Effect of formulary policy decisions on antimicrobial drug utilization in British Columbia

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Background: Formularies are used routinely for management of drug expenditures yet evaluations of their impact remain rare. The objective of this study was to analyse the impact of addition or deletion of antimicrobials from the provincial formulary on drug utilization.

Methods: We obtained data from the British Columbia PharmaNet database on all outpatient oral antimicrobial prescriptions from 1996 to 2000 and converted them to their defined daily dose (DDD) equivalents according to the ATC system. Trends in utilization associated with a changing formulary status of new antimicrobial agents were analysed. Maximum likelihood estimation was used to determine the rate of increase in utilization resulting from addition to the formulary. Models were adjusted for seasonal and temporal trends as well as serial correlation.

Results: During this time period, clarithromycin was on formulary, later delisted, and then relisted again. Valaciclovir and famciclovir were also added to the formulary. During the time clarithromycin was off the formulary, the rate of change in its monthly consumption was 0.0061 DDD/1000 population/day; following its relisting, the rate of change increased by 818% to 0.0560 DDD/1000 population/day (P < 0.002). After the listing of valaciclovir on the formulary, the rate of change in its monthly consumption increased 57% from a baseline of 0.0014 to 0.0022 DDD/1000 population/day (P < 0.07). A similar effect was seen with the addition of famciclovir to the formulary whereby the rate of change in monthly consumption increased from 0.0008 (before addition to the formulary) to 0.0018 (after addition to the formulary) (P < 0.001).

Conclusions: Listing of antimicrobials on provincial or countrywide formularies is followed temporally with increased utilization. However, before governmental agencies can institute reference-based pricing or co-payment programmes, the effect of such a programme on the emergence of antimicrobial resistance and on patient outcomes needs further study.

Keywords: antimicrobial consumption, macrolides, clarithromycin, valaciclovir, famciclovir

Introduction

Publicly funded formularies have been created in an attempt to maintain a system where the population receives cost-effective therapy. By achieving these goals, national and provincial formularies can curtail the total expenditures of their prescription drug plans. Since 1997, drugs in Canada have exceeded physicians’ services as the second largest category of health expenditure after hospital services. In 2002, expenditures on prescription drugs were estimated to reach $14.6 billion (CDN), representing 80.3% of total drug expenditure. This corresponds to an increase of 10% since 1990, when prescribed drugs occupied 70.3% of total drug expenditure.

In North America, efforts to control increases in drug costs focus on instituting restrictive formularies, cost-sharing programmes (e.g. co-payments, reference-based pricing),
developing expert Drug and Therapeutics committees to advise health ministers, and academic detailing to give drug information to health professionals. Alternatively, in Europe, the focus is more on developing provincial or country-wide drug surveillance programmes, which track utilization over time and the impact of various policy decisions on use of therapeutic agents.

Within British Columbia, Pharmacare provides financial assistance to residents for eligible prescriptions in the form of reimbursement for prescriptions of approved products. During the analytical horizon of our study (1996–2000), all new products underwent separate reviews of efficacy and cost effectiveness by the Therapeutic and Pharmacoeconomic Initiatives of British Columbia, respectively. These independent groups’ expert committees provided a critical appraisal regarding the product’s relative efficacy and cost effectiveness in comparison to currently funded treatments utilized by the decision making drug benefit committee of Pharmacare in their formulary inclusion/exclusion decision.

The British Columbia Centre for Disease Control (BCCDC) has recently adopted a similar strategy to track antimicrobial utilization for the province. The methodology of data extraction and patterns of use for the province of BC have been published elsewhere. This paper describes how policy decisions to add or delete various antimicrobials from the provincial formulary impact on their use by clinicians. The hypothesis of the study was that introduction of the new antimicrobial agents on the provincial formulary would result in increased utilization. In contrast, utilization of the older antimicrobial agent within the same therapeutic class (which was already on formulary) would decrease. In addition, overall antimicrobial consumption would increase since the prescribing physician will take into account the formulary or reimbursement status of the newer more expensive product.

Materials and methods

PharmaNet is a province-wide network linking all pharmacies into a central set of data systems. British Columbia’s College of Pharmacists mandates that every community prescription, regardless of formulary status of the prescribed agent, be entered in this database at the time of dispensing. Underreporting and misclassification in this type of database have been shown to be minimal. The data provided to the BCCDC by PharmaNet were from September 1995 to December 2000 and included the patient’s age, sex, the antimicrobial agent prescribed according to the ATC classification system, the date, dose and quantity dispensed.

Antimicrobials included in the database were from ATC categories: J01, antibacterials for systemic use; J02, antimycotics for systemic use; and J05, antivirals for systemic use. The following groups of antibiotics were included in the database: β-lactamase-sensitive penicillins (ATC code J01CE— benzylpenicillin and phenoxymethylpenicillin); β-lactamase-resistant penicillins (ATC code J01CF— cloxacillin); aminopenicillins (ATC code J01CA— amoxicillin, ampicillin, pivampicillin, bacampicillin); β-lactam/β-lactamase inhibitor combinations (ATC code J01CR— co-amoxiclav); macrolides (ATC code J01FA); tetracyclines (ATC code J01AA); cephalosporins (J01DA); fluoroquinolones (J01MA); lincosamides (J01FF); trimethoprim, either alone or in combination (J01EA); and sulphonamide-containing antibiotics (J01EE). Antiviral agents (J05AB) included aciclovir, famiclovir and valaciclovir.

For this study, we looked at utilization of macrolides and antiviral agents because the only new additions to the formulary during the study timeframe (1995–2000) were clarithromycin, valaciclovir and famciclovir. In fact, by September 1995, among other antimicrobial agents, clarithromycin was already on the provincial formulary as a regular benefit agent, it was removed from the Pharmacare formulary on November 17, 1996 but subsequently relisted on July 17, 1999. During the study timeframe, erythromycin was always on the provincial formulary but azithromycin, although marketed in Canada, was not added to the BC formulary until 2001. Valaciclovir (500 mg caplet) and famciclovir (500 mg tablet) were added to the BC formulary on May 26, 1997 and May 20, 1998, respectively.

All drug utilization data were expressed in daily defined doses (DDD) using the Anatomical Therapeutic Chemical (ATC) classification system of the World Health Organization. Daily defined dose is the assumed average maintenance dose per day for a drug used for its main indication for an average adult. This was conducted by creating a data dictionary to classify the antimicrobials and assign their DDD; the PharmaNet database was then merged with the data dictionary (using the statistical software SAS). All antimicrobial consumption rates were expressed in DDD/1000 population/day.

Maximum likelihood estimation was used to estimate the trends and correlations in the data. All drugs included a linear time trend to adjust for long-term changes in consumption rates. Changes in formulary status were included as indicator variables and were allowed to interact with the slope of the linear time trend, while a sine and cosine wave with a period of 1 year was included as a predictor for the seasonal trend in macrolides. The error term was modelled as a first-order autoregressive process which was determined by examining the autocorrelation and partial autocorrelation function of the detrended data.

Results

The entire database consisted of 15 273 324 records of prescription antimicrobials dispensed from September 1995 to December 2000 (0.73 prescriptions/person/year). Of these records, 1 419 893 (9.3%) were for erythromycin, 575 529 (3.8%) for clarithromycin, 215 751 (1.4%) for aciclovir, 77 403 (0.5%) for valaciclovir, and 42 174 (0.3%) for famciclovir. Throughout the 5 year period, 57% of prescriptions were for women, the mean age of recipients was 37.6 years (S.D. 23.8), and 16.3% were ≥65 years of age.

Clarithromycin and erythromycin

Figure 1 shows the monthly consumption rate of clarithromycin and erythromycin. The two consumption patterns track each other closely. In fact, during non-respiratory seasons, the month of lowest consumption is always the same for both drugs over the 5 years of the study. During each respiratory season, the peak consumption of clarithromycin and erythromycin also coincided except for 1996 when clarithromycin was delisted in November. That year, the peak for clarithromycin occurred in October, 1 month before being delisted from the formulary, and the peak for erythromycin occurred in December, 1 month after delisting of clarithromycin. The consumption rate of clarithromycin was noticeably lower than that of erythromycin until clarithromycin was relisted in July 1999. Leading into the respiratory season at the end of 1999, the consumption rate of
clarithromycin moved closer to the consumption rate of erythromycin and finally surpassed it in the winter of 2000.

The immediate impact of delisting and relisting clarithromycin on the provincial formulary after adjusting for seasonal and temporal trends is shown in Table 1. When clarithromycin was delisted off the formulary in November 1996, there was an immediate decline in its monthly consumption rate of 0.2929 DDD/1000 population/day (S.E.M. = 0.1409, \( P = 0.038 \)) while the effect on erythromycin was a significant increase of 0.3449 DDD/1000 population/day (S.E.M. = 0.1647, \( P = 0.036 \); Figures 2 and 3). However, the relisting of clarithromycin on the formulary was not associated with an immediate increase in its consumption rate nor a significant decline in the consumption of erythromycin, perhaps due to the season of relisting which was the summer month of July.

In addition to the immediate impact of delisting and relisting on the provincial formulary, the model estimated the change in the monthly consumption rate of clarithromycin (Table 2). During the time clarithromycin was off the provincial formulary, the change in the monthly consumption was 0.0061 DDD/1000 population/day, representing a decrease of 0.0037 DDD/1000 population/day (S.E.M. = 0.0152, \( P > 0.20 \)). After it was relisted, the change in the monthly consumption rate of clarithromycin increased to 0.0560 DDD/1000 population/day, representing a significant increase of 0.0499 DDD/1000 population/day (S.E.M. = 0.0158, \( P = 0.0016 \)). However, there was no significant change in the monthly consumption rate of erythromycin when clarithromycin was relisted (Table 2 and Figure 3).

Valaciclovir, famciclovir and aciclovir

Table 1 shows the immediate increase in the use of both valaciclovir and famciclovir once they were introduced onto the provincial formulary in May 1997 and May 1998, respectively. During that time, aciclovir use declined by 17% from a rate of 0.156 DDD/1000 population/day before May 1997 to 0.130 DDD/1000 population/day after May 1998. For valaciclovir, the monthly consumption rate appeared to immediately jump from 0.0173 DDD/1000 population/day to 0.0240 DDD/1000 population/day in May 1997, an increase of 0.0067 (S.E.M. = 0.0032, \( P = 0.034 \)) or 42% (Figure 4). The effect of being listed on the provincial formulary in May 1998 was even more dramatic for famciclovir.

![Graph](https://academic.oup.com/jac/article-abstract/55/1/95/777038)

**Figure 1.** Effect of delisting and relisting clarithromycin on the provincial formulary before adjusting for seasonal and temporal trends. Marketed indicates when clarithromycin was marketed in Canada (250 mg on May 8, 1992 and 500 mg on August 25, 1994). Clarithromycin was placed on the provincial formulary soon after marketing. Delisted indicates the time when clarithromycin was taken off the provincial formulary (November 17, 1996), and relisted indicates when clarithromycin was placed back on the provincial formulary (July 7, 1999). CAP indicates when the guidelines for treatment of community-acquired pneumonia were published (April 1998 and August 2000).

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**Table 1.** Immediate impact of delisting and relisting of clarithromycin, valaciclovir and famciclovir on the provincial formulary

<table>
<thead>
<tr>
<th>Change in formulary</th>
<th>Drug</th>
<th>Effect</th>
<th>S.E.M.</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delisting of clarithromycin(^a)</td>
<td>clarithromycin</td>
<td>−0.2929</td>
<td>0.1409</td>
<td>0.038</td>
</tr>
<tr>
<td></td>
<td>erythromycin</td>
<td>0.3449</td>
<td>0.1647</td>
<td>0.036</td>
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<tr>
<td>Relisting of clarithromycin(^b)</td>
<td>clarithromycin</td>
<td>0.0147</td>
<td>0.1448</td>
<td>&gt;0.20</td>
</tr>
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<td>erythromycin</td>
<td>−0.0628</td>
<td>0.1360</td>
<td>&gt;0.20</td>
</tr>
<tr>
<td>Listing of valaciclovir(^c)</td>
<td>valaciclovir</td>
<td>0.0067</td>
<td>0.0032</td>
<td>0.034</td>
</tr>
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<td></td>
<td>aciclovir</td>
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<td>0.0065</td>
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<tr>
<td>Listing of famciclovir(^d)</td>
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<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>aciclovir</td>
<td>−0.0058</td>
<td>0.0061</td>
<td>&gt;0.20</td>
</tr>
</tbody>
</table>

\(^a\)Delisted indicates the time when clarithromycin was taken off the provincial formulary (November 17, 1996).

\(^b\)Relisted indicates the time when clarithromycin was placed back on the provincial formulary (July 7, 1999).

\(^c\)Listed indicates the time when valaciclovir 500 mg was placed on the provincial formulary (May 26, 1997).

\(^d\)Listed indicates the time when famciclovir 500 mg was placed on the provincial formulary (May 20, 1998).
where was an immediate increase in the monthly consumption rate from 0.0346 DDD/1000 population/day to 0.0600 DDD/1000 population/day, an increase of 0.0254 DDD/1000 population/day (S.E.M. 0.0024, \( P < 0.0001 \)) (Figure 5).

During the times when valaciclovir was off the provincial formulary, the model estimated the change in the monthly consumption rate to be 0.0014 DDD/1000 population/day (Figure 4). After listing onto the formulary in May 1997, the change in the monthly consumption rate was estimated to have increased by 0.0008 DDD/1000 population/day (S.E.M. 0.0004, \( P = 0.069 \)). The increase in the change in monthly consumption rate was dramatic when famciclovir was listed on the formulary (Figure 5). This was estimated to be 0.0010 DDD/1000 population/day after listing, an increase of 0.0010 (S.E.M. 0.0002, \( P < 0.0001 \)) or 125%.

Table 2. Change in monthly consumption rate of macrolide and antivirals when placed on provincial formulary

<table>
<thead>
<tr>
<th>Change in formulary</th>
<th>Drug</th>
<th>Change in monthly consumption rate (DDD/1000 population/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Drug</td>
</tr>
<tr>
<td>Delisting of clarithromycin(^a)</td>
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</tr>
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<td></td>
<td>erythromycin</td>
<td>-0.0170</td>
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<td>Relisting of clarithromycin(^b)</td>
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<td></td>
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<td>Listing of valaciclovir(^c)</td>
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<td>0.0008</td>
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<tr>
<td></td>
<td>aciclovir</td>
<td>-0.0013</td>
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<td>Listing of famciclovir(^d)</td>
<td>famciclovir</td>
<td>0.0010</td>
</tr>
<tr>
<td></td>
<td>aciclovir</td>
<td>0.0012</td>
</tr>
</tbody>
</table>

\(^a\)Delisted indicates the time when clarithromycin was taken off the provincial formulary (November 17, 1996).

\(^b\)Relisted indicates when clarithromycin was placed back on the provincial formulary (July 7, 1999).

\(^c\)Listed indicates the time when valaciclovir 500 mg was placed on the provincial formulary (May 26, 1997).

\(^d\)Listed indicates the time when famciclovir 500 mg was placed on the provincial formulary (May 20, 1998).
Policy decisions and antimicrobial consumption

Figure 4. Monthly consumption rates for valaciclovir before and following listing on the provincial formulary. The fitted line comes from a regression model with effects for listing status and linear trend and an AR(1) error structure. Marketed indicates when valaciclovir 500 mg (May 1, 1996) was marketed in Canada. Listed indicates the time when valaciclovir 500 mg (May 26, 1997) was placed on the provincial formulary. Herpes guidelines refer to the Center for Disease Control guidelines for treatment of genital herpes infections (January 1998) and the Canadian guidelines for treatment of sexually transmitted diseases (July 1998).

The effect of policy decisions around placing antimicrobials on the provincial formulary can be clearly seen with clarithromycin. Health Canada approved the 250 mg tablet of clarithromycin in May 1992 and then the 500 mg tablet in August 1994. Pharmacare was not able to provide us with a reason why clarithromycin was delisted in November 1996, but it is clear that the delisting of the provincial formulary resulted in a decline in use despite its continued availability in the Canadian marketplace. The landmark guidelines on the use of antibiotics for treatment of community-acquired pneumonia were first published in April 1998 and then August 2000.13–15 These guidelines promoted the use of macrolides, particularly clarithromycin for treatment of community-acquired pneumonia infections. Our data do not show a large increase in the use of clarithromycin for the respiratory season (i.e. November 1998–March 1999) following introduction of the guidelines. However, utilization of clarithromycin did increase substantially for the 1999–2000 respiratory season, following its introduction on the provincial formulary. Although we did not have the complete data for the 2000 respiratory season, it is evident that clarithromycin use increased even further for that respiratory season and this may have been due to the publication of the community-acquired pneumonia guidelines in August 2000, as well as its availability on the formulary.

Our study shows that placing valaciclovir and famciclovir on the provincial formulary was followed by increased utilization by clinicians. Valaciclovir had been in the marketplace for approximately 1 year before placement on the formulary. Valaciclovir received its Notice of Compliance (NOC) from Health Canada for suppression of genital herpes (1000 mg once daily) on May 1, 1996 and for treatment of recurrent herpes infection (500 mg twice daily for 5 days) on October 8, 1996. In contrast, famciclovir had been on the Canadian market for 3 years before being placed on the formulary. Famciclovir 500 mg received its NOC from Health Canada on July 31, 1995 for treatment of herpes zoster infections (500 mg thrice daily for 7 days). Although the use of valaciclovir and famciclovir was increasing after being marketed, there was a large jump in their utilization after being placed on the formulary. Other confounders which may have contributed to the large increase in utilization of the antiviral agents include the publication of guidelines for management of genital herpes infections which identify aciclovir, valaciclovir and famciclovir as primary treatment for genital herpes. The Centers for Disease Control (CDC) and Canadian guidelines on treatment of sexually transmitted diseases were published in January 1998 and July 1998, respectively.16,17 However, the large increase seen in valaciclovir use occurred before the publication of those guidelines but coincides with the listing of the agent on the BC formulary (May 1997). Although the publication of the CDC guidelines occurred 6 months before the listing of valaciclovir on the formulary, the large jump in utilization of valaciclovir coincides with the listing of the agent on the provincial formulary rather than publication of the guidelines 6 months before.

Of the three antimicrobial agents evaluated in this study, the increased use of clarithromycin is most concerning since macrolide resistance among Gram-positive organisms such as Streptococcus pneumoniae, the most common cause of community-acquired pneumonia, is increasing in Canada and the United States.18–20 Furthermore, this increase in macrolide resistance has been shown to be strongly correlated with increased consumption. For example, Hyde et al. from the Centers for Disease Control and Prevention showed that in a setting of increasing macrolide use (the number of prescriptions increased by 13%...
from 1993 to 1999), the prevalence of resistance among pneumococci doubled from 1995 to 1999.\textsuperscript{21} In Europe, increasing consumption of the macrolides has not only been linked to resistance in pneumococci but also with \textit{Streptococcus pyogenes}, a common pathogen in pharyngitis.\textsuperscript{22,23} There is also some suggestion that macrolide agents with a low $C_{\text{max}}$ and long half-life (like once daily azithromycin and twice daily clarithromycin) are likely to produce a longer selective window, which means longer bacterial exposure to resistance-selective concentrations.\textsuperscript{24,25}

Our study had a number of limitations. We could not determine patient outcomes nor the impact on pathogen susceptibility of adding clarithromycin on the BC formulary. Based on the literature, we can surmise that increased use of clarithromycin would lead to increased resistance. Unfortunately, due to lack of laboratory surveillance data on community-acquired pathogens for this province, we were unable to demonstrate the effect of increased clarithromycin usage on $S. \text{pneumoniae}$, $S. \text{pyogenes}$ and \textit{H. influenzae} resistance. In addition, the development of resistance within a community depends on many factors and not just on the total amount of antibiotic used. These factors include drug class, dose and regimen, public behaviour and social conditions. Thus, the addition of newer agents may have been beneficial by diverting use away from older, more toxic therapies and thus result in improved compliance. For example, the addition of clarithromycin to the BC formulary may have had a positive impact on health outcomes through the avoidance of adverse events and a subsequent improved compliance over the poorly tolerated erythromycin. Similarly, the use of valaciclovir and famciclovir, which are dosed less frequently than aciclovir, may have promoted increased compliance and a better patient outcome. Finally, there may have been other potential confounders such as manufacturer detailing or increased journal advertisements at the time of formulary listing that impacted on utilization rates.

Our study showed that adding antimicrobials to the provincial formulary increased their consumption while other studies have shown a link between antimicrobial consumption and resistance. To date, various strategies including campaigns promoting appropriate antibiotic use, development of practice guidelines and critical pathways have been used to decrease consumption with a subsequent decline in resistance.\textsuperscript{26,27} Other methods of decreasing drug consumption include reference-based pricing or co-payment programmes. Although these have been widely used for cardiovascular diseases,\textsuperscript{28–31} to date, they have not been applied to antimicrobial agents nor has there been a full evaluation of the effects of these policies on other end points such as health outcomes, utilization of healthcare resources and overall total costs to the healthcare system.

The use of reference-based pricing or co-payment programmes may be appropriate for certain antibiotics to decrease overuse and subsequent resistance. This is particularly true with the introduction of the respiratory fluoroquinolones—based on our study findings, we would expect use of these agents to increase dramatically once on the BC formulary. Resistance to levofloxacin has already been described in Canada and other parts of the world, a problem which will only be expected to get worse with overuse of this important class of drugs. However, introduction of a policy to regulate antibiotic consumption would need further evaluation to determine its impact on health outcomes.

Conclusions

The addition of antimicrobial agents to national or provincial formularies is followed temporally by an increase in their utilization. Governmental agencies could consider instituting reference-based pricing or limiting reimbursement for antimicrobial agents through co-payment programmes in order to decrease utilization and subsequent potential for resistance once their impact on patient outcome has been evaluated.

References


