

Decision and cost analysis of empirical antibiotic therapy of acute sinusitis in the era of increasing antimicrobial resistance: do we have an additional tool for antibiotic policy decisions?

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Abstract

OBJECTIVE: No previous analyses have attempted to determine optimal therapy for upper respiratory tract infections on the basis of cost-minimization models and the prevalence of antimicrobial resistance among respiratory pathogens in Slovakia. This investigation compares macrolides and cephalosporines for empirical therapy and look at this new tool from the aspect of potential antibiotic policy decision-making process.

METHODS: We employed a decision tree model to determine the threshold level of macrolides and cephalosporines resistance among community respiratory pathogens that would make cephalosporines or macrolides cost-minimising. To obtain information on clinical outcomes and cost of URTIs, a systematic review of the literature was performed. The cost-minimization model of upper respiratory tract infections (URTIs) treatment was derived from the review of literature and published models.

RESULTS: We found that the mean cost of empirical treatment with macrolides for an URTIs was €93.27 when the percentage of resistant *Streptococcus pneumoniae* in the community was 0%; at 5%, the mean cost was €96.45; at 10%, €99.63; at 20%, €105.99, and at 30%, €112.36. Our model demonstrated that when the percentage of macrolide resistant *Streptococcus pneumoniae* exceeds 13.8%, use of empirical cephalosporines rather than macrolides minimizes the treatment cost of URTIs.

CONCLUSIONS: Empirical macrolide therapy is less expensive than cephalosporines therapy for URTIs unless macrolide resistance exceeds 13.8% in the community. Results have important antibiotic policy implications, since presented model can be use as an additional decision-making tool for new guidelines and reimbursement processes by local authorities in the era of continual increase in antibiotic resistance.

INTRODUCTION

Acute sinusitis (or rhinosinusitis) represents one of the most common diagnoses in ambulatory care, and one of the most frequent causes for prescription of antibiotic treatment (Schappert & Burt 2006). The choice of antibiotic therapy is empiric, in most cases, among agents potentially effective against the most frequently encountered upper respiratory tract pathogens, including *Streptococcus pneumoniae*, *Haemophilus influenzae* and, particularly in children, *Moraxella catarrhalis* (Gwaltney 1996; Masaryk 2016). Rhinosinusitis is an extremely common condition. In US health survey conducted during 2008, nearly 1 in 7 (13.4%) of all non-institutionalized adults aged 18 years were diagnosed with rhinosinusitis within the previous 12 months. Incidence rates among adults are higher for women than men (1.9-fold), and adults between 45 and 74 years are most commonly affected (Pleis *et al.* 2008). The prevalence of a bacterial infection during acute rhinosinusitis is estimated to be 2%–10%, whereas viral causes account for 90–98% (Gwaltney *et al.* 2004). Despite this, antibiotics are frequently prescribed for patients presenting with symptoms of acute rhinosinusitis, being the fifth leading indication for antimicrobial prescriptions by physicians in office practice (Anand 2004). The total direct healthcare costs attributed to a primary medical diagnosis of sinusitis in 1996 were estimated to exceed \$3 billion per year (Ray *et al.* 1999). US survey of antibiotic prescriptions for URTIs in the outpatient setting showed that antibiotics were prescribed for 81% of adults with acute rhinosinusitis (Gill *et al.* 2006; Young *et al.* 2008).

Experts are concerned about overuse of macrolides leading to increased prevalence of macrolide-resistant pathogens that has major implications for the treatment of mainly upper respiratory tract infections (URTIs) (Doern *et al.* 2005; Lynch & Zhanel 2002). Resistance to the macrolide antibiotics (e.g., erythromycin, clarithromycin, and azithromycin) escalated in tandem with penicillin resistance (Doern *et al.* 2005; Lynch & Zhanel 2002). In addition, macrolide resistance can develop independently of penicillin resistance (Lynch & Martinez 2002; Geslinet *et al.* 1992). In many parts of the world, macrolide-resistant *Streptococcus pneumoniae* is more common than PRSP (penicillin resistant *Streptococcus pneumoniae*) (Song *et al.* 2004; Felmingham *et al.* 2002). Cefotaxime and ceftriaxone are the most active cephalosporines against pneumococci (Lynch & Martinez 2002). Despite marked escalation in PRSP, rates of resistance to cefotaxime (MICs $\geq 2 \mu\text{g/mL}$) globally remain low (1 to 7%) (Karlowsky *et al.* 2003; Jones *et al.* 2007).

We have no information about previous analyses that would have attempt to determine optimal therapy for URTIs on the basis of cost-minimization models and the prevalence of antimicrobial resistance among respiratory pathogens in Slovakia. This investigation

compares macrolides and cephalosporines for empirical therapy of URTIs. We performed a cost-minimization and sensitivity analysis comparing cephalosporines and macrolides to determine the threshold level of antimicrobial resistance for which each of these antibiotics becomes cost-minimizing.

Previously, we have compared in small randomized trial therapy with ceftibuten, ofloxacin and azithromycin for pneumonia and acute exacerbation of chronic bronchitis. No statistical differences between 3rd generation cephalosporines and macrolides were observed. Limitation of this trial was small sample size of patients and good general performance of patients. We didn't observed statistical differences in occurrence of adverse events and drug-drug interactions (Thornberry *et al.* 1982).

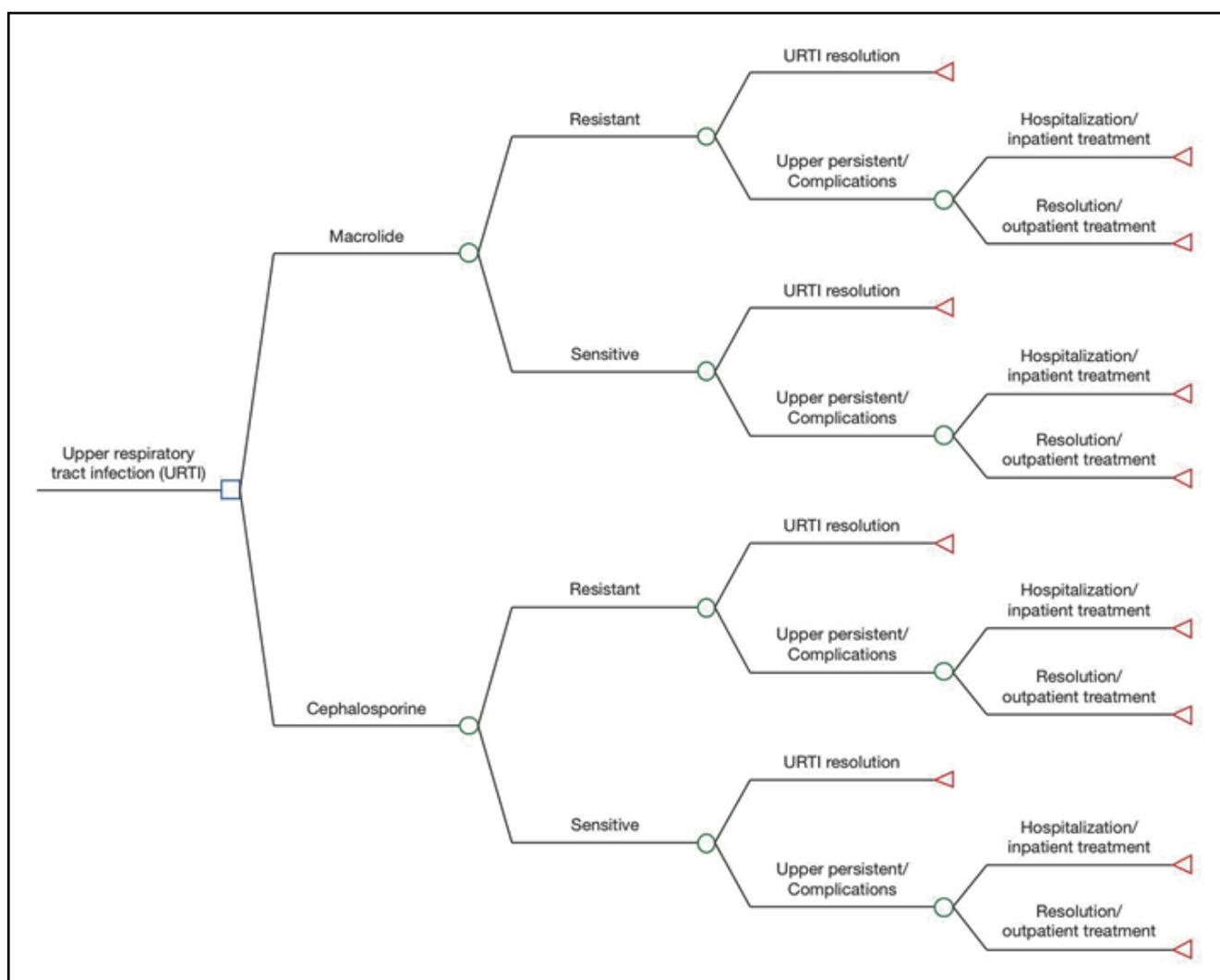
METHODS

To determine the threshold level of macrolides and cephalosporines resistance among community respiratory pathogens that would make cephalosporines or macrolides cost-minimizing, we employed a decision tree model using the TreeAge Pro software (Version 2013). The model is based on a clinical pathway model of acute bacterial rhinosinusitis treatment in adults (Chow *et al.* 2012). To obtain information on clinical outcomes and cost of URTIs, a systematic review of the literature was performed. We searched PUBMED articles through June 2014, with the key words *respiratory*, *upper-respiratory*, *rhinosinusitis* and combine these words with *cost*, *efficacy*, *response* or *cure*. Similar systematic searches were conducted using Medline and Cochrane Library databases. Reviewers assessed abstracts and if an abstract suggested that the article contained data on clinical cure rates of URTIs or rhinosinusitis based on antimicrobial susceptibility, the article was reviewed. We reviewed also Slovak published articles using same methodology, since we needed to detect most relevant resistance and cost data applicable to local conditions (Masaryk 2015).

The cost-minimization model of URTI treatment was derived from the review of literature and published models (Chow *et al.* 2012; McKinnell *et al.* 2011; Le & Miller 2001). In the model it was assumed that clinicians would choose to empirically treat URTIs with 3 to 10 day course of macrolides or 5-day course of cephalosporines 3rd generation (Table 1). We assumed that empirical treatment involved a physician visit and clinical examination to confirm the presence of URTI and that microbiology tests were not performed initially, as recommended by IDSA guidelines (Chow *et al.* 2012). Our model assumed that all infections were ultimately cured, although some treatments for URTI would initially fail to respond, but would later resolved after treatment of complications and/or would lead to adverse effects that were subsequently cured.

Tab. 1. Cost of interventions to treat an URTI caused by *Streptococcus pneumoniae* that were used in model and subsequent sensitivity analyses.

Description of therapy	Days of treatment or Number of items	Dosage	Mean cost per unit or per item (in EUR)	References
Azithromycin	3	500 mg	3.87	20
Clarithromycin	10	500 mg	4.46	20
Ceftibuten	5	400 mg	12.6	20
Cefixime	5	200 mg	13	20
Amoxicillin & Clavulanic Acid	7	625 mg	6.24	20
Clindamycin	4	300 mg	3.43	20
Hospitalization (URTIs complications)	1	n.a.	550	Mean payment for 1 hospitalization in Kosice, Bratislava and Nove Zamky at the E.N.T. department
Initial visit to a physician for URTI	1	n.a.	42	21
Microbiologie culture & procedure	1	n.a.	12.97	27
Follow-up physician visit	1	n.a.	42	21
Follow-up microbiologie culture & proc	1	n.a.	12.97	27

**Fig. 1.** Decision tree diagram that shows intermediate and final outcomes for an URTI (upper respiratory tract infection) caused by *Streptococcus pneumoniae* treated with either macrolide or cephalosporine.

The decision analysis model for the comparison of macrolides and cephalosporines is shown in Figure 1. We have identified four main scenarios, depending on the agent used and whether organism had in vitro susceptibility (Figure 1). The first scenario examined treatment of macrolide resistant *Streptococcus pneumoniae* infection with macrolide, resulting in recovery or initial clinical failure. Initial clinical failure led to a scenario for a complicated course outcome. Potential intermediate outcome included hospitalization for complications due to URTIs, outpatient treatment for complication associated with URTI and persistence of rhinosinusitis symptoms resulting in change or in addition of other antibiotic either before or after culture results were available.

In the second scenario, we examined the outcomes for a patient treated with macrolides for infection caused by a macrolide susceptible *Streptococcus pneumoniae* using similar schema. In subsequent scenarios we examined URTIs cause by *Streptococcus pneumoniae* treated with cephalosporines. When cephalosporines treatment failed to resolve the symptoms, the cephalosporines treatment was either continued until culture results dictated treatment or empirically changed to a regimen aimed against cephalosporines resistant *Streptococcus pneumoniae*.

Costs

Costs used in this model were based on the systematic review of the literature and a survey of costs derived from national and local sources (Table 1). Antibiotic costs were acquired from official reimbursement list published each month in Slovak republic (MZSR 2014). Costs of hospitalization were compiled from a national survey and incorporated the average cost of a single

hospitalization (Table 1). Costs of physician visits were derived from the literature (HPI 2014).

Probabilities

Probabilities for clinical events were obtained from multiple published estimates with use of the mean value as the point estimate in the model (Hadley *et al.* 2010; Stalman *et al.* 1997; Varonen *et al.* 2003; Williamson *et al.* 2007; Bucher *et al.* 2003; Hansen *et al.* 2000; Haye *et al.* 1998; Lindbaek & Hjortdahl 1998; De Sutter *et al.* 2002; Gananca & Trabulsi 1973; Kaiser *et al.* 2001; Lindbaek *et al.* 1996; Merenstein *et al.* 2005; van Buchem *et al.* 1997; Stone *et al.* 2000). Clinical response was derived from prospective clinical trials, investigations and from local clinical experts experience where we had less than 1 source, to minimize authors' bias.

Sensitivity analyses

One-way sensitivity analyze was performed for the comparison of mean cost of empirical treatment with macrolides vs. cephalosporines. In addition, a 2-way sensitivity analysis was performed to determine how changing the values of each cost and resistance probability in the model would affect the cost-minimization threshold (Table 1). Table 1 summarizes the costs employed in our model. In each case we consider an initial costs including office visit and clinical examination by doctor (HPI 2014). Sensitivity analysis was also performed to determine how changing the values of each cost and resistance probability in the model would affect the cost minimization threshold. For costs, a range incorporating 50% and 200% of the point estimate was used (Table 2). For all probabilities, the range probabilities for clinical events found in the literature survey was used (Chow *et al.* 2012; Babela *et al.* 2012;

Tab. 2. Values of cost of interventions used for 2-way sensitivity analysis with extremes of range tested (50% and 200%).

Description	Range of probability tested (in EUR)	Change in cost-minimization threshold at extremes of range tested with >5% change (macrolides)	Change in cost-minimization threshold at extremes of range tested with >5% change (céphalosporines)
macrolides (Azithromycin/Clarythromycin)	2.08–8.33		
céphalosporines (Ceftibuten/Cefixime)	6.4–25.6		X
Amoxicillin & Clavulanic Acid	3.12–12.48		
Clindamycin	1.715–6.86		
Hospitalization (URTIs complications)	275–1100	X	X
Initial visit to a physician for URTI	21–84	X	X
Microbiologie culture & procedure	6.49–25.94		
Follow-up physician visit	21–84	X	X (at 200% only)
Follow-up microbiologie culture & procedure	6.49–25.94		

Hadley *et al.* 2010; Stalman *et al.* 1997; Varonen *et al.* 2003; Williamson *et al.* 2007; Bucher *et al.* 2003; Hansen *et al.* 2000; Haye *et al.* 1998; Lindbaek & Hjortdahl 1998; De Sutter *et al.* 2002; Gananca & Trabulsi 1973; Kaiser *et al.* 2001; Lindbaek *et al.* 1996; Merenstein *et al.* 2005; van Buchem *et al.* 1997).

RESULTS

We found that the mean cost of empirical treatment with macrolides for an URTI was €93.27 when the percentage of resistant *Streptococcus pneumoniae* in the community was 0%; at 5%, the mean cost was €96.45; at 10%, €99.63; at 20%, €105.99, and at 30%, €112.36. At the current level of cephalosporines 3rd generation resistance among *Streptococcus pneumoniae* isolates [Babela *et al.* 2012], mean cost of empirical treatment with cephalosporines is €102.02. On the basis of our model, our sensitivity analysis demonstrated that when the percentage of macrolide resistant *Streptococcus pneumoniae* exceeds 13.8%, use of empirical cephalosporines rather than macrolides minimizes the treatment cost of URTIs (Figure 2).

For the comparison of macrolides and cephalosporines, the sensitivity analysis demonstrated that, when the percentage of macrolide resistant exceeds 13.8%, empirical treatment with cephalosporines becomes cost-minimizing. Below that level, macrolides are cost minimizing compared to cephalosporines (Figure 2). At the current level of national macrolide resistance among *Streptococcus pneumoniae* in community isolates, the mean cost of empirical treatment with macrolides is €112.36. [Babela *et al.* 2012). At the 13.8% macrolide resistance breakpoint, the mean total cost of empirical treatment of URTIs with cephalosporines is cost-minimizing (€102.02).

For the 2-way sensitivity analysis we use comparable methodology published by McKinnell *et al.* (2011). In our 2-way sensitivity analyses we examined extreme values, the 13.8% threshold did not differ by >5% for the costs of the following services or treatments: empirical antibiotic treatment, additional antibiotic treatment, microbiologic testing and follow-up microbiology tests. Variables that had more impact included the cost hospitalization, initial visit to a physician and the cost of a return medical visit (Table 2), which changed the threshold by more than 5%.

In 2-way sensitivity analyses, extreme values of the probabilities negligibly affected (<5%) the threshold: proportion of macrolide resistant infections treated with macrolides that were cured, changing antibiotics after lack of clinical response to macrolides, changing antibiotics after lack of clinical response to cephalosporines. However, the proportions of cephalosporines susceptible, macrolide susceptible, and macrolide resistant *Streptococcus pneumoniae* infections clinically cured had a relatively larger impact on our break point. When the proportion of cepha-

losporines resistant *Streptococcus pneumoniae* in the community increased to 10%, the 13.8% threshold climbed to 16.3%.

When the proportion of macrolide susceptible *Streptococcus pneumoniae* infections cured with macrolides reached 100%, the threshold was not reached. In the reverse manner, when the clinical cure rate for cephalosporines susceptible *Streptococcus pneumoniae* infections cured with cephalosporines therapy was 100%, it lowered the threshold to 11.3%.

Considering same level of resistance evolution for both categories of antibiotics, we found that until 22% of *Streptococcus pneumoniae* resistance in community it would be cost-minimising to use macrolides compared to cephalosporines (€107.27 vs €107.42, respectively). From 23% resistance threshold empirical treatment with cephalosporines would be cost-minimising compared to macrolides (€107.74 vs €107.90, respectively).

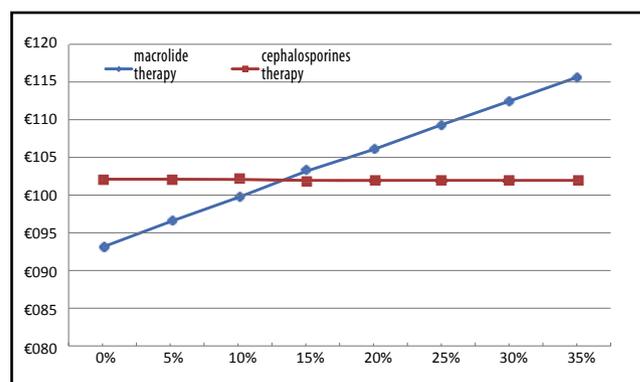


Fig. 2. Comparison of the mean cost of treatment of URTIs caused by *Streptococcus pneumoniae* with macrolides vs the community prevalence of macrolide resistant *Streptococcus pneumoniae*. The threshold for macrolide resistance when cephalosporines (3rd generation) becomes cost-minimizing was 13.8% with an estimated cost of €102.02 to the payer. Left is cost per one patient and on the bottom line is resistance in %.

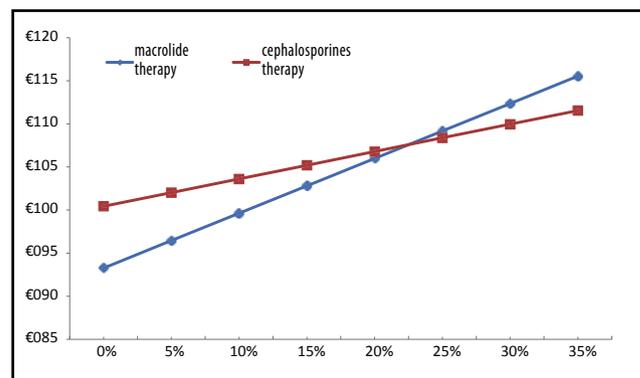


Fig. 3. Comparison of the mean cost of treatment of *Streptococcus pneumoniae* URTIs (rhinosinusitis) with macrolides and cephalosporines in the community with same level of resistance. The threshold for macrolide resistance above which cephalosporines (3rd generation) becomes cost-minimizing is 23% with an estimated cost of €107.90 to the payer compared to €107.74 for cephalosporines. Left is cost per one patient and on the bottom line is resistance in %.

This simulation is only hypothetical, since current level of cephalosporines resistance (3rd generation) is no more than 5% nationwide (Babela *et al.* 2012).

DISCUSSION

Using a cost-based model performed in several other studies (McKinnel *et al.* 2011; Le & Miller 2001), we have performed what we believe to be the first cost and sensitivity analysis to determine what level of macrolide resistance in the community should trigger a switch of empirical therapy for URTIs from macrolide to cephalosporine. To our knowledge, our investigation is also the first to employ decision analysis to explore the relationship between antimicrobial resistance and clinical decision-making in local settings. Decision analyses are ideal for answering questions that are difficult or impossible to resolve in a clinical trial. Our investigation demonstrated that when the proportion of macrolide resistant *Streptococcus pneumoniae* exceeds 13.8% in a community, then empirical cephalosporines therapy becomes less expensive than initial therapy with macrolides.

There are several strengths to our investigation. First, our model employed data obtained by a systematic review of the medical literature, complemented by data from official sources. Second, we directly addressed the impact of antimicrobial resistance on empirical antibiotic choices for rhinosinusitis, building upon previous investigations and employing a more detailed decision tree that incorporated more intermediate health outcomes. Finally, we employed 2-way sensitivity analyses, which have not been used in any of previous analyses locally examining the cost of treating URTIs. Similar and older cost analyses published elsewhere [Anand 2004; Ray *et al.* 1999], employed only 1 source for costs or probabilities were limited by the values used in their models, which may be imprecise.

Our study has several limitations. First, any decision analysis is potentially limited by its inherent simplicity. Uncommon outcomes like drug allergies or adverse events were not considered in our model. Another limitation in our model was that we studied only URTIs caused by *Streptococcus pneumoniae*. However, this organism causes most of URTIs and thus is responsible for the vast majority of cost. Data which describe incidence of the other pathogens than *Streptococcus pneumoniae* vary from study to study. In the most complex clinical observation from Czech republic was incidence of atypical pathogens very high and thus is responsible for the vast majority of cost (Kolek *et al.* 2002). Our model also does not respect the influence of vaccination of elderly and risky patients with conjugate 13-valent antipneumococcal vaccine, which is now available in Slovak and Czech conditions (Chlíbek 2013; Pneumokok 2014). Routine vaccination of children with conjugate vac-

cine had impact to occurrence of some serotypes of *Streptococcus pneumoniae* not only in children age hood, but also in elderly. Vaccination led to decrease incidence of pneumococcal diseases in elderly and it is associated with decreasing of resistance antibiotics to of *Streptococcus pneumoniae* (Richter & Heilmann 2013). Our model was also limited because published data on clinical response to cephalosporines were confined to studies in which not all currently available cephalosporines were used.

Finally, our results are derived from an economic model. Clearly, other important factors should help determine the antimicrobial of choice for a URTIs, such as potential to alter local resistance patterns. To reduce the selective pressure driving the emergence of cephalosporine resistance in communities, antibiotic policy makers may wish to use a threshold higher than the level we found, up to 15%. Conversely, arguments could be made for lowering the threshold to 12% to minimize uncommon complications and absenteeism from work and school. Our 2-way sensitivity analyses led to several important observations. The only costs that significantly impacted our break points (>5%) were those of cephalosporines, hospitalization and follow-up physician visits. This supports the adequacy of the model, given the inherent methodological problems with measuring costs of medical services (Le & Miller 2001; Stone *et al.* 2000). Probabilities of clinical cure for macrolide susceptible, macrolide resistant and cephalosporines susceptible *Streptococcus pneumoniae* also had significant effects on our break point. Sometimes, microbiological susceptibility may correlate weakly with clinical outcomes (Le & Miller 2001; Thornsberry *et al.* 1982; Fuchs *et al.* 1989). Future research should be aimed at better delineating clinical cure rates based on respiratory antimicrobial susceptibilities (Zareba-Szczudlik *et al.* 2016). Our results would be enhanced by more reports on the prevalence of resistance in respiratory pathogens causing URTIs and more accurate cost data mainly from hospitalization cost aspect (HPI 2014; Babela *et al.* 2012).

Longer duration of antibiotic treatment might have disadvantages, compared with equally effective shorter duration treatment (offered for example by 3rd generation cephalosporines), including higher toxicity, promotion of bacterial drug resistance and greater overall economic burden. Regarding toxicity, the most common adverse events reported in the RCTs included in Falagas *et al.* (2008) meta-analysis were gastrointestinal in nature, consisting primarily of diarrhoea and nausea/vomiting. Although these are frequently non-severe, they can cause considerable patient discomfort and decrease compliance with therapy. Prolonged antimicrobial therapy is often associated with poor patient compliance after the resolution of symptoms or because of toxicity; a fact that may lead to inappropriately low drug levels, thus facilitating the emergence of resistance (Kardas 2002; Schwartz *et al.* 1981). Last, but not least,

the economic benefits of shortened effective treatment should not be disregarded, since at a community level the cost of even 2 extra days of therapy may be appreciable (Harris & Lloyd 1994).

CONCLUSION

We conclude that empirical macrolide therapy is less expensive than cephalosporines therapy for URTIs unless macrolide resistance exceeds 13.8% in the community. From a payer perspective and from the antibiotic policy decision-maker perspective, we constructed important model, which can serve as important add-on tool for decision-making process, especially given the current prevalence of macrolides resistance among *S. pneumoniae* in community that reached 30% level, nationwide (Babela *et al.* 2012). Although 13.8% break point is based purely on economic considerations, concerns of inducing further cephalosporines resistance in communities suggest that this threshold may need to be raised even further to 15% or 18%. The paucity of information on clinical cure rates following treatment against antibiotic susceptible and antibiotic resistant pathogens highlights the need for further data analysis on this issue.

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