EMPIRICAL THERAPY FOR RESPIRATORY TRACT INFECTIONS IN AN ERA OF INCREASING ANTIMICROBIAL RESISTANCE: A DECISION AND COST ANALYSIS

Robert Babela
St. Elizabeth University
DHEHA, Bratislava, Slovakia

BACKGROUND
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 [1]. 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 sinusitis, Moraxella catarrhalis [2]. Rhinosinusitis is an extremely common condition. In US health survey conducted during 2008, nearly 1 in 17 (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 [3]. The prevalence of a bacterial infection during acute rhinosinusitis is estimated to be 2%-10%, whereas viral causes account for 90%–98% [4]. 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 [5]. The total direct healthcare costs attributed to a primary medical diagnosis of sinusitis in 1998 were estimated to exceed $3 billion per year [6]. US survey of antibiotic prescriptions for URIs in the outpatient setting showed that antibiotics were prescribed for 81% of adults with acute rhinosinusitis [7,8].

Experts are concerned about overuse of macrolides leading to increased prevalence of macrolide-resistant pathogens that has major implications for the treatment of many upper respiratory tract infections (URTI). Resistance to the macrolide antibiotic (e.g., erythromycin, clarithromycin, and azithromycin) escalated in tandem with penicillin resistance [9,10]. In addition, macrolide resistance can develop independently of penicillin resistance [11,12]. In many parts of the world, macrolide-resistant Streptococcus pneumoniae is more common than PRSP [13,14]. Cefotaxime and ceftriaxone are the most active cephalosporines against pneumococci [11]. Despite marked escalation in PNSP, cefotaxime and ceftriaxone are the most active cephalosporines for empirical therapy of URTIs. We performed a cost-minimization and sensitivity analysis comparing macrolide and cephalosporines treatment for URIs. We performed a cost-minimization and sensitivity analysis comparing cephalosporines to macrolide, and to determine the threshold level of antimicrobial resistance for which these antibiotics become cost-minimizing.

METHODS
To determine the threshold level of macrolide and cephalosporines resistance among community respiratory pathogens that would make cephalosporines cost-minimizing, we employed a decision tree model using the FreeAge Pro software (Version 2015). The model is based on a clinical pathway model of acute bacterial rhinosinusitis treatment [7]. Model uses a payer perspective for the study. To obtain information on clinical outcomes and cost of URIs, a systematic review of the literature and local sources was performed. The cost-minimization model of URIs treatment on scenarios was derived from the review of the literature and published models [18,19]. In the model, infection would resolve with initial therapy or would fail to respond to initial therapy (Figure 1). In the latter case, the URTI would resolve after continuation with that treatment or the original antibiotic treatment would be extended. Potential complications of clinical non-response included hospitalization due to rhinosinusitis complications. The decision analysis model for the comparison of macrolide and cephalosporines treatment is shown in Figure 1. Because cephalosporines resistance is generally determined relatively stable in Slovakia and Europe, cefotaxime resistance was held constant at 0.5% for the model [15,16].

RESULTS
For the comparison of macrolides and cephalosporines, the sensitivity analysis demonstrated that, when the percentage of macrolide resistant exceeds 15%, empirical treatment with cephalosporines becomes cost-minimizing. At that level, macrolides are cost-muching compared to cephalosporines (Figure 4). At the 15% macrolide resistance breakpoint, the total cost of empirical treatment of URIs with macrolides was 79 EUR.

CONCLUSIONS
A number of antibiotic resistance may have disadvantages, compared with equally effective shorter duration treatment (e.g., in the case of the 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 gastrointestinal (23,24). Last, but not least, the economic benefits of shortening effective treatment should not be disregarded, since at a community level the cost of even 2 extra days of therapy may be appreciable [25]. We believe we have performed the first cost-based model and sensitivity analysis to determine what level of macrolide resistance in the community prevents macrolides from being cost-effective for empirical therapy for URIs from macrolides to cephalosporines in Slovakia. Our investigation also employed decision analysis to explore the relationship between antimicrobial resistance and clinical decision making in URIs. From a payer perspective, cephalosporines appears to be a reasonable alternative to macrolides for empirical treatment of URIs, especially given the current prevalence of macrolide resistance among S. pneumoniae in community that reached 30% level [26].