Impact of a Multipronged Education Strategy on Antibiotic Prescribing in Quebec, Canada

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Background. Antibiotic overuse and resistance have become a major threat in the last 2 decades. Many programs tried to optimize antibiotic consumption in the inpatient setting, but the outpatient environment that represents the bulk of antibiotic use has been challenging. Following a significant rise of Clostridium difficile infections, all the health care stakeholders in the province of Quebec, Canada initiated a global education program targeting physicians and pharmacists.

Methods. A bundle approach was used; 11 user-friendly guidelines were produced by a group of experts and sent to all physicians and pharmacists in Quebec in January 2005. Downloadable versions of guidelines were posted on a dedicated Web site. They were promoted by professional organizations, universities, and experts during educational events, and there was strong acceptance by the pharmaceutical industry with a willingness to follow the recommendations in their marketing. The Intercontinental Medical Statistics (IMS) database was used to analyze and compare Quebec’s total outpatient prescriptions per 1000 inhabitants with those in the other Canadian provinces for 2 time periods: preintervention (January 2003 to December 2004), and postintervention (February 2005 to December 2007).

Results. In 2004, antibiotic consumption per capita was 23.3% higher in Canada generally than in Quebec. After the guidelines dissemination, the gap between Quebec and the other Canadian provinces increased by 4.1 prescriptions/1000 inhabitants ($P = .0002$), and the trend persisted 36 months later. Antibiotic costs fell $134.5/1000 inhabitants in Quebec compared with the rest of Canada ($P = .054$).

Conclusions. The implementation of guidelines significantly reduced antibiotic prescriptions in Quebec compared with the rest of the country, and there was a strong trend toward significant cost reduction.

Antibiotic resistance is a growing and emerging threat to the entire world population [1, 2]. It represents a very dynamic process unique to this class of drugs as antibiotic prescription at the individual level will ultimately impact the community at large. Antibiotics are the only class of drugs that has such an impact at the population level even when prescribed individually, because antibiotics will influence the global bacterial ecology. Cost of outpatient infections, length of hospital stay, and mortality for inpatients increase with some antibiotic-resistant bacteria [3–6]. Antibiotic resistance can lead to increased morbidity but mostly renders obsolete a wide array of agents with proven track records, and this has consequences everywhere, especially in poorer countries where resources are limited.

Antibiotic resistance is associated with both the total amount of antibiotics used and the inappropriate use of antibiotics, but there are still some unanswered questions, and the exact relationship is more complex than had been thought [7–9]. Increasing ease and volume of travel also facilitates the propagation of resistance on a worldwide scale.

The number of new antimicrobial agents released on the market has dropped significantly during the last decade, which represents a worrisome challenge for the medical community with fewer potential therapeutic options in the future. Infectious diseases still represent a major cause of death throughout the world, although
showing different faces, appearing as historical infectious entities in the developing world but with a growing trend of debilitating and costly nosocomial infections in the richest nations.

The association between antibiotic use, resistance, and inappropriate prescribing trends for common infections has led many experts to recommend a more judicious use of antibiotics. For instance, in 1997, a Canadian task group recommended the reduction of overall antibiotic prescriptions by 25% within 3 years by focusing on community-acquired respiratory tract infections [10]. Similar recommendations have been put forward in the United States and the European Union.

Different types of interventions to change prescribing practices have been tested. The available medical literature shows that educational interventions can be useful in selective targeted clinical conditions, or closed environments, such as hospitals, but are much more difficult to implement on a large scale [6, 11–13]. Issuing new guidelines requires a favorable environment in which several factors are critical for success. These critical factors are a favorable context where the need for the guidelines is shared and expected, the development of guidelines by credible organizations, evidence-based guidelines, endorsement of guidelines by recognized professional organizations, broad and active dissemination of guidelines, and user-friendly format.

Between 2002 and 2004, the province of Quebec, Canada, was severely affected by an outbreak of mostly hospital-associated cases of *Clostridium difficile* infections caused by the new strain NAP 001 [14]. The Quebec Ministry of Health, in partnership with physicians and pharmacists associations, decided to implement an extensive educational program to promote a better use of antibiotics. Although *C. difficile* infections have been an overwhelmingly hospital-based issue, antibiotic prescription in the community was initially targeted, because this represents in volume >80% of all antibiotics prescribed.

The main objective of this study was to assess the impact of a multipronged, mostly Web-based education strategy on the per capita number and cost of antibiotic prescriptions in the province of Quebec and to compare the trends with those of the other 9 Canadian provinces.

**METHODS**

The province of Quebec, Canada (2009 population, 7.8 million) has a universal health care insurance program in which medical visits, required investigations, and treatments (whether outpatient or inpatient) are provided free of charge to all citizens. In 1997, the Quebec government instituted a universal drug plan in which everybody has to be covered by either private insurance obtained through his or her employer (57% of the population) or by the public plan (43% of the population). Other provinces have similar drug plans, but not as extensive as that in Quebec.

**Education Strategy**

In the fall of 2004, at the request of the Quebec Minister of Health, the Quebec Medication Council (Conseil du Médicament du Québec, Quebec City), with the help of designated physicians and pharmacists, issued a first series of guidelines targeting the most common infectious conditions in the outpatient setting. Eleven 2-page highly graphic guidelines providing clinical information (diagnosis, investigation) and antibiotic recommendations were published and sent to all physicians (including medical residents), and pharmacists in January 2005 (http://www.cdm.gouv.qc.ca/site/aid=166.phtml). The topics included upper (pharyngitis, otitis media, sinusitis) and lower (bronchitis, community-acquired pneumonia) respiratory tract infections, urinary tract infections and *C. difficile* infections in adults and children. Emphasis was placed not only on proper antibiotic regimens but also on not using antibiotics when viral infections were suspected and on prescribing the shortest possible duration of treatment.

A letter signed by all key stakeholders in Quebec (Minister of Health, College of Physicians, College of Pharmacists, and Medical associations) accompanied the initial mailing explaining the reasons supporting the process and the importance of prescribing antibiotics appropriately. There were no compulsory rules or specific prescription limitations imposed on anyone, but physicians were strongly encouraged to follow the guidelines. Possible auditing by the College of Physicians, which strongly endorsed the guidelines, was the only potential control measure.

Pharmaceutical companies were well aware of the process and had to adapt their marketing in Quebec to the recommendations. Promotion of guidelines by expert speakers was heavily encouraged at all CME events whether organized by pharmaceutical companies or professional organizations (eg, College of Physicians, University-sponsored educational sessions). In addition, the deans of the 4 schools of medicine in Quebec were strongly encouraged to include proper antibiotic prescribing behavior in their curriculum. Seven additional guidelines (surgical prophylaxis, intra-abdominal infections) were published in December 2005.

Approximately 30 000 printed copies of the initial 11 guidelines were distributed to all Quebec physicians (including residents) and pharmacists in January 2005. From April 2005 to December 2007, about 193 500 copies of the guidelines were downloaded from the Web site (54 500 in PDF format, 139 000 in PDA format), for a monthly average of 533 downloads per clinical guide. Although similar initiatives may have occurred during the same period elsewhere in Canada, no other province implemented a full-fledged strategy like that in Quebec.

**Data and Measures**

Data on the number and cost of antibiotic prescriptions were obtained for the period from January 2003 to December 2007.
from the Canadian CompuScript Audit database of IMS Health Canada, which contains data collected from >5000 retail pharmacies, representing two-thirds of all Canadian retail pharmacies and 82% of all prescriptions filled in Canada. Pharmacies are stratified by province, type of outlet (independent affiliation or with a chain), and size (small or large). Based on standardized sampling weights and after passing through various quality-control checks, monthly estimates for the dispensing of individual drugs are calculated for each province. IMS CompuScript data are not patient specific; however, the data provided on prescription volume and class can be used to estimate trends in drug use at provincial and national levels. Also available is the cost of the prescription as dispensed (including all markups and the pharmacist’s professional fee) representing the specific amount paid to the pharmacist by the public plan and the portion paid by the patient. For the purpose of this article, the rates of antibiotic prescriptions and costs were measured on a monthly basis per 1000 inhabitants in Quebec and in the other Canadian provinces for all antibiotics, individually and per class. Population data was obtained from Statistics Canada (http://www.statscan.gc.ca). The following antibiotics classes were included in the analysis: cephalosporins (cephalexin, cefadroxil, cefuroxime, cefaclor, cefprozil, cefixime), macrolides and its derivatives (erythromycins, azithromycin, clarithromycin, telithromycin), penicillins (amoxicillin, penicillin, amoxicillin-clavulanate, pivampicilline), fluoroquinolones (norfloxacin, ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin), and others (metronidazole, oral vancomycin, tetracyclines, trimethoprim-sulfamethoxazole, clindamycin).

**DESIGN AND STATISTICAL ANALYSIS**

Segmented regression analysis of interrupted time series was used to estimate the effect of the guidelines dissemination on antibiotic prescription and costs [15]. Two segments were defined: the preintervention period (from January 2003 to December 2004) and the postintervention period (from February 2005 to December 2007). Observations for January 2005 were omitted because the guidelines dissemination took place during this month. We first calculated, for each month, the difference in the rates of antibiotic prescriptions and costs in Canadian dollars per 1000 inhabitants by subtracting the rate for the province of Quebec from the rates in the other Canadian provinces. We used the “generalized least squares” model to test for any significant change in level or trend in the time series after the implementation of the guidelines, controlling for any preintervention differences in level and trend. A stepwise elimination of nonsignificant terms was conducted to obtain the most parsimonious models. The final models also included any significant autoregressive terms to control for correlation over time. Estimates are presented with their 95% confidence intervals (CIs). Analysis was performed using the Autoreg procedure in SAS software (version 9.2; SAS Institute).

**RESULTS**

**Prescribing Rates**

Table 1 presents the yearly number of outpatient antibiotic prescriptions per 1000 population in Quebec and the other Canadian provinces between 2003 and 2007. The total number of prescriptions per 1000 population was 10.5% lower in Quebec in 2007 than in 2003 (471 vs 526 per 1000 population), while it was 1.4% higher in the other provinces (652 vs 643 per 1000 population). Figure 1 shows the time series of monthly prescribing rates for any antibiotic in Quebec and in the other provinces.

For the preintervention period, prescribing in Quebec was lower than in the other provinces and the difference increased by 0.2 prescriptions/1000 inhabitants monthly. The gap between Quebec and the other provinces significantly increased by 4.1 prescriptions per 1000 inhabitants (95% CI, –6.6 to –1.6) immediately after the guidelines dissemination (Table 2). After this level change, there was no further significant fluctuation in the difference between Quebec and the other provinces during the postintervention period. For each class of antibiotics, there was an immediate significant level change after the implementation of the guidelines, and this change was maintained until the end of the postintervention period measured at 36 months.

In Quebec, the number of outpatient antibiotic prescriptions per 1000 population, which represents the bulk of antibiotic use decreased by 4.2% in the year after the guidelines dissemination (2005), compared with the year before the dissemination (2004). By contrast, in the other Canadian provinces, the number of prescriptions increased by 6.5% during the same period (Table 1).

**Prescription Cost**

Table 3 presents the yearly cost of antibiotics per 1000 population in Quebec and the other Canadian provinces between 2003 and 2007. The cost per 1000 population decreased by $2402 ($18 539 vs $16 137) or 13% in Quebec during that period, whereas it barely decreased in the other provinces ($18 637 vs $18 550) (all costs in Canadian dollars). Figure 2 shows the monthly cost of antibiotics included in the study in Quebec and in the other Canadian provinces. During the preintervention period, antibiotics prescription costs were higher in Quebec from January to May 2003, but they were higher in the other provinces from June to December 2004. Immediately after the guidelines dissemination, there was an increase of $134.5/1000 inhabitants (95% CI, –$270.5 to $1.6) in the difference between Quebec and the rest of Canada, the costs being lower in Quebec (Table 2). This level change was close to the statistical significance level (P = .054). For the rest of the postintervention period, Quebec's costs were lower than in the other provinces.
period, there was no other significant change in the difference between Quebec and the other provinces.

We found no significant level change in costs for macrolides after dissemination of the guidelines. For cephalosporins, fluoroquinolones, and the other antibiotics, there was a significant level change immediately after the implementation of the guidelines that was maintained until the end of the post-intervention period. An immediate change in the level of penicillin costs was also observed, but was not maintained over time, the difference between Quebec and the rest of Canada being similar at the end of the postintervention period to the difference observed just before the guidelines were implemented.

**DISCUSSION**

The province of Quebec already had the lowest antibiotic consumption rate per capita in Canada in 2003, but the introduction of this multipronged, mostly Web-based education strategy with user-friendly guidelines enabled the province to improve its situation compared with the rest of the country even more. In spite of the controversy surrounding fluoroquinolones use and the occurrence of *C. difficile* infections, there were no major changes in terms of overall prescription of this class. Yet, between 2003 and 2007, Quebec did not see any significant increase, whereas Canada’s consumption grew by 15.1%. Fluoroquinolones are the only class of antibiotics for which Quebec had a higher consumption in 2004 than the rest of the country. The Quebec guidelines insisted on the fact that fluoroquinolones are very appropriate and safe when used in the right situation, usually in patients with underlying medical conditions, but also stressed the importance of prescribing the shortest possible duration of treatment (ie, moxifloxacin has an indication of 5 days in acute exacerbation of chronic bronchitis and a 3-day treatment course of ciprofloxacin in uncomplicated urinary tract infections).

![Figure 1](cid:2011:53 (1 September))

**Figure 1.** Monthly prescribing rates (no. of prescriptions/1000 inhabitants) for all antibiotics in Quebec (QC) and in the other Canadian provinces.

### Table 1. Outpatient Antibiotic Prescriptions per 1000 Population in Quebec (QC) and the Other Canadian Provinces (CAN) From 2003 to 2007

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalosporins</td>
<td>70</td>
<td>92</td>
<td>67</td>
<td>90</td>
<td>61</td>
<td>95</td>
<td>62</td>
<td>94</td>
<td>58</td>
<td>92</td>
</tr>
<tr>
<td>Macrolides</td>
<td>134</td>
<td>144</td>
<td>127</td>
<td>135</td>
<td>123</td>
<td>148</td>
<td>122</td>
<td>141</td>
<td>110</td>
<td>137</td>
</tr>
<tr>
<td>Penicillins</td>
<td>155</td>
<td>229</td>
<td>143</td>
<td>213</td>
<td>140</td>
<td>229</td>
<td>141</td>
<td>226</td>
<td>141</td>
<td>224</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>101</td>
<td>79</td>
<td>101</td>
<td>83</td>
<td>99</td>
<td>88</td>
<td>99</td>
<td>89</td>
<td>101</td>
<td>91</td>
</tr>
<tr>
<td>Others</td>
<td>66</td>
<td>99</td>
<td>63</td>
<td>97</td>
<td>57</td>
<td>98</td>
<td>59</td>
<td>102</td>
<td>61</td>
<td>108</td>
</tr>
<tr>
<td>Total</td>
<td>526</td>
<td>643</td>
<td>501</td>
<td>618</td>
<td>480</td>
<td>658</td>
<td>483</td>
<td>652</td>
<td>471</td>
<td>652</td>
</tr>
</tbody>
</table>

**NOTE.** * CANadian provinces other than Quebec.
Table 2. Absolute Change in Antibiotic Use and Costs Between Quebec and the Other Canadian Provinces Immediately After Dissemination of Guidelines in January 2005

<table>
<thead>
<tr>
<th>Class of antibiotics</th>
<th>Prescriptions/1000 inhabitants (95% CI)</th>
<th>P</th>
<th>Prescription cost, CAD/1000 inhabitants (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalosporins</td>
<td>–1.0 (–1.5 to –0.6)b</td>
<td>&lt;.001</td>
<td>–44.3 (–62.6 to –25.9)a</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Macrolides</td>
<td>–2.1 (–2.7 to –1.6)b</td>
<td>&lt;.001</td>
<td>–53.4 (–125.0 to 18.2)c</td>
<td>.142</td>
</tr>
<tr>
<td>Penicillins</td>
<td>–1.3 (–1.8 to –0.7)a</td>
<td>&lt;.001</td>
<td>–20.7 (–35.0 to –6.5)c</td>
<td>.006</td>
</tr>
<tr>
<td>Quinolones</td>
<td>–0.9 (–1.2 to –0.7)a</td>
<td>&lt;.001</td>
<td>–53.5 (–76.6 to –30.5)h</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Other antibiotics</td>
<td>–0.4 (–0.5 to –0.3)d</td>
<td>&lt;.001</td>
<td>–13.7 (–22.3 to –5.0)c</td>
<td>.003</td>
</tr>
<tr>
<td>All antibiotics</td>
<td>–4.1 (–6.6 to –1.6)c</td>
<td>.002</td>
<td>–134.5 (–270.5 to 1.6)c</td>
<td>.054</td>
</tr>
</tbody>
</table>

**NOTE.** CAD, Canadian dollars; CI, confidence interval. Terms left in the final parsimonious models are listed in the footnotes below, where Yt = monthly number of prescriptions or prescription costs per 1000 inhabitants, β0 = intercept (baseline level), β1 = preintervention trend, β2 = level change immediately after dissemination of guidelines, β3 = postintervention trend, interventiont = indicator for time t occurring before intervention (0) or after intervention (1) dissemination of guidelines, t = a continuous variable indicating time in months at time t from the start of the observation period, time after interventiont = continuous variable counting the number of months after dissemination of guidelines at time t.

a Yt = β0 + β1*interventiont.
b Yt = β0 + β1*interventiont + β2*time after interventiont (corresponding to full segmented regression model).
c Yt = β0 + β1*interventiont + β2*time after interventiont + β3*time after interventiont.
d Yt = β0 + β1*time after interventiont + β2*interventiont.

Media interventions in Quebec in 2003–2004 about *C. difficile* infections and nosocomial infections in general increased the awareness level of the general population but also of health care professionals in relation to antibiotic use. This probably contributed to better acceptance of the published guidelines. There are no published data showing that decreasing antibiotic use in Quebec compared with the rest of the country was associated with more clinical failure or any signal of increased morbidity due to infections (eg, hospitalizations, outbreaks). This would be very surprising in the outpatient setting, where morbidity and mortality are usually very low.

The way to measure antibiotic consumption is still a matter of some debate. Defined daily doses are usually considered a standard method, but this information is not yet easy to collect on a very large and continuous scale, especially in an ambulatory setting. Although imperfect, consumption adjusted per capita (prescriptions/1000 inhabitants) is a tool that offers a view of global antibiotic consumption at the macro level.

Despite the lower number of prescriptions in Quebec in 2003, the cost per 1000 population was comparable to that in the rest of Canada. This can be explained by the faster acceptance of newer agents on the provincial formulary in Quebec at that time. In general, Quebec physicians were able to prescribe newer molecules more easily than their Canadian counterparts (ie, clarithromycin or azithromycin instead of erythromycins, cefprozil instead of older cephalosporins). In addition, cost includes management and professional fees, and not just the drug itself. These fees can vary from province to province. Antibiotics costs are very similar between Canadian provinces, and major changes, such as the arrival of a generic brand, will have the same impact throughout the country. There was indirectly no major changes in terms of length of therapy during the study period.

Table 3. Costs of Outpatient Antibiotic Prescriptions per 1000 Population in Quebec (QC) and the Other Canadian Provinces (CAN) From 2003 to 2007

<table>
<thead>
<tr>
<th>Class of antibiotics</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>QC</td>
<td>CAN</td>
<td>QC</td>
<td>CAN</td>
<td>QC</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>2824</td>
<td>2640</td>
<td>2790</td>
<td>2669</td>
<td>2541</td>
</tr>
<tr>
<td>Macrolides</td>
<td>6299</td>
<td>6265</td>
<td>6129</td>
<td>6216</td>
<td>6144</td>
</tr>
<tr>
<td>Penicillins</td>
<td>2753</td>
<td>3490</td>
<td>2508</td>
<td>3297</td>
<td>2490</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>5177</td>
<td>4327</td>
<td>4958</td>
<td>4201</td>
<td>4214</td>
</tr>
<tr>
<td>Others</td>
<td>1486</td>
<td>1915</td>
<td>1692</td>
<td>1972</td>
<td>1602</td>
</tr>
<tr>
<td>Total</td>
<td>18 539</td>
<td>18 637</td>
<td>18 077</td>
<td>18 355</td>
<td>16 991</td>
</tr>
</tbody>
</table>

**NOTE.** CAD, Canadian dollars.

a Canadian provinces other than Quebec.

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because the total cost of antibiotics use went down in Quebec with no major shift in terms of brand names or generic drugs overall. A decreasing number of prescriptions per capita in Quebec cannot be offset by a lengthening of treatment duration and therefore consumption.

Antibiotics represented 3.5% of the total retail drug market in Canada in 2007, with a total value of $665 million [16]. The average per capita spending for all outpatient prescription drugs in Canada and Quebec in 2007 was $58 and $76, respectively. Quebec had higher than average spending per capita for cardiovascular, neurologic, and acid-reducing drugs, which represented the 3 most important categories. However, in terms of antibiotics, the per capita spending was $20.20 in Canada and $18.1 in Quebec (11.6% below the national average) [16].

Numerous clinical trials have looked at antibiotic consumption within the hospital setting, a much smaller and controlled environment [6, 13, 17–19]. Limited success was sometimes achieved using a multifaceted approach. However, this cannot be easily extended to the community at large [20–22]. Focusing on respiratory tract infections is another approach, because they represent the bulk of antibiotic prescriptions but health care professionals have to face many hurdles that are not solely medical (cultural beliefs, patient requests, new drugs) [11, 12, 20, 23].

The major impact of this strategy took place in January 2005, and it had a sustained effect on antibiotic prescriptions even 36 months later. The 4.1 prescriptions/1000 population change in January 2005 saved roughly 370 thousand antibiotic prescriptions per year in Quebec. Although antibiotic prescriptions were decreasing in both Quebec and Canada when 2003 and 2004 were compared, the trend completely disappeared in Canada in 2005. The decrease was sustained only in Quebec, where a global approach to improve antibiotic use was implemented. It is therefore possible to obtain successful long-term results in the challenging field of outpatient antibiotic use. With the advent of hand-held electronic devices and their increasing use by all categories of health care professionals, information disseminated by this mean becomes instantly available, reaching private offices and remote areas. Geographic and site-of-care barriers do not exist anymore with these approaches.

This study has a number of limitations; we did not take into account samples given to physicians, but they represent a very small percentage of the total amount of antibiotics, and filling an antibiotic prescription at a community pharmacy does not guarantee that the patient will finish the entire treatment. The Quebec antibiotic guidelines were produced in a period when health care professionals, government authorities, and perhaps the population as a whole were highly aware of the risks associated with antibiotic overuse (C. difficile infections). Thus, external factors besides the guidelines themselves may have influenced antibiotic prescribing practices.

Our results demonstrated that user-friendly guidelines, based on rigorous scientific content, presented in a concise and attractive format, prepared by a credible organization, endorsed by professional colleges and associations, and actively promoted and disseminated through various means (notably the Internet), can have a sustained impact on antibiotic prescribing practices.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed in the Acknowledgments section.

References