ORIGINAL ARTICLE

Longitudinal surveillance of outpatient quinolone antimicrobial use in Canada

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INTRODUCTION: Because antimicrobial use is commonly associated with the development of antimicrobial resistance, monitoring the volume and patterns of use of these agents is important.
OBJECTIVE: To assess the use of quinolone antimicrobials within Canadian provinces over time.
METHODS: Antimicrobial prescribing data collected by IMS Health Canada were acquired from the Canadian Integrated Program for Antimicrobial Resistance Surveillance and the Canadian Committee for Antimicrobial Resistance, and were used to calculate two yearly metrics: prescriptions per 1000 inhabitant-days and the mean defined daily doses (DDDs) per prescription. These measures were used to produce linear mixed models to assess differences among provinces and over time, while accounting for repeated measurements.
RESULTS: The quinolone class of antimicrobials is used similarly among Canadian provinces. Year-to-year increases in quinolone prescribing occurred from 1995 to 2010, with a levelling off in the latter years. Year-to-year decreases in the DDDs per prescription were found to be significant from 2000 to 2010.
DISCUSSION: Although the overall use of antimicrobials differs significantly among Canadian provinces, the use of the quinolone class does not vary at the provincial level. Results suggest that prescribing of ciprofloxacin may be a potential target for antimicrobial stewardship programs; however, decreases in the average DDDs per prescription suggest continued uptake of appropriate treatment guidelines.

Key Words: *Antimicrobial use; Drug utilization; Quinolones; Surveillance*

La surveillance longitudinale de l'utilisation d'antimicrobiens de la classe des quinolones en consultations externes au Canada

INTRODUCTION : Puisque l'utilisation d'antimicrobiens s'associe souvent à l'apparition d'une résistance antimicrobienne, il est important d'en surveiller le volume et le mode d'utilisation.
OBJECTIF : Évaluer l'utilisation d'antimicrobiens de la classe des quinolones au sein des provinces canadiennes au fil du temps.
MÉTHODOLOGIE : Les chercheurs ont acquis les données de prescription d'antimicrobiens colligées par IMS Health Canada auprès du Programme intégré canadien de surveillance de la résistance aux antimicrobiens et du Comité canadien sur la résistance aux antibiotiques et les ont utilisées pour calculer deux mesures annuelles : les prescriptions par 1 000 habitants-jours et les doses quotidiennes définies (DTD) moyennes par prescription. Ils les ont utilisées pour produire des modèles linéaires mixtes afin d'évaluer les différences entre les provinces et au fil du temps, tout en tenant compte des mesures répétées.
RÉSULTATS : Les antimicrobiens de la classe des quinolones sont utilisés de manière similaire dans les provinces canadiennes. Les prescriptions annuelles de quinolone ont augmenté de 1995 à 2010, mais ont plafonné au cours des dernières années. Les DTD par prescription ont diminué annuellement de manière significative entre 2000 et 2010.
EXPOSÉ : Même si l'utilisation globale d'antimicrobiens diffère de manière significative entre les provinces canadiennes, l'utilisation de la classe des quinolones ne varie pas sur la scène provinciale. D'après les résultats, la prescription de ciprofloxacine peut être une cible potentielle des programmes de gestion des antimicrobiens. Cependant, les diminutions des DTD moyennes par prescription sont indicatrices d'une assimilation continue des directives thérapeutiques pertinentes.

In the current article, data regarding the use of the quinolone class of antimicrobial drugs by the outpatient population in Canada, defined by the WHO's Anatomical Therapeutic Classification system as group J01M (1), are presented. Previous reports have described differences in antimicrobial use according to Canadian provinces and according to antimicrobial class at the national level (2). However, provincial patterns of use at the quinolone class and drug level are not currently available in the literature. Therefore, the objective of the present article was to detail trends in use in Canada of the quinolone class and the 10 individual drugs within the class from 1995 to 2010, and to determine whether significant differences in quinolone use at the provincial level are present. Trends were assessed using two measures of antimicrobial consumption: prescriptions per 1000 inhabitant-days (PrIDs) and the mean defined daily doses (DDDs) per prescription.

A secondary objective of the present study was to compare the use of quinolone antimicrobials in Canada with use reported by European countries in 2009 through the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) (3,4).

METHODS

Antimicrobial prescribing and extended unit data for all individual quinolones dispensed in Canadian provinces from 2000 to 2010 were collected by IMS Health Canada and acquired by the Public Health Agency of Canada's Canadian Integrated Program for Antimicrobial Resistance. In addition, supplemental prescription counts per province for ciprofloxacin, grepafloxacin, levofloxacin, nalidixic acid, norfloxacin, ofloxacin and trovafloxacin for 1995 to 1999 were also collected by IMS Health Canada and acquired from the former Canadian Committee on Antimicrobial Resistance (5). The Canadian

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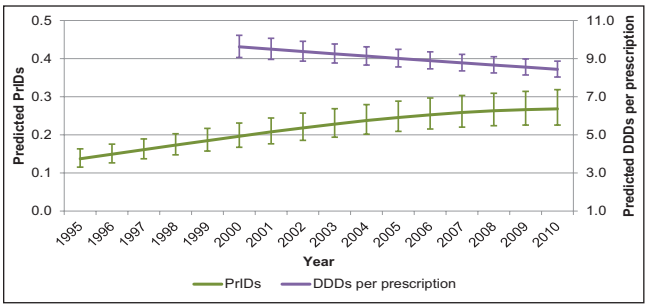

Figure 1) *Predicted values and 95% CIs for the models describing quinolone prescriptions per 1000 inhabitant-days (PrIDs) (1995 to 2010) and defined daily doses (DDDs) per prescription (2000 to 2010) in Canadian provinces*

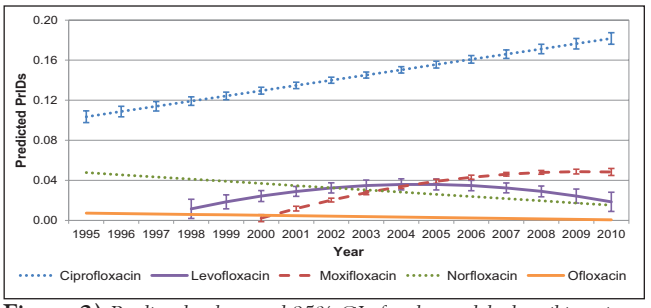

Figure 2) *Predicted values and 95% CIs for the models describing ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin and ofloxacin prescriptions per 1000 inhabitant-days (PrIDs) at the national level in Canada, 1995 to 2010*

CompuScript dataset is developed by accessing all marketed outpatient drug data dispensed via prescriptions by 5900 geographically representative retail pharmacies across Canada, with provincial-level coverage ranging from 51% to 88%. Geospatial extrapolation is used to infer use across all 8800 pharmacies (current to May 2013). The extrapolation stratifies according to pharmacy size, type and province (6). This methodology nullifies any variance in store coverage over time and across geography. All data were reported monthly according to province for all new and refilled prescriptions. The Canadian CompuScript dataset included individual drug-level prescription count information, but also included manufacturer name, extended units prescribed (total number of tablets, capsules, millilitres, etc), drug strength, volume of active ingredient and patient acquisition cost. Data from Newfoundland and Labrador and Prince Edward Island were combined for the years 1999 to 2004. In 2005 and subsequent years, data from these provinces were provided individually. The prescription counts were combined with population data from Statistics Canada to develop two population-standardized measures: PrIDs and the DDDs per 1000 inhabitant-days (DIDs) (7). The volume of active ingredient, number of extended units dispensed and the strength of the product were also acquired for all observations during the 2000 to 2010 time period. These additional data allowed for the development of the DID, and DDD per prescription measures. Data for grepafloxacin and trovafloxacin were not used for the analysis in the present study because data were only available for the years 1995 to 1998.

Linear mixed models were developed in a forward step-wise fashion to assess differences in use according to province over the 1995 to 2010 study frame, and to describe provincial differences in quinolone prescribing and the average DDDs per prescription over time. Province and year were assessed as predictors for use at $P<0.05$ and assessed for confounding effects using a 25% change cut-off in any significant coefficient. Quadratic terms for year were assessed at $P<0.05$ where visually appropriate to model a curvilinear relationship between time and the outcome, as well as interaction terms between province and year, and province with the quadratic term for year. Repeated measures were accounted for by assigning a first-order autoregressive correlation structure, and the natural logarithm transformation was applied to the outcome variable to meet the assumption of homoscedasticity where required. Normality was assessed and met, and residual analyses were performed to highlight outlying observations. Data for any outlying observations were assessed to assure that recording errors were not present; however, models were built using all observations to limit any potential bias.

Linear models were developed to describe the use of ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin and ofloxacin PrIDs at the national level from 1995 to 2010. Predicted values from all models were used to develop figures to visualize significant patterns of use.

Antimicrobial use data from 2009 were acquired from ESAC-Net, and rankings performed such that the country with lowest use was assigned a rank of 1. Comparisons were made using three use measurements: DIDs, PrIDs and DDDs per prescription. All calculations and analyses were performed using SAS version 9.3 (SAS Institute Inc, USA) for Windows 2010 (Microsoft Corporation, USA), and graphs were produced in Excel (Microsoft Corporation, USA).

RESULTS

There were 10 quinolone antimicrobial drugs dispensed from Canadian outpatient pharmacies during the 1995 to 2010 time frame: ciprofloxacin, gatifloxacin, gemifloxacin, grepafloxacin, levofloxacin, moxifloxacin, nalidixic acid, norfloxacin, ofloxacin and trovafloxacin. The majority of quinolone prescribing was for ciprofloxacin, which represented >56% of PrIDs in all years examined.

New antimicrobials were introduced in the quinolone class during the study period. The first prescriptions for levofloxacin and moxifloxacin were dispensed in 1998 and 2000, respectively; the steady uptake of these drugs results in them representing >27% of quinolone PrIDs in 2010. In contrast, norfloxacin PrIDs were reduced by 24% from 1995 to 2010.

After accounting for the significant effects of year and its quadratic term in the PrID model, no significant differences in use were found among the provinces. For the PrIDs, a steady increase was observed from 1995 to 2007, followed by a slight levelling from 2008 to 2010 (Figure 1). Similarly, no significant provincial differences were found in the DDD per prescription model. However, a different trend over time appeared in the DDD per prescription model, with significant yearly decreases (Figure 1).

The individual drug linear models showed that significant increases in prescribing of ciprofloxacin occurred from year to year in Canada (Figure 2). The prescribing of levofloxacin increased from 1995 to 2004, followed by a decline from 2005 to 2010, which was modelled using year and its quadratic term (Figure 2). Similarly, year and its quadratic term were significant in the model describing moxifloxacin prescribing, which increased from 2000 to 2007, followed by a levelling off in use from 2007 to 2010 (Figure 2). The models describing norfloxacin and ofloxacin use each included year as a significant predictor, which showed that significant decreases in prescribing of these drugs occurred from 1995 to 2010 (Figure 2).

In 2009, the use of quinolones in Canada was relatively high in comparison with the reporting European countries according to all measures assessed (Table 1). According to the PrID measure, Canada ranked 26 of 33, while the DID and DDD per prescription measures ranked Canada 12 of 18 and 14 of 18, respectively (Table 1).

DISCUSSION

Despite declining overall rates of antimicrobial use in Canada (2), prescribing within the quinolone class of antimicrobials has been increasing since 1995. Ciprofloxacin and moxifloxacin dominate this trend of increased prescribing rates, with an increase of >125% in the prescribing of these two drugs from 1995 to 2010, and representing >84% of quinolone class prescribing in Canada in 2010. In contrast, the prescription rate for norfloxacin decreased by >65% from 1995 to 2010. Interestingly, however, in Canada in 2011, a review of provincial

formularies conducted by the authors showed that the quinolones are the most restricted antimicrobial class in terms of financial reimbursement. Restrictions are placed on antimicrobial reimbursement by non-listing of drugs, whereby the provincial drug plan will not reimburse prescriptions for that particular drug or by placing requirements on the prescription. These requirements may involve a particular diagnosis or a special authorization for reimbursement criteria to be met and, therefore, drugs with restrictions are expected to be prescribed at lower rates than those listed as general benefits of the provincial plans.

On March 4, 2001, the formulary for the Ontario Drug Benefit was changed such that ciprofloxacin and ofloxacin prescriptions went from being general (reimbursable) benefits to requiring a limited use (LU) authorization (8). This LU authorization requires that physicians add an appropriate numerical code to the prescription, which reflects a given diagnosis or condition (9). Furthermore, although LU designation was in place for levofloxacin, additional restrictions were added for the use of LU codes for prescribing for levofloxacin, while norfloxacin remained a general benefit (8,9). The expectation was that increased LU stipulations would result in the reduction of inappropriate prescribing of ciprofloxacin, levofloxacin and ofloxacin due to the increased 'burden of proof' required for financial reimbursement to the patient at the point of prescription receipt. Marshall et al (10) showed that a significant reduction in the number of prescriptions for ciprofloxacin in Ontario occurred subsequent to the LU requirement using time-series model methodologies for data spanning January 1999 and September 2002. However, viewing the data over a longer time frame and adjusting for population changes showed that this change did not produce significantly different prescribing rates between Ontario and any of the other provinces. Similar utilization initiatives were introduced in Canada with the exception of British Columbia, Newfoundland and Labrador, and Quebec for ciprofloxacin and ofloxacin. In addition, British Columbia did not provide benefit coverage for levofloxacin, while New Brunswick did not cover expenses related to ofloxacin.

Decreases in the average DDDs per prescription for the quinolone class from 2000 to 2010 may reflect shorter durations for pneumonia as well as increasing adherence to suggested treatment guidelines for urinary tract infections (UTIs). Because ciprofloxacin is the most commonly used drug within the class, the dynamics of ciprofloxacin use are expected to drive class-level dynamics and, although not suggested as an empirical treatment, ciprofloxacin is a commonly chosen treatment for UTIs in Canada (11,12). Suggestions for reducing treatment duration have been made for ciprofloxacin treatment of uncomplicated UTIs (13), therefore, also suggesting a reduction in the average DDDs per prescription. However, prescription-level data are required to confirm this expectation and may be an avenue for future analysis of quinolone use in Canada. In addition, further work is needed to better understand the appropriateness of prescribing use practices and whether they are used appropriately because this information is currently not available to the authors.

In comparison with reporting European countries, use of quinolone antimicrobials in 2009 was relatively high in Canada. Canada ranked among the upper one-third of countries according to all three measures of use, with measures approximately four times the magnitude of the lowest-ranked country. These results highlight that quinolone prescribing is a potential stewardship target in the medical community.

Many reports have been published on the increase of quinolone-resistant infections around the world, particularly those related to previous use of fluoroquinolones (14-18). In particular, a study conducted in the Swiss canton of Geneva (15) produced information regarding how increases in the use of ciprofloxacin impacted the increase of community-acquired ciprofloxacin-resistant isolates. The findings indicated that for every 1% increase in ciprofloxacin use, there would be an immediate increase of 1.3% in the number of community-acquired ciprofloxacin-resistant isolates and an additional 0.97% one month later. Although the majority of reports on the impact of quinolone use on resistance rates appear to be focused on UTIs (16), *Staphylococcus aureus* (17) and other hospital-acquired organisms (14), there has been at least one report discussing the impact of this use on food-borne diseases such as illness caused by *Campylobacter*. In Denmark, Koningstein et al (18) found an increase in the risk for previous exposure to fluoroquinolones and diagnosis with campylobacteriosis. These risks increased when the infection was caused by a resistant strain compared with a susceptible strain.

In Canada, antimicrobial resistance among pathogens causing UTIs continue to rise. Data reported by a national surveillance study conducted between 2007 and 2009 showed that resistance to amoxicillin-clavulanic acid and sulfamethoxazole-trimethoprim drugs continue to increase (19). However, resistance to ciprofloxacin showed a greater relative increase compared with sulfamethoxazole-trimethoprim resistance identified in a 1998 survey of outpatient UTI isolates. These increases correlate well with reported increased use of quinolones for treatment of lower UTIs (20). In British Columbia, between 1996 and 2010, consumption of quinolones for the treatment of lower UTIs has doubled from 0.125 DID to 0.24 DID.

TABLE 1
Comparison of total quinolone use among Canada and the reporting European Surveillance of Antimicrobial Consumption Network countries according to defined daily doses (DDDs) per 1000 inhabitant-days (DIDs), prescriptions per 1000 inhabitant-days (PrIDs) and DDD per prescription measures in 2009 (lowest use ranking = 1)

	DIDs		PrIDs		DDDs per prescription	
Country	Value	Rank	Value	Rank	Value	Rank
Austria	1.33	16	0.22	10	6.16	9
Belgium	2.61	28	0.31	13	8.35	17
Bulgaria	1.97	22	0.36	14	5.51	5
Canada	2.04	26	0.26	12	7.70	14
Croatia	1.33	17	0.19	8	6.87	11
Cyprus	4.13	33	NR	NR	NR	NR
Czech Republic*	1.27	15	0.19	9	6.57	10
Denmark	0.52	3	0.07	1	7.57	13
Estonia	0.79	5	0.14	5	5.54	6
Finland	0.87	8	0.12	4	7.39	12
France	2.00	23	NR	NR	NR	NR
Germany	1.48	19	NR	NR	NR	NR
Greece	2.63	29	0.57	17	4.64	2
Hungary	1.79	21	NR	NR	NR	NR
Iceland	0.55	4	NR	NR	NR	NR
Ireland*	0.94	10	0.16	6	5.89	8
Israel	1.44	18	NR	NR	NR	NR
Italy†	3.61	32	1.60	18	2.25	1
Latvia	0.85	7	NR	NR	NR	NR
Lithuania	1.23	12	0.26	11	4.70	3
Luxembourg	2.81	30	NR	NR	NR	NR
Malta	1.66	20	NR	NR	NR	NR
Norway	0.51	2	NR	NR	NR	NR
Poland	1.25	13	NR	NR	NR	NR
Portugal	3.04	31	0.37	15	8.14	16
Romania	1.26	14	NR	NR	NR	NR
Russian Federation	2.01	24	0.40	16	4.96	4
Slovakia	2.03	25	NR	NR	NR	NR
Slovenia	1.08	11	0.18	7	5.87	7
Spain	2.42	27	NR	NR	NR	NR
Sweden	0.79	6	0.09	2	8.48	18
The Netherlands	0.89	9	0.11	3	7.85	15
United Kingdom	0.48	1	NR	NR	NR	NR

**Data from 2007; †Data from 2008; NR Not reported*

We acknowledge the limitations to our study, which include the lack of DDD information for the 1995 to 1999 time period and the potential for nonrepresentativeness of measured pharmacies. However; despite missing DDD (and, therefore, DDD per prescription) measurements from 1995 to 1999, the 2000 to 2010 data supply sufficient information to describe a significant decreasing trend over time. Furthermore, the large proportion of pharmacies represented in the dataset (>67% of all the Canadian pharmacies in September 2011), and the extensive extrapolation method used by IMS Health Canada supports our belief that these data truly reflect the use of quinolone antimicrobials in Canada (2,5).

DISCLAIMER: The analyses, conclusions, opinions and statements expressed are those of the authors and not those of IMS Health Canada Inc.

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