Antibiotic Resistance and Prescribing in Children Hospitalized with Community-Acquired Pneumonia

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This thesis is dedicated to Luis, Lilliam, Luis, Millicent, Xavier, and Jennifer Ambroggio and Barry and Genevieve Campbell. Thank you for inspiring me to become the scholar I've always wanted to be and for helping me laugh throughout the process.

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Abstract

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Lilliam Vanessa Ambroggio

Pneumonia causes more deaths in children under 5 years old worldwide than malaria, AIDS and measles combined. Community-acquired pneumonia occurs annually in about 4 million children under 5 years old in the United States and is typically caused by *Streptococcus pneumoniae*. Substantial variability exists in the management of this disease. The variability in the management of pediatric pneumonia is due to all aspects of the disease, including but not limited to the numerous agents that cause the disease, the lack of a gold standard diagnostic test and the lack of national guidelines regarding treatment. This variability in treatment has resulted in the use of unnecessarily broad spectrum antibiotics leading to more resistant organisms becoming more prevalent in the community. The prevalence of penicillin resistance in *S. pneumoniae* has increased over the past decade, but penicillin is found to be still effective clinically in treating nonsusceptible pneumococci. Accredited hospitals in the U.S. document antibiotic susceptibility patterns of *S. pneumoniae* and it is unclear whether the hospital-reported susceptibility patterns influence the clinician's prescribing patterns. It is also unknown if prescribing broader spectrum antibiotics to patients have similar outcomes to patients who are prescribed narrower spectrum antibiotics, for instance penicillin alone. This research examines the variability that exists in managing pediatric pneumonia by using

existing data from 20,000 patients collected from over 30 tertiary care children's hospitals across the United States.

Chapter 1: Literature review of pediatric community acquired pneumonia

1.1 INTRODUCTION

Community-acquired pneumonia occurs annually in about 156 million children under 5 years old, worldwide. In the United States alone, approximately 4 million children are diagnosed with pneumonia resulting in greater than 150,000 hospitalizations each year in the United States, with approximately 60,000 attributable to *Streptococcus pneumoniae* [1-3]. Empiric therapy is the most common way to treat pediatric pneumonia as the causative agent is usually unknown due to the difficulty of specimen collection. As a consequence, there is substantial variability in empiric therapy.

CAP is a highly treatable disease. Typically, treatment decisions are made based on clinical manifestations of the disease present in the patient and the known epidemiology of potential pathogens that exist in the community. Substantial variability exists in the management of pediatric CAP due to all aspects of the disease, such as the numerous agents that can cause CAP, the lack of a gold standard diagnostic test, and the lack of national guidelines for the management of childhood pneumonia. Tools such as hospital antibiograms were created to disseminate information on drug resistant pathogens, either bacterial or viral, that have been isolated in the hospital. This information can guide the physician with the decision of which treatment to administer. The actual influence of hospital antibiograms in guiding prescribing practices has not been well described or quantified in the literature.

The aim of this review was to present the most recent epidemiology, etiology, and diagnostic findings for childhood pneumonia with a specific focus on antibiotic prescribing practices.

1.2 EPIDEMIOLOGY

Community-acquired pneumonia (CAP) can be defined as "the presence of fever, acute respiratory symptoms, or both, plus evidence of parenchymal infiltrates [change in soft tissue in the lung] on chest radiography" due to microbial agents acquired outside of the hospital [4, 5]. Pneumonia accounts for 20% of mortality in children worldwide [6]. In developing countries the incidence of pneumonia is tenfold higher than in developed countries; 70% of these deaths occur in sub-Saharan Africa and South East Asia [7, 8]. The annual incidence of pneumonia in children under 5 in the U.S. ranges from 20 to 55 cases per 1000 and 16 to 22 cases per 1000 for children 5 years or older [6].

In developed countries less than 1% of pediatric CAP cases are fatal, but morbidity associated with CAP can be quite substantial [9]. CAP is estimated to account for 3-18% of all pediatric admissions into hospitals in the developed world [10]. Morbidity associated with CAP may be measured by "length of symptoms, time off school and, for those admitted to hospital, time in hospital, duration of oxygen requirement, numbers requiring intensive care and time to recovery as well as complications of the disease and of the treatment" [10]. Certain risk factors, such as children who are predisposed to respiratory tract infections (children with asthma or cystic fibrosis), immunocompromised patients , sickle cell disease, malignancy, or who were born with congenital anomalies lead to a more complicated form of the disease [6].

1.3 ETIOLOGY

The etiology of CAP is difficult to obtain on an individual-level basis therefore physicians depend on etiological studies that have been stratified by the age of the child **(TABLE 1)**. The majority of CAP cases in newborns (birth to 20 days of age) are caused by group B streptococci, gram negative enteric bacteria, cytomegalovirus, *Listeria monocytogenes,* or herpes simplex virus acquired perinatally. In infants (21 days to 3 months of age), CAP is typically caused by *Chlamydia trachomatis*, different respiratory viruses (e.g. respiratory syncytial virus, influenza A or B, parainfluenza viruses 1, 2, and 3, and adenovirus), *bordetella pertussis,* or *staphylococcus aureus*. In young children (3 months to 5 years) and school-aged children (5 to 15 years), the most typical bacterial cause of CAP is *Streptococcus pneumoniae* and, less commonly, respiratory viruses, *Haemophilus influenzae, Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* [4, 6, 7]. Tuberculosis, although a relatively uncommon cause in all age groups, is also considered a potential cause in endemic areas [11]. The etiology of pneumonia is also highly influenced by seasonal patterns, with influenza being more common as a causative agent in winter months [9, 11]. The leading bacterial cause of pneumonia in all age groups, with the exception of newborns, is *Streptococcus pneumoniae* [4, 9].

Of one hundred eighty-four immunocompetent children, ages 2 months to 17 years (median: 33 months), who were admitted to Children's Medical Center in Dallas, TX for CAP, 60% of these children were found to have typical respiratory bacteria as the causative agent; 73% of these bacterial cases were caused by *Streptococcus pneumoniae.* In addition 23% of the overall cases were found to be caused by mixed bacterial and viral infections [12]. A similar study conducted in children hospitalized for pneumonia in Finland, found that 37% of the total cases (n=254) with ages ranging from 1 month to

children older than 5 years old were infected with *S. pneumoniae* and only 7% were infected *Mycoplasma pneumoniae* [13].

Although there has been a 90% reduction in the incidence of invasive pediatric pneumonia and a 23% reduction of non-invasive pediatric pneumonia due to bacterial pathogens, specifically *S. pneumoniae,* since the introduction of heptavalent pneumococcal vaccine (PCV-7) licensed in 2000 [6, 9], *S. pneumoniae* still causes 17,000 cases annually of invasive disease in children under 5 years old in the U.S. which results in about 200 fatalities [6]. In addition more resistant strains of bacterial pneumonia continue to pose a problem especially as more antibiotics are introduced into the community to treat these bacterial agents [12].

1.4 DIAGNOSTICS

Determining the etiology of pneumonia for children is difficult in practice. Less than 10% of children with pneumonia have live bacteria present in the blood stream, limiting the effectiveness of blood cultures as a diagnostic. In addition the majority of children do not produce enough sputum to test, "and there are no definitive tests that are noninvasive and accurate" [4, 10, 12]. For instance, testing bacterial antigens generally lacks sensitivity and specificity, and bacterial antibodies in children are "either absent (in the case of nontypable *H. influenzae* and *Moraxella catarrhalis*) or severely limited (*S. pneumoniae*)" [4]. Invasive procedures such as lung punctures or thoracentesis where fluid or air is removed from the pleural space in the lung are reserved for very severe cases of pneumonia. The definitive determination of the etiology of pediatric pneumonia is generally reserved for children who are hospitalized with a severe case of pneumonia who are not responding to empirical therapy [10]. For the majority of pediatric CAP

patients, clinicians diagnose patients based on their symptoms and their chest radiography findings [4].

Chest radiography determines the presence and "the location of a pulmonary infiltrate in all children with suspected CAP evaluated in the emergency department as well as those requiring hospitalization" [1]. It is important to note that chest radiographs do not distinguish between viral or bacterial pathogens [4]. Even though the intraobserver agreement for pediatric radiologists in detecting presence or absence of pneumonia was found to be good (Kappa statistic=0.87; 95% CI 0.60-0.99), the interobserver agreement for pediatric radiologists was less convincing (kappa=0.51, 95% CI: 0.39-0.64) [14]. These results suggest that chest radiographs cannot be used exclusively in determining care of for pediatric pneumonia patients. The resulting care for these patients is largely determined by the clinical manifestations of the disease and the subsequent decisions made by the attending physician.

The clinical presentation of pneumonia includes dyspnea, shallow or grunting respirations, "the sudden onset of fever, cough, and tachypnea [abnormally fast breathing]" [1, 9]. The distinction between a viral and bacterial pathogen-causing pneumonia can be less evident upon examination. Bacterial pneumonia is characterized by tachypnea, crackling noises and hard breathing heard upon physical examination[1]. Viral pneumonia is suspected when wheezing is present, but children with asthma but not viral pneumonia may present with similar symptoms thereby masking the true etiology of the pneumonia [1, 12].

Patients with asthma receive different empiric therapy than patient without asthma possibly because of this difficult separation of asthma-related symptoms and pneumonia-

related symptoms. Recently different phenotypes and risk factors have been shown to be associated with three different "types" of wheezing in children between ages 2-6 years old has been found. The first type "early wheezing" is defined as having been diagnosed with one lower respiratory tract infection (LRTI) with presentation of wheezing in the first 2 years of life and having no wheezing in the previous 12 months, the second type is "persistent wheezing" which is defined as one LRTI with wheezing in the first 2 years of life and presenting with wheezing in the past 12 months, and the third type is labeled "late onset wheezing" which is defined as no LRTI during the first 2 years of life and wheezing present in the last 12 months[15]. The fact that the risk factors are different for the three types of wheezing (e.g. maternal asthma being a substantial risk factor for children with persistent wheezing, but less so for the other types)[15], could be due to different etiologies that caused their initial LRTI, further confounding the relationship between asthma, wheezing and pneumonia even further. Once CAP is diagnosed and the pathogen is suspected to be bacterial, either typical or atypical, empiric therapy is administered.

1.5 TREATMENT

Currently there are no official national guidelines in the United States for prescribing empiric therapy for CAP, however some antibiotics are more commonly recommended by various organizations, such as the World Health Organization (WHO) and the British Thoracic Society (BTS) **(Table 1)** [1, 4, 16]. Typically penicillin derivatives (e.g. ampicillin, amoxicillin, or penicillin) which are part of the beta-lactam class (which also include cephalosporins, such as cefuroxime, ceftriaxone, and ceftaxime), are considered to be the best first line therapy for CAP as it is highly effective against *S.*

pneumoniae, the most likely pathogen [6]. Macrolides such as azithromycin, clarithromycin, or erythromycin, are generally recommended in addition to a beta-lactam to treat patient who present with wheezing, a sign of an atypical infection. Broad spectrum antibiotic coverage, such as beta-lactam and macrolide combination therapy, risks exposing the patient to additional toxic drug effects and increases the risk for antibiotic resistance in the community. Although beta-lactam monotherapy and in certain cases beta-lactam and macrolide combination therapy are recommended across published guidelines, the amount and quality of evidence to support these recommendations in children with CAP is limited[5].

Few comparative effectiveness studies have been done specifically in children. These studies generally have found no statistical difference in length of stay or clinical failure between the use of beta-lactam monotherapy and beta-lactam and macrolide combination therapy however may be underpowered to find a true difference in outcomes (**Table 2**). These studies range from 116 to 893 patients. Stratification by therapy reduces the numbers to as few as 24 patients per therapy group. In addition to small sample sizes, these studies also vary in the characteristics of their study populations, including age, ambulatory versus outpatient settings, and even country of origin.

There are significantly more comparative effectiveness studies done in the adult population and many time clinicians review the results from these studies to guide empiric prescribing in children. There is much less agreement between studies in the adult population **(Table 2)**. While some studies have found a decrease in 30 day mortality when treating patients with beta-lactam and macrolide combination therapy when compared to beta-lactam monotherapy, others have not [17-22]. These varying results

in adults could be due to the heterogeneity of inclusion criteria among the various studies, including differences in patient age, study setting (i.e., community- or long-term care facility-dwelling), and presence of comorbid conditions. Although these studies are used to inform prescribing practices in children, they are not directly generalizable to the pediatric population. It is also unknown the degree to which empirically selecting antibiotic and the side effects of the antibiotics affect the clinical outcome of children with pneumonia [1].

There are side effects to all antibiotic therapies, judiciously prescribed or not, which vary in severity and can include "anaphylaxis, organ toxicity, serum sickness, Stevens Johnson syndrome [a serious disorder where the skin and mucous membranes of the patient develop a painful rash that spreads and blisters, killing that layer of skin], Clostridium difficile colitis [bacterial infection that can cause inflammation of the colon], and the promotion of antibiotic resistance" [6]. Non-judicious prescribing of antibiotics, such as prescribing broad spectrum antibiotics (a beta-lactam and a macrolide) when a narrow spectrum antibiotic (a beta-lactam therapy alone) would be as effective, can increase the risk of not only antibiotic resistance, but also the financial cost to the patient for medications, length of stay in the hospitals, general resource utilization and likelihood of developing *Clostridium difficile colitis*[11]. In general it has been estimated that about 50% of all antibiotic use is inappropriate and pathogens are becoming resistant to antibiotics faster than new antibiotics can be developed to target these pathogens [6]. Currently the research agenda for Centers for Disease Control and Prevention and the National Institute of Allergy and Infectious Diseases is focused on developing new

antibiotics and promoting partnerships between physicians, health departments and parents to diminish the unnecessary prescribing of broad spectrum antibiotics [23].

1.6 ANTIBIOTIC RESISTANCE

In the United States, hospitals create an annual antibiogram which is "a periodic summary of antimicrobial susceptibilities of local bacterial isolates submitted to the hospital's microbiology laboratory" [24]. Antibiograms are required to be done in order to be accredited by the Joint Commission on Accrediation of Healthcare Organizations (JCAHO) as a quality assurance measure [25, 26]. These accredited hospitals create antibiograms on organisms in specimens that have been obtained at the hospital's microbiology laboratory and are required to make these antibiograms available to their staff [27]. These antibiograms are distributed to physicians within the hospital to aid them in their choice of empiric antibiotic therapy as well as to aid the hospitals in tracking trends of antibiotic resistance over time.

The antibiograms report the minimum inhibitory concentration (MIC) for each drug and organism combination. MIC "is the lowest concentration of drug necessary to inhibit growth of a particular organism" [6]. MIC is usually determined by putting a range of concentrations of a particular antibiotic (usually doses that are therapeutically available) on each organism [28]. MIC therefore determines the *in vitro* level of drug resistance for that specific organism which does not always correspond directly to the *in vivo* levels.

There are some antibiotics, for instance, that are still effective against organisms *in vivo* that have a high MIC *in vitro* (i.e. organisms that are considered resistant to the antibiotic). For instance, penicillin resistant *S. pneumoniae* has occurred due to "genetic

alterations in the affinity of *S. pneumoniae* penicillin binding proteins", but high-doses of penicillin, amoxicillin or ampillicin are still effective against this organism and have been shown to be safe to use [6]. The prevalence of penicillin resistance among pneumococci has increased in the past decade. In adults penicillin has been shown to still be effective in treating nonsusceptible *S. pneumoniae* [29]. Yu et al. suggests that *in vitro* resistance does not necessarily correlate to *in vivo* resistance thereby decreasing the necessity of using an antibiotic other than penicillin or an equivalent antibiotic in the beta-lactam class. If other antibiotics are being commonly used to treat CAP caused by *S. pneumoniae* then there is a greater risk that the organism will develop resistance to these drugs. As a consequence more nonsusceptible strains will exist and greatly limit the number of effective antibiotics that can be used. For instance, it has been reported that macrolide-resistant *S. pneumoniae* has increased in the past decade [30]. The emerging resistance of *S. pneumoniae* to two different antibiotic classes is alarming. An important factor for physicians and health departments to take into account when prescribing antibiotics is the regional antibiotic susceptibility patterns, but it is unclear how antibiograms are used in hospital settings in dictating prescribing practices [31]. It has been noted that antibiograms should not be used alone to select optimal empiric therapy as other individual-level patient information is needed; such as severity of the disease, causative agent if known, patient medical history and prior antibiotic use [24].

1.7 CONCLUSION

Community-acquired pneumonia is a treatable childhood disease with several treatment options. The variability in treatment may exist for multiple reasons. These reasons include the limited number of comparative antibiotic therapy studies done in

children and the unknown effectiveness of tools, such as antibiograms, in guiding empiric antibiotic prescribing. Further studies are needed in these areas to standardize prescribing practices and to reduce broad spectrum antibiotic resistance in the community.

TABLES

Table 1: Recommended empiric therapy in published guidelines for children with community-acquired pneumonia[a]		
Author or Society (Year)	First-line therapy	Second-line therapy
World Health Organization (2009)	Amoxicillin	Amoxicillin-clavulanic acid with or without macrolide
South African Thoracic Society (2005)	Amoxicillin, Ampicillin, Aminoglycoside, Macrolide,	Second or third generation cephalosporin, Amoxicillin-clavulanic acid
Brazilian Society of Pediatrics (2004)	Amoxicillin, Ampicillin, penicillin, second or third generation cephalosporin	Amoxicillin-clavulanic acid, macrolide
Canadian Medical Association (1997)	Amoxicillin, Macrolide, second generation cephalosporin	Third generation cephalosporin

[a] Table modified from Nascimento-Carvalho, CM.[16]

Table 2: Summary of epidemiologic studies of empiric antibiotic therapy in patients with community-acquired pneumonia

Author (Year)	Patient Population	Study Design	Number of Patients	Antibiotic Exposure	Outcome Measurement	Main Conclusion
Kogan et al. (2003)[32]	Children (1mo-14 years) Pakistan	Randomized Control Trial	47 Bacterial Pneumonia 59 Atypical bacterial pneumonia	Bacterial: azithromycin (n=23) or amoxicillin (n=24) Atypical: azithromycin (n=33) or erythromycin (n=26)	No fever or improvement of 75% or more on X-ray examination on day 7	1.Azithromycin and amoxicillin behaved similarly in cases with bacterial pneumonia, both had 100% clearage on x-ray at day 14 2. Azithromycin and amoxicillin behaved similarly in atypical bacterial cases except azithromycin had slightly better clearage on x-ray at day 14 (100% vs. 81%, p-value 0.059)
Aurangzeb et al. (2003)[33]	Children (3mos-6 years) Chile	Randomized Control Trial	124 children	Amoxicillin (n=43) cefuroxime (n=41) clarithromycin (n=42)	Clinical outcome: no clinical improvement after 48 hours of treatment LOS	1. Amoxicillin was found to be the most cost effective in treating non-severe and severe CAP. 2. No statistical difference in median LOS (3 days) or in clinical outcome between the three therapies.

Table 2 (continued): Summary of epidemiologic studies of empiric antibiotic therapy in patients with community-acquired pneumonia

Author (Year)	Patient Population	Study Design	Number of Patients	Antibiotic Exposure	Outcome Measurement	Main Conclusion
Zhang et al. (2008)[34]	Children (29 days-12 years) Brazil	Retrospective Cohort	893 children	Penicillin, cephalosporin and "other" monotherapies Combination therapy (unclear what antibiotics this includes)	Antibiotic failure (initial antibiotic was changed 72 hours or more after no clinical improvement was shown) LOS	1. In an unadjusted comparison, empiric antibiotic therapy failed in 43 cases or 4.8%. 2. No statistically significant difference in mean LOS (p-value=0.08)

Table 2 (continued): Summary of epidemiologic studies of empiric antibiotic therapy in patients with community-acquired pneumonia

Author (Year)	Patient Population	Study Design	Number of Patients	Antibiotic Exposure	Outcome Measurement	Main Conclusion
Gleason et al. (1999)[22]	Adults (≥65 years old) Medicare patients in US	Retrospective Cohort	9751 community-dwelling adults 3194 long-term facility adults	Penicillin, 1st, 2nd, 3rd-generation cephalosporin, macrolides, and fluroquinolones	30 day mortality 30 day readmission LOS	1. 77% higher likelihood of 30 d mortality when treated with a beta-lactam and macrolide combination therapy compared to a non-pseudonomal 3rd-generation cephalosporin, but beta-lactam alone not associated with greater mortality 2. No regimen was independently associated with decreased rehospitalization, and only aminoglycoside plus another agent was associated with an increased rehospitalization rate. 3. No regimen was significantly associated with a shorter LOS

Table 2 (continued): Summary of epidemiologic studies of empiric antibiotic therapy in patients with community-acquired pneumonia

Author (Year)	Patient Population	Study Design	Number of Patients	Antibiotic Exposure	Outcome Measurement	Main Conclusion
Dudas et al. (2000)[20]	Children and adults (1-105 years old) AmeriNet patients in US	Prospective Cohort	2963	Non-severe CAP: 2nd or 3rd-generation cephalosporin or beta-lactam with or without macrolide Severe CAP in ICU: Macrolide and 3rd generation cephalosporin with antipseudonomal activity	Mortality LOS	1. Patients who received 2nd or 3rd generation cephalosporin monotherapy or beta-lactam with a macrolide are independently associated with a decreased probability of mortality. (OR: 0.4; 95% CI: 0.2 to 0.8) 2. Patients who received 2nd or 3rd generation cephalosporin monotherapy or beta-lactam with a macrolide are independently associated with a decreased LOS (p-value: 0.0003).

Table 2 (continued): Summary of epidemiologic studies of empiric antibiotic therapy in patients with community-acquired pneumonia

Author (Year)	Patient Population	Study Design	Number of Patients	Antibiotic Exposure	Outcome Measurement	Main Conclusion
Houck et al. (2001)[19]	Adults (≥ 65 years old) Medicare, US	Retrospective Cohort	10,069	1. Monotherapy with beta-lactam (2^{nd}, 3^{rd}, 4^{th} cephalosporin) 2. Macrolide monotherapy 3. Fluroquinolone monotherapy 4. Fluroquinolone + beta-lactam combination therapy 5. Any other antibiotic 6. beta-lactam + macrolide combination therapy	30 day mortality	1. No statistical difference in 30 d mortality between patients who received beta-lactam and macrolide combination therapy to patients who received beta-lactam monotherapy in the adjusted model.

Table 2 (continued): Summary of epidemiologic studies of empiric antibiotic therapy in patients with community-acquired pneumonia

Author (Year)	Patient Population	Study Design	Number of Patients	Antibiotic Exposure	Outcome Measurement	Main Conclusion
Brown et al. (2003)[21]	Adults (> 18 years) HBSI database, US	Retrospective Cohort	44814	25,996 received monotherapy (ceftriaxone, macrolides, fluorinated quinolones, other cephalosporins, penicillin) 18,818 received dual therapy (ceftriaxone + macrolide, fluorinated quinolones + macrolide, other cephalosporins + macrolide, penicillin + macrolide)	LOS Cost of hospital charges 30 day mortality rate	1. Penicillin was statistically similar in LOS for monotherapy and dual therapy. 2. Increased 30 day mortality in patient who received penicillin monotherapy compared to dual therapy. 3. Ceftriaxone and macrolide generally had shortest LOS, lowest hospital charges, and no statistical difference in 30 day mortality.

Table 2 (continued): Summary of epidemiologic studies of empiric antibiotic therapy in patients with community-acquired pneumonia

Author (Year)	Patient Population	Study Design	Number of Patients	Antibiotic Exposure	Outcome Measurement	Main Conclusion
Lodise et al. (2007)[18]	Adults (≥ 65 years old) Veterans Integrated Services Network 2, US	Retrospective Cohort	515	Extended beta-lactam monotherapy Extended beta-lactam and macrolide combination therapy	14 day mortality 30 day mortality	1. No statistical difference in mortality at either 14 day or 30 day between monotherapy and dual therapy in patients who had a PSI of IV or lower (i.e. non severe pneumonia). 2. Combination therapy significantly reduced 14 day and 30 day mortality in patients who had a PSI class of V (i.e. severe pneumonia).

Table 2 (continued): Summary of epidemiologic studies of empiric antibiotic therapy in patients with community-acquired pneumonia

Author (Year)	Patient Population	Study Design	Number of Patients	Antibiotic Exposure	Outcome Measurement	Main Conclusion
Bratzler et al. (2008)[17]	Adults (≥ 65 years old) Medicare, US	Retrospective Cohort	27,730	1. Macrolide 2. Fluoroquinolone 3. beta-lactam 4. Aminoglycosides 5. 2nd generation cephalosporin 6. 3rd generation cephalosporin 7. Other 8. Macrolide and Cephalosporin 9. Fluoroquinolone and Cephalosporin 10. Macrolide and beta-lactam	30 day mortality	1. Fluoroquinolone monotherapy and cephalosporin plus a macrolide combination therapy significantly decreased 30d mortality in patients with severe pneumonia (PSI class IV or V). 2. No statistical difference in 30 d mortality in non-severe pneumonia cases, regardless of empiric therapy.

Chapter 2: Comparative effectiveness of beta-lactam monotherapy and beta-lactam- macrolide combination therapy in children hospitalized with community-acquired pneumonia

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2.1 ABSTRACT

Objective: To determine the comparative effectiveness of beta-lactam monotherapy and beta-lactam and macrolide combination therapy on clinical outcomes in the treatment of children hospitalized with community-acquired pneumonia (CAP).

Methods: A retrospective cohort study was conducted using the Pediatric Health Information System (PHIS) database during 2006-2008. Associations between empiric antibiotic therapy and hospital readmission for the same episode of pneumonia were estimated using logistic regression. Associations between empiric antibiotic therapy and length of hospital stay were estimated using a negative binomial generalized estimating equation. Potential confounders such as age, principal payer, asthma status, and severity of illness were considered.

Results: There were 20,743 patients hospitalized with CAP. Of these, 24% received beta-lactam and macrolide combination therapy upon admission. Compared to children who received beta-lactam monotherapy, children who received beta-lactam and macrolide combination therapy were 20% less likely to stay in the hospital an additional day (RR: 0.80; 95% CI: 0.75, 0.86) but did not have a different readmission rate (RR: 0.68; 95% CI: 0.42, 1.09). The effect of combination treatment on reducing LOS is stronger with increasing patient age.

Conclusion: Patients hospitalized with CAP who receive beta-lactam and macrolide combination therapy have a shorter length of stay and similar rates of readmission when compared to patients who receive beta-lactam monotherapy.

2.2 INTRODUCTION

Community-acquired pneumonia (CAP) is a common and serious infection in children, resulting in greater than 150,000 hospitalizations each year in the United States, with approximately 60,000 attributable to *Streptococcus pneumoniae* [2, 3]. Wide variations in antimicrobial prescribing practices exist for children hospitalized with CAP, partially because the causative organism is rarely identified in clinical practice. Empiric treatment is therefore prescribed based on the predicted pathogens as assessed by the child's age, clinical presentation upon admission, and local epidemiology of pneumonia-causing pathogens [6]. However, the optimal empiric treatment for children hospitalized with CAP is not known.

Beta-lactam monotherapy is the recommended first-line therapy for children hospitalized with CAP [16, 35]. Beta-lactam therapies are effective against the most common bacterial causes of childhood CAP, including *S. pneumoniae* [11]. Among hospitalized adults and older school-aged children, macrolide therapy is sometimes added to beta-lactam therapy in order to cover atypical pathogens such as *Mycoplasma pneumoniae* [27, 36]. Few studies have compared the effectiveness of beta-lactam monotherapy to beta-lactam and macrolide combination therapy in treating CAP in the pediatric population[20, 32-34].

Published guidelines exist for the management of community-acquired pneumonia in adults; however variability in empiric therapy prescribing is still common, in part because studies have yielded conflicting results [22, 36]. While some studies have found a decrease in 30 day mortality with beta-lactam and macrolide combination therapy compared with monotherapy, others have not [17-22]. These varying results in adults could

be due to the heterogeneity of inclusion criteria among the various studies, including differences in patient age, study setting (i.e., community- or long-term care facility-dwelling), and presence of comorbid conditions. Although these studies are used to inform prescribing practices in children, they are not directly generalizable to the pediatric population.

The objective of this multicenter analysis was to determine the comparative effectiveness of beta-lactam monotherapy compared with beta-lactam and macrolide combination therapy for children hospitalized with CAP. The secondary objective of this study was to determine the comparative effectiveness of narrow- and broad-spectrum antibiotic therapy.

2.3 METHODS

DATA SOURCE

This retrospective cohort study used data obtained from the Pediatric Health Information System (PHIS). PHIS is a national administrative database containing resource utilization from 38 freestanding, tertiary care children's hospitals affiliated with the Child Health Corporation of America (Shawnee Mission, KS). Participating hospitals account for 20% of all tertiary care children's hospitals. For the purposes of external benchmarking, participating hospitals provide discharge data including patient demographics, diagnoses, and procedures. Billing data detail all of the drugs, radiologic imaging studies, laboratory tests, and supplies charged to each patient. Data quality and reliability are assured through a joint effort between Child Health Corporation of America and participating hospitals as previously described [37, 38]. The study protocol was

approved by Institutional Review Boards of The Children's Hospital of Philadelphia and the Drexel University College of Medicine with a waiver of informed consent.

PARTICIPANTS

Children, 1-18 years of age, with CAP were eligible if they were discharged from any participating hospital between January 1, 2006 and December 31, 2008. Subjects were included if they received beta-lactam antibiotics (i.e. penicillin, 2nd and 3rd generation cephalosporins), alone or in combination with macrolides (i.e., erythromycin, clarithromycin, azithromycin) on the first day of hospitalization and if they satisfied one of the following International Classification of Diseases, 9th Revision (ICD-9), discharge diagnosis code criteria: 1) primary diagnosis of pneumonia (ICD-9 codes 481-483.8, 485-486); 2) primary diagnosis of a pneumonia-related symptom (ICD-9 codes 780.6 or 786.00-786.52 [except 786.1]) and a secondary diagnosis of pneumonia, empyema (510.0, 510.9), or pleurisy (511.0, 511.1, 511.9); or 3) primary diagnosis of empyema or pleurisy and a secondary diagnosis of pneumonia.

Children younger than one year of age were excluded because they experience a high rate of viral respiratory infections that are difficult to distinguish clinically from bacterial pneumonia. Patients with comorbid conditions that predisposed them to severe or recurrent pneumonia (e.g. cystic fibrosis, malignancy, sickle cell disease) were excluded using a previously reported classification method [39]. Patients with severe illness at admission were also excluded as these children are likely to require broad-spectrum antibiotics. Severe illness was defined as intensive care admission or receipt of any one of the following on the first day of hospitalization: pleural fluid drainage procedure, vasoactive infusions (dobutamine, dopamine, epinephrine, norepinephrine), blood

product transfusion (packed or washed red blood cells, fresh-frozen plasma, and coagulation factors), invasive (endotracheal intubation) and noninvasive (continuous positive airway pressure) mechanical ventilation.

PATIENT CHARACTERISTICS

Patient characteristics assessed included were age, sex, principal payer, and underlying asthma. We identified children with asthma in two ways. Asthma-related hospitalizations were defined by an ICD-9 code for asthma (493.0-493.2) in any discharge diagnosis field during any prior hospitalization in the 24 months before the current hospitalization. Chronic asthma controller medication use was defined by treatment with inhaled corticosteroids (e.g., fluticasone) or leukotriene receptor antagonists on the first day of hospitalization for CAP, which suggested that these medications were a continuation of baseline therapy. Other medications prescribed for asthma included beta-agonist (i.e. albuterol) therapy or systemic corticosteroids on the first day of their hospitalization. Systemic corticosteroids (either oral or intravenous) were defined by receipt of dexamethasone, hydrocortisone, methylprednisolone, prednisolone, or prednisone. Testing of arterial blood gases and additional radiologic imaging on the first day of hospitalization were included as measures of illness severity. Additional radiologic imaging included receiving chest computed tomography or ultrasound.

TREATMENT MEASURES

The primary exposure of interest was empiric antibiotic therapy, classified as beta-lactam monotherapy or a beta-lactam plus a macrolide (i.e., combination therapy). A subanalysis was performed among subjects comparing individual antibiotic categories for

monotherapy (i.e. penicillin or aminopenicillins, 2nd generation cephalosporin or 3rd generation cephalosporins) and for combination therapy (i.e., penicillin or aminopenicillin in combination with macrolide, 2nd generation cephalosporin in combination with macrolide, and 3rd generation cephalosporin in combination with a macrolide).

OUTCOME MEASURES

The main outcome measures were hospital length of stay (LOS) and readmission within 14 days of the index hospital discharge. LOS was defined as the discharge date minus the admission date. We chose 14-day readmissions because readmissions after initial discharge for pneumonia beyond this time frame are typically not related to pneumonia [40].

DATA ANALYSIS

Continuous variables were described using median, range, and interquartile range (IQR) values and were compared across groups using the Wilcoxon rank sum test. Categorical variables were cross-tabulated by treatment groups and differences tested using the chi-square statistic.

Graphical analysis of LOS showed positive skew. The distribution of LOS was compared using Poisson and negative binomial distributions. When fit to the data, the negative binomial distribution had the lowest Quaslikelihood Information Criterion (QIC) indicating a better fit [41]. Further assessment of overdispersion indicated that the true variance was larger than the mean, confirming overdispersion and the use of negative binomial regression [41-43]. Because patient LOS is correlated within hospitals a generalized estimating equation (GEE) was used to account for this in standard error estimates. The

negative binomial regression model produces the log of expected counts of days stayed in the hospital which are used to estimate a length of stay ratio (by exponentiation of the beta coefficient) of >1 that indicates an association with a longer LOS on average. These estimates can be thought of a ratio of probability ratios of staying one more day in the combination therapy group compared to monotherapy. Interaction terms between age and antibiotic therapy and asthma and antibiotic therapy were tested as these variables might modify the effect of therapy on LOS. These interaction terms remained in the final models if the interaction terms were statistically significant with p-value determined a priori of <0.05 and if their inclusion improved overall model fit (i.e. resulted in a smaller QIC).

Associations between treatment and readmission within 14 days were estimated using logistic regression models. Potential confounders, such as age, sex, principal payer, and asthma status remained in the model if their inclusion changed the effect estimate of the empiric therapy by greater than ≥10% [44, 45]. These variables were analyzed as they have been previously shown to be significantly associated with empiric therapy and hospital LOS or hospital readmission [3, 46, 47]. Interaction terms were not tested in the readmission models as there were few readmission events. All statistical analyses were performed using SAS statistical software (version 9.2, SAS Institute Inc, Cary, N.C.).

2.4 RESULTS

PATIENT CHARACTERISTICS

A total of 20,743 patients hospitalized with CAP during the study period received beta-lactam therapy, alone or in combination with a macrolide. Beta-lactam monotherapy was given to 15,809 (76%) of children while beta-lactam and macrolide combination

therapy was given to the remaining 4934 (24%) children (**Table 3**). Patients receiving beta-lactam monotherapy were similar in respect to sex and prior hospitalization for asthma when compared with patients who received combination therapy **(Table 4)**.

LENGTH OF HOSPITAL STAY

The median LOS for the total cohort was 2 days (IQR: 2-3 days); 10% of patients had a LOS of 6 days or greater. The median LOS was 2 days (IQR: 2-4 days) for patients who received beta-lactam monotherapy and 2 days (IQR: 1-3 days; p=0.057) for patients who received beta-lactam and macrolide combination therapy. Results are presented for the unadjusted model and fully adjusted model in **Table 5**. In the adjusted analysis, patients who received combination therapy were on average 20% less likely to stay an additional day in the hospital when compared with patients who received monotherapy as empiric treatment for their episode of CAP (**Table 5**). No significant differences in LOS were found when comparing individual antibiotics among those who received monotherapy and individual combinations among those who received combination therapy (**Table 5**).

Interaction between combination therapy and age was found to be statistically significant (p-value <0.001). Children ages 12-18 years old who were treated with combination therapy were 31% less likely to stay one extra day in the hospital compared to children 12-18 years, who received monotherapy. Children ages 1-5 years old who received combination therapy were only 4% less likely to stay in the hospital one extra day when compared to children, 1-5 years, who received monotherapy. As shown in Table 6 the effect of combination therapy on reduced LOS is stronger with increasing patient age.

HOSPITAL READMISSION

Readmission within 14 days of index hospital discharge occurred in 0.5% of those who received beta-lactam monotherapy and in 0.6% of those who received beta-lactam and macrolide combination therapy. Odds of readmission within 14 days of index hospitalization were reduced among those receiving combination therapy compared with those receiving monotherapy; however this difference was not statistically significant **(Table 7)**. A subanalysis was conducted among patients who received beta-lactam monotherapy as empirical treatment. In the adjusted analysis, the probability of readmission within 14 days of index hospitalization was not statistically different between patients receiving either 2nd or 3rd generation of cephalosporin when compared with patients receiving aminopenicillin alone **(Table 7)**. The confidence intervals around the odds ratio estimated in the subanalysis were wider. This is most likely due to the small number of readmission events once the analysis was stratified by receipt of monotherapy (n=91) and may bias our results toward the null. None of the interaction terms tested met our criteria for inclusion in the final model.

2.5 DISCUSSION

In this multicenter study, patients who received beta-lactam and macrolide combination therapy had a significantly shorter LOS compared with patients who received beta-lactam monotherapy. The magnitude of the effect for combination therapy in reducing LOS was greater in children ≥ 6 years old compared with children 1-5 years. However, among the individual therapies there was no significant difference in LOS. Beta-lactam and macrolide combination therapy resulted in reduced hospital readmission within 14 days of index discharge but the association was not statistically significant.

No prior studies have compared the effectiveness of beta-lactam monotherapy to beta-lactam and macrolide combination therapy in children. In our study older children receiving combination beta-lactam and macrolide therapy had a shorter LOS compared with those receiving beta-lactam monotherapy. There was less of a reduction in LOS in younger children, ages 1-5, who received combination therapy compared with younger children who received monotherapy. These findings suggest a role for the addition of macrolide-class antibiotics in older children hospitalized with community-acquired pneumonia. The benefit may be explained by the higher prevalence of *Mycoplasma pneumoniae* and other atypical bacteria in older children with pneumonia [5].

There are two randomized, unblinded, controlled trials conducted that compared beta-lactam monotherapy to macrolide monotherapy [5, 32, 33]. These two studies found that children who were treated with amoxicillin (a penicillin derivative similar to aminopenicillin) had similar cure rates to those children who were treated with a macrolide therapy [32, 33]. However, both of these studies had small sample sizes (47 children in one study[32] and 87 in the other[33]) and it is unclear how the treatments were allocated [5]. In one study older children were disproportionately given macrolide therapy [32]. Although these studies support the use of beta-lactam monotherapy , these studies had too few participants to identify specific populations or subpopulations that might benefit from either monotherapy or combination therapy.

There are several limitations to our study. First we used ICD-9 discharge diagnosis codes to identify study patients with pneumonia. We attempted to limit misclassification of a pneumonia diagnosis by using a previously validated ICD-9 coding algorithm [48-51]. Additionally we restricted the study to those who on the first day of their

admission received antibiotics that are typically used to treat CAP. Our inability to ascribe the cause of pneumonia to a particular organism mirrors clinical practice where the causative organism is rarely identified.

Second, our adjustment for clinical characteristics of an atypical infection (e.g., wheezing) used surrogate measures such as receipt of asthma therapies. Atypical bacteria, such as *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae,* are more common in patients with asthma exacerbations or who present with wheezing [52]. Therefore it is possible that the significant difference in LOS between children who received beta-lactam monotherapy and those who received beta-lactam and macrolide combotherapy was due to inadequate adjustment for patients who were presumed to be infected with an atypical bacterium in which case the addition of a macrolide might be recommended. Although beta-agonists and steroid therapies are specific for treating patients with asthma and/or present with wheezing they may have been administered for alternate reasons in which case we may have underestimated the effect that beta-lactam and macrolide combination therapy had in treating patients with atypical bacterial pneumonia.

Third, despite our attempts to adjust for severity through restriction and multi-variable adjustment, it is possible that residual confounding exists. This study was restricted to children who did not have factors associated with disease severity and complications upon admission, such as admission to the ICU, comorbid conditions, and receipt of a pleural fluid drainage procedure. There is currently no pneumonia severity index available for children therefore additional measures of disease severity were identified based on ICD-9 codes for discharge diagnoses, laboratory tests, procedures,

and radiologic imaging. It is possible that there are other measures of severity that we were unable to restrict or adjust for completely.

Finally, all participants in this study were hospitalized at a free-standing children's hospital. Children typically have longer hospital stays and more expensive hospital stays when admitted to a children's hospital compared with non-children's hospital when controlling for primary diagnosis [53]. Therefore the results from this study are only generalizable to pediatric populations that do not have underlying conditions in addition to their pneumonia diagnosis that are admitted at children's hospitals.

This study is one of the only multicenter comparative effectiveness studies conducted in hospitalized pediatric patients with CAP in a developed country. We found a significant difference in LOS, but no statistical difference in hospital readmission in patients who received beta-lactam monotherapy and in those who received beta-lactam and macrolide combination therapy. These findings suggest the need for a randomized clinical trial comparing beta-lactam and macrolide therapies in treating children hospitalized with CAP to identify populations or subpopulations that benefit from combination antibiotic therapy.

TABLES

Table 3: Patient characteristics by exposure[a]

	Total Cohort (n=20743)	**Monotherapy (n=15809)**	**Combination Therapy (n= 4934)**	**P-value [b]**
Age				
1-5 years	14672 (71)	12008 (76)	2664 (54)	<0.0001
6-11 years	4168 (20)	2633 (17)	1535 (31)	
12-18 years	1903 (9)	1168 (7)	735 (15)	
Sex				
Male	9980 (48)	7597 (48)	2383 (48)	0.7659
Principal Payer				
Government	10227 (49)	7936 (50)	2291 (46)	<0.0001
Asthma				
Prior Hospitalization for Asthma	2689 (13)	2024 (13)	665 (13)	0.2178
Chronic Asthma Medication	3768 (18)	2762 (17)	1006 (20)	<0.0001
Systemic Corticosteroid Medication	7020 (34)	5176 (33)	1844 (37)	<0.0001
Beta Agonist Therapy	11371 (55)	8400 (53)	2971 (60)	<0.0001
Other Variables for Degrees of Disease				
Arterial Blood Gases (ABG)	1436 (8)	1018 (7)	418 (9)	<0.0001
Intensive Imaging	279 (1)	198 (1)	81 (2)	0.0383

[a]Unless otherwise noted, data are expressed in counts (percentages) of patients
[b]P-value obtained via chi-square for categorical variables

Table 4: Empiric antibiotic therapies

Empiric Antibiotic Therapy	**Number of Patients (%)**
Beta-lactam Monotherapy (n=15809)	
Aminopenicillin	1977 (12)
2nd Generation Cephalosporins	2949 (19)
3rd Generation Cephalosporins	10833 (69)
Beta-lactam and Macrolide Combination Therapy (n=4934)	
Aminopenicillin plus Macrolide	359 (7)
2nd Generation Cephalosporin plus Macrolide	677 (14)
3rd Generation Cephalosporin plus Macrolide	3898 (79)

Table 5: Length of stay according to empiric antibiotic therapy

	Unadjusted RR (95% CI)	**Adjusted RR (95% CI)** [a,b,c]
Antibiotic Categories		
Monotherapy	Reference	Reference
Combination Therapy	0.91 (0.87, 0.96)	0.80 (0.75, 0.86)
Monotherapy Therapy		
Aminopenicillin	Reference	Reference
2nd Generation Cephalosporin	1.06 (0.96, 1.17)	1.01 (0.91, 1.12)
3rd Generation Cephalosporin	1.16 (1.05, 1.28)	1.03 (0.94, 1.14)
Combination Therapy		
Aminopenicillin + Macrolide	Reference	Reference
2nd Generation Cephalosporin +Macrolide	1.03 (0.93, 1.15)	1.01 (0.90, 1.13)
3rd Generation Cephalosporin + Macrolide	0.88 (0.77, 1.01)	0.91 (0.79, 1.04)

[a] Results for main analysis were adjusted for age, principal payer, prior hospitalization for asthma, receipt of chronic asthma therapy, systemic corticosteroid medication, beta agonist therapy, testing for arterial blood gases, intensive imaging testing and interaction of therapy and age.
[b] Results for monotherapy subanalysis were adjusted for age, principal payer, prior hospitalization for asthma, receipt of chronic asthma therapy, systemic corticosteroid medication, beta agonist therapy, testing for arterial blood gases, and intensive imaging testing.
[c] Results for combination therapy subanalysis were adjusted for age, principal payer, prior hospitalization for asthma, receipt of chronic asthma therapy, systemic corticosteroid medication, beta agonist therapy, testing for arterial blood gases, and intensive imaging testing.

Table 6: Interaction effect of age and empiric antibiotic therapy on LOS

Age Category	**Adjusted RR (95% CI)** [a,b]
1-5 years	0.96 (0.86, 1.06)
6-11 years	0.85 (0.79, 0.91)
12-18 years	0.69 (0.49, 0.98)

[a] Results are for patients who received combination therapy with monotherapy as the reference category

[b] Results are adjusted for principal payer, prior hospitalization for asthma, receipt of chronic asthma therapy, systemic corticosteroid medication, beta agonist therapy, testing for arterial blood gases, intensive imaging testing

Table 7: Readmission within 14 days of index hospitalization according to empiric antibiotic therapy

	Unadjusted OR (95% CI)	**Adjusted OR (95% CI)** [a, b]
Antibiotic Categories		
Monotherapy	Reference	Reference
Combination Therapy	0.77 (0.49, 1.23)	0.68 (0.42, 1.09)
Monotherapy		
Aminopenicillin	Reference	Reference
2nd Generation Cephalosporin	1.27 (0.73, 2.23)	1.68 (0.93, 3.01)
3rd Generation Cephalosporin	1.07 (0.70, 1.63)	1.31 (0.84, 2.06)

[a] Results for main analysis were adjusted for age
[b] Results for monotherapy subanalysis were adjusted for age, and testing for arterial blood gases

Chapter 3: Antibiotic susceptibility patterns influence on empiric antibiotic prescribing for children hospitalized with community acquired pneumonia

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3.1 ABSTRACT

Objective: A multi-level, random intercept, logistic regression was used to explain the influence of hospital-level pneumococcal penicillin non-susceptibility patterns on individual-level antibiotic prescription using data from 33 children's hospitals.

Patients and Methods : A multi-level cross-sectional study in 33 children's hospitals, among children, 1-18 years of age, with CAP discharged in 2006. Hospital-level antibiotic susceptibility data was collected from surveys and patient-level data was obtained from an administrative database. The primary exposure was the proportion of penicillin non-susceptible pneumococcal isolates reported by each hospital. A secondary exposure included using the proportion of penicillin-resistant pneumococcal isolates to determine if a threshold of susceptibility existed. Receipt of narrow spectrum empiric antibiotic therapy (i.e., penicillins or aminopenicillins) was the main outcome measure.

Results: 5,033 children diagnosed with community-acquired pneumonia (CAP) were eligible. The proportion of penicillin non-susceptible isolates ranged from 9%-70% across hospitals while the proportion of penicillin resistant isolates ranged from 0%-60%. Narrow spectrum antibiotics were prescribed to 7% of patients; 41% of patients received cephalosporin class antibiotics alone. There was no significant association between the proportion of penicillin nonsusceptible pneumococcal isolates at individual hospitals and narrow spectrum prescribing. However, every 10% increase in penicillin-resistant pneumococcal isolates was associated with a 28% decrease in narrow spectrum antibiotic prescribing (adjusted odds ratio, 0.72; 95% confidence interval: 0.56-0.88).

Conclusion: There was substantial variability in empiric antibiotic prescribing for CAP among children's hospitals in the U.S. High- (i.e., resistant) but not modest-levels (i.e.,

intermediate susceptibility) of penicillin resistance were associated with broad spectrum antibiotic prescribing.

3.2 INTRODUCTION

Antibiotic resistance is a major public health problem. Infections caused by drug-resistant bacteria lead to worse clinical outcomes than infections caused by susceptible bacteria [54]. Furthermore, the rise of antibiotic resistant organisms has rapidly limited the availability of effective therapies for some infections [54]. Therefore, reducing antibiotic resistance is a major focus of many national and international organizations [23, 54, 55]. Improving antibiotic prescribing practices is an important part of the global strategy to reduce antibiotic resistance. Studies aimed at improving antibiotic prescribing, including encouraging narrower spectrum antibiotic prescribing, have traditionally focused on persuasive (e.g., educational) or restrictive (e.g., formulary restriction) interventions [56]. These approaches, while often successful, yield only modest improvements in prescribing practices.

Hospital "antibiograms," bacteria-specific antimicrobial susceptibility profiles, are often used to support the need for *improving* antibiotic prescribing practices. However, antibiograms may also be used to *influence* antibiotic prescribing [57]. Antibiograms are disseminated to physicians by hospitals at varying intervals, though usually at the end of each calendar year. These antibiograms are based on Clinical and Laboratory Standards Institute (CLSI) breakpoints,[58] the minimum inhibitory concentration (MIC) cut-off values that determine the level at which an organism is susceptible to specific antibiotics. The categories, susceptible, intermediate, and resistant, correspond to the likelihood of successful or unsuccessful *in vitro* inhibition of bacterial growth [58, 59]. Physicians use antibiograms to guide empiric prescribing of broad spectrum antibiotics for common infections. In some cases, breakpoints are altered to better align

with clinical outcomes. For example, the CLSI changed the breakpoints for *Streptococcus pneumoniae*, the most common bacterial cause of community-acquired pneumonia (CAP), in 2008 after studies demonstrated that narrow spectrum antibiotics, such as penicillin and aminopenicillins, were effective in treating non-central nervous system (CNS) pneumococcal infections even when classified as non-susceptible *in vitro* [59]. The proportion of pneumococcal isolates now reported as "susceptible" to penicillin has increased as a result of the change, however, the impact of hospital antibiograms on antibiotic prescribing for community-acquired infections is not known.

The aim of this multicenter study was to determine the association between pneumococcal penicillin susceptibility testing results, as reported by hospital antibiograms, and physicians' prescribing practices for children hospitalized with CAP. We used antibiograms incorporating 2005 pneumococcal susceptibility patterns, as these antibiograms would be available to physicians when prescribing antibiotics for CAP in 2006.

3.3 METHODS

Study Design And Data Sources

This multi-level cross-sectional study used hospital-level data collected from surveys and patient-level data obtained from an administrative database. The Pediatric Health Information System (PHIS) was used to identify hospitals that contributed group-level data and was used to gather prescribing information for patient-level data. PHIS is a national administrative database containing resource utilization from 38 freestanding, tertiary care children's hospitals affiliated with the Child Health Corporation of America (Shawnee Mission, KS). Participating hospitals account for 20% of all tertiary care

children's hospitals. For the purposes of external benchmarking, participating hospitals provide discharge data including patient demographics, diagnoses, and procedures. Billing data detail all of the drugs, radiologic imaging studies, laboratory tests, and supplies charged to each patient. Data quality and reliability are assured through a joint effort between Child Health Corporation of America and participating hospitals as previously described [37, 38]. The study protocol was approved by Institutional Review Boards of The Children's Hospital of Philadelphia and the Drexel University College of Medicine.

Group-level Data. Hospital-level antibiotic susceptibility patterns for *S. pneumoniae* were determined via written surveys sent to the microbiology laboratories of each hospital. The surveys requested information regarding antibiotic susceptibility patterns for pneumococcal isolates tested in 2005 in aggregate and, when available, by specific site (i.e., blood isolates, respiratory isolates). The cutpoints were defined using MICs for *S. pneumoniae* susceptibility as established by the CLSI for 2005 as follows: $\leq$0.06 mcg/mL, susceptible; 0.12-1.0 mcg/mL, intermediate; and $\geq$2.0 mcg/mL, resistant[9]. An isolate was considered non-susceptible if it was classified as either intermediate or resistant.

Individual-level Data. Patient-level information for the calendar year 2006 was retrieved from the PHIS database. Children, 1-18 years of age, with CAP were eligible if they were discharged from any participating hospital between January 1 and December 31, 2006. Subjects were included if they received antibiotic therapy on the first day of hospitalization and if they satisfied one of the following International Classification of Diseases, 9th Revision (ICD-9), discharge diagnosis code criteria: 1) Primary diagnosis of

pneumonia (ICD-9 codes 481-483.8, 485-486); 2) Primary diagnosis of a pneumonia-related symptom (ICD-9 codes 780.6 or 786.00-786.52 [except 786.1]) and a secondary diagnosis of pneumonia, empyema (510.0, 510.9), or pleurisy (511.0, 511.1, 511.9); or 3) Primary diagnosis of empyema or pleurisy and a secondary diagnosis of pneumonia. Only patients receiving antibiotics considered conventional treatment for childhood CAP (i.e. penicillin, macrolide, cephalosporin, vancomycin, and clindamycin) on the first day of hospitalization were included.

We identified children with asthma in two ways. Asthma-related hospitalizations were defined by an ICD-9 code for asthma (493.0-493.2) in any discharge diagnosis field during any prior hospitalization in the 24 months before the current hospitalization. Chronic asthma controller medication use was defined by treatment with inhaled corticosteroids (e.g., fluticasone) or leukotriene receptor antagonists on the first day of hospitalization for CAP, which suggested that these medications were a continuation of baseline therapy.

Data from five of the thirty-eight hospitals were excluded because of incomplete patient-level information (n=3) or an incomplete antibiogram was returned (n=2). Children younger than one year of age were excluded because they experience a high rate of viral respiratory infections that are difficult to distinguish clinically from bacterial pneumonia. Patients with comorbid conditions that predisposed them to severe or recurrent pneumonia (e.g. cystic fibrosis, malignancy, sickle cell disease) were excluded using a previously reported classification scheme [39].

MEASURED EXPOSURES

The primary exposure of interest was the proportion of penicillin *non-susceptible* pneumococcal isolates reported by each hospital. Secondary exposures included using the proportion of penicillin-*resistant* pneumococcal isolates to determine if a threshold of susceptibility existed, as well as restricting the exposures to blood or respiratory penicillin non-susceptible pneumococcal isolates as these isolates were more likely than aggregated isolates to represent invasive disease.

Measured Outcomes

The primary outcome was the receipt of empiric narrow spectrum antibiotic therapy (i.e., penicillin or aminopenicillins).

Data Analysis

Categorical variables were described using frequencies and percentages. Chi-square analysis was used to compare the between hospital distribution of individual level variables.

We used multi-level, random intercept, logistic regression to explain the influence of hospital-level penicillin non-susceptible pneumococcal patterns on individual-level antibiotic prescription for several reasons. First, the observations are not independent as patients admitted to the same hospital are similar in regards to both their exposure and outcome, precluding a simple logistic regression (rather than multi-level) modeling approach. Second, the variability within and between hospitals in the PHIS database is of interest and a generalized estimating equation (GEE) (rather than random effects) approach would treat the heterogeneous patient population in each hospital as a nuisance factor [60]. Third, the inference with a random-effects model is made for a specific patient in a specific hospital while the inference with a GEE approach results in a population

effect averaged over all the hospitals. The population average inference of the GEE approach does not allow for interpretation of the influence from the complex heterogeneities that exist between hospitals [61, 62].

The first model, considered the 'empty' model, contained the random-intercept only and no other predictor variables. This model accounted for the probability of receiving penicillin or aminopenicillin alone only as a function of which hospital the patient attended. The second model, an extension of the 'empty' model, added the proportion of penicillin non-susceptible pneumococcal isolates. The proportion of penicillin non-susceptible pneumococcal isolates was grand-mean centered at 52% (standard deviation [SD]: 11.4) [63]. This model determined the amount of variance explained by the addition of susceptibility patterns reported from each hospital. In the additional sub-analyses, the exposures were grand-mean centered at 26% (SD: 15.1) for penicillin-resistant *S. pneumoniae*, 43% (SD: 15.3) for penicillin-nonsusceptible *S. pneumoniae* blood isolates, and 54% (SD: 13.9) for penicillin nonsusceptible *S. pneumoniae* respiratory isolates.

The third model tested individually the inclusion of potential effect modifiers, age and asthma status. These interaction terms, determined *a priori*, remained in the model if the main effect of non-susceptible pneumococcal patterns and aminopenicillin prescribing changed by 10% or more [64]. The models were compared using Akaike's information criterion (AIC) [65]. The model with the smallest AIC was chosen. Other variables describing the severity of illness (e.g. empyema) were not considered as either confounders or effect modifiers, as severity of illness for CAP rather than hospital-

reported antibiotic susceptibility patterns likely determine broad spectrum antibiotic prescribing [11].

The median odds ratio (OR) was calculated to quantify the heterogeneity between different hospitals. The median OR, calculated using the variance of the hospitals in each model, is the median value of the ORs when comparing all possible pairs of patients with similar covariates admitted to different hospitals [66, 67]. A median OR equal to 1 indicates that there is no difference between hospitals in the probability of receiving narrow spectrum antibiotics and a median OR larger than 1 indicates large variation in the probability of receiving narrow spectrum antibiotics between hospitals. This measure is not dependent on the prevalence of narrow spectrum antibiotic prescribing and can therefore be compared with future studies. All statistical analyses were performed using SAS statistical software (version 9.2, SAS Institute Inc, Cary, N.C.).

3.4 RESULTS

HOSPITAL-LEVEL EXPOSURE

Hospitals reported the percentage of pneumococcal isolates tested in 2005 that were susceptible to penicillin, overall and, when available, by specific site (i.e., blood isolates, respiratory isolates) (**Table 8**).

PATIENT CHARACTERISTICS

There were 5,033 patients from 33 hospitals. The median age of this cohort was 3 years (interquartile range: 2-7). Narrow spectrum antibiotic therapy was prescribed to 349 (7%) of the 5,033 children with CAP. Patients who received a narrow spectrum antibiotic were younger and more likely to have a prior asthma-related hospitalization than those receiving empiric broad spectrum antibiotic therapies (**Table 9**).

Variability in Antibiotic Prescribing

Commonly used antibiotics were classified into 7 categories based on their spectrum of antibacterial activity to describe hospital-level variability in antibiotic prescribing (**Figure 1**). Overall, 41% (n=2224) of all the patients received cephalosporins as empiric therapy for CAP; cephalosporins were also the most commonly prescribed antibiotic within each hospital. One exception was a hospital where penicillins or aminopenicillins alone were prescribed at a much higher rate, 57%, compared with other hospitals, in which penicillins or aminopenicillin alone accounted for 6% of the total proportion of antibiotics prescribed for CAP during the study period.

Association of Resistance and Prescribing

In the adjusted analysis there was no association between the proportion of penicillin-non-susceptible pneumococcal isolates and narrow spectrum antibiotic prescribing, either overall or when restricted to blood or respiratory isolates (**Table 10**). However, the association between the proportion of penicillin-*resistant* pneumococcal isolates and narrow spectrum antibiotic prescribing was significant; patients were 28% less likely to receive narrow spectrum antibiotics for every 10% increase in penicillin-resistant pneumococcal isolates (**Table 10**). The interaction effects did not meet the inclusion criteria and, therefore, were not included in the final models.

One of the hospitals was unique in its prescribing practices (**Figure 1**) and its inclusion increased the variance component in the models. There was no association between proportion of penicillin non-susceptible *S. pneumoniae* isolates and narrow spectrum prescribing when this hospital was excluded (adjusted OR: 0.94; 95 % confidence interval: 0.73, 1.21) but the overall fit of the model improved (AIC with the

outlier was 2171.8 versus 2011.1 without the outlier). This finding indicates that some, but not all, of the variability between hospitals is due to this hospital which had a disproportionate amount of narrow spectrum antibiotic prescribing.

The median OR for penicillin non-susceptible isolates, overall and site-specific, indicated large variability between hospitals in narrow spectrum prescribing (**Table 11**). In contrast, there was much less variability between hospitals in the probability of prescribing narrow spectrum antibiotics when adjusting for penicillin-resistant pneumococcal isolates; on average a patient had 1.62 higher odds of receiving a narrow spectrum antibiotic solely based on which hospital they were admitted. By comparing the median OR of the different models it can be deduced that the variability in prescribing practices between hospitals decreases significantly when adjusting for the proportion of penicillin-resistant *S. pneumoniae* isolates.

3.5 DISCUSSION

This multicenter study found substantial variability in empiric antibiotic prescribing for CAP among children's hospitals in the U.S. High- (i.e., resistant) but not modest-levels (i.e., intermediate susceptibility) of penicillin resistance were associated with broad spectrum antibiotic prescribing. As narrow spectrum antibiotics effectively treat most non-CNS pneumococcal infections, our findings suggest that strategies to optimally align antibiotic susceptibility patterns and clinical outcomes can lead to meaningful decreases in broad spectrum antibiotic prescribing.

The degree of variability in empiric therapy prescribing for CAP in this study is similar to prior studies investigating general antibiotic prescribing [68]. In our study, broad spectrum antibiotics were more commonly prescribed as empiric therapy for CAP than

narrow spectrum antibiotics, such as penicillin. This is in contrast to recommended first line therapy for a child who is hospitalized with CAP, even in hospitals with reported penicillin non-susceptible *S. pneumoniae* [69]. Studies in adults[29] and children[70] demonstrated that *in vitro* resistance did not correlate with *in vivo* resistance for non-CNS pneumococcal infections, thereby decreasing the necessity of using an antibiotic other than penicillin. Findings such as these informed the CLSI decision to change the breakpoints in 2008 to better mirror the clinical effectiveness of penicillin for non-CNS pneumococcal infections [71]. Our study supports the rationale behind the decision of the CLSI, as we found an association between penicillin resistance and penicillin prescribing.

The Centers for Disease Control and Prevention reported that the number of non-meningitis pneumococcal isolates categorized as resistant decreased from 10.3% to 1.2% using the 2008 CLSI breakpoints [59]. Given that only high levels of resistance seemed to influence prescribing practices, this relatively low level of resistance under the new breakpoints should influence physicians to prescribe narrow spectrum antibiotics to treat *S. pneumoniae*. In previous studies, however, clinicians typically used antibiograms to prescribe broader spectrum empiric therapy and continued broad spectrum antibiotic therapy even when the bacteria were identified as susceptible to narrower spectrum antibiotics [72]. This limited use of a potentially powerful tool contributes to the public health problem of antibiotic resistant bacteria.

CLSI determined breakpoints by reviewing the MICs, the pharmacokinetic and pharmacodynamic information for each antimicrobial/pathogen combination, and the data from clinical trials or well documented case series [73]. The site from which the isolate originates (e.g. blood, respiratory secretions, CNS) is not always taken into account when

developing the breakpoints. Therefore the breakpoints do not always accurately reflect the potency of the antimicrobial in inhibiting the growth of the infecting pathogen at those specific sites of infection.

CLSI breakpoints that define the interpretative categories in antibiograms must align with clinical outcomes as they influence the choice of empiric therapy. Antibiograms are known to overestimate drug resistance in the community and prompt broad spectrum prescribing. Urinary tract infections, predominantly caused by *Escherichia coli,* are example of how breakpoints determined *in vitro* may contribute to broad spectrum antibiotic prescribing [74]. This "false" equating of drug resistance with clinical treatment failure promotes a culture of broad spectrum antimicrobial prescribing for pathogens that are otherwise susceptible to narrower spectrum drugs in clinical settings. Urinary tract infections, however, also offer an opportunity for intervention whereby aligning *in vitro* susceptibility results with clinical outcomes could encourage narrower spectrum antibiotic use.

This study had several limitations. First, there is no information on the patients from whom these isolates were obtained and reported in the antibiograms. Variability in reported susceptibility patterns across hospitals may be due in part to the differences in the underlying patient populations [57]. Antibiograms may overestimate community-level resistance because isolates are obtained from patients with specific indications for invasive testing and from patients with chronic medical conditions and consequently greater antibiotic exposure. Better measures of community-level resistance and better diagnostic tests to identify the cause of CAP in the emergency department or hospital settings are needed.

Second, we assumed that the proportion of resistant or non-susceptible pneumococcal isolates reported by each hospital was the only measure that was disseminated to physicians and, consequently, influencing their prescribing practices. The outlier hospital in our study reported 46% of pneumococcal isolates to be nonsusceptible to penicillin, however this hospital had the highest proportion of aminopenicillin prescribing, 69%, when compared to the other hospitals. Therefore there are other determinants that affect antimicrobial prescribing which include hospital policies to direct prescribing (e.g. formulary restriction or prior authorization required), the preference of antibiotic in each subspecialty, the dynamic and expertise of the team of health professionals providing care [75].

Third, the use of ICD-9 codes to identify patients with CAP may result in misclassification of the disease. However, the ICD-9 codes used in this study are similar to previous studies that have shown a relatively high sensitivity and specificity for identifying CAP compared with medical record review [30, 31]. Additional criteria that likely increased the specificity of these algorithms included restriction of the cohort to those receiving antibiotics conventionally used to treat CAP in children on the first day of hospitalization and exclusion of children with comorbid conditions. Children who received something other than conventional antibiotics made up less than 7% (n=369) of the original cohort. While this approach may have lead to the exclusion of some previously healthy children with CAP, such as those with delayed recognition of CAP, these exclusions likely have a negligible influence on the overall estimates produced from this analysis. Fourth, this study was limited to freestanding children's hospitals. The results, therefore, may not be generalizable to other healthcare settings.

Lastly, limitations exist in the use of multi-level analysis. The fixed variables available for this analysis may not have accounted for all the different factors that drive a physician's prescribing practice (i.e. the patient's medical history). However, these unmeasured variables are by default incorporated into the random intercept in the model and could also explain some of the variability that was seen in the model [62].

In conclusion, high levels of resistance reported in an antibiogram were associated with broad spectrum empiric antibiotic therapy. This finding supports a strategy of better aligning antibiotic susceptibility reports and clinical outcomes to reduce broad spectrum antibiotic prescribing. Future studies using data after the CLSI breakpoints changed in 2008 need to be conducted to confirm these findings.

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TABLES

Table 8: Variability in proportion of penicillin-nonsusceptibility in *Streptococcus pneumoniae* across all hospitals[a]

Main Exposure	**Hospital Reported Data (No.)**	**Median (%)**	**Interquartile Range (%)**	**Range (%)**
Penicillin-nonsusceptible *S. pneumoniae*				
All isolates	33	52	46-60	9-70
Blood isolates	17	48	37-54	14-69
Respiratory isolates	14	56	48-65	4-72
Penicillin-resistant *S. pneumoniae*				
All isolates	20	25	18-30	0-60

[a]All numbers in table are the median percentages of the hospitals

Table 9: Characteristics of children hospitalized with community-acquired pneumonia stratified by empiric therapy

Characteristics	**All Patients (N=5033)**	**Narrow Spectrum Antibiotic (N=349)**	**Broad Spectrum Antibiotic (N=4684)**	**P-Value[a]**
Median age (years) (IQR)	3 (2-7)	2 (1-4)	4 (1-7)	<0.0001
Male sex	2734 (54)	196 (56)	2538 (54)	0.5
Asthma status				
Prior asthma hospitalization	644 (13)	61 (18)	583 (12)	0.01
Chronic asthma medication[b]	1040 (21)	92 (26)	948 (20)	0.0064

Data are presented as number (percent) or median (interquartile range).
Abbreviation: IQR, interquartile range.
[a]Compared between Narrow Spectrum and Broad Spectrum Antibiotic
[b]Patients were considered to be on chronic asthma therapy if they received an inhaled steroid or a leukotriene-receptor antagonist on admission.

Table 10: Random-intercept multilevel model predicting the probability of being prescribed aminopenicillin[c]

Exposure	**Unadjusted Odds Ratio (95% CI)**	**Adjusted Odds Ratio[a] (95% CI)**
Penicillin-nonsusceptible *S. pneumoniae*		
All isolates	0.89 (0.67, 1.17)	0.89 (0.60, 1.18)
Blood isolates	1.01 (0.70, 1.48)	1.03 (0.61, 1.44)
Respiratory isolates	0.91 (0.64, 1.31)	0.90 (0.50, 1.30)
Penicillin-resistant *S. pneumoniae*		
All isolates[b]	0.71 (0.61, 0.83)	0.72 (0.56, 0.88)

Abbreviations: CI, confidence interval
[a]Adjusted for age, prior hospitalization for asthma, and chronic asthma medication
[b]The outlier hospital did not report overall resistance and therefore is not included in this model
[c]Odds ratios are given for every 10% change in penicillin-nonsusceptible or resistant pneumococcal isolate

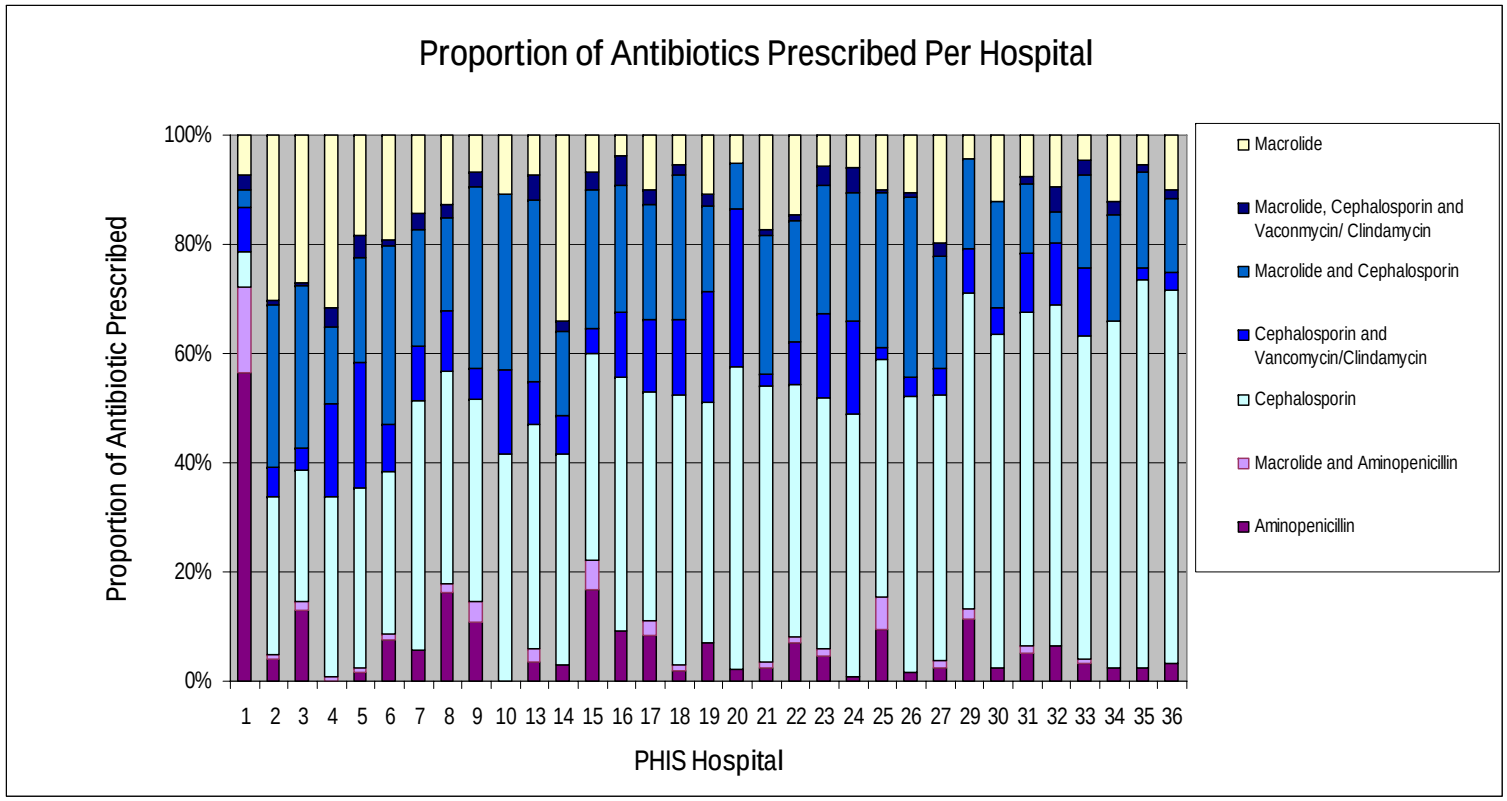
Table 11: Median odds ratio for unadjusted and adjusted models

Exposure	**Unadjusted Median Odds Ratio (95% CI)**	**Adjusted Median Odds Ratio[a] (95% CI)**
Penicillin-nonsusceptible *S. pneumoniae*		
All isolates	2.67 (1.41, 5.04)	2.69 (1.41, 5.13)
Blood isolates	2.98 (1.03, 8.65)	3.04 (1.01, 9.10)
Respiratory isolates	2.98 (0.99, 8.99)	3.05 (0.97, 9.58)
Penicillin-Resistant *S. pneumoniae*		
All isolates[b]	1.71 (1.23, 2.38)	1.67 (1.23, 2.26)

Abbreviations: CI, confidence interval
[a]Adjusted for age, prior hospitalization for asthma, and chronic asthma medication
[b]The outlier hospital did not report overall resistance and therefore is not included in this model

FIGURES

Figure 1. Common antibiotic treatment prescribed per hospital



*Please note that PHIS Hospital number was randomly generated and is not correlated to the hospital numbers in the actual database. Also, hospital numbers 11, 12, and 28 were not included in this graph as discussed in the methods section.

Chapter 4: Conclusions and recommendations

This thesis addressed two significant gaps in the existing literature on childhood pneumonia: 1. limited evidence exists to support the international recommendations for empiric therapy prescribed to children diagnosed with community-acquired pneumonia and 2. limited evidence exists on the true influence of antibiograms (hospital-reported susceptibility patterns) on antibiotic prescribing. These gaps were addressed using information submitted to a national database of freestanding, tertiary care children's hospitals.

Evidence from the comparative effectiveness study conducted for this thesis demonstrates that patients who received beta-lactam and macrolide combination therapy on average had a shorter LOS compared to patients who received beta-lactam monotherapy. Children who were ≥ 6 years had a shorter LOS compared with children 1-5 years old. There were no significant differences in LOS among the individual therapies. In addition, beta-lactam and macrolide combination therapy resulted in reduced hospital readmission within 14 days of index discharge, but the association was not statistically significant.

Antibiograms are associated with broad spectrum (i.e. non-penicillin) prescribing but only when high-levels (i.e. resistant) but not modest-levels (i.e. intermediate susceptibility) of penicillin-resistant *Streptococcus pneumoniae* were reported. This study also demonstrated that substantial variability exists in empiric antibiotic prescribing for CAP among children's hospitals in the U.S. Variability in prescribing is a well-known driver of antibiotic resistance in the community.

Recommendations from these studies are: 1. a randomized control trial is needed to address the benefit of combination therapy among older children; 2. strategies are needed to optimally align antibiotic susceptibility patterns and clinical outcomes as these can lead to meaningful decreases in broad spectrum antibiotic prescribing; and 3. further studies are needed to understand the reasons behind the variability that exists in empiric prescribing practices for childhood pneumonia.

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Appendix A: Detailed study criteria

A1. VALIDATION OF ICD-9CM DISCHARRGE DIAGNOSIS CODES FOR CAP

Errors in coding for hospital discharge records can occur at various points during the process: diagnosing by the physician, medical record keeping, filing the discharge abstract form by the treating physician and the interpretation by the coding clerk [48].Many studies have been conducted evaluating the accuracy of using ICD-9 CM codes in identifying patients with pneumonia **(TABLE 12)**. A study conducted in the Netherlands by van de Garde et al. found that when ICD-9 CM codes were used as the principal diagnosis of patients with pneumonia (ICD-9 CM codes: 481, 482.x, 483.x, 485, and 486) excluding patients who had cystic fibrosis, immunosuppressive conditions, or cancer, there was a sensitivity of 72.4% when the diagnosis was confirmed by microbiological analysis of the causative agent (specificity was not reported in this study) [48]. In a similar study conducted in an adult population who were admitted to the emergency department at a hospital in Utah, three different algorithms were created using combinations of ICD-9 CM codes for pneumonia and/or pneumonia-like symptoms [51]. When only including the most common pneumonia ICD-9 CM codes (Algorithm 1: 480-483 and 485-487.0) for in-patients only, the investigators found a sensitivity of 54.8% and a specificity of 99.1%. The next algorithm included a wider spectrum of ICD-9 CM codes to include more possible cases of pneumonia cases and found a sensitivity and specificity for in patients of 68.3% and 99.0% respectively [51].

The range of ICD-9 CM codes used in this study are not as extensive as those in the second algorithm but are more extensive than the ones stated in the first algorithm, therefore the sensitivity and specificity of this combination of ICD-9 CM codes would most likely be somewhere between 54-68% and 99-99.1% respectively. However these studies did not specifically try to differentiate between community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP). ICD-9 CM codes for pneumonia do not differentiate as to how the pneumonia was acquired.

Whittle et al. and Guevara et al. conducted studies to determine the accuracy of using ICD-9 CM codes in combination with other exclusion criteria in identifying CAP. Patients were included in the Whittle et al. study if they had symptoms compatible with pneumonia with 24 hours of hospital admission and had a chest radiograph performed within 48 hours of admission that confirmed the presence of pneumonia. The exclusion criteria included pneumonia that was diagnosed with 10 days of discharge or if symptoms compatible with pneumonia were diagnosed after the initial 24 hour period of hospitalization or they had a diagnosis code indicating a major trauma or elective surgery as these cases are indicative of HAP. In addition patients were excluded if they had a diagnosis code of HIV/AIDS or organ transplantation as the pneumonia in these patients is clinically distinct from CAP [49]. The sensitivity and specificity of the diagnostic criteria in patients with a principal diagnosis code of pneumonia only was 84% and 86% respectively or a sensitivity and specificity of 89% and 80% respectively if patients had a principal diagnosis code related to pneumonia when cases were confirmed with medical chart reviews [49].

Guevara et al. conducted a study in not only detecting CAP from ICD-9 CM codes but specifically CAP pneumococcal pneumonia caused by *Streptococcus pneumoniae*, the most prevalent cause of pneumonia [50]. This study included adult patients who had no other hospitalization within 30 days of the pneumonia diagnosis and had a chest radiograph taken with 48 hours of admission which was consistent with a diagnosis of pneumonia. The causative agent of pneumonia was confirmed with microbiological findings as indicated in the medical chart review. In general the most sensitive ICD-9 CM code to detect pneumococcal pneumonia was 481.00. However sensitivity was increased when more commonly cited ICD-9 CM codes were used (i.e. 38.00, 38.20, 38.80, 482.30, 486.00 and 518.81)[50].

Table 12: Comparison of ICD-9 Algorithms in identifying patients with pneumonia

Author (Year)	Study Population	Validation Test	ICD-9 Algorithm	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
van de Garde et al. (2007)[48]	293 adult patients discharged from 7 Netherland hospitals	Sputum samples and blood samples for specific etiology	481-483, 485-486	72.4	NR	NR	NR
Whittle et al. (1997)[49]	212 adult patients discharged from Presbyterian University Hospital (US)	Chart review of symptoms compatible with pneumonia present within 24 hours of admission and official reading of chest radiography	NR	89	80	89	NR

Table 12 (continued): Comparison of ICD-9 Algorithms in identifying patients with pneumonia

Author (Year)	Study Population	Validation Test	ICD-9 Algorithm	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Guevara et al. (1999)[50]	4,385 adult patients in 15 acute-care hospitals in Ohio (US)	*Streptococcus pneumonia* isolated from blood or pleural isolates	Group 1: 38.20	8.38	99.95	95.92	88.15
			Group 2: 38.20, 481.00	55.61	97.41	75.91	93.73
			Group 3: 38.20, 481.00, 38.00	60.96	96.97	74.67	94.42
			Group 4: 38.20, 481.00, 38.00, 482.30	72.19	96.05	72.84	95.93
			Group 5: 38.20, 481.00, 38.00, 482.30, 518.81	72.19	96.03	72.71	95.92
			Group 6: 38.20, 481.00, 38.00, 482.30, 518.81, 486.00	85.03	44.53	18.36	95.30

Table 12 (continued): Comparison of ICD-9 Algorithms in identifying patients with pneumonia

Author (Year)	Study Population	Validation Test	ICD-9 Algorithm	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Aronsky et al. (2005)[51]	199 patients admitted in LDS Hospital in Utah (US)	Chart review	Algorithm 1: 480-483	54.8	99.1	84.5	96.1
			Algorithm 2: 480-487.0, 507	68.3	99.0	85.5	97.2
			Algorithm 3: 480-483, 485-487.0, 507	69.8	98.9	84.8	97.3

Table 13 and table 14 describe the ICD-9CM codes that were used to define the cohort for this dissertation.

Table 13: Pneumonia-related ICD-9CM* discharge diagnosis coding used for this dissertation to identify Community Acquired Pneumonia patients

Diagnosis	ICD-9CM Code
Pneumonia	481-483.8, 485-486
Pneumonia-related Symptoms:	
Fever	780.6
Respiratory abnormality, unspecified	786.00
Shortness of breath	786.05
Tachypnea	786.06
Wheezing	786.07
Cough	786.2
Hemoptysis	786.3
Abnormal Sputum	786.4
Chest Pain	786.50
Precordial Pain	786.51
Painful Respiration	786.52
Empyema or pleurisy	510.0, 510.9, 511.0, 511.1, 511.9

**International Classification of Diseases, 9th Revision, Clinical Modification*

Table 14: Summary of Exclusion Criteria in this study	
Diagnosis	**ICD-9CM Code***
Human Immunodeficiency Virus	042
Malignancy	140.x-165.x, 170.x-172.x, 174-175.9, 19.x-208.x
Cystic Fibrosis	277.00, 277.01, 277.02, 277.03, 277.09
Immune Mechanism Disorder	279.00- 279.13,279.19, 279.2, 279.3, 279.4, 279.8, 279.9, 334.8
Sickle Cell	282.60-282.64, 282.68, 282.69
Disease of White Blood Cells	288.00-288.59, 288.8, 288.9
Encounter for Radiation, Chemotherapy	V58.0, V58.11, V58.12
Transplant	V42.0-V42.89
Other Lung Conditions	507.0, 507.1, 507.8, 517.1, 517.2, 517.3, 517.8
Congenital Heart Defects	745.0, 745.10, 745.11, 745.12, 745.19, 745.2, 745.3, 745.4, 745.5, 745.60, 745.61, 745.69, 745.7, 745.8, 745.9, 746.0, 746.01, 746.02, 746.09, 746.1, 746.2, 746.3, 746.4, 746.5, 746.6, 746.7, 746.81, 746.82, 746.83, 746.84, 746.85, 746.86, 746.87, 746.89, 746.9, 747.0, 747.11, 747.20, 747.21, 747.22, 747.29, 747.3, 747.40, 747.41, 747.42, 747.49, 747.83
Prematurity	765.0, 765.1, 765.20-765.25
***International Classification of Diseases, 9th Revision, Clinical Modification*	

A2. OUTCOME MEASURES FOR PEDIATRIC PNEUMONIA

Since mortality is a rare consequence of pediatric CAP in the U.S., other indicators have been used in previous studies to quantify a more positive or more negative resolution of disease. These indicators include length of stay in hospital, total hospital charges and rates of hospital readmission for the same episode of pneumonia.

Length of hospital stay has been used previously in research that uses administrative claims data as a way to evaluate the quality of medical care within hospitals [53, 76]. This measure may be drastically different for two individuals who receive the same primary diagnosis due to non-clinical factors such as age of the patient, type of insurance, race of the patient, and the location and teaching-status of the hospital [53]. It has been argued that for pediatric care, freestanding children's hospitals are most important when specialty care is needed (i.e. uncommon surgeries, oncology, and rare conditions) and are not any better equipped medically than other hospitals in regards to common conditions such as asthma or pneumonia. It has been assumed that patients seen at children's hospitals have generally longer length of stays and greater hospital charges when compared to patients seen at other hospitals for the same diagnosis. In a study conducted by Merenstein et al., no statistical difference was found in the median length of stay when comparing freestanding children's hospitals to other hospitals but freestanding children's hospitals did have significantly higher hospital charges compared to other hospitals when adjusting for the non-clinical patient characteristics mentioned above [53]. This illustrates the importance in adjusting for these factors when comparing patients from different hospitals even if the patients have similar conditions.

Hospital readmission rates are dependent on multiple factors such as age, insurance status and longer lengths of stay during the initial admission [46, 77]. In one study twenty-four percent of adults who were diagnosed with CAP were readmitted to the hospital within thirty days of their index discharge [77]. It is unclear whether a similar rate of readmission exists in children.

A study where adult patients (65 years and older) hospitalized with CAP were given antibiotics according to the Infectious Disease Society of America (IDSA) 2009 Guidelines for adult pneumonia, found that these patients had a shorter length of stay, a decrease in CAP-related mortality and a shorter amount time to reaching clinical stability compared to a similar population of patients who did not receive antibiotics according to IDSA guidelines [78]. Similar results would be favorable in the pediatric population; however no such national guidelines currently exist for children with CAP. This lack of national guidelines in clinical management of pediatric pneumonia leads to large variability within the field.

A3. COMPARISON OF SEVERITY INDEX MEASURES

Severity index measures are useful for two reasons: 1. they aid in the identification of subpopulations who are comparably more ill and 2. They allow for epidemiologist to adjust for severity of illness more accurately. For patients diagnosed with pneumonia, the Pneumonia Severity Index (PSI) is the gold standard in identifying patients with different risk factors who have a higher 30-day mortality rate. Patients are assigned to one of five risk classes based on their overall PSI score. Points are assigned for the presence of different symptoms, such as older age, coexisting illness, higher temperature, high respiratory rate, etc. The higher the overall score the higher the risk of 30-day mortality. Although the PSI was created in 1997 and has since been extensively studied, it has only been validated in adults. It is not possible for PSI to be validated in children since many of the measures used to obtain the overall score do not directly apply to children. The Charlson Index which has also been validated in adults is only useful in predicting mortality based on comorbid conditions but less than 1% of children diagnosed with pneumonia die from the disease. Therefore the usefulness of this measure in predicting disease severity for children with pneumonia is limited. The Pediatric Risk of Mortality (PRISM) Score is the most well known severity score for children. It is similar to PSI in its use of different risk factors found on physical finding to calculate a risk score to predict ICU mortality. Similar to the Charlson Index, PRISM is validated in predicting mortality risk for children admitted to the ICU. Generally only a small proportion of children are admitted to the ICU with a diagnosis with pneumonia and the majority of these children have an underlying comorbid condition which makes their treatment drastically different than children who are otherwise healthy except for their diagnosis of pneumonia. Therefore there is a great need for a pneumonia severity index specifically

created and validated in children. This pneumonia index for children should be informed by the other measures that have been developed and well validated.

Table 15: Severity index measures

Index Measure	Population in which Validated	Variables	Predicted Outcome
Pediatric Risk of Mortality (PRISM) Score[79] (Pollack et al. 1988)	Children	Systolic Blood Pressure Diastolic Blood Pressure Heart Rate Respiratory Rate PaO2/FIO2 PaCO2 Glasgow Coma Score Pupillary Reactions PT/PTT Total Bilirubin Potassium Calcium Glucose Bicarbonate	Predicts ICU mortality risk in children.

Table 15 (continued): Severity index measures

Index Measure	Population in which Validated	Variables	Predicted Outcome
Charlson Index[80] (Charlson et al., 1987)	Adults	Myocardial Infarction Congestive Heart Failure Peripheral Vascular Disease Cerebrovascular Disease Dementia Chronic Pulmonary Disease Connective Tissue Disease Ulcer Disease Diabetes Hemiplegia Moderate or Severe Renal Disease Diabetes with End Organ Damage Any Tumor Leukemia Lymphoma Moderate or Severe Liver Disease Metastatic Solid Tumor AIDS	Predicts mortality based on comorbid conditions.

Table 15 (continued): Severity index measures

Index Measure	Population in which Validated	Variables	Predicted Outcome
Pneumonia Severity Index (PSI)[81] (Fine et al, 1997)	Adults	Age Neoplastic Disease Congestive Heart Failure Cerebrovascular Disease Renal Disease Liver Disease Altered Mental Status Pulse Respiratory Rate Systolic Blood Pressure Temperature Nursing Home Resident Arterial pH BUN Sodium Glucose Hematocrit Partial Pressure of Arterial Oxygen Pleural Effusion	Predicts severity risk and mortality risk for patients diagnosed with community-acquired pneumonia.

Appendix B: Additional analysis for the comparative effectiveness study

B1. ACRONYMS

LOS: length of stay

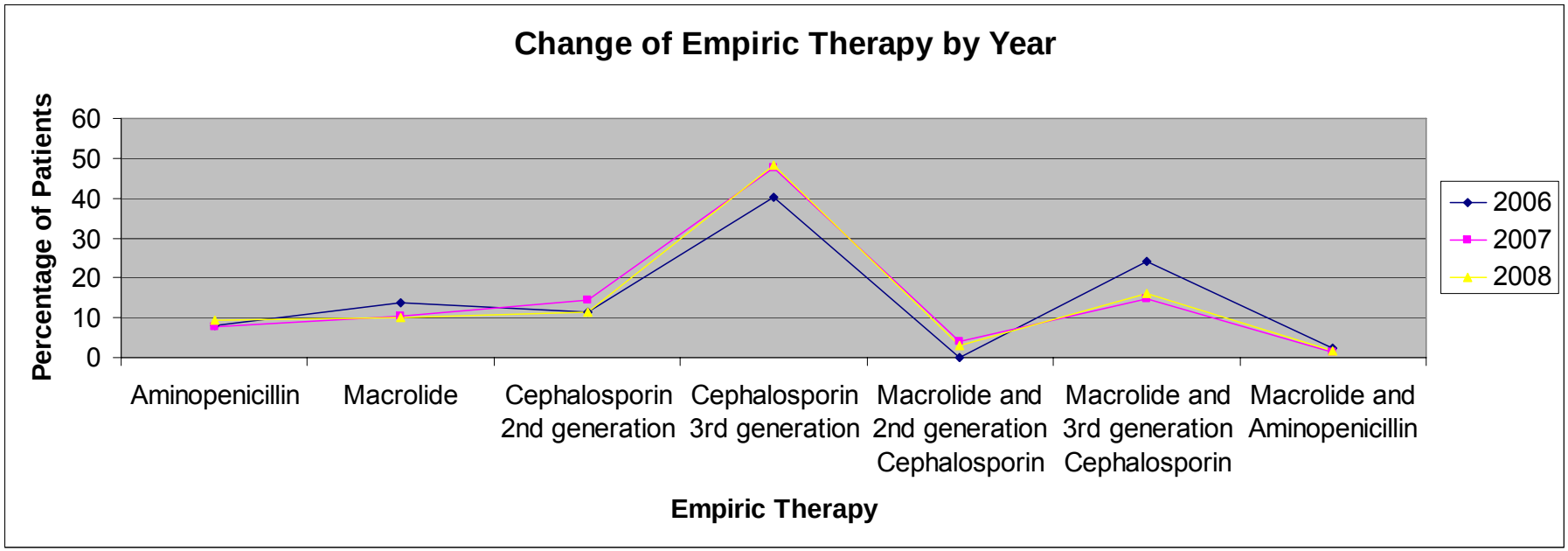
Prior Hospitalization: Any hospitalization within the prior 24 months (to their hospitalization with CAP) where there was a diagnosis of asthma.

Chronic Asthma Med: Treatment with inhaled corticosteroids (e.g., fluticasone) or leukotriene receptor antagonists on the first day of hospitalization for CAP

Systemic Steroid: Systemic (either oral or intravenous) corticosteroids (e.g. dexamethasone, hydrocortisone, methylprednisolone, prednisolone, and prednisone received on the first day of hospitalization for CAP.

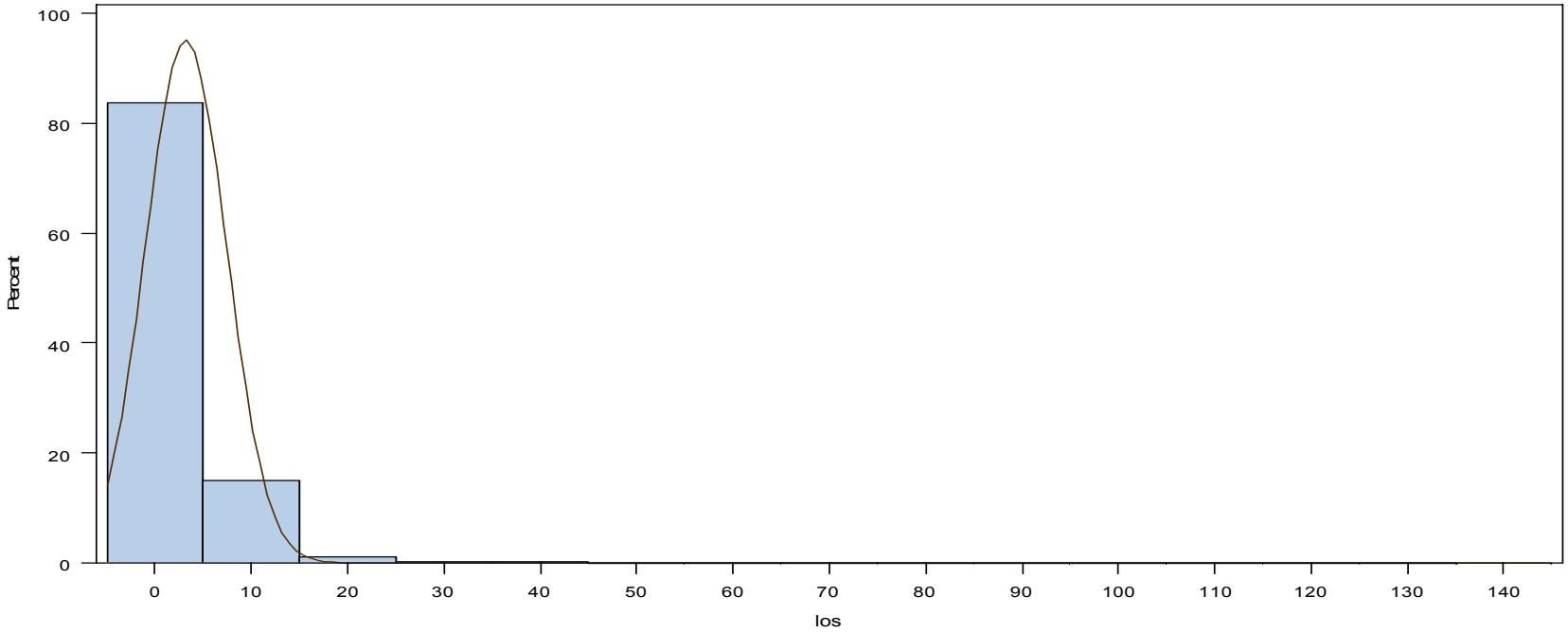
Acute Wheeze: Receipt of beta agonist therapy on the first day of hospitalization for CAP

Figure 2: Change of empiric therapy by year



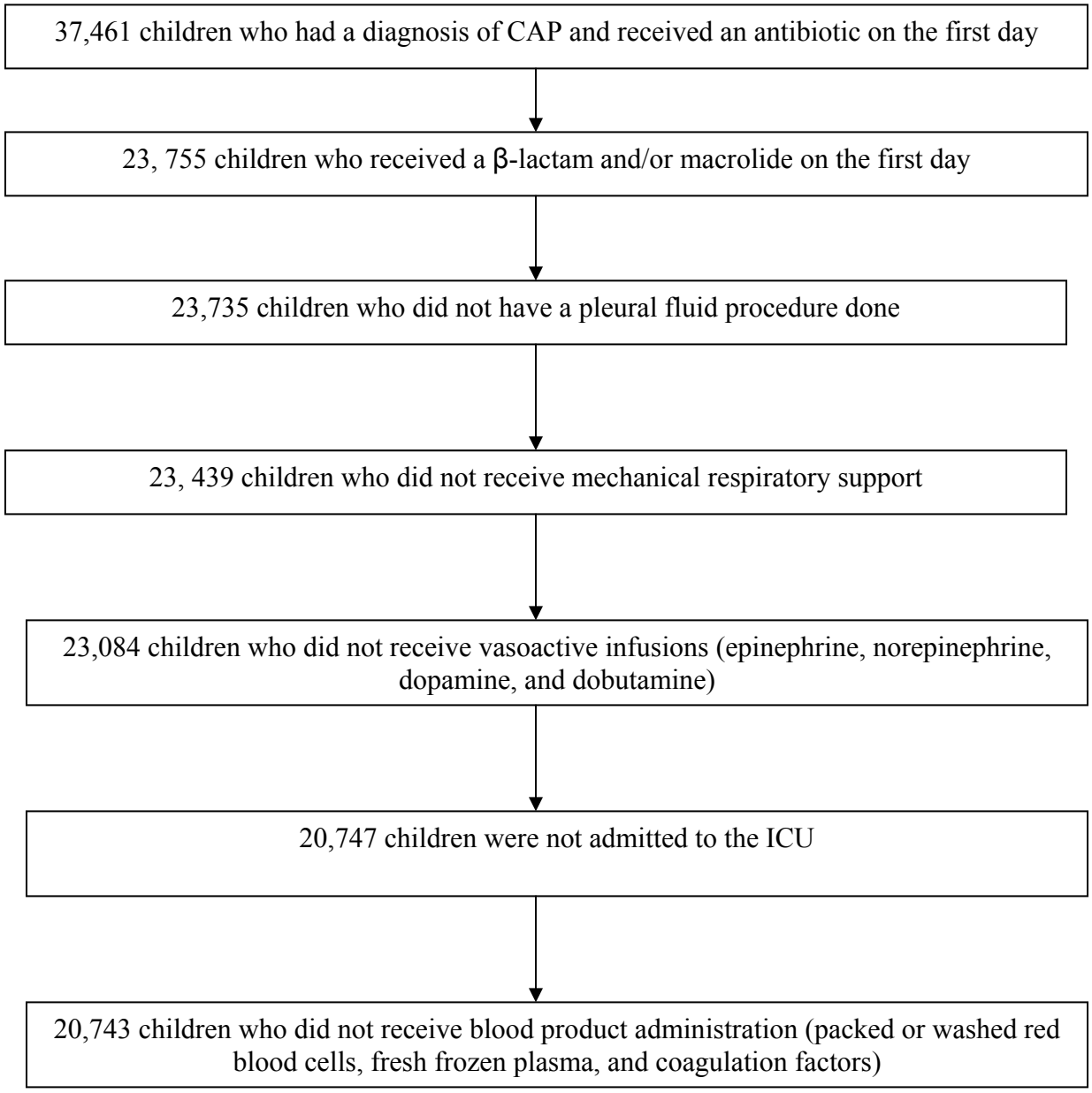
Linear trend test showed no statistically significant differences in year prescribed for any of the therapies prescribed.

Figure 3: Distribution of LOS



Note: Kolmogorov-Smirnov test p-value <0.010 so statistically different than a normal Gaussian curve. Right skewed and over dispersed around 1-2 days.

Figure 3: Exclusion criteria flow chart



B3. UNIVARIATE ASSOCIATIONS

Table 16: Univariate associations of hospital readmission within 14 days among patients who received beta-lactam-macrolide combination compared to beta-lactam monotherapy

	Combo Therapy (Reference: Monotherapy) OR (95% CI)	Confounder OR (95% CI)	% Change in Combo Therapy Effect Estimate *Unadj. for other variables
Combo Therapy (Reference: Monotherapy)	0.774 (0.485, 1.234)	N/A	
Length of Stay	0.793 (0.497, 1.266)	1.036 (1.022, 1.051)	2%
Age-in-years	0.678 (0.421, 1.092)	1.060 (1.018, 1.103)	12%
Principal Payer (Reference: Government)			
Non-Government	0.772 (0.484, 1.231)	1.114 (0.727, 1.709)	0.3%
Other		0.838 (0.511, 1.373)	
No Charge		2.338 (0.320, 17.104)	
Asthma (Reference: No)			
Prior Hospitalization	0.771 (0.484, 1.230)	1.451 (0.894, 2.356)	0.4%
Chronic Asthma Med	0.763 (0.478, 1.218)	1.501 (0.978, 2.305)	1%
Systemic Steroid	0.785 (0.492, 1.253)	0.711 (0.468, 1.081)	1%
Acute Wheeze	0.795 (0.498, 1.269)	0.684 (0.472, 0.993)	3%
Other Variables (Reference: No)			
Arterial Blood Gases	0.763 (0.472, 1.231)	1.601 (0.875, 2.928)	1%
Intensive Imaging	0.773 (0.485, 1.232)	1.343 (0.330, 5.460)	0.1%
Combo Therapy (Reference: Monotherapy)	0.738 (0.451, 1.205)	Fully Adjusted	5%

Table 16 (continued): Univariate associations of hospital readmission within 14 days among patients who received beta-lactam-macrolide combination compared to beta-lactam monotherapy

	Combo Therapy (Reference: Monotherapy) OR (95% CI)	Confounder OR (95% CI)	% Change in Combo Therapy Effect Estimate *Unadj. for other variables
Interaction Terms (Tested in model adjusted for age only)*			
Combo and Anydx_prior_24mo	0.679 (0.402, 1.147)	1.00 (0.30, 3.38)	0.1%
Combo and Chronic_asthma_med	0.658 (0.39, 1.12)	1.15 (0.423, 3.13)	3%
Combo and Systemic_steroid_00	0.721 (0.413, 1.26)	0.86 (0.30, 2.47)	6%
Combo and Acute_wheeze_1	0.637 (0.321, 1.265)	1.21 (0.47, 3.08)	6%

*Difference tested from main effect estimate in model adjusted for age only

Table 17: Univariate associations of hospital readmission within 14 days among patients who received beta-lactam monotherapy

	2nd Gen. Cephalosporin (Ref: Ampcn) OR (95% CI)	3rd Gen. Cephalosporin (Ref: Ampcn) OR (95% CI)	% Δ 2nd Gen Ceph	% Δ 3rd Gen Ceph	Confounder OR (95% CI) or P-Value for Int. Terms
2nd Gen Ceph (Ref: Ampcn)	1.274 (0.728, 2.231)	-	0%	N/A	N/A
3rd Gen Ceph (Ref: Ampcn)	-	1.071 (0.704, 1.629)	N/A	0%	N/A
Length of Stay	1.279 (0.730, 2.241)	1.043 (0.685, 1.587)	0.4%	3%	1.037 (1.022, 1.052)
Age-in-years	1.415 (0.803, 2.493)	1.147 (0.751, 1.749)	11%	7%	1.056 (1.015, 1.098)
Principal Payer (Ref: Government)					
Non-Government	1.268 (0.724, 2.222)	1.073 (0.705, 1.634)	0.5%	0.2%	1.110 (0.723, 1.702)
Other	-	-			0.841 (0.513, 1.380)
No Charge	-	-			2.357 (0.321, 17.292)
Asthma (Ref: No)					
Prior Hospitalization	1.285 (0.734, 2.250)	1.083 (0.712, 1.647)	0.9%	1%	1.454 (0.895, 2.361)
Chronic_Asthma_Med	1.301 (0.743, 2.280)	1.088 (0.715, 1.655)	0.9%	1.6%	
Systemic Steroid	1.266 (0.723, 2.217)	1.033 (0.678, 1.574)	0.6%	4%	0.703 (0.462, 1.071)

Table 17 (continued): Univariate associations of hospital readmission within 14 days among patients who received beta-lactam monotherapy

	2nd Gen. Cephalosporin (Ref: Ampcn) OR (95% CI)	3rd Gen. Cephalosporin (Ref: Ampcn) OR (95% CI)	% Δ 2nd Gen Ceph	% Δ 3rd Gen Ceph	Confounder OR (95% CI) or P-Value for Int. Terms
Acute Wheeze	1.262 (0.721, 2.210)	1.032 (0.678, 1.572)	0.9%	4%	0.676 (0.465, 0.981)
Other Variables (Ref: No)					
Arterial Blood Gases	1.513 (0.847, 2.703)	1.227 (0.785, 1.918)	19%	15%	1.577 (0.863, 2.883)
Intensive Imaging	1.274 (0.727, 2.230)	1.071 (0.704, 1.628)	0%	0%	1.323 (0.325, 5.380)
Partially Adjusted Model	1.675 (0.931, 3.013)	1.314 (0.837, 2.063)	31%	23%	Adjusted for age and ABG
Fully Adjusted Model*	1.627 (0.904, 2.929)	1.227 (0.779, 1.933)	3%	7%	Fully adjusted model
Interaction Terms (Tested in model adjusted for age and ABG)**					
Monoabx and Anydx_prior_24mo	1.67 (0.88, 3.17)	1.25 (0.76, 2.05)	0.3%	5%	Abx2*Prior:0.97 Abx3*Prior:0.62
Monoabx and Chronic_Asthma_Med	1.58 (0.84, 2.97)	1.12 (0.69, 1.81)	6%	15%	Abx2*chronic: 1.35 (0.45,4.09) Abx3*chronic: 1.95 (1.10, 3.45)
Monoabx and Systemic_steroid_00	1.70 (0.83, 3.48)	1.36 (0.79, 2.33)	1%	4%	Abx2*Sys:0.90 Abx3*Sys:0.64

Table 17 (continued): Univariate associations of hospital readmission within 14 days among patients who received beta-lactam monotherapy

	2nd Gen. Cephalosporin (Ref: Ampcn) OR (95% CI)	3rd Gen. Cephalosporin (Ref: Ampcn) OR (95% CI)	% Δ 2nd Gen Ceph	% Δ 3rd Gen Ceph	Confounder OR (95% CI) or P-Value for Int. Terms
Monoabx and Acute_wheeze_1	1.37 (0.57, 3.29)	1.39 (0.75, 2.59)	18% (only 8% from unadj. model)	6%	Abx2*Wheeze: 0.56 Abx3*Wheeze: 0.65

*Difference tested from main effect estimates in partially adjusted model

**Difference tested from main effect estimates in model adjusted for age and ABG only

Table 18: Univariate associations of LOS among patients who received Beta-lactam-macrolide combination compared to Beta-lactam monotherapy

	Combo Therapy (Reference: Monotherapy) RR (95% CI)	Confounder RR (95% CI)	% Change in Combo Therapy Effect Estimate *Unadj. for other variables
Combo Therapy (Reference: Monotherapy)	0.9125 (0.8689, 0.9583)	N/A	0%
Age-in-years	0.8348 (0.7904, 0.8818)	1.046 (1.0367, 1.0552)	9%
Principal Payer (Reference: Government)			
Non-Government	0.9165 (0.8727, 0.9625)	0.8780 (0.8200, 0.9402)	0%
Other	0.9165 (0.8727, 0.9625)	0.8487 (0.7839, 0.9188)	
No Charge	0.9165 (0.8727, 0.9625)	0.7162 (0.6562, 0.7817)	
Asthma (Reference: No)			
Prior Hospitalization	0.9109 (0.8680, 0.9559)	1.2373 (1.1692, 1.3094)	0%
Chronic Asthma Medication	0.9105 (0.8674, 0.9558)	1.0816 (1.0071, 1.1617)	
Systemic Steroid	0.9239 (0.8811, 0.9687)	0.8052 (0.7596, 0.8537)	1%
Acute Wheeze	0.9191 (0.8760, 0.9644)	0.9129 (0.8691, 0.9589)	1%
Other Variables (Reference: No)			
Arterial Blood Gases	0.9024 (0.8562, 0.9511)	1.3391 (1.2363, 1.4505)	1%
Intensive Imaging	0.9009 (0.8542, 0.9502)	1.5832 (1.3692, 1.8306)	1%
Combo Therapy (Reference: Monotherapy)	0.8446 (0.8008, 0.8907)	Fully Adjusted Model	8%

Table 18 (continued): Univariate associations of LOS among patients who received Beta-lactam-macrolide combination compared to Beta-lactam monotherapy

	Combo Therapy (Reference: Monotherapy) RR (95% CI)	Confounder RR (95% CI)	% Change in Combo Therapy Effect Estimate *Unadj. for other variables
Interaction Terms (Tested in fully adjusted model)			
Combo and Anydx_prior_24mo	0.8456 (0.7917, 0.9032)	1.00 (0.91, 1.10)	7%
Combo and Chronic Asthma Medication	0.8419 (0.7883, 0.8991)	0.99 (0.89, 1.10)	8%
Combo and Systemic_steroid_00	0.8595 (0.8153, 0.9601)	1.12 (1.05, 1.20)	6%
Combo and Acute_wheeze_1	0.8413 (0.7974, 0.8878)	1.05 (0.95, 1.15)	8%

Table 19: Univariate associations of LOS among patients who received beta-lactam monotherapy

	2nd Gen. Cephalosporin (Ref: Ampcn) RR (95% CI)	3rd Gen. Cephalosporin (Ref: Ampcn) RR (95% CI)	% Δ 2nd Gen Ceph	% Δ 3rd Gen Ceph	Confounder RR (95% CI) or P-value for Int. Terms unless stat. sig.
2nd Gen Ceph (Ref: Ampcn)	1.06 (0.96, 1.17)	-	0%	N/A	N/A
3rd Gen Ceph (Ref: Ampcn)	-	1.16 (1.05, 1.28)	N/A	0%	N/A
Age-in-years	1.06 (0.97, 1.16)	1.11 (1.02, 1.21)	0%	4%	1.05 (1.04, 1.06)
Principal Payer (Ref: Government)					
Non-Government	1.04 (0.95, 1.15)	1.14 (1.03, 1.26)	2%	2%	0.90 (0.84, 0.97)
Other	-	-			0.85 (0.78, 0.94)
No Charge	-	-			0.73 (0.68, 0.79)
Asthma (Ref: No)					
Prior Hospitalization	1.07 (0.97, 1.18)	1.17 (1.06, 1.30)	1%	1%	1.24 (1.16, 1.33)
Chronic Asthma Med	1.07 (0.97, 0.97)	1.16 (1.05, 1.29)	1%	0%	1.09 (1.00, 1.19)
Systemic Steroid	1.05 (0.95, 1.15)	1.12 (1.01, 1.24)	1%	3%	0.79 (0.74, 0.85)
Acute Wheeze	1.06 (0.96, 1.17)	1.15 (1.04, 1.28)	0%	1%	0.91 (0.85, 0.96)
Other Variables (Ref: No)					
Arterial Blood Gases	1.02 (0.92, 1.14)	1.11 (0.99, 1.24)	4%	3%	1.35 (1.23, 1.48)
Intensive Imaging	1.02 (0.91, 1.13)	1.11 (0.99, 1.24)	4%	3%	1.61 (1.36, 1.91)
Fully Adjusted Model	1.01 (0.91, 1.12)	1.03 (0.94, 1.14)	5%	11%	Fully adjusted model
Interaction Terms (Tested in fully adjusted model)*					

Table 19 (continued) : Univariate associations of LOS among patients who received beta-lactam monotherapy

	2nd Gen. Cephalosporin (Ref: Ampcn) RR (95% CI)	3rd Gen. Cephalosporin (Ref: Ampcn) RR (95% CI)	% Δ 2nd Gen Ceph	% Δ 3rd Gen Ceph	Confounder RR (95% CI) or P-value for Int. Terms unless stat. sig.
Monoabx and Anydx_prior_24mo	0.99 (0.88, 1.12)	1.08 (0.95, 1.22)	7%	7%	Abx1*Prior:0.2446 Abx2*Prior: 0.0988
Monoabx and Chronic_asthma_med	0.99 (0.88, 1.11)	1.08 (0.96, 1.21)	7%	7%	Abx1*Chronic: 1.17 (0.97, 1.42) Abx2*Chronic: 1.23 (1.13, 1.34)
Monoabx and Systemic_steroid_00	1.01 (0.93, 1.11)	1.04 (0.95, 1.13)	5%	10%	Abx1*Sys: 0.4735 Abx2*Sys: 0.6976
Monoabx and Acute_wheeze_1	1.00 (0.90, 1.12)	1.03 (0.93, 1.14)	6%	11%	Abx1*Wh-RR: 1.24 (1.03, 1.49) Abx2*Wh-RR: 1.15 (1.03, 1.28)
Mon0abx * Chronic and Monoabx*Acute	0.98 (0.84, 1.13)	1.05 (0.92, 1.21)			Abx*Chronic (0.47 & 0.0005) Abx* Wheeze (0.08 & 0.11)

Table 20: Univariate associations of LOS among patients who received beta-lactam-macrolide combination

	2nd Gen. Cephalosporin +Macrolide (Ref: Ampcn+Macrolide) RR (95% CI)	3rd Gen. Cephalosporin+Macrolide (Ref: Ampcn+Macrolide) RR (95% CI)	% Δ 2nd Gen Ceph	% Δ 3rd Gen Ceph	Confounder RR (95% CI) or P-values for interaction terms
2nd Gen Ceph + Macrolide (Ref: Ampcn+Macrolide)	1.03 (0.93, 1.15)	-	0%	N/A	N/A
3rd Gen Ceph +Macrolide (Ref: Ampcn+Macrolide)	-	0.88 (0.77, 1.01)	N/A	0%	N/A
Age-in-years	1.01 (0.91, 1.12)	0.87 (0.76, 0.99)	2%	1%	1.03 (1.02, 1.04)
Principal Payer (Ref: Government)					
Non-Government	1.03 (0.93, 1.15)	0.89 (0.77, 1.03)	0%	1%	0.81 (0.73, 0.91)
Other					0.85 (0.78, 0.92)
No Charge					0.79 (0.72, 0.87)
Asthma (Ref: No)					
Prior Hospitalization	1.03 (0.93, 1.14)	0.87 (0.75, 0.99)	0%	1%	1.26 (1.19, 1.33)
Chronic Asthma Med	1.03 (0.93, 1.15)	0.87 (0.76, 1.00)	0%	1%	1.07 (0.97, 1.17)
Systemic Steroid	1.02 (0.92, 1.14)	0.90 (0.79, 1.03)	1%	2%	0.88 (0.82, 0.95)
Acute Wheeze	1.03 (0.93, 1.15)	0.88 (0.77, 1.01)	0%	0%	0.96 (0.89, 1.04)
Other Variables (Ref: No)					
Arterial Blood Gases	1.03 (0.91, 1.15)	0.90 (0.79,l 1.03)	0%	2%	1.29 (1.18, 1.41)
Intensive Imaging	1.02 (0.91, 1.15)	0.90 (0.79, 1.03)	1%	2%	1.51 (1.23, 1.86)
Fully Adjusted Model	1.01 (0.90, 1.13)	0.91 (0.79, 1.04)	2%	3%	Fully Adjusted

Table 20 (continued): Univariate associations of LOS among patients who received beta-lactam-macrolide combination

	2nd Gen. Cephalosporin +Macrolide (Ref: Ampcn+Macrolide) RR (95% CI)	3rd Gen. Cephalosporin+Macrolide (Ref: Ampcn+Macrolide) RR (95% CI)	% Δ 2nd Gen Ceph	% Δ 3rd Gen Ceph	Confounder RR (95% CI) or P-values for interaction terms
Interaction Terms (Tested in fully adjusted model)					
Comboabx and Anydx_prior_24mo	1.01 (0.87, 1.16)	0.90 (0.76, 1.08)	2%	2%	Abx1*Prior: 0.86 Abx2*Prior: 0.88
Comboabx and Chronic_asthma_med	1.00 (0.88, 114)	0.89 (0.79, 1.00)	3%	0%	Abx1*Chronic:0.35 Abx2*Chronic: 0.42
Comboabx and Systemic_steroid_00	1.00 (0.88, 1.13)	0.91 (0.79, 1.04)	3%	3%	Abx1*Sys:0.40 Abx2*Sys:0.67
Comboabx and Acute_wheeze_1	1.01 (0.90, 1.13)	0.90 (0.79, 1.02)	2%	2%	Abx1*Wheeze: 0.56 Abx2*Wheeze: 0.34

B4. Model Diagnostics

Figure 5. Hospital readmission model:

No influential points or outliers in the readmission model after adjustment for age and ABG.

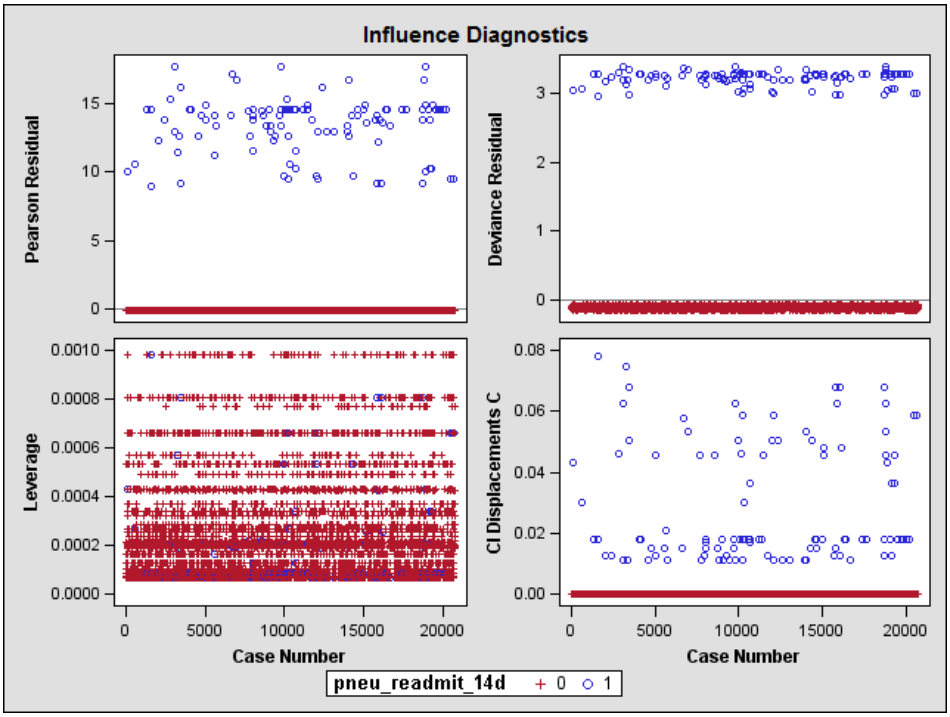


Figure 5 (continued). Hospital readmission model:

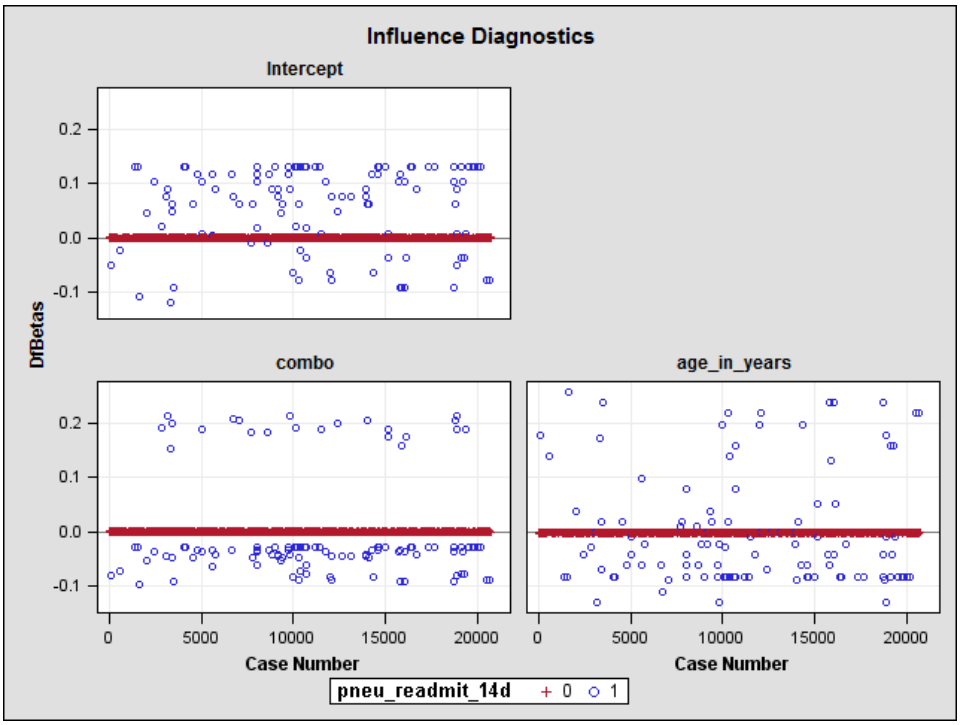
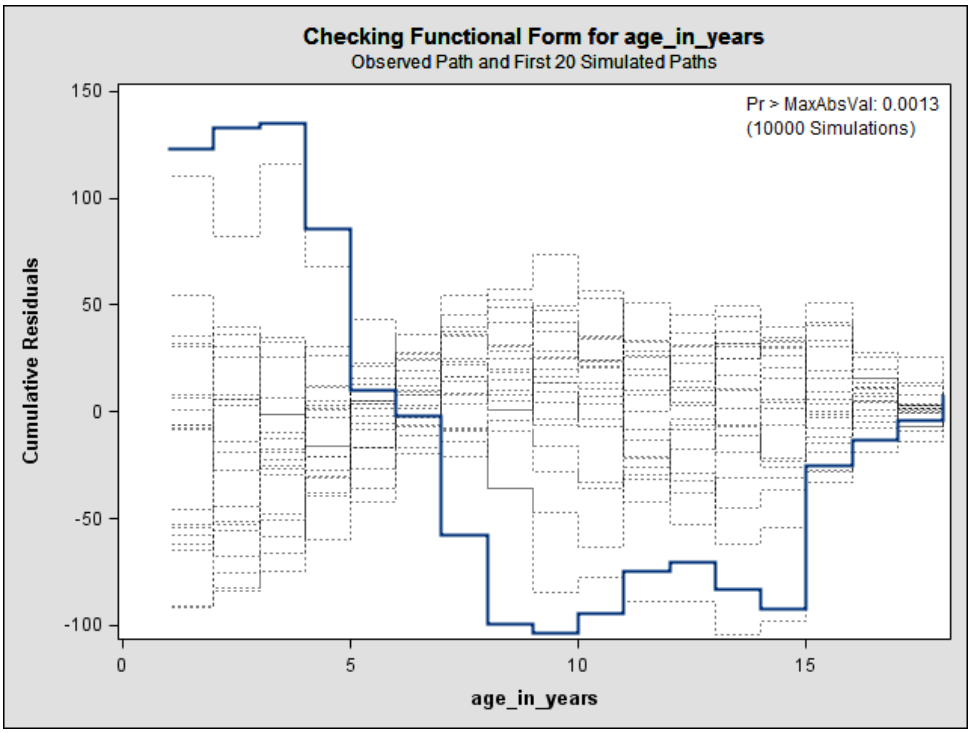


Figure 6. LOS Model



Note: Age adequately fits the LOS fully adjusted model

Appendix C: Additional analysis for antibiogram study

C1. ACRONYMS

PNNS_ALL: Penicillin-Nonsusceptible *S. pneumoniae* (all isolates)

PNNS_BLOOD: Penicillin-Nonsusceptible *S. pneumoniae* (isolates from blood only)

PNNS_RESP: Penicillin-Nonsusceptible *S. pneumoniae* (isolates from respiratory secretions only)

PNRES_ALL: Penicillin-Resistant *S. pneumoniae* (all isolates)

Anydx_prior_24mo: Any hospitalization within the prior 24 months (to their hospitalization with CAP) where there was a diagnosis of asthma.

Systemic_steroid_00: Systemic (either oral or intravenous) corticosteroids (eg. dexamethasone, hydrocortisone, methylprednisolone, prednisolone, and prednisone received on their first day of hospitalization for CAP.

AIC: Akaike Information Criterion

C2. ANTIBIOGRAM SURVEY

Figure 7: Antibiogram survey sent to participating hospitals

Survey of 2005 *Streptococcus pneumoniae* Antibiotic Resistance

Antibiotic	CSF			Blood			Resp. Secretion			Pleural Fluid			Overall*		
	% S	% I	% R	% S	% I	% R	% S	% I	% R	% S	% I	% R	% S	% I	% R
Amoxicillin/ Ampicillin															
Amoxicillin/ Clavulanate															
Azithromycin															
Cefotaxime															
Ceftriaxone															
Cefuroxime															
Clarithromycin															
Clindamycin															
Eyrthromycin															
Imipenem															
Levofloxacin															
Meropenem															
Penicillin															
Trimethoprim-Sulfamethoxazole															
Vancomycin															

***Note**: If your lab does not report site-specific resistance data, please fill in only the "Overall" column on the far right.

Legend: **% S** = % fully susceptible to antibiotic **% I** = % intermedidate resistance to antibiotic **% R** = % fully resistant to antibiotic

How often is your antibiogram updated? ☐ Monthly ☐ Quarterly ☐ Annually ☐ Other (specify) _____

What test(s) did your laboratory use to determine antibiotic susceptibility for pneumoccous in 2005? ☐ E-test ☐ MicroScan ☐ In-house BMD ☐ Broth Macrodilution ☐ Sensititer ☐ Vitek ☐ Agar Dilution ☐ Other (specify) _____

How is antibiogram information disseminated to clinicians? ☐ Post to Intranet ☐ Email ☐ Hard copy ☐ Other (specify) _____

Multiple specimens from same patient were: ☐ Reported separately ☐ Pooled together as one report

C3. TRANSFORMATION ANALYSIS OF MAIN EXPOSURE

Table 21a: Transformations of PNNS_ALL Variable with Outlier

Regressor	**Model 1 (SE)**	**Model 2 (SE)**	**Model 3 (SE)**	**Model 4 (SE)**
Intercept	*-2.2272 (0.9688)*	-0.3209 (3.4437)	-3.8292 (3.7887)	*-3.0235 (0.2014)*
PNNS_ALL (Continuous)	-0.01561 (0.0182)	-	0.05246 (0.1567)	-
PNNS_ALL (Log Transformed)	-	-0.6916 (0.8802)	-	-
PNNS_ALL (Quadratic)	-	-	-0.00069 (0.001576)	-
PNNS_ALL (Grand Mean Centered)	-	-	-	-0.01562 (0.01862)
-2 Log Likelihood Test (df)	2235.1 (1)	2235.2 (1)	2234.9 (2)	2235.1 (1)
Test Statistic (p-value)	1.0 (>0.05)	0.9 (>0.05)	1.2 (>0.05)	1.0 (>0.05)
Variance*	*1.0610 (0.3329)*	*1.0634 (0.3235)*	*1.0647 (0.3258)*	*1.0610 (0.3229)*
AIC	2241.1	2241.2	2242.9	2241.1

Table 21b: Transformations of PNNS_ALL Variable without Outlier

Regressor	**Model 1 (SE)**	**Model 2 (SE)**	**Model 3 (SE)**	**Model 4 (SE)**
Intercept	*-2.6107 (0.7903)*	-1.02874 (2.7837)	-2.1267 (3.0700)	*-3.0847 (0.1680)*
PNNS_ALL (Continuous)	-0.00929 (0.01513)	-	-0.02997 (0.1276)	-
PNNS_ALL (Log Transformed)	-	-0.4599 (0.7110)	-	-
PNNS_ALL (Quadratic)	-	-	0.000210 (0.001287)	-
PNNS_ALL (Grand Mean Centered)	-	-	-	-0.00947 (0.01518)
-2 Log Likelihood Test	2052.6 9 (1)	2052.6 (1)	2052.6 (2)	2052.6 (1)
Test Statistic (p-value)	0.6 (>0.05)	0.6 (>0.05)	0.6 (>0.05)	0.6 (>0.05)
Variance*	*0.6313 (0.2195)*	*0.6295 (0.2191)*	*0.6285 (0.2192)*	*0.6360 (0.2222)*
AIC	2058.6	2058.6	2060.6	2058.6

NOTE: PNNS_ALL (Grand Mean Centered) was the chosen form of the variable to be included in all following models. There was not much difference between Model 4 and Model 1 in either set of models, but the interpretability of penicillin-nonsusceptible pneumococcal isolates grand mean centered at 52% (as baseline) was better than the interpretability of 0% nonsusceptibility.

C4. Comparison of models

Table 22a: Penicillin-nonsusceptible (all isolates) *S. pneumoniae* beta coefficient table (with outlier)—main effects and interaction

Regressor	**Model 1 (SE)**	**Model 2 (SE)**	**Model 3 (SE)**	**Model 4 (SE)**	**Model 5 (SE)****	**Model 6 (SE)**	**Model 7 (SE)**	**Model 8 (SE)**	**Model 9 (SE)**
Intercept	*-3.0251 (0.2018)*	*-3.0235 (0.2014)*	*-2.4697 (0.2125)*	*-2.5193 (0.2130)*	*-2.6360 (0.2202)*	*-2.5882 (0.2281)*	*-2.6360 (0.2202)*	*-2.6375 (0.2204)*	*-2.6349 (0.2201)*
PNNS_ALL (Centered-Continuous)	-	-0.01562 (0.01862)	-0.01413 (0.01873)	-0.01418 (0.01868)	-0.01402 (0.01865)	-0.01379 (0.01864)	-0.01392 (0.01962)	-0.01668 (0.01879)	-0.01140 (0.01938)
Age (Continuous)	-	-	*-0.1353 (0.01910)*	*-0.1387 (0.01929)*	*-0.1377 (0.01934)*	*-0.1381 (0.01934)*	*-0.1377 (0.01935)*	*-0.1377 (0.01935)*	*-0.1379 (0.01936)*
Anydx_prior_24mo	-	-	-	*0.4575 (0.1619)*	*0.3916 (0.1645)*	*0.3977 (0.1649)*	*0.3916 (0.1645)*	*0.3912 (0.1643)*	*0.3926 (0.1646)*
Systemic_steroid_00	-	-	-	-	*0.2673 (0.1235)*	*0.3246 (0.1444)*	*0.2673 (0.1236)*	*0.2658 (0.1235)*	*0.2651 (0.1236)*
Acute_wheeze_1	-	-	-	-	-	-0.1168 (0.1503)	-	-	-
PNNS_ALL*AGE	-	-	-	-	-	-	-0.00003 (0.001899)	-	-
PNNS_ALL*Anydx_prior_24mo	-	-	-	-	-	-	-	0.01806 (0.01501)	-

Table 22a (continued): Penicillin-nonsusceptible (all isolates) *S. pneumoniae* beta coefficient table (with outlier)—main effects and interaction

Regressor	**Model 1 (SE)**	**Model 2 (SE)**	**Model 3 (SE)**	**Model 4 (SE)**	**Model 5 (SE)****	**Model 6 (SE)**	**Model 7 (SE)**	**Model 8 (SE)**	**Model 9 (SE)**
PNNS_ALL*Systemic_steroid_00	-	-	-	-	-	-	-	-	-0.00555 (0.01124)
Variance*	*1.0673 (0.3221)*	*1.0610 (0.3229)*	*1.0738 (0.3254)*	*1.0650 (0.3227)*	*1.0600 (0.3214)*	*1.0577 (0.3211)*	*1.0599 (0.3213)*	*1.0619 (0.3219)*	*1.0589 (0.3212)*
AIC	2240.1	2241.1	2179.9	2174.4	2171.7	2173.1	2173.7	2172.2	2173.5

*Italics=p-value<0.05
**Final Model shaded in grey

Table 22b: Penicillin-nonsusceptible (all isolates) *S. pneumoniae* beta coefficient Table (without outlier)- Main Effects

Regressor	**Model 1 (SE)**	**Model 2 (SE)**	**Model 3 (SE)**	**Model 4 (SE)****	**Model 5 (SE)**
Intercept	*-3.0867 (0.1672)*	*-3.0847 (0.1680)*	*-2.6287 (0.1812)*	*-2.7184 (0.1905)*	*-2.6306 (0.2001)*
PNNS_ALL (Centered-Continuous)	-	-0.00947 (0.01518)	-0.00763 (0.01492)	-0.00754 (0.01494)	-0.00763 (0.01492)
Age (Continuous)	-	-	*-0.1242 (0.02055)*	*-0.1237 (0.02060)*	*-0.1242 (0.02058)*
Anydx_prior_24mo	-	-	*0.4497 (0.1697)*	*0.3939 (0.1730)*	*0.4490 (0.1718)*
Systemic_steroid_00	-	-	-	0.2110 (0.1306)	-
Acute_wheeze_1	-	-	-	-	0.003178 (0.1358)
Variance*	*0.6289 (0.2169)*	*0.6360 (0.2222)*	*0.6062 (0.2118)*	*0.6078 (0.2121)*	*0.6063 (0.2118)*
AIC	2057.2	2058.6	2011.8	2011.2	2013.8

*Italics=p-value<0.05

**Final Model chosen shaded in grey

Note: Interaction terms were tested without the outlier and similar results were seen as with the outlier therefore they were not included in this table for simplicity.

Table 23: Penicillin-resistant *S. Pneumoniae* beta coefficients—main effects and interaction Table
(Hospitals reporting resistant category n=20)

Regressor	**Coefficient Symbol**	**Model 1 (SE)**	**Model 2 (SE)**	**Model 3 (SE)**	**Model 4 (SE)**	**Model 5 (SE)****	**Model 6 (SE)**	**Model 7 (SE)**	**Model 8 (SE)**
Intercept	B0	*-3.0345 (0.2125)*	*-2.3790 (0.3064)*	*-1.8753 (0.3123)*	*-1.9428 (0.3078)*	*-2.1364 (0.3157)*	*-2.0914 (0.3372)*	*-2.1499 (0.3166)*	*-2.1309 (0.3359)*
PCNRES_ALL (Continuous)	B1	-	*-0.03424 (0.01104) p-value=0.0059*	*-0.03341 (0.01077)*	*-0.03315 (0.01056)*	*-0.03364 (0.01047)*	*-0.03794 (0.01217)*	*-0.03491 (0.01049)*	*-0.03606 (0.01238)*
Age (Continuous)	B2	-	-	*-0.1243 (0.02751)*	*-0.1286 (0.02787)*	*-0.1283 (0.02810)*	*-0.1086 (0.04080)*	*-0.08539 (0.02245)*	*-0.08537 (0.02245)*
Anydx_prior_24mo	B3	-	-	-	*0.5700 (0.2167)*	0.4436 (0.2215)	0.3895 (0.1962)	0.2131 (0.3478)	0.3858 (0.1960)
Systemic_steroid_00	B4	-	-	-	-	*0.4661 (0.1768)*	*0.7227 (0.1595)*	*0.7182 (0.1593)*	*0.6363 (0.2709)*
PCNRES_ALL*Age	B5	-	-	-	-	-	0.001145 (0.001659)	-	-

Table 23 (continued): Penicillin-resistant *S. Pneumoniae* beta coefficients—main effects and interaction Table
(Hospitals reporting resistant category n=20)

Regressor	**Coefficient Symbol**	**Model 1 (SE)**	**Model 2 (SE)**	**Model 3 (SE)**	**Model 4 (SE)**	**Model 5 (SE)****	**Model 6 (SE)**	**Model 7 (SE)**	**Model 8 (SE)**
PCNRES_ALL*Anydx_prior_24mo	B6	-	-	-	-	-	-	0.009026 (0.01468)	-
PCNRES_ALL*Systemic_steroid_00	B7	-	-	-	-	-	-	-	0.00417 (0.01173)
Variance*	U	*0.6343 (0.2688)*	0.3197 (0.1680) p-value=0.0723	0.2948 (0.1570)	0.2735 (0.1491)	0.2619 (0.1447)	0.2892 (0.1481)	0.2900 (0.1481)	0.2907 (0.1486)
Change in Variance from Model 2	-	N/A	0%	7.8%	14.5%	18.1%	9.5%	9.3%	9.1%
AIC	-	1410.1	1168.7	1145.0	1140.7	1135.7	1365.8	1365.9	1366.1

*Italics=p-value<0.05
**Final Model in gray.

Table 24: Penicillin-nonsusceptible (blood isolates) *S. Pneumoniae* beta coefficients—main effects and interaction table (Hospitals reporting blood isolates n=17)

Regressor	**Model 1 (SE)**	**Model 2 (SE)**	**Model 3 (SE)**	**Model 4 (SE)**	**Model 5 (SE)**	**Model 6 (SE)**	**Model 7 (SE)**	**Model 8 (SE)**	**Model 9 (SE)****
Intercept	*-2.8467 (0.2189)*	*-2.9354 (0.8524)*	*-2.3490 (0.8665)*	*-2.4179 (0.8655)*	*-2.5921 (0.8667)*	*-2.5571 (0.8668)*	*-2.7826 (0.9061)*	*-2.5625 (0.8733)*	*-3.1577 (0.9373)*
PCNNS_Blood (Continuous)	-	0.001472 (0.01889)	0.001799 (0.01912)	0.002315 (0.01908)	0.002557 (0.01901)	0.002127 (0.01902)	0.007285 (0.01994)	0.001902 (0.01916)	0.01520 (0.02041)
Age (Continuous)	-	-	*-0.1429 (0.02460)*	*-0.1461 (0.02482)*	*-0.1434 (0.02488)*	*-0.1407 (0.02469)*	*-0.07131 (0.08079)*	*-0.1436 (0.02490)*	*-0.1416 (0.02475)*
Anydx_prior_24mo	-	-	-	0.4475 (0.2183)	0.3556 (0.2218)	-	-	0.1896 (0.6726)	-
Systemic_steroid_00	-	-	-	-	*0.3591 (0.1637)*	*0.4036 (0.1608)*	*0.4021 (0.1609)*	*0.3603 (0.1637)*	*1.5185 (0.5877)*
PCNNS_Blood *Age	-	-	-	-	-	-	-0.00156 (0.001795)	-	-
PCNNS_Blood *Anydx_prior_24mo	-	-	-	-	-	-	-	0.003801 (0.01447)	-
PCNNS_Blood *Systemic_steroid_00	-	-	-	-	-	-	-	-	-0.02453 (0.01230)
Variance*	0.5452 (0.2742)	*1.3216 (0.5436)*	*1.3528 (0.5542)*	*1.3460 (0.5512)*	*1.3345 (0.5465)*	*1.3370 (0.5478)*	*1.3381 (0.5482)*	*1.3338 (0.5462)*	*1.3630 (0.5591)*
Change in Variance from Model 2	58.7%	0%	2.4%	1.8%	1.0%	1.2%	1.2%	0.9%	3.1%
AIC	1245.3	1282.2	1241.2	1239.3	1236.4	1236.9	1238.2	1238.4	1234.7

*Italics=p-value<0.05 & **Final Model in gray.

Table 25: Penicillin-Nonsusceptible (respiratory isolates) *S. Pneumoniae* beta coefficients—main effects and interaction (Hospitals reporting respiratory isolates n=14)

Regressor	**Model 1 (SE)**	**Model 2 (SE)**	**Model 3 (SE)**	**Model 4 (SE)**	**Model 5 (SE)**	**Model 6 (SE)****	**Model 7 (SE)**	**Model 8 (SE)**
Intercept	*-2.8484 (0.2274)*	*-2.3515 (1.0914)*	-1.7733 (1.1124)	-1.8046 (1.1108)	-2.0700 (1.1111)	-1.4616 (1.1683)	-1.9805 (1.1150)	*-2.5812 (1.1955)*
PCNNS_RESP (Continuous)	-	-0.00889 (0.02020)	-0.00943 (0.02050)	-0.00958 (0.02047)	-0.00916 (0.02039)	-0.02071 (0.02157)	-0.01096 (0.02049)	0.000519 (0.02186)
Age (Continuous)	-	-	*-0.1299 (0.02660)*	*-0.1317 (0.02678)*	*0.2295 (0.2616)*	*-0.3215 (0.1208)*	*-0.1262 (0.02695)*	*-0.1267 (0.02687)*
Anydx_prior_24mo	-	-	-	0.3643 (0.2580)	0.5287 (0.1895)	-	-0.9636 (1.1954)	-
Systemic_steroid_00	-	-	-	-	*0.5287 (0.1895)*	*0.5595 (0.1873)*	*0.5273 (0.1897)*	1.5366 (0.7431)
PCNNS_RESP*Age	-	-	-	-	-	0.003711 (0.002181)	-	-
PCNNS_RESP*Anydx_prior_24mo	-	-	-	-	-	-	0.02203 (0.02130)	-
PCNNS_RESP*Systemic_steroid_00	-	-	-	-	-	-	-	-0.01853 (0.01355)
Variance*	0.4708 (0.2543)	*1.3211 (0.5631)*	*1.3667 (0.5814)*	*1.3601 (0.5783)*	*1.3443 (0.5715)*	*1.3743 (0.5839)*	*1.3501 (0.5735)*	*1.3520 (0.5756)*
Change in Variance from Model 2	64.4%	0%	3.5%	3.0%	1.8%	4.0%	2.2%	2.3%
AIC	870.3	953.6	926.3	926.4	920.6	918.4	921.5	919.4

*Italics=p-value<0.05 & **Final Model in gray.

C5. MODEL DIAGNOSTICS

Figure 8: Normality of random effects
The normal probability plot of the random effects in the main model satisfies the normality assumption of random effects. (PCNNS_ALL)

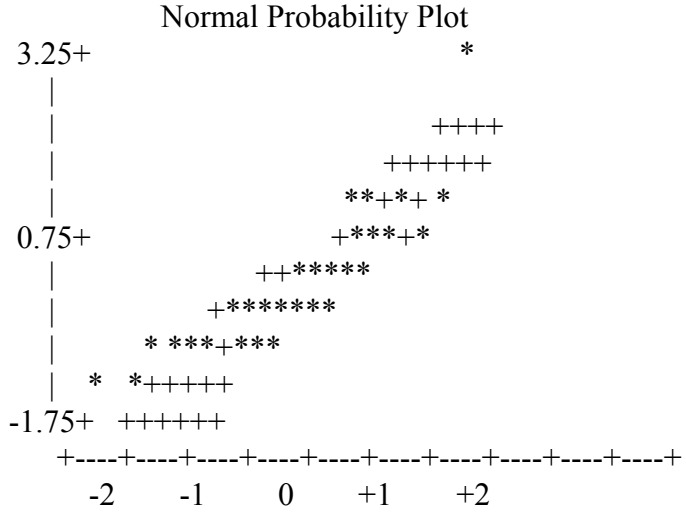
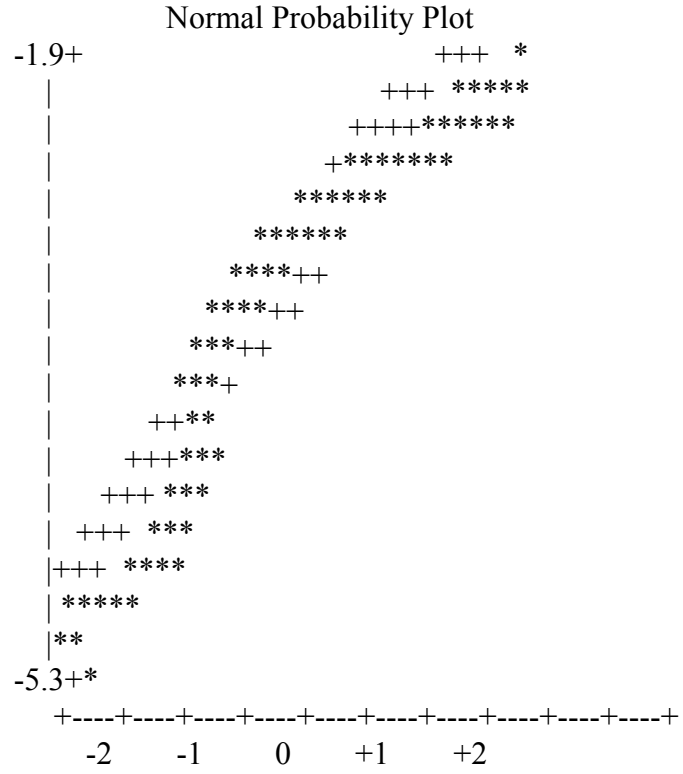


Figure 9: Normality of fixed effects
The normal probability plot of the fixed effects in the main model satisfies the normality assumption of fixed effects. (PCNNS_ALL)



Vita

EDUCATION

2008-June 2011 Drexel University Philadelphia, PA

Doctor of Philosophy, Epidemiology

Dissertation: Antibiotic Resistance and Prescribing in Children Hospitalized with Community-Acquired Pneumonia

2006-2008 Drexel University Philadelphia, PA

Master of Public Health, Concentration in Epidemiology

Thesis: Herpes Simplex Virus in Neonates and Young Infants

999-2003 University of Washington Seattle, WA

Bachelor of Science, Molecular and Cellular Biology

WORK EXPERIENCE

Jan. 2008 –2011 Drexel University SPH Philadelphia, PA

Teaching Assistant for graduate courses and instructor for undergraduate courses

- Introduction to Epidemiology, Intermediate Epidemiology, Infectious Diseases, Biostatistics Computing, Behavioral Assessment, Principles of Epidemiology, Community Health Assessment, Clinical Trials

Lead review sessions, lectured on new material and lead in class discussions, graded all assignments

INTERNSHIPS

June –Aug. 2007 Concern for Health Options: Information, Care, and Education (CHOICE) Philadelphia, PA

Latino Adolescent Sexual Health Preference Study

Facilitated Focus Groups with clients served by Latino organizations in North Philadelphia and reported findings to the Samuel S. Fels Fund

March –June 2007 Esperanza Health Center Philadelphia, PA

Practicum

- Created Access database to collect data on current patients with diabetes

Assisted with implementing Project Dulce-a Type II educational program

AWARDS AND PUBLICATION

- Member of the Hygeia Academic Honor Society of Drexel University School of Public Health
- Excellence in Communication Award, Drexel University, 2008

Ambroggio, L., Lorch, S.A., Mohamad, Z., Mossey, J., Shah, S.S. (2009). Congenital Anomalies and Resource Utilization in Neonates Infected with Herpes Simplex Virus. *Sexually Transmitted Diseases.* **36** (11): 680-685