Respiratory tract infections are accompanied by significant morbidity, impaired quality of life, and mortality. The scientific literature and international guidelines recommend antibiotic therapy in patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD) (Gold stages II to IV and/or acute respiratory failure) and community-acquired pneumonia (CAP) [3-5]. 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 [6]. In fact, the added value of antibiotics for therapeutic purposes has been so persuasive that many older antibiotics never underwent controlled clinical trials [7]. On the other hand, systematic reviews published by the Cochrane Collaboration have found no benefit of antibiotic therapy in upper respiratory tract infections because the cause of such infections is generally viral and, thus, the use of antibiotics is not indicated [8,9].

Antibiotics have made a significant contribution to improving the health of patients suffering from respiratory tract infections. The scientific literature and international guidelines recommend antibiotic therapy in patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD) (Gold stages II to IV and/or acute respiratory failure) and community-acquired pneumonia (CAP) [3-5]. 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 [6]. In fact, the added value of antibiotics for therapeutic purposes has been so persuasive that many older antibiotics never underwent controlled clinical trials [7]. On the other hand, systematic reviews published by the Cochrane Collaboration have found no benefit of antibiotic therapy in upper respiratory tract infections because the cause of such infections is generally viral and, thus, the use of antibiotics is not indicated [8,9].

A range of antibiotics such as penicillins, macrolides, cephalosporins, co-trimoxazol, tetracyclines, and fluoroquinolones can be used to treat respiratory tract infections in ambulatory care. Fluoroquinolones are a class of antibiotics developed in the 1980s. Fluoroquinolones initially demonstrated their effectiveness against Gram-negative bacteria (H. influenzae, Moraxella catarrhalis), whereas newer fluoroquinolones have increased activity against Gram-positive bacteria, including S. pneumoniae, and against atypical micro-organisms (Mycoplasma pneumoniae, Chlamydia spp. and Legionella pneumophila). Moreover, moxifloxacin has increased activity against Staphylococcus aureus and anaerobes.

In an era of spiralling health care costs and limited resources, policy makers and health care payers are concerned about the costs of antibiotics in addition to their effectiveness. Rising consumption of antibiotics is contributing to increasing pharmaceutical expenditure [10]. Furthermore, the quality of antibiotic use has been questioned, with studies suggesting that up to 50% of antibiotic use is inappropriate [11,12]. For instance, a Belgian survey of general practitioners and pulmonologists compared actual management of AECOPD with GOLD recommendations [13]. The authors concluded that antibiotics were overused in the treatment of exacerbations and that their use should be limited to those exacerbations where bacterial infection is likely to be present. Inappropriate use of antibiotics contributes to the appearance of resistance [14]. Antibiotic resistance is associated not only with worse clinical outcomes, but also with higher treatment costs [15]. For instance, a survey of 122 U.S. hospitals revealed that antibiotic resistance was the most commonly cited reason for increases in antibiotic expenditure [16].

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 [17]. Resistance to fluoroquinolones is still low, but if these antibiotics become more widely used in the community for the treatment of respiratory tract infections, resistance is expected to spread with the potential
induction of cross-resistance even to the new fluoroquinolones. Resistance may also develop as a result of unnecessary antibiotic therapy and inappropriate dose, duration and/or frequency of administration of antibiotics.

The aim of this chapter is to address specific aspects of the treatment of respiratory tract infections with fluoroquinolones in ambulatory care in Belgium by: a) mapping fluoroquinolone consumption in ambulatory care in Belgium over time and breaking down consumption by infection type; b) discussing the role of fluoroquinolones as recommended by Belgian guidelines on the treatment of respiratory tract infections in ambulatory care; c) documenting the level of in vitro resistance of *S. pneumoniae* to fluoroquinolones in Belgium over time; and d) reviewing the current evidence on the cost-effectiveness of treating respiratory tract infections with fluoroquinolones in ambulatory care in Belgium.

### 2. Fluoroquinolones and consumption

In Belgium, fluoroquinolones made up 9% of the average annual volume of antibiotic consumption [18]. The share of fluoroquinolones increased from 7% in 1993 to 12% in 2003, but then fell to 10% in 2009. The volume of fluoroquinolone consumption increased from 1.75 defined daily doses per 1,000 inhabitants per day (DID) in 1993 to 3.00 DIDs in 2003, but then fell to 2.66 DIDs in 2009 (see Figure 1).

In the 1990s, consumption was dominated by norfloxacin, although this fluoroquinolone was increasingly replaced by ciprofloxacin and ofloxacin in the second half of the 1990s. Although pefloxacin contributed to fluoroquinolone consumption in the 1990s, this antibiotic is no longer commercialized in Belgium. The growth in consumption in the 1990s originated from increased consumption of ciprofloxacin, and accelerated with the introduction of levofloxacin in 2000 and moxifloxacin in 2002.

The decrease in consumption since 2003 can be attributed to falling consumption of norfloxacin and ofloxacin, although the consumption of ciprofloxacin, levofloxacin and moxifloxacin has remained relatively stable. In 2009, consumption of fluoroquinolones was made up of 1.07 DIDs of ciprofloxacin (40% of fluoroquinolone consumption), 0.78 DIDs of moxifloxacin (29%), 0.33 DIDs of levofloxacin (13%), 0.27 DIDs of norfloxacin (10%), and 0.21 DIDs of ofloxacin (8%).

Looking at the annual consumption of fluoroquinolones valued at public prices, this increased from 24.1 million € in 1993 to a maximum of 44.4 million € in 2002, and then decreased to 35.0 million € in 2009.

With respect to the type of infection, levofloxacin was used for treating respiratory tract infections prior to the introduction of moxifloxacin, and for treating gastro-intestinal and urinary tract infections after its introduction [18]. Moxifloxacin was typically used in the treatment of respiratory tract infections. The principal use of fluoroquinolones was in the treatment of urinary tract infections (36% of consumption, volume of 0.95 DIDs) and lower respiratory tract infections (26% of consumption, volume of 0.70 DIDs). Management of upper respiratory tract infections with fluoroquinolones amounted to 8% of consumption (volume of 0.21 DIDs). This suggests that fluoroquinolones are primarily used in those indications where they have been shown to yield clinical benefit [19,20].

Future consumption patterns of fluoroquinolones and other antibiotics are likely to be influenced by a number of factors. A recent analysis suggested that the worldwide antibiotic market is stagnating and increasingly subjected to generic substitution [21]. While little activity is taking place developing new antibiotics for the community setting, the antibiotic market is shifting towards the hospital sector. Generic competition is likely to affect older classes of antibiotics such as cephalosporins and penicillins to a greater extent than the newer class of fluoroquinolones.
Nonetheless, the consumption of generic fluoroquinolones in Belgium has steadily increased to 24% of consumption in DIDs and 17% of consumption in Euro in 2009 [18]. Patents covering levofloxacin and moxifloxacin will expire in the next five years. The danger exists that the lower price of generic medicines may incite physicians to increase overall consumption, thereby possibly negating the effect of Belgian information campaigns to rationalize the use of antibiotics.

3. Fluoroquinolones and guidelines

The role of fluoroquinolones in the treatment of respiratory tract infections in ambulatory care is discussed in guidelines issued by the Belgian Antibiotic Policy Coordination Committee [22] and by the Belgian Infectious Disease Advisory Board [23,24].

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 β-lactam allergy or severe intolerance to β-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 β-lactam allergy or severe intolerance to β-lactam antibiotics.

The use of antibiotics in AECOPD remains a subject of controversy. The Belgian Infectious Disease Advisory Board 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 AECOPD outside the hospital. Oral moxifloxacin 400mg OD is proposed as first choice in case of IgE-mediated β-lactam allergy or severe intolerance to β-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, 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 β-lactamase producing pathogens. Oral moxifloxacin 400mg OD is proposed in case of IgE-mediated β-lactam allergy or severe intolerance to β-lactam antibiotics.

4. Fluoroquinolones and resistance

Fluoroquinolones inhibit bacterial DNA synthesis by inhibiting DNA gyrase and topoisomerase IV [25]. Fluoroquinolone resistance is generally related to mutations in the Quinolone Resistance-Determining Region (QRDR). In *S. pneumoniae*, resistance to the new fluoroquinolones mostly requires at least two mutation events, one in DNA gyrase and one in topoisomerase IV.

In Belgium, surveillance studies from 1995 to 2005 have consistently found 0% resistance of *S. pneumoniae* to moxifloxacin [26,27]. One of these studies focused on fluoroquinolone consumption and pneumococcal resistance rates [26]. Data on fluoroquinolones sold by wholesalers in Belgium were obtained from IMS Health. Also, the susceptibility of 600 isolates of *S. pneumoniae* collected from 1998 to 2003 was tested. The *S. pneumoniae* strains were isolated in Belgian laboratories participating in the National Surveillance Programme. The volume of consumption of fluoroquinolones in ambulatory care in Belgium nearly doubled from 1993 to 2003. The growth in consumption accelerated with the introduction of levofloxacin in 2000 and moxifloxacin in 2002. However, the use of levofloxacin and moxifloxacin, and the ongoing use of older fluoroquinolones did not lead to increased pneumococcal resistance: it remained below 1% for levofloxacin and was 0% for moxifloxacin.

A more recent surveillance study of blood isolates from the Belgian Pneumococcal Reference Laboratory showed that moxifloxacin is the most potent fluoroquinolone available for treatment of lower respiratory infections in Belgium with MIC90 of 0.19 mg/L [18]. Also, the use of fluoroquinolones has not led, to date, to an increase in the rate of pneumococcal resistance to fluoroquinolones. A rightward shift in the minimum inhibitory concentration (MIC) distributions of fluoroquinolones was not observed during 2004-2009, indicating that first-step mutants have not become more prevalent in Belgian strains. Data on the activity of antibiotics (including fluoroquinolones) against non-invasive isolates of *S. pneumoniae* pointed to similar resistance rates as those observed in this sample of blood isolates.

These results mirror the findings of a recent survey of antibiotic resistance in *S. pneumoniae* collected from 3,262 non-invasive clinical isolates in Belgium from 1995 to 2008 [28]. Resistance of *S. pneumoniae* to levofloxacin and to moxifloxacin was less than 1% and no rightward shift in the MIC distributions of the fluoroquinolones was noted. The percentage of *S. pneumoniae* that are not susceptible to selected antibiotics in 2008 was 29.7% for erythromycin, 22.9% for tetracycline, 11.6% for penicillin, 9.2% for cefuroxime, 5.1% for ciprofloxacin, 2.0% for cefotaxime, 0.7% for levofloxacin, 0.4% for moxifloxacin, 0% for amoxicillin, and 0% for telithromycin.
Antibiotic resistance can have a substantial impact on the cost-effectiveness of treating respiratory tract infections with antibiotics (cfr. infra). For instance, four economic evaluations assessed the cost-effectiveness of moxifloxacin for CAP taking into account antibiotic resistance in CAP pathogens and multi-drug resistance in *S. pneumoniae* isolates [29-32]. These studies were conducted in countries with different levels of antibiotic resistance: Germany, which has a low level of antibiotic resistance in CAP pathogens; Belgium, Canada and the United States, which have an intermediate level of resistance; France and Spain, which have a high level of resistance. These studies indicated that antibiotic resistance affected costs and clinical outcomes, but first-line treatment with moxifloxacin remained more effective and less expensive than all other treatment strategies in Belgium, France, Germany, Spain and the United States. In Canada, a 50% increase in fluoroquinolone resistance would raise the incremental cost-effectiveness ratio of first-line moxifloxacin treatment as compared with azithromycin to CAN$ 101.47 per first-line clinical failure avoided. Canada has faced a steady increase in macrolide resistance over time, and further increase in macrolide resistance rates cannot be ruled out. Increase in macrolide resistance would result in more favourable cost-effectiveness ratios for first-line treatment with moxifloxacin.

5. Fluoroquinolones and cost-effectiveness

Economic evaluation is a technique that can be used to determine whether antibiotic treatment adds sufficient value to justify its costs. An economic evaluation is a comparative analysis of at least two health technologies in terms of both their costs and outcomes. Evidence derived from economic evaluations is used to inform antibiotic pricing/reimbursement decisions in many countries. Antibiotics that provide better value for money are rewarded by means of a more favourable price/reimbursement. The requirement for economic evaluation fits within an overall trend towards evidence-based decision making in health care.

An economic evaluation focused on the treatment of CAP with fluoroquinolones in ambulatory care in Belgium [30]. 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. As this economic evaluation was carried out from the perspective of the third-party payer, the analysis considered direct health care costs only and did not include indirect costs due to productivity loss.

The economic evaluation was based on the premise that clinical failure can 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.

The decision-analytic model employed in the economic evaluation reflected empirical antibiotic treatment. 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. However, if the aetiology cannot be discriminated clinically, first-line treatment of CAP with moxifloxacin is the most cost-effective option.

To date, economic evaluations assessing the cost-effectiveness of treating respiratory tract infections with fluoroquinolones or other 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 pharmaco-economic considerations. International evidence supports the value of treating respiratory tract infections with fluoroquinolones [33,34]. However, the cost-effectiveness of fluoroquinolones is influenced by the local frequency

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of causative pathogens, the pattern of antibiotic resistance, and risk factors for resistant bacteria. Therefore, it may be advisable to identify patient subgroups in which treatment with fluoroquinolones is cost-effective and should be recommended by guidelines.

In addition to information about the cost-effectiveness of treating respiratory tract infections with fluoroquinolones in Belgium, the budgetary impact of fluoroquinolones needs to be considered. Treatment with fluoroquinolones benefits from a lower resistance rate, an equal or higher clinical success rate, a similar or higher bacteriological eradication rate, and a shorter time to resolution of symptoms as compared with other antibiotics. This may translate into cost savings due to a shorter course of antibiotic treatment, a lower hospitalization rate, a shorter duration of intravenous therapy and hospital stay. These cost savings more than offset the higher drug acquisition costs of fluoroquinolones. Therefore, the management of respiratory tract infections with fluoroquinolones saves money, freeing up resources to be invested in other health technologies in Belgium.

A recent study evaluated the impact of three interventions for physicians in order to implement guidelines for sequential therapy (i.e. intravenous to oral conversion) with fluoroquinolones in a Belgian university hospital [35]. This study was not an economic evaluation, focused on fluoroquinolone use in general (not limited to respiratory tract infections), and examined the impact of interventions for guideline implementation rather than of fluoroquinolones. The three interventions were: 1) hospital-wide publication of guidelines in local drug letter to all prescribers; 2) a once-only educational interactive session by infectious disease specialists to medical staff; and 3) a proactive conversion programme by pharmacists. The outcome measures were the ratio of intravenous versus total fluoroquinolone consumption (as measured in daily defined doses per 1,000 bed days) and the number of days that intravenous therapy continued beyond the day that the patient fulfilled the criteria for sequential therapy as assessed by an expert panel. To calculate the potential financial impact, the cost of continuing intravenous therapy when oral fluoroquinolones could have been used was determined. The study did not consider other costs associated with labour in drug preparation and administration, supplies for administration, avoidance of infusion-related complications, length of hospital stay etc. It should be noted that this study had limited statistical power due to the small sample size and employed a pre- and post-study design (without control group for the second and third intervention) rather than a controlled before-and-after study design.

The study observed that the mean ratio of intravenous versus total fluoroquinolone consumption decreased from 44.5% before the publication of the guidelines to 41.2% in the following 24 months (p = 0.011). This intervention had a gradual rather than an instant effect (learning effect observed following six months) which may decline over time (decay effect). The number of excess days of intravenous therapy was 4.1 days in the baseline period, 3.5 days with the educational session and 1.0 days with the conversion programme (p = 0.006). The mean additional cost for excess intravenous therapy decreased from 188 € in the baseline period to 103 € with the educational session and 44 € with the conversion programme (p = 0.037). These results show that the educational session had a clear, but not significant impact; whereas the proactive conversion programme by a pharmacist reduced the duration of intravenous treatment and antibiotic costs. Finally, the authors noted that the majority of physicians were not aware of the bio-equivalence of and the cost difference between intravenous and oral fluoroquinolones.

6. Conclusions

Belgian data on the treatment of respiratory tract infections with antibiotics in ambulatory care showed that fluoroquinolone use remains well controlled. 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 β-lactam allergy or severe intolerance to β-lactam antibiotics when treating COPD exacerbations or when treating upper respiratory tract infections on the rare occasion that antibiotic treatment is warranted. The MIC distribution of moxifloxacin and levofloxacin in S. pneumoniae isolates remained stable during 2004-2009 and resistance to moxifloxacin and levofloxacin was low (≤ 1%) in Belgium. 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.

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