Treatment costs associated with community-acquired pneumonia by community level of antimicrobial resistance

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Received 19 October 2007; returned 4 November 2007; revised 24 January 2008; accepted 1 February 2008

Introduction: The aim is to quantify community-acquired pneumonia (CAP) treatment outcomes and costs from a managed care perspective by the level of macrolide resistance corresponding to the metropolitan statistical area (MSA) where patients lived.

Materials and methods: A retrospective analysis was conducted using the i3 Magnify database (05/2000–05/2005) and the Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin (PROTEKT) database. Continuously enrolled patients aged 18 years and older residing in MSAs with PROTEKT data that had an outpatient CAP-related ICD-9 code and with one antibiotic pharmacy claim within 7 days were included. Patients were excluded for having a prior condition or drug treatment that could mimic CAP or precipitate infections, or for recent hospitalizations. Treatment costs by the level of resistance in the patient’s MSA, by treatment outcome and by initial treatment were measured and adjusted for differences in baseline patient characteristics.

Results: The final study included 9446 CAP cases (average age of 47.6 years, 52.2% male). The majority (56.1%) resided in an MSA with macrolide resistance rates of <25%. Treatment success rates were 82.5% and 80.5% for MSAs with resistance levels being <25% and ≥25%, respectively (P < 0.001). Treatment failure resulting in hospitalization was higher in resistance areas ≥25% at 13.1% versus 8.0% in areas with resistance <25% (P < 0.001). Average adjusted treatment costs were 33% higher for those treated in areas with resistance levels ≥25% than for those treated in areas where resistance was <25%. Treatment success was associated with average adjusted costs that were 58% less than those whose initial treatment failed, controlling for level resistance (P < 0.001).

Conclusions: This study observed an association between community-level macrolide resistance and treatment and economic outcomes. Treatment failure costs were higher for CAP patients treated in areas with macrolide resistance rates ≥25% than for those treated in areas where resistance was ≤25%.

Keywords: infectious disease, antibiotics, macrolides, quinolones

Introduction

Community-acquired respiratory tract infections (RTIs), including community-acquired pneumonia (CAP), are prevalent conditions and constitute a substantial socio-economic burden. In particular, CAP represents a particular public health concern owing to the morbidity and mortality associated with this infection.1–3 In the USA, the incidence of CAP ranges from 4 to 5 million cases per year, with ~25% requiring hospitalization resulting in annual costs of approximately $12.2 billion (US).3

Common causative agents for bacterial CAP include Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis.4 Unfortunately, antimicrobial resistance among these agents has emerged. Penicillin resistance to...
S. pneumoniae in the USA overall has been reported to be 26.4% (38.9% with reduced susceptibility), whereas the percentage of H. influenzae that produced β-lactamase was 28.3%. In addition, resistance to macrolides and quinolones is also emerging. The S. pneumoniae erythromycin resistance rate in the USA was found to be 31.0%, whereas the rate of fluoroquinolone resistance was 0.8%. However, surveillance data have indicated that antimicrobial resistance has regional variation. Thus, the development and spread, and geographical variability of antibiotic resistance among respiratory pathogens, particularly S. pneumoniae, represent a challenge in the management of CAP.

Antimicrobial resistance can also impact CAP patient clinical and economic outcomes. One study of hospitalized CAP cases found that 24% of the treatment failures were related to a persistent causative agent, which includes those resistant to initial treatment, and were most likely caused by antimicrobial resistance. Studies have demonstrated that inpatient costs and pharmacy costs were higher for CAP patients with resistant strains of S. pneumoniae than those with susceptible strains.

Incorporation of resistance information into clinical practice is challenging in the area of RTIs, including CAP. Much of the CAP treatment is empirical as guidelines consider microbiological testing optional in routine outpatient cases. Thus, in the primary care setting, clinicians treat on the basis of patient history such as prior antimicrobial therapy co-morbid conditions, social factors, local CAP aetiology and antimicrobial resistance patterns. Another consequence of empirical treatment is the difficulty it presents for conducting real-world, observational studies of CAP antimicrobial resistance and treatment outcomes in the absence of patient-level microbiological data.

An ecological research design can be used to study antimicrobial resistance and treatment outcomes when patient-level data are scarce. Ecological studies are group-level evaluations that are often conducted to generate hypotheses about the relationships between environmental factors and population outcomes. Thus, ecological designs have been used to help establish whether there are correlations in local antimicrobial resistance, and local treatment outcomes and healthcare resource utilization where patient-level microbiological data are lacking. Therefore, the purpose of this study is to address whether higher CAP treatment failure rates and treatment costs in a defined geographical region are associated with higher levels of S. pneumoniae erythromycin resistance in that area using an ecological design.

Materials and methods

An ecological analysis was conducted using data from 23 defined metropolitan statistical areas (MSAs) from 1 May 2001 to 31 May 2005. Treatment outcome and cost data were obtained from the i3 Magnify database, a pharmacy and administrative claim database with data on 1.5 million members from six Independent Practice Association model health plans, commercial insurers which pay providers on a discounted fee-for-service basis. The associated 13 health plans are located in the Midwest, Northeast, Southeast and Western geographical regions of the USA. Health plan members are of all ages; however, those 65 and older represent a small percentage as individuals in this age group are eligible for Medicare, a government-sponsored health plan for senior citizens.

Community-level antimicrobial resistance information was obtained from the Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin (PROTEKT) database. The PROTEKT study is a global, longitudinal, international surveillance programme established in 1999 to study the antimicrobial susceptibility of common bacterial pathogens associated with community-acquired RTIs. Specimens are acceptable for PROTEKT inclusion if they are isolated from patients with a defined RTI or from hospitalized patients within 48 h of admission. Isolates from patients with nosocomial infections are excluded. From 2001 to 2002, ~60% of the PROTEKT isolates in the USA were S. pneumoniae and 16% were H. influenzae.

The i3 and PROTEKT databases overlapped in 23 MSAs. Thus, subjects in the i3 database were included in the analysis if enrolment data indicated that the patient resided in one of the 23 MSAs where there were corresponding PROTEKT data, were 18 years of age or older, and were continuously enrolled in the health plan for 12 months prior to the first CAP-related diagnosis date and 3 months following the diagnosis date. In addition, included subjects had an outpatient medical claim with a CAP-related diagnosis code (International Classification of Diseases, Ninth Revision, Clinical Modification codes of 481, 482.2, 482.3, 482.9, 483.xx, 485.xx, or 486.xx) and an outpatient pharmacy claim for an antibiotic used in the CAP treatment on or within 7 days after the CAP-related diagnosis. The first identified prescription was labelled as first-line therapy, and the earlier of the first antibiotic fill or the CAP diagnosis was defined as the episode index date.

CAP episodes were excluded from the study if they had a prescription for an anti-infective within 90 days prior to the episode index date and had been prescribed more than one antibiotic to treat CAP on the antibiotic index date. In addition, patients with conditions that mimic pneumonia or with conditions or drug treatment that can make them susceptible to pneumonia or other pulmonary condition prior to the CAP episode were excluded from the analysis. Cases with documentation during the 12 months prior to the CAP episode date of pulmonary embolism, congestive heart failure, lung cancer, hypersensitivity pneumonitis, tuberculosis, chronic obstructive pulmonary disease, granulomatosis disease, fungal infections, systemic lupus erythematosus, polymyositis, polyarteritis nodosa, HIV infection, tuberculosis, cystic fibrosis, or with an organ or bone marrow transplant were excluded. Episodes were also excluded for treatment with cytotoxic agents, non-steroidal anti-inflammatory drugs, antiarrhythmics such as amiodarone or tocainide, select chemotherapeutic agents, biological modifiers or anticonvulsants within 3 months of the CAP episode date. Cases with a claim for hospitalization or a long-term care facility stay the month prior to the CAP diagnosis date were also excluded to avoid cases of nosocomial pneumonia.

Upon population identification, all episodes treated with an antimicrobial in which there were 100 cases or fewer receiving such treatment were excluded. Only quinolones and macrolides were prescribed in 100 or more CAP episodes, and thus cases with initial treatment with all other antimicrobial classes were excluded from the analysis. A CAP episode was defined as the period from the diagnosis date to 45 days post-episode index date. Treatment success was defined as receiving only one antimicrobial prescription with no subsequent hospitalization during the CAP episode period. A patient may have experienced multiple episodes of CAP during the study period.

Treatment failure was determined by a hospitalization after the first day of the episode and before the end of the episode period, or a second antimicrobial prescription for either the same antibiotic or a different regimen 1 day or more after the initial prescription but
before the end of the episode. However, if a medical claim with a different respiratory diagnosis appeared 7 days before or after the fill date of the second antibiotic prescription, the second antimicrobial treatment event did not constitute treatment failure.

Treatment costs were calculated for each episode and included outpatient clinic services, hospitalization (inpatient >24 h), emergency department/urgent care visit (<24 h) and antimicrobial prescriptions. If no treatment failure occurred, treatment costs included the index antibiotic claim, and physician and facility claims for the assigned prescribing condition if such claims occurred within 7 days of the episode index date. Treatment costs related to treatment failure included the initial treatment costs plus subsequent antimicrobial therapy and medical costs occurring during the episode period if the primary diagnosis on the claim was the same as the CAP episode diagnosis. All costs in this study were reported from the perspective of the managed care payer.

Antimicrobial resistance for each MSA was based on the percentage of macrolide (erythromycin)-resistant *S. pneumoniae* isolates, based on CLSI (formerly NCCLS) methodologies that define erythromycin resistance as an MIC >1 mg/L, from the MSA included in the PROTEKT database. Macrolide was selected as the resistance measure because it is recommended as first-line treatment in previously healthy patients with no risk factors for drug resistance, a clinical situation representative of a relatively young, healthy managed care population. Because there is no standard in the literature for categorizing resistance, it was determined that antimicrobial resistance would be categorized on the basis of the distribution of MSA resistance levels. Our goal was to achieve an equal distribution of episodes between resistance groups, although having multiple MSAs within a category to ensure a geographical mix. On the basis of the data distribution, resistance was dichotomized to <25% and ≥25%.

Statistical analysis
Baseline characteristics were identified overall and stratified by percentage of macrolide-resistant isolates in the episode MSA (Table 1). Treatment success or failure was reported by the level of erythromycin resistance and further stratified by quinolone or macrolide treatment. Episode treatment costs were identified by treatment success or failure and stratified by antimicrobial treatment, quinolone or macrolide, as well as by the MSA level of erythromycin resistance. Pearson’s χ² and one-way analysis of variance were used to determine differences in baseline characteristics by the level of resistance as well as overall differences in treatment outcomes and cost for categorical variables, whereas independent t-tests were used to test continuous variables.

In order to ensure unbiased comparisons between macrolide resistance categories, a linear regression analysis was conducted to estimate the effect of antimicrobial resistance in the MSA of treatment on costs, adjusting for factors that could influence outcomes. Independent variables utilized to adjust costs included age at episode date, gender, initial treatment (i.e. quinolone or macrolide), specialty of the diagnosing physician, the number of respiratory-related ambulatory care visits the year prior to the CAP episode, and baseline co-morbidities as defined by the Deyo adaptation of the Charlson co-morbidity index (CCI). Because cost data were not normally distributed, costs were log-transformed. Logged coefficients and standard errors were retransformed to provide estimates of the percentage difference in cost relative to the referent group. The regression analysis was repeated for episodes receiving macrolide treatment or quinolone treatment, controlling for treatment success or failure, and demographic and clinical characteristics defined earlier.

All statistical tests were performed at a 0.05 significance level using Stata SE v. 9 (StataCorp, College Station, TX, USA) and SAS v. 9 (SAS Institute, Cary, NC, USA).

Results
Of the 2.67 million patients in the i3 database from May 2000 to May 2005, 112 625 CAP episodes were identified in the study MSAs and in patients aged 18 and older. A total of 9965 cases were identified in patients with a minimum of 12 months continuous eligibility in the database prior to the CAP episode and at least 3 months continuous activity post-CAP episode and who were treated with an antimicrobial agent within 7 days of diagnosis. As only quinolones and macrolides were prescribed in 100 or more CAP episodes, cases with initial treatment with all other antimicrobial classes were excluded from the analysis. Thus, the final study population included 9446 CAP episodes, of which a majority of cases (56%) were treated with a macrolide (erythromycin, clarithromycin, azithromycin or telithromycin) and 44% of the cases were treated with a quinolone (ciprofloxacin, levofloxacin or moxifloxacin). The cases excluded due to a
low number of treated episodes were distributed across amoxicillin/clavulanate (40 cases; 0.4%), telithromycin (25 cases; 0.3%), or other antimicrobials (classes combined: 454 cases; 4.6%).

Baseline characteristics of the study population are described in Table 1. The episode population was 52.2% males with an average age of 47.6 years (Table 1). The majority of the study cases (56.1%) resided in an area where the macrolide resistance rate was ≤25%. When evaluating baseline characteristics by antimicrobial resistance, populations varied by gender and initial treatment. The percentage of male episodes was higher in the areas with resistance ≤25% (P, 0.05). Macrolides were prescribed for a majority of CAP cases in areas where resistance was ≤25% (61%), whereas quinolones were prescribed more commonly in areas where resistance was >25% (55.1%). Co-morbidities as measured by the CCI did not differ by the level of resistance, with an average CCI of 0.7 for both groups. However, the average CCI for macrolide cases was 0.5, whereas the CCI was 0.9 for quinolone cases (P < 0.001; data not shown).

Overall CAP treatment success rate was 81.6%. The success rate was 82.5% for MSAs with resistance levels ≤25%, which was significantly higher than that for areas with resistance levels >25% (80.5%; P < 0.05) (Table 2). Treatment failure resulting in hospitalization was higher in resistance areas >25% with 13.1% of failures resulting in hospitalization versus 8.0% in areas with resistance ≤25% (P < 0.001).

Macrolides and quinolones did not differ overall by treatment success or failure; however, a significantly higher proportion of quinolone treatment failures resulted in hospitalization than macrolide treatment failures (P < 0.001). This result may reflect the differences in the average CCI (0.5 for macrolides versus 0.9 for quinolones) as described earlier, suggesting that the prognosis for quinolone users was worse. When macrolide and quinolone treatment success or failure was evaluated by the MSA level of resistance, treatment failure was higher for macrolide cases in MSAs where erythromycin resistance was >25% (19.5%) than in areas with erythromycin resistance ≤25% (17.5%; P < 0.05). More macrolide treatment failures in MSAs where resistance was >25% resulted in hospitalization (11.4%) than those in MSAs where resistance was ≤25% (4.4%; P < 0.05). There was no difference in quinolone treatment success or failure or the portion of quinolone failures resulting in hospitalization by the level of erythromycin resistance.

### Table 2. Unadjusted treatment success and failure rates stratified by resistance and by antimicrobial class

<table>
<thead>
<tr>
<th>Resistance level</th>
<th>n</th>
<th>Treatment success (%)</th>
<th>Treatment failures (%)</th>
<th>antimicrobial re-treatment (%)</th>
<th>hospitalized (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>9446</td>
<td>7711 (81.6)</td>
<td>1735 (18.4)</td>
<td>1555 (89.6)</td>
<td>180 (10.4)</td>
</tr>
<tr>
<td>Resistance level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25%</td>
<td>5303</td>
<td>4377 (82.5)</td>
<td>926 (17.5)</td>
<td>852 (92.0)</td>
<td>74 (8.0)</td>
</tr>
<tr>
<td>≥25%</td>
<td>4143</td>
<td>3334 (80.5)</td>
<td>809 (19.5)</td>
<td>703 (86.9)</td>
<td>106 (13.1)</td>
</tr>
<tr>
<td>Antimicrobial treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>macrolides</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>resistance level &lt;25%</td>
<td>3237</td>
<td>2689 (83.1)</td>
<td>548 (16.9)</td>
<td>524 (95.6)</td>
<td>24 (4.4)</td>
</tr>
<tr>
<td>resistance level ≥25%</td>
<td>1861</td>
<td>1500 (80.6)</td>
<td>361 (19.4)</td>
<td>320 (88.6)</td>
<td>41 (11.4)</td>
</tr>
<tr>
<td>quinolones</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>resistance level &lt;25%</td>
<td>2066</td>
<td>1688 (81.7)</td>
<td>378 (18.3)</td>
<td>328 (86.8)</td>
<td>50 (13.2)</td>
</tr>
<tr>
<td>resistance level ≥25%</td>
<td>2282</td>
<td>1834 (80.4)</td>
<td>448 (19.6)</td>
<td>383 (85.5)</td>
<td>65 (14.5)</td>
</tr>
</tbody>
</table>

*aLowest recorded MSA resistance, 19.5%.

<table>
<thead>
<tr>
<th>Treatment costs, $ (SD)</th>
<th>n</th>
<th>resistance level &lt;25%</th>
<th>n</th>
<th>resistance level ≥25%</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment success</td>
<td>4377</td>
<td>1334 (4372)</td>
<td>3334</td>
<td>2193 (5706)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>926</td>
<td>2841 (9635)</td>
<td>809</td>
<td>3918 (10 245)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Macrolides</td>
<td>4189</td>
<td>949.75 (2833.2)</td>
<td>909</td>
<td>2130.00 (7966.60)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Quinolones</td>
<td>3522</td>
<td>2603.70 (6628.30)</td>
<td>826</td>
<td>4678.50 (11585.00)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*aLowest recorded MSA resistance, 19.5%.

Test used: t-test.
The unadjusted average CAP-related treatment cost for successful treatment was $1334 versus $2841 for treatment failure in episodes from MSAs with erythromycin resistance levels <25%. Unadjusted average treatment costs in MSAs with resistance levels ≥25% were $2192 and $3918 for treatment success and failure, respectively. Unadjusted costs for treatment success were significantly less than that for treatment failure, regardless of the level of erythromycin resistance (P < 0.001) or initial CAP treatment (Table 3), and costs regardless of outcome were lower in areas with resistance <25% than in areas with resistance ≥25% (P < 0.05). Unadjusted mean treatment costs for macrolide and quinolone treatment were significantly less in MSAs with macrolide resistance <25% ($949 and $2603, respectively) than in MSAs with resistance ≥25% ($2130 and $4679, respectively; P < 0.001 for both).

Multiple linear regression with log transformation of cost data was utilized to adjust initial treatment costs for patient demographic and clinical characteristics that could influence treatment outcomes. The analysis found that treatment success was associated with average costs that were ~58% less than those whose initial treatment failed, controlling for the patient characteristics described above and by MSA level of resistance (P < 0.001). In addition, study subjects treated in areas with erythromycin resistance ≥25% experienced treatment costs that were ~33% higher than those treated in areas where erythromycin resistance was <25%, controlling for age, gender, initial treatment, treatment outcome, specialty of the diagnosing physician, the number of respiratory-related ambulatory care visits in the prior year and baseline CCI. The same trends were seen in the treatment subgroup analysis. However, the effect of MSA resistance ≥25% relative to resistance level <25% tended to be higher for macrolides than for quinolones (36% versus 30%).

Discussion

This study was designed to evaluate the CAP treatment success rates and outcomes by S. pneumoniae macrolide resistance levels in the inpatient’s MSA of residence. Of 2.67 million patients in the i3 database from May 2000 to May 2005, 9466 subjects met all study inclusion criteria. A majority of the study episodes (56.1%) occurred in an area with macrolide resistance rates of <25%.

The study found that the treatment failure rate was 2% higher in MSAs with erythromycin resistance levels ≥25% than in MSAs with lower resistance levels (P < 0.001). Furthermore, the macrolide treatment failure rate was higher in MSAs with erythromycin resistance ≥25%, whereas the quinolone failure rate did not differ by the MSA level of resistance, which is not unexpected as quinolone treatment outcomes are not related to erythromycin resistance.

To the best of our knowledge, this is the first study that correlates community macrolide resistance levels with treatment outcomes for CAP. Community-level resistance and treatment outcomes for suppurative acute otitis media, acute sinusitis and acute exacerbation of chronic bronchitis, however, have been evaluated. This study, conducted by Furuno et al.,13 did not find an association between resistance level and outcomes, with the exception of a positive correlation between non-susceptibility to erythromycin isolates and macrolide treatment resolution (P = 0.04).

Furuno, however, included penicillin non-susceptibility in addition to erythromycin non-susceptibility, and the evidence is somewhat inconclusive on whether penicillin resistance is associated with CAP treatment outcomes.17 In fact, most of the literature regarding the relationship between S. pneumoniae resistance to antimicrobials and clinical outcomes evaluates the impact of penicillin resistance, with only one additional small retrospective study identified that conducted an evaluation of macrolide treatment failure and macrolide resistance in adults with CAP.17 In a case-based study of 12 S. pneumoniae CAP patients with antibiotic treatment failure, Kelley et al.18 found there were four treatment failures with clarithromycin. Isolates from all four cases revealed a high level of macrolide resistance.

Other studies have evaluated S. pneumoniae resistance to erythromycin in pneumococcal infections and established a relationship between erythromycin resistance, macrolide treatment and bacteraemia breakthrough. In a case–control study of hospitalized patients by Lonks et al.,19 86 cases with erythromycin-resistant or -intermediately resistant S. pneumoniae bacteraemia [65 (76%) were pneumonia episodes] were matched to 114 controls [111 (97%) were pneumonia episodes] with susceptible S. pneumoniae bacteraemia. This study found that 24% of the cases, but none of the controls, were being treated with a macrolide when the bacteraemia broke-through. Thus, the authors concluded that breakthrough bacteraemia was more likely to occur in patients with an erythromycin-resistant pneumococcal infection treated with a macrolide.

In the economic analysis of the current study, treatment costs were 57.0% lower with treatment success than with treatment failures in the overall population, controlling for differences in patient demographic and clinical characteristics between groups (P < 0.001). Adjusted treatment costs were 33.1% higher in the MSAs with erythromycin resistance ≥25% controlling for treatment outcome (P < 0.001), with the effect of resistance greater for macrolide cases. Unadjusted treatment costs were notably higher for quinolones than for macrolides for treatment success and failure. This difference could be explained by drug costs, as there are more generic alternatives for macrolides than for quinolones. However, this cost difference could also be explained by the baseline characteristics of the quinolone group, which had a higher CCI than macrolides and thus may have been sicker and more prone to poor CAP outcomes. The finding of increased hospitalization/costs in the fluoroquinolone group may be due to the fact that fluoroquinolones are recommended and widely used for the treatment of patients with CAP who are at risk for infection due to macrolide-resistant S. pneumoniae and other drug-resistant S. pneumoniae. So by indication, this group of patients is at higher risk of having an infection that leads to hospitalization. Besides, there is an emerging resistance to fluoroquinolone treatment, and treatment failures may add to the increased hospitalization rate at baseline in the fluoroquinolone group.

These economic findings, although generally intuitive, are also consistent with the literature that evaluates CAP costs relative to treatment success or failure. In a retrospective, observational, cohort, single-centre study of hospitalized CAP patients infected with S. pneumoniae, Klepser et al.8 found that total treatment costs were higher in the group with a non-susceptible strain of S. pneumoniae than those infected with a susceptible strain ($27958 versus $19372; P < 0.05). The economic variance was driven by differences in utilization for hospital room,
nursing and pharmacy resources. A second case-control study of hospitalized patients by Einarsson et al.\textsuperscript{9} found that those with non-susceptible \textit{S. pneumoniae} CAP had significantly higher average antibiotic costs than those whose CAP was caused by a susceptible strain ($736 versus $213; P < 0.001). Although these studies evaluated economic outcomes specific to \textit{S. pneumoniae} penicillin resistance and CAP treatment costs versus the current study’s evaluation of macrolide resistance, the data provide evidence that CAP treatment failure is associated with significantly higher treatment costs.

When treatment costs were evaluated by initial treatment, the MSA level of erythromycin resistance continued to be a significant predictor of cost, with macrolide treatment costs, \textasciitilde36\% higher in MSAs where macrolide resistance was $\geq 25\%$. This cost difference is likely to be driven by higher failure rates and a higher proportion of failure MSAs with erythromycin resistance $\geq 25\%$ resulting in hospitalization than in MSAs with resistance $< 25\%$. Although quinolone failure rates were not associated with the level of erythromycin resistance, treatment costs for the quinolone episodes were also higher in MSAs with higher resistance ($\textasciitilde 30\%$). These findings suggest that other unmeasured factors may contribute to costs in the MSAs with macrolide resistance levels $\geq 25\%$, such as higher rates of non-\textit{S. pneumoniae} CAP cases or more aggressive treatment patterns related to higher expectation of treatment failure.

There are several limitations to this study that must be mentioned. First, a well-known limitation of ecological studies is that effects measured at the population level may not represent the association at the individual level.\textsuperscript{1,2} Thus, it would not be appropriate to draw conclusions about how community-level antimicrobial resistance impacts individual CAP patient outcomes as unmeasured effects may confound the findings. However, we do not believe that the design of the study should discount the importance of these findings. Most CAP cases are initially treated empirically, and a proportion of all outpatient cases are treated entirely on an empirical basis. Thus, this study suggests that local macrolide resistance levels may be associated with clinical and economic outcome trends in the area, evidence that clinicians may choose to consider when making treatment decisions.

Several limitations are related to the study population and data source. Due to the scope of the study database, the study population for establishing treatment success and failure rates and economic data was limited to managed care patients of select geographical regions and, as such, is not reflective of the overall US population. Thus, generalizing these results beyond the geographies that they represent or to non-managed care patients should be undertaken with caution. In addition, being based on a managed care population, the study likely underrepresents the Medicare age population (age 65+), who would have a higher incidence of CAP, have more co-morbidities, may have different resistance patterns due to prior antimicrobial exposure and thus be more likely to experience poor outcomes.

Another data-related limitation of the study is that the data do not allow for complete adjustment for all factors that could impact outcomes, including severity of illness. The study designed attempted to control these factors by including only non-hospitalized episodes and adjusting for age, the number of respiratory-related ambulatory care visits in the year prior to the CAP episode, and baseline co-morbidities. However, data regarding the time from onset of CAP to treatment, vital signs and other biological indicators or disease severity are not captured in the i3 administrative database and thus could not be incorporated into the analysis.

Another limitation is related to the resistance data used from the PROTEKT database. Study data were limited to macrolide resistance for \textit{S. pneumoniae}, which is the most common causative microbe associated with CAP. However, there are numerous causative bacteria in CAP, and thus differences in the distribution of causative organisms between MSAs may confound correlations between treatment outcomes and \textit{S. pneumoniae} resistance levels.

In addition, bacterial CAP is a challenging disease to study due to the empirical nature of initial treatment and assessment. Thus, as a disease, CAP is susceptible to misdiagnosis due to pneumonias resulting from non-bacterial causes. Although this study took a thorough approach to excluding patients who have underlying conditions or other medical and pharmacological treatments that can mimic pneumonia, it remains possible that not all cases included in this study were truly CAP. In contrast, the thorough inclusion and exclusion criteria may have excluded initial CAP episodes.

Conclusions

This current study quantified CAP-related treatment outcomes and treatment costs by the level of macrolide resistance in select geographical areas and found positive correlations between macrolide resistance rates of 25\% or higher, treatment failure and treatment costs. As an ecological analysis, it is not possible to establish causation between CAP resistance and patient-level outcomes; however, this study provides insight into the potential role community antimicrobial resistance plays in overall clinical and economic outcomes. This is particularly relevant in a treatment paradigm in which antimicrobial treatment decisions are made empirically and thus local resistance levels are the most specific resistance data available to clinicians at the time of treatment. Furthermore, this study provides value in providing additional theoretical support for clinical trials or cohort studies to more thoroughly investigate the relationship between macrolide resistance and treatment outcomes.

Acknowledgements

We thank Brian Oberg for his role as data analyst for this study.

Funding

This study was funded by Sanofi-Aventis Pharmaceuticals.

Transparency declarations

B. S. is an employee of Sanofi-Aventis and holds stocks. C. A. and C. D. M. have acted as consultants for Sanofi-Aventis in the past, but they did not act as consultants in relation to this manuscript. Other authors: none to declare.
References


