23.7	584	26.3	0.05
Initial Adjunctive Therapies					
IV or oral steroids	698	31.4	748	33.6	0.11
Short-acting beta-agonists	1264	56.8	1283	57.7	0.56
Intravenous fluids	1437	64.6	1422	63.9	0.64
Chronic asthma medications	328	14.7	375	16.9	0.05
Intensive care unit admission	61	2.7	78	3.5	0.14
Non-invasive ventilation	12	0.5	11	0.5	0.83
Intubation and ventilation	3	0.1	1	0.0	0.32

Table 8. Adjusted and unadjusted models for length of stay and total hospital costs among children treated with ceftriaxone in addition to a macrolide relative to ceftriaxone alone.

	Length of stay		**Total hospital cost**	
Ages 1-4 years	Relative Risk (95% CI)	p-value	Cost Ratio (95% CI)	p-value
Unadjusted	1.00 (0.97, 1.03)	0.88	1.08 (1.05, 1.11)	<0.0001
Covariate adjusted	0.98 (0.95, 1.01)	0.31	1.04 (1.01,1.07)	<0.01
Propensity score & covariate adjusted	0.99 (0.96, 1.02)	0.38	1.04 (1.01,1.07)	<0.01
Propensity score matched*	1.02 (0.99, 1.05)	0.32	1.07 (1.03, 1.10)	<.0001
Ages 5-17				
Unadjusted	0.96 (0.93, 0.99)	0.01	1.03 (0.99, 1.06)	0.12
Covariate adjusted	0.95 (0.92,0.98)	<0.01	1.01 (0.98, 1.04)	0.60
Propensity score & covariate adjusted	0.95 (0.92, 0.98)	<0.01	1.01 (0.98, 1.04)	0.55
Propensity score matched**	0.96 (0.93, 0.99)	<0.01	1.01 (0.98,1.04)	0.62

* Adjusted for unbalanced covariates which included race, urban/rural hospital location, hospital teaching status, hospital bed size, hospital type, and tests for viral respiratory pathogens

** Adjusted for unbalanced covariates which included age group, insurance status, hospital geographic region and disorders of fluids and electrolytes

Figure 2. Adjusted and unadjusted models for length of stay and total hospital costs among children treated with ceftriaxone in addition to a macrolide relative to ceftriaxone alone.

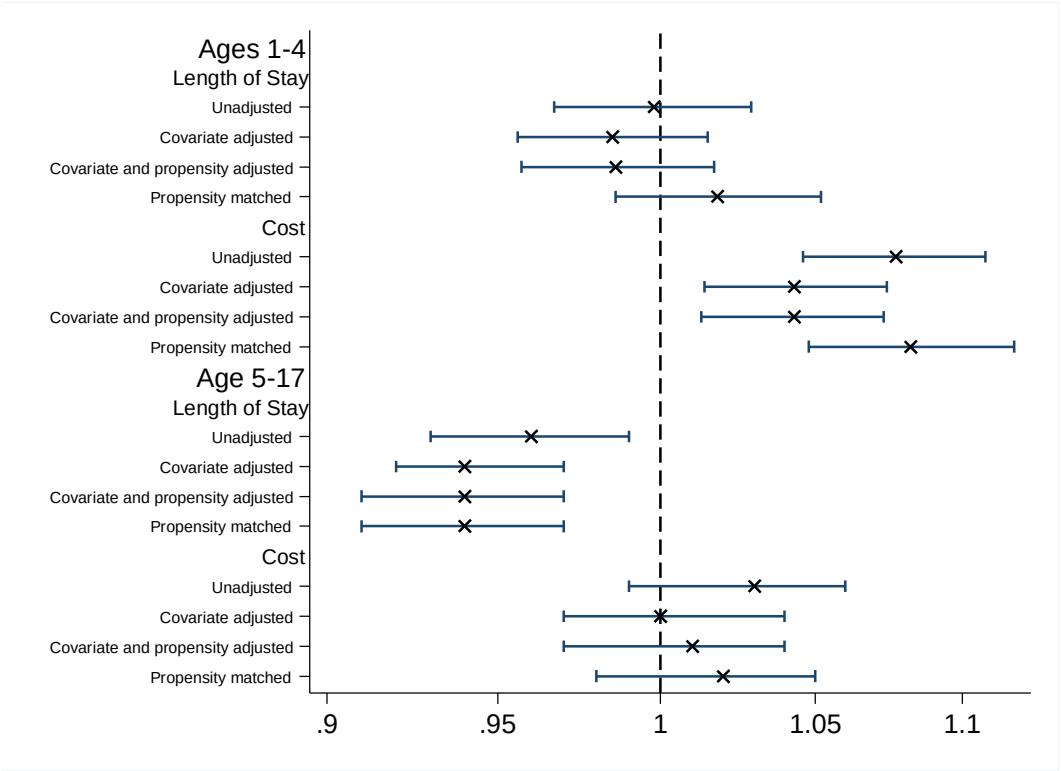

Figure 3. Distribution of propensity scores among subjects who received ceftriaxone alone and ceftriaxone in combination with a macrolide by age strata. Figure A illustrates the strata of children 1-4 yers of age in our cohort, and B illustrating the strata of children 5-17 years of age.