Antibiotic Treatment of Respiratory Tract Infections in Ambulatory Care in Belgium

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Abstract: This study aims to analyse antibiotic treatment of respiratory tract infections in ambulatory care in Belgium by: a) mapping antibiotic consumption over time and breaking down antibiotic consumption by infection type; b) discussing antibiotic treatment as recommended by Belgian guidelines; and c) reviewing the current evidence on the cost-effectiveness of antibiotic treatment. IMS Health data showed that the total volume of antibiotic consumption in ambulatory care in Belgium has increased over the years. Antibiotic consumption mainly originated from the use of broad-spectrum penicillins. The volume of fluoroquinolone use remains well controlled. Policy makers need to target the main drivers of inappropriate antibiotic consumption rather than a specific class of antibiotics when they aim to promote better use of antibiotics in ambulatory care. A ß-lactam-based therapy for CAP is recommended as first choice in Belgian guidelines and moxifloxacin is advocated for CAP outpatients with comorbid conditions or outpatients in whom infection with atypical pathogens needs to be considered. Because of its high eradicating power against the target organisms and because *H. influenzae* is the main pathogen to be covered, amoxicillin-clavulanic acid may be a first choice to treat COPD exacerbations, although this choice is subject to debate. Moxifloxacin is recommended in case of IgE-mediated ß-lactam allergy or severe intolerance to ß-lactam antibiotics for the treatment of COPD exacerbations or for the treatment of upper respiratory tract infections on the rare occasion that antibiotic treatment is warranted. One study supported the cost-effectiveness of first-line treatment of CAP with moxifloxacin in Belgium.

Keywords: Ambulatory care, antibiotics, Belgium, Consumption, Cost-effectiveness, Guidelines, Respiratory tract infections.

INTRODUCTION

Antibiotics have made a significant contribution to improving the health of patients suffering from bacterial infections. The scientific literature and international guidelines recommend antibiotic therapy in patients with acute exacerbations of chronic obstructive pulmonary disease (COPD) (GOLD stages II to IV and/or acute respiratory failure) and community-acquired pneumonia (CAP) [1,2]. Also, antibiotics appear effective in improving cure rates and decreasing duration of some upper respiratory tract infections in patients who have a microbiological diagnosis of bacterial infection or severe disease [3].

In an era of scarce health care resources, policy makers and health care payers focus on the costs of antibiotics in addition to their effectiveness. Rising consumption of antibiotics is contributing to increasing pharmaceutical expenditure. Furthermore, the quality of antibiotic use has been questioned, with studies suggesting that up to 50% of antibiotic use is inappropriate [4,5]. Inappropriate use of antibiotics contributes to the appearance of resistance [6]. Antibiotic resistance is associated not only with worse clinical outcomes, but also with higher treatment costs [7].

The resistance of respiratory pathogens to commonly prescribed antibiotics such as macrolides and tetracyclines is relatively high in Belgium, and there has been some concern about the decrease in susceptibility of *S. pneumoniae* to ß-lactam antibiotics [8]. In contrast, newer "respiratory" fluoroquinolones (e.g. levofloxacin, moxifloxacin), so-called because of the enhanced activity against *S. pneumoniae*, have several attributes that make them excellent choices for the therapy of lower respiratory tract infections. They have a rapid bactericidal activity with a spectrum covering the main pertinent pathogens (*S. pneumoniae*, *H. influenzae*, *M. catarrhalis* and the 'atypical' respiratory pathogens *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Legionella*) [9]. Furthermore, the bioavailability after oral administration is excellent (nearly 100%), which makes

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these antibiotics suitable for use in ambulatory care. However, the use of fluoroquinolones can potentially lead to several drawbacks: these antibiotics are not without side effects and more importantly there is a possible danger for increasing resistance among the major respiratory pathogens, *S. pneumoniae* in particular [10].

The aim of this study is to analyse the treatment of respiratory tract infections with antibiotics in ambulatory care in Belgium. This is addressed by: a) mapping antibiotic consumption in ambulatory care in Belgium over time and breaking down antibiotic consumption by infection type; b) discussing antibiotic treatment of respiratory tract infections in ambulatory care as recommended by Belgian guidelines; and c) reviewing the current evidence on the cost-effectiveness of treating respiratory tract infections with antibiotics in ambulatory care in Belgium.

MATERIALS AND METHODOLOGY

Antibiotic Consumption

Belgian data on antibiotic consumption in ambulatory care in Belgium from 1993 to 2009 were derived from IMS Health. This database brings together information on oral antibiotics sold by wholesalers. Volume of consumption was expressed in terms of the number of defined daily doses per 1,000 inhabitants per day (DID). Defined daily doses of antibiotics originated from the World Health Organisation. The defined daily dose refers to the assumed average daily dose of a drug needed to treat its main indication in an adult person weighing 70 kg. This measure of volume is suited for comparing consumption volume between antibiotics as it is independent of differences in preparation and quantity per prescription, and is suited for international comparison. Volume of consumption was valued at public prices pertaining to the year or month of consumption.

IMS Health consumption data by type of infection originated from a panel of 500 physicians of all specialities offering general medical services, except for hospital inpatients. The composition of the panel of physicians corresponded to the distribution of the Belgian population of physicians by speciality and by region. When extrapolating the number of antibiotic prescriptions by type of infection issued by the panel of 500 physicians to antibiotic consumption in the Belgian population, care was taken that the frequency of results adheres to the Gauss curve as closely as possible.

Belgian Guidelines

The research team accessed the guidelines issued by the Belgian Antibiotic Policy Coordination Committee (BAPCOC) and by the Infectious Disease Advisory Board (IDAB) relating to the treatment of respiratory tract infections in ambulatory care. The most recent BAPCOC guidelines on the management of lower respiratory tract infections were issued in 2008 [11]. IDAB issued its most recent guidelines in 2005 for CAP [12], and in 2007 for AECOPD [13]. IDAB ended its activities in spring 2008.

Cost-Effectiveness

Studies were identified by searching Medline (PubMed), EMBASE, Centre for Reviews and Dissemination databases, Cochrane Database of Systematic Reviews, and EconLit (OVID) up to February 2011. The bibliography of included studies was checked for other relevant studies. Additionally, the research team searched the database of research papers presented at meetings of the International Society for Pharmaco-economics and Outcomes Research, and the Tufts-New England Center Cost-Effectiveness Analysis Registry.

Search terms included 'respiratory tract infection', 'chronic bronchitis', 'chronic obstructive pulmonary disease', 'acute exacerbation', 'community-acquired pneumonia', 'acute sinusitis', 'antibiotic', 'antimicrobial', 'pharmaco-economics', 'economic evaluation', 'cost-effectiveness', 'cost-minimisation', 'cost-consequence', 'cost-utility', 'cost-benefit' alone and in combination with each other.

The literature search included articles published in peer-reviewed journals and congress abstracts. Articles could be published in English, Dutch, French or German. No restrictions were imposed on the publication date of articles. To be included in the review, a study had to conduct an economic evaluation comparing the use of an antibiotic in respiratory tract infections with an alternative health technology in terms of both costs and consequences in Belgium [14]. Relevant alternative health technologies were other antibiotics or placebo.

RESULTS

Antibiotic Consumption

The annual volume of antibiotic consumption in ambulatory care in Belgium from 1993 till 2009 is displayed in Fig. (**1**). Annual consumption increased from 22.6 DIDs in 1994 to 26.9 DIDs in 1998, but dropped to 21.6 DIDs in 2004. Since then, consumption has again risen to 27.3 DIDs in 2009.

Antibiotic consumption in ambulatory care mainly originated from the use of broad-spectrum penicillins, which accounted for an average annual volume of 11.2 DIDs (or 45% of average annual consumption). The share of consumption held by broad-spectrum penicillins has steadily increased from 37% in 1993 to 60% in 2009. The consumption of tetracyclines has consistently fallen from 4.6 DIDs in 1993 to 1.9 DIDs in 2009, a decrease of 59%. Average annual consumption of cephalosporins was higher in the 1990s than in the 2000s. Consumption of macrolides was fairly constant over time. Fluoroquinolones constituted a modest part of antibiotic consumption, representing 9% of average annual consumption. The share of fluoroquinolones increased from 7% in 1993 to 12% in 2003, but then fell to 10% in 2009. Amphenicols, sulphonamides, narrow-spectrum antibiotics, aminoglycosides and other antibiotics were marginal drivers of antibiotic consumption in ambulatory care in Belgium.

In 2009, antibiotic consumption consisted of 16.5 DIDs of broad-spectrum penicillins (60% of consumption), 3.3 DIDs of macrolides (12%), 2.7 DIDs of fluoroquinolones (10%), 1.9 DIDs of tetracyclines (7%), 1.8 DIDs of cephalosporines (6%), 0.8 DIDs of sulphonamides (3%), and 0.4 DIDs of narrow-spectrum penicillins (1.5%).

The value of antibiotic consumption increased from 210 million € in 1994 to 233 million € in 1998, dropped to 155

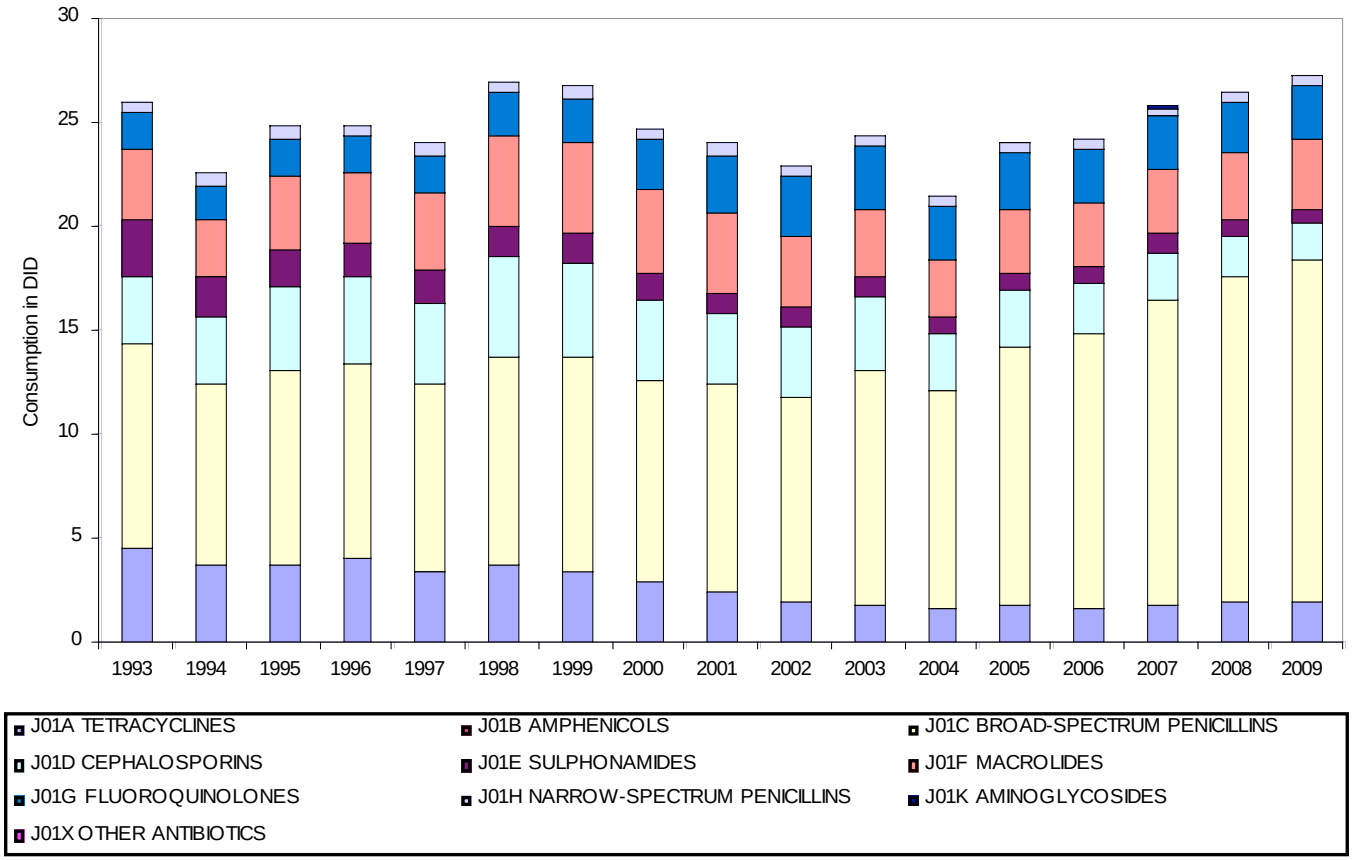

Fig. (1). Consumption of antibiotics in ambulatory care in Belgium.

million € in 2004 and has remained constant at that level until 2009.

A breakdown of the volume of antibiotic consumption by type of infection in ambulatory care in Belgium in 2009 is portrayed in Fig. (**2**). Even though the use of antibiotics in treating upper respiratory tract infections is more controversial than their use in managing lower respiratory tract infections [3,15-17], the data indicate that the volume of antibiotic consumption in treating upper respiratory tract infections (40% of consumption, volume of 11.1 DIDs) exceeded the volume of antibiotics used in managing lower respiratory tract infections (31% of consumption, volume of 8.3 DIDs) in 2009. This finding may be expected given that upper respiratory tract infections are far more frequent than lower respiratory tract infections. Also, the availability of generic antibiotics may play a role: the market share of generic antibiotics amounted to 50% in managing upper respiratory tract infections as compared to 43% in managing lower respiratory tract infections in 2009.

Belgian Guidelines

For patients with mild to moderate CAP who can be treated outside the hospital, the choice of antibiotics will depend on their age and the presence of comorbid illnesses. In younger (age <65y), previously healthy patients with pneumonia (CAP1) oral amoxicillin 1g TID is the preferred choice. Oral moxifloxacin 400mg OD or telithromycin 800mg OD are proposed in case of IgE-mediated ß-lactam allergy or severe intolerance to ß-lactam antibiotics. In older (age ≥65y) patients and/or patients with comorbidities (CAP2) oral amoxicillin-clavulanic acid, either 875/125 mg TID or 2000/125 mg 'Retard formulation' BID, is recommended. Oral moxifloxacin 400mg OD is proposed in case of IgE-mediated ß-lactam allergy or severe intolerance to ß-lactam antibiotics.

The use of antibiotics in COPD exacerbations remains a subject of controversy [18]. IDAB recommends oral amoxicillin-clavulanic acid, either 875/125 mg TID or 2000/125 mg 'Retard formulation' BID, as the preferred choice for the empiric antibiotic treatment of a COPD exacerbation outside the hospital. Oral moxifloxacin 400mg OD is proposed as first choice in case of IgE-mediated ß-lactam allergy or severe intolerance to ß-lactam antibiotics. In COPD patients with a history of frequent exacerbations (≥3 in the previous year) cycling between amoxicillin-clavulanic acid and moxifloxacin is recommended.

Most upper respiratory tract infections such as acute rhinosinusitis, acute pharyngitis, acute laryngitis, and acute bronchitis are self-limiting illnesses caused by viruses. Treatment with antibiotics is not warranted unless complications due to secondary bacterial infection occur (mastoiditis, meningitis, …). In more severe cases of bacterial sinusitis [19], antibiotic therapy can be indicated and oral amoxicillin 1g TID is recommended as the preferred choice. When clinical evolution is unfavourable after 2 days a switch to oral amoxicillin-clavulanic acid, either 875/125 mg TID or 2000/125 mg 'Retard formulation' BID, is advised to also cover ß-lactamase producing pathogens. Oral

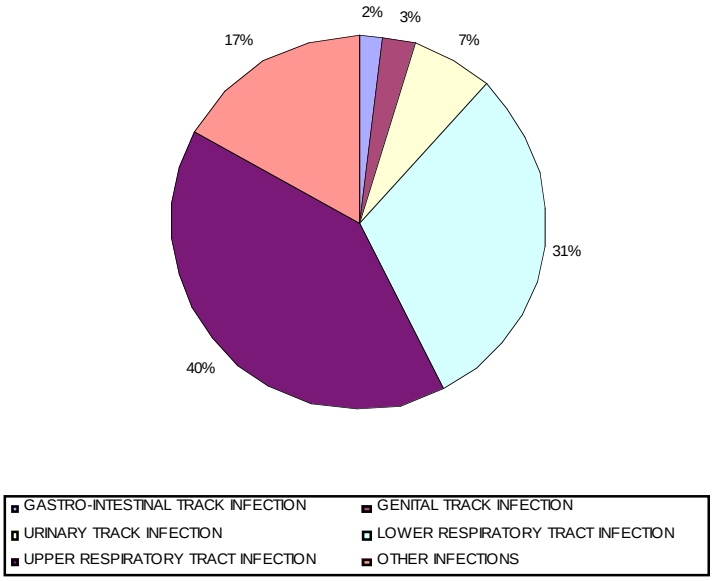

Fig. (2). Antibiotic consumption by type of infection in Belgium in 2009.

moxifloxacin 400mg OD is proposed in case of IgE-mediated ß-lactam allergy or severe intolerance to ß-lactam antibiotics.

Cost-Effectiveness

The literature search generated only one economic evaluation investigating the cost-effectiveness of treating respiratory tract infections with antibiotics in ambulatory care in Belgium from the perspective of the third-party payer. This particular study focused on the antibiotic treatment of CAP in ambulatory care [20]. The study employed a decision-analytic model to evaluate the cost-effectiveness of empirical antibiotic treatment of patients suffering from mild-to-moderate CAP. Treatment strategies involved oral antibiotics (i.e. moxifloxacin, co-amoxiclav, cefuroxime or clarithromycin), were recommended by clinical practice guidelines and reflected prevailing treatment pathways in Belgium. First-line treatment was initiated in the community, with failure resulting in second-line treatment in the community or hospitalization. The analysis calculated the cost-effectiveness of antibiotic treatment in the presence of resistance.

Clinical failure could occur due to two main reasons: lack of response to treatment in patients with susceptible pathogens and failure due to the presence of antibiotic-resistant pathogens. The failure rate in susceptible pathogens was estimated on the basis of antibiotic success rates from published clinical trials in CAP. The failure rate in antibiotic-resistant pathogens was estimated on the basis of antibiotic resistance data from published surveillance studies. Antibiotic resistance data related to Belgium or were derived from published sources in the absence of Belgian data.

First-line treatment of CAP with moxifloxacin turned out to be more effective in terms of first-line clinical failure, need for second-line treatment, hospitalization and mortality as compared with first-line treatment with co-amoxiclav, cefuroxime or clarithromycin. The rate of first-line failure was 5%, 16%, 19% and 18% for these four treatment strategies, respectively. The rate of second-line treatment amounted to 4%, 13%, 16% and 15%, respectively. The hospitalization rate was 1%, 4%, 4% and 4%, respectively. The death rate was 0.01%, 0.04%, 0.03% and 0.03%, respectively. As a consequence, total health care costs of treating a CAP episode with moxifloxacin were lower than costs of comparator strategies, despite the higher drug cost of moxifloxacin. Costs of treating a CAP episode amounted to 144 € with moxifloxacin, 222 € with co-amoxiclav, 211 € with cefuroxime, and 193 € with clarithromycin. The extensive sensitivity analyses corroborated these results in nearly all scenarios.

The authors argued that the absence of resistance to moxifloxacin and the high clinical success rate associated with moxifloxacin leads to moxifloxacin being the most effective and least expensive option in most cases. Therefore, it appears to be more cost-effective to select an antibiotic as first-line treatment that is more effective, i.e. with lower resistance and a higher clinical success rate.

This specific study has demonstrated that first-line empirical treatment of CAP with moxifloxacin is the most cost-effective option. However, empirical treatment does not always correspond to real clinical practice where data on the pathogen and the susceptibility may be available following first-line treatment failure. If the physician can adopt with a high degree of reliability the antibiotic treatment strategy according to the cause, the most cost-effective treatment strategy may vary [21].

DISCUSSION

This study has examined the use of antibiotics in treating respiratory tract infections in ambulatory care in Belgium over time. The data indicated that the volume of antibiotic consumption fluctuated from 1993 to 2003, but then has steadily risen from 2004 to 2009. During the same period, the value of antibiotic consumption remained constant, pointing to price decreases of antibiotics. The trend of rising

volume of antibiotic consumption and price decreases can be explained by the availability of generic antibiotics: the market share of generic antibiotics increased from 26% in 2004 to 45% in 2009. However, the role of generic antibiotics needs to be better taken into account in pharmaco-economic evaluations. For instance, Belgian guidelines state that, if the comparator covers two kinds of medicines with a different price but equal outcomes (i.e. an originator and generic off-patent antibiotic), the least expensive medicine should be used in an economic evaluation because such a medicine is more cost-effective than the more expensive medicine [22].

Decision makers tend to focus on fluoroquinolones due to their high acquisition costs as compared to other classes of antibiotics. Our analysis shows that fluoroquinolones constituted a modest part of antibiotic consumption, representing 10% of annual consumption. Although the volume of fluoroquinolone consumption has nearly doubled from 1993 to 2003, it has fallen consistently in the following years. This may originate from the fact that an agreement was struck between representatives of physicians and health insurance funds in 2003 to make an increase in physician fees conditional on curbing the growth in fluoroquinolone consumption [23].

Such an approach focusing on one class of antibiotics runs the risk of producing a switch in physician prescribing behaviour away from fluoroquinolones to other classes of antibiotics, rather than have an impact on overall consumption [24]. Indeed, this seems to have happened: although fluoroquinolone consumption decreased since 2003, consumption of broad-spectrum penicillins and overall antibiotic consumption increased. Therefore, this study recommends to identify those indications, such as upper respiratory tract infections, where the use of antibiotics is not recommended and introduce policy measures such as clinical guidelines, peer review with feedback, educational campaigns or financial incentives to discourage the use of antibiotics in the treatment of those infections [24].

The optimal treatment of respiratory tract infections continues to challenge clinicians, and the prospect of resistance in the community offers future obstacles. Therefore, our study has reviewed the recommendations of Belgian guidelines governing antibiotic treatment of respiratory tract infections in ambulatory care.

ß-lactam-based therapy covers the most common pathogens in CAP and acts as one of the first-line standard treatments. As antibiotic resistance has increased in recent years, it should be noted that these resistance mechanisms which inactivated antibiotics such as penicillins, cephalosporins and macrolides did not interfere with the antibacterial activity of the respiratory fluoroquinolones, and cross-resistance with other antibiotic classes is therefore not likely [25]. Several studies have shown that moxifloxacin monotherapy has similar clinical efficacy and favorable microbiological treatment success rates as compared with ß-lactam-based standard therapy for CAP [26]. The high bioavailability of this agent provides a treatment option that could avoid hospitalization in some 'borderline' patients by providing a safe, effective and convenient outpatient regimen. Furthermore, surveillance results have shown that resistance of CAP pathogens to moxifloxacin is low (≤1%) and has remained stable over time [21]. Although current data point to a series of adverse events with moxifloxacin, these are mostly minor and not more frequent than with any other comparator antibiotic in clinical trials [27,28].

It should be noted that the Belgian guidelines for antimicrobial therapy of outpatient CAP do not fully reflect international guidelines [21]. For instance, amoxicillin or tetracyclines are recommended for the treatment of CAP in the community by the guidelines of the European Respiratory Society [2]. If there is clinically relevant resistance against first-choice agents, treatment with moxifloxacin or levofloxacin may be considered. Based on guidelines by the Infectious Diseases Society of America/American Thoracic Society [1], an advanced macrolide or doxycycline is recommended to treat CAP in the community for a healthy person without risk factors for drug-resistant *Streptococcus pneumoniae*. In patients with comorbidities or recent antimicrobial use, a respiratory fluoroquinolone (moxifloxacin, gemifloxacin or levofloxacin [750 mg]) or a β-lactam plus a macrolide (e.g. high-dose amoxicillin [1 g 3 times daily] or amoxicillin-clavulanate [2 g 2 times daily]) is recommended.

The debate surrounding the use of antibiotics in COPD exacerbations arises from the observation that 30-50% of COPD exacerbations are not caused by bacterial infection and, hence, do not require antibiotic therapy. It is, however, difficult to differentiate these patients on clinical grounds from those whose exacerbation is caused by a bacterial infection. Because of its high eradicating power against the target organisms and because *H. influenzae* is the main pathogen to be covered, amoxicillin-clavulanic acid may be a first choice to treat COPD exacerbations, although this choice is subject to debate. Amoxicillin has poor activity against ß-lactamase producing microorganisms, i.e. 15-20% of *H. influenzae* and almost all *M. catarrhalis* strains, which make out a large proportion of bacterial COPD exacerbations, and is therefore not an acceptable treatment option. Thanks to its rapid and extensive eradicating power, studies with moxifloxacin have been instrumental in emphasizing the importance of reducing the bacterial load in reducing exacerbation frequency [29,30] and, hence, possibly also subsequent decline in lung function. However, overuse of fluoroquinolones needs to be avoided in view of selection of mutant strains and resistance. Therefore, moxifloxacin is only recommended as first choice in case of IgE-mediated ß-lactam allergy or severe intolerance to ß-lactam antibiotics. We also propose moxifloxacin as an alternative to amoxicillin-clavulanic acid in patients with frequent exacerbations (≥3 in the previous year). Cycling of antibiotics has been defined as alternatively using an antibiotic of a different class with each subsequent exacerbation. It can offer a means to reduce the risk of selection of less sensitive or resistant microorganisms.

Most upper respiratory tract infections are caused by viral infection and do not require antibiotic treatment [15,17]. As overuse and misuse of fluoroquinolones needs to be avoided, these antibiotics are contra-indicated for treating upper respiratory tract infections. Only on the rare occasion that antibiotic treatment is warranted and standard β-lactam therapy is not an option due to IgE-mediated allergy of

severe intolerance to β-lactams, moxifloxacin is an acceptable alternative for treating upper respiratory tract infections [19].

These recommendations reflect empirical outpatient treatment in that treatment is initiated in the absence of information about the causative pathogen involved and the antibiotic susceptibility pattern of the isolated organism. This is because antimicrobial treatment in the community is often empirical and empirical treatment is also the prevailing method of drug selection [20]. However, empirical treatment inhibits the selection of an appropriate antibiotic and does not always reflect real clinical practice where data on the pathogen and the susceptibility may be available following first-line treatment failure.

Only one economic evaluation investigated the cost-effectiveness of treating respiratory tract infections with antibiotics in ambulatory care in Belgium. This study supported the cost-effectiveness of first-line treatment of CAP with moxifloxacin in Belgium [20]. A review of the international literature supported the cost-effectiveness of moxifloxacin in the treatment of respiratory tract infections: treatment with moxifloxacin was equally or more effective, and less expensive than treatment with other antibiotics [31]. This conclusion applied to CAP, acute exacerbations of chronic bronchitis and acute bacterial sinusitis. The cost-effectiveness of moxifloxacin originates from its low resistance rates and its high clinical success rate in outpatients. Although worldwide moxifloxacin resistance is low in general, resistance does appear in some regions with a high prevalence of multi-drug resistant *Streptococcus pneumoniae* [21]. Therefore, continued vigilance with regard to the use of moxifloxacin and the evolution of resistance to moxifloxacin is recommended and it may be advisable to identify patient subgroups in which moxifloxacin is particularly cost-effective [21].

To date, economic evaluations assessing the cost-effectiveness of treating respiratory tract infections with antibiotics are not taken into account in Belgian (or international) clinical guidelines. In addition to the best available evidence on safety and effectiveness, treatment guidelines should take into account cost-effectiveness considerations by assessing whether a treatment adds sufficient value to justify its costs. Also, there is a need for more and comprehensive economic evaluations examining the cost-effectiveness of treating respiratory tract infections with antibiotics in Belgium.

CONCLUSION

This study has shown that the total volume of antibiotic consumption in ambulatory care in Belgium has increased over the years, but the volume of fluoroquinolone use remains well controlled. Policy makers need to target the main drivers of inappropriate antibiotic consumption rather than a specific class of antibiotics when they aim to promote better use of antibiotics in ambulatory care. Belgian guidelines have recommended moxifloxacin for CAP outpatients with comorbid conditions or outpatients in whom infection with atypical pathogens needs to be considered. Moxifloxacin is recommended in case of IgE-mediated ß-lactam allergy or severe intolerance to ß-lactam antibiotics for the treatment of COPD exacerbations or for the treatment of upper respiratory tract infections on the rare occasion that antibiotic treatment is warranted. As the cost-effectiveness of moxifloxacin is influenced by the causative pathogens involved and resistance patterns, it may be advisable to identify patient subgroups in which moxifloxacin is cost-effective.

CONFLICT OF INTEREST

None declared.

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