Per Capita Antibiotic Consumption: How Does a North American Jurisdiction Compare with Europe?

David M. Patrick, Fawziah Marra, James Hutchinson, Dominique L Monnet, Helen Ng, and William R. Bowie

1Centre for Disease Control and 2Department of Medicine, University of British Columbia, Vancouver, and 3Department of Medicine, Memorial University, St. John’s, Newfoundland, Canada, and 4Statens Serum Institut, Copenhagen, Denmark

Antibiotic consumption in populations affects the emergence of resistant organisms. We compared 1996–2000 trends in consumption in British Columbia, Canada, with those in Europe. Prescription data from the British Columbia PharmaNet database were converted into SAS files and classified using the Anatomical Therapeutic Chemical system, and weights of antibiotics were converted into defined daily doses (DDDs) using the 2001 definitions from the World Health Organization Collaborating Center for Drug Statistics Methodology. During 1996–2000, consumption in British Columbia decreased from 19.5 to 17.9 DDDs/1000 inhabitant-days. Although antibiotic consumption in British Columbia was less than the European median in 2000, it exceeded that in northern European countries with established antibiotic surveillance and control programs. The consumption rates for fluoroquinolones, newer macrolides, and cephalosporins in British Columbia exceeded those in Denmark (1.44 vs. 0.15, 1.59 vs. 0.92, and 1.86 vs. 0.02 DDDs/1000 inhabitant-days, respectively). The observed increase in and pattern of consumption associated with newer antimicrobials may increase the risk for emergence of antimicrobial-resistant organisms in British Columbia.

Overuse of antibiotics has contributed to the emergence and spread of antimicrobial-resistant organisms (AROs). AROs are a global threat affecting industrialized and developing nations [1, 2]. Until recently, the major emphasis for study of bacterial resistance was confined to hospital-acquired microorganisms, such as Staphylococcus aureus, enterococci, and Pseudomonas aeruginosa [3–5]. However, increasing resistance has been observed in community-acquired microbes such as Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis, which are key pathogens in respiratory tract infections; Escherichia coli, which is a common pathogen in urinary tract infections; and group A streptococci, the cause of streptococcal pharyngitis and many skin and soft-tissue infections [4–9].

Factors contributing to antimicrobial resistance include natural selection imposed by widespread use of antimicrobial agents in humans [10–12]. Reasons cited for antimicrobial overuse include defensive and unnecessary prescribing, perceived or real pressure from patients and parents of patients to prescribe drugs, inadequate knowledge of the proper indications for some drugs, lack of awareness of prescription guidelines, lack of time to explain to the patient that antimicrobials are not needed, lack of education about resistance patterns in the community, and fee-for-service remuneration of physicians [2, 13, 14].

Enhanced antimicrobial surveillance is one of the strategies that can be used to guide control of antimicrobial overuse or misuse. This is because the ability to study population-based patterns of antimicrobial use provides a more comprehensive understanding of how the physician and patient use these agents. Countries such as Denmark and Spain have databases containing information on antimicrobials prescribed for all patients in the country. Prescription information for various populations (e.g., children versus adults) and between jurisdictions (i.e., provinces within the country)
METHODS

British Columbia’s PharmaNet system is a population-based prescription drug database that captures nearly all antimicrobial consumption by outpatient residents of the province on a prescription-by-prescription basis. Oral and parenteral antimicrobials may only be accessed by prescription at pharmacies, all of which are required to enter drug and dosage information into the Web-based PharmaNet system. A central database repository is held at the British Columbia Ministry of Health. Underreporting and misclassification appear to be minimal. Outpatient drugs that are not so captured are those dispensed by the BC sexually transmitted diseases control program (0.02 defined daily doses [DDDs] per 1000 inhabitant-days; BC Centres for Disease Control pharmacy, unpublished data) and antiretroviral agents dispensed by the BC HIV treatment program (not cogent to this analysis). Samples of antibiotics distributed by physician offices represent small but unmeasured additional contributions.

The data examined spanned September 1995 through December 2000 and included the patients’ age and sex; the antimicrobial agent prescribed, according to the Anatomical Therapeutic Chemical (ATC) classification system; and the date and total quantity dispensed. The format of the downloaded data from British Columbia PharmaNet allowed for precise measurement of the total dose consumed by each patient but did not allow discernment of the total dose and dosage for each individual prescription.

Drugs were classified according to the 5 different levels of the ATC classification. For example, azithromycin would be classified as follows: first level, general anti-infective drug for systemic use; second level, antibacterial therapy for systemic use; third level, macrolide and lincosamide; fourth level, macrolide; and fifth level, azithromycin.

Antimicrobials included in the database were for systemic use (ATC code J01). For this study, we evaluated trends for penicillins (ATC code J01C), macrolides (J01FA), tetracyclines (J01AA), cephalosporins (J01DA), fluoroquinolones (J01MA), lincosamides (J01FF), trimethoprim and derivatives (J01EA), and combinations of sulfonamides and trimethoprim (J01EE).

Dosage trends were standardized using the ATC/DDD index for international drug consumption studies [23]. The DDD is a technical unit based on the “assumed average maintenance dose per day for a drug used for its main indication in adults.” The consumption rate is most commonly expressed as the number of DDDs per 1000 inhabitants per day. Population estimates were provided by British Columbia Stats.

Raw data from 9,481,043 records of aggregate antimicrobial use spanning September 1995 through December 2000 were received from British Columbia PharmaNet on 192 separate Excel spreadsheets (Microsoft). Data were imported into SAS software (version 8.02; SAS Institute) and reviewed for completeness of fields. Frequency tables were produced to quantify missing variables in all records. Less than 0.1% of data were missing for each field used in these analyses. The generic sequencing numbers (GCNs; 5-digit codes that uniquely identify specific drug/form/strength combinations in the raw data set) were extracted, and a data dictionary was created by assigning the appropriate ATC category and DDD conversion factor to each GCN. DDD conversion factors were based on the 2001 version of the ATC/DDD index produced by the World Health Organization Collaborating Center for Drug Statistics Methodology [23].

The analyses were performed using SAS software and focused on data recorded between 1996 and 2000. Consumption was plotted by year, age group, sex, geographic region, and antibiotic class or compound. Published comparisons were obtained using data posted on the Web by the European Surveillance of Antimicrobial Consumption Study [24–31], DANMAP [32], and direct communication with a coauthor (D.L.M.) of one of the ESAC studies [30]. Statistical tests suitable for assessing the accuracy of inference for a sample were

![Figure 1. Median antibiotic consumption in British Columbia (BC) and Europe, 1996–2000.](image-url)
not employed, because British Columbia and European data used in this and comparative publications represented total population ambulatory use and were not obtained from a sampling framework.

RESULTS

Overall antibiotic consumption. During 1996–2000, the rate of antibiotic consumption (ATC group J01) in British Columbia decreased 8.2%, from 19.5 to 17.9 DDDs/1000 inhabitant-days (figure 1). This was just below the median European consumption rate (19–20 DDDs/1000 inhabitant-days) between 1998 and 2000. However, figure 2 underscores the heterogeneity of consumption within Europe. British Columbia is consuming fewer DDDs of antibiotics per capita than are high-consumption European countries (e.g., France and Greece). Yet antibiotic consumption in British Columbia considerably exceeded that in northern European countries with more-developed antimicrobial-control programs.

Seasonality, age, and sex distribution. An association between seasonality and antibiotic consumption was revealed by the finding that peak use occurred between January and March of each year of the study (figure 3). The mean seasonal variation for British Columbia, calculated by comparing antibiotic consumption during quarters 1 and 4 with that during quarters 2 and 3 over this period, was 21.6%. Year 2000 consumption rates by age and sex for the province are displayed in figure 4. Recall that the apparent lower rates among children are an artifact of the DDDs being based on typical adult doses. Overall, female patients consumed 17% more antibiotics during 2000 than did male patients (19.3 vs 16.5 DDDs/1000 inhabitant-days). Overall antibiotic consumption was higher for patients aged 15–19 and >65 years than for those in other age groups.

Class-specific trends. Figure 5 illustrates trends in consumption of the major classes of antibiotics for 1997–2000 in British Columbia and Denmark. The rate of consumption was ~50% higher in British Columbia during each year of the study.
Although overall $\beta$-lactam use was similar in the 2 jurisdictions, comparatively few cephalosporins were used for outpatient care in Denmark. It is also notable that the rate of outpatient fluoroquinolone consumption in British Columbia exceeded that in Denmark by nearly 10-fold.

A comparison of antimicrobial use in British Columbia in 1996 and 2000 showed that $\beta$-lactams accounted for a high but decreasing proportion of overall antibiotic consumption (45% [8.77 DDDs/1000 inhabitant-days] vs. 42% [7.47 DDDs/1000 inhabitant-days]). Overall tetracycline and macrolide consumption remained stable between 1996 and 2000, but a dramatic 44% increase in the fluoroquinolone consumption rate (1.01 vs. 1.44 DDDs/1000 inhabitant-days) was observed (figure 6). Of note, most of the overall increase in fluoroquinolone consumption was accounted for by the use of 1 drug: ciprofloxacin consumption increased from 0.68 to 1.02 DDDs/1000 inhabitant-days during 1996–2000.

Although overall macrolide consumption has not changed substantially in British Columbia, there has been increased use of the newer macrolides azithromycin and clarithromycin, with a far greater consumption of the latter drug in British Columbia than in Denmark (figure 7). Consumption of these compounds increased 67% during 1996–2000, whereas consumption of erythromycin steadily decreased.

**DISCUSSION**

To our knowledge, this is the first report of population-based rates of antibiotic consumption in a province or state in North America. The existence of a population-based pharmaceutical prescription database and the earlier development by others of widely accepted standards and methodology facilitated the work.

Although British Columbia experienced an 8.2% decrease in the rate of antibiotic prescribing between 1996 and 2000, antibiotics were consumed at a rate of 17.9 DDDs/1000 inhabi-
tant-days during 2000, which was 46% higher than the consumption rate of 12.3 DDDs/1000 inhabitant-days recorded in Denmark. Indeed, consumption rates in British Columbia consistently exceed those in northern European countries, such as Denmark, Sweden, and the United Kingdom.

Of more concern than the overall rate of consumption is that patients in British Columbia consumed proportionately more DDDs of fluoroquinolones and newer macrolides per capita than did patients in northern European countries. This increase may be accounted for in part by the greater emphasis on adherence to recent respiratory infection guidelines [33]. However, it is also likely that aggressive marketing of newer agents and a lack of comprehensive antibiotic-control programs have had an effect on consumption rates. These data do not allow us to comment conclusively on whether this difference is due to inappropriate prescription, but the magnitude of the difference between British Columbia and a country, Denmark, that has similar life expectancy and similar rates of reporting of infectious diseases and infectious diseases–specific mortality raises questions. The potential for emergence of resistance among community-acquired organisms, especially pneumococci, to these classes of agents is of concern. In contrast, although β-lactams comprise a high but decreasing proportion of antibiotics prescribed, a high rate of use would seem to be appropriate because of their role as first-line therapy for many common indications.

Further work planned by our group will address reasons for the prescription of specific compounds. We also need to correlate antimicrobial consumption among humans with rates of identification and emergence of antimicrobial-resistant organisms in British Columbia. It should be recognized that, although use of antimicrobials in human populations may indeed drive resistance, other variables also play a role. Population density, the effect of importation and subsequent spread of antibiotic-resistant organisms from countries with established problems, and antimicrobial use in animals may also influence the emergence of resistance among humans [2, 13, 34].

A few other observations are worthy of comment. The observed pattern of seasonal variation in British Columbia (22% increase between quarters 1 and 4 and quarters 2 and 3) is a pattern typical in northern European countries with lower overall antibiotic use [24]. Countries with higher use often see a more marked (i.e., >30%) seasonal swing.

Consumption by female patients exceeded that by male patients, especially during the reproductive years. Females are known to more actively seek health care and to attend physicians’ offices more frequently. Some classes of infection, such as urinary tract infection, are also objectively more common among females.

This study has a number of limitations. First, the format of the download from British Columbia PharmaNet allowed for precise measurement of total amounts of drugs consumed but not discernment of the total dose, dosage, and volume of each individual prescription. As a result, it was not possible to es-
imate how many individual prescriptions were supplied (e.g., to children). This will be addressed with future data exchanges. The inability to count prescriptions in children leads to a reliance on describing consumption on the basis of DDDs for adults. This creates a systematic underestimate of the extent of antimicrobial consumption in infants and young children. These deficiencies will be addressed in future downloads from and collaborations with British Columbia PharmaNet.

We have reported the first population-based study of antimicrobial consumption in a North American province or state and, in doing so, have demonstrated a measurably higher rate of antimicrobial consumption in British Columbia than that in northern Europe. This is a critical first step in designing approaches to prevent the emergence of antimicrobial resistance through measurement and guidance of antimicrobial prescribing.

Acknowledgments

We thank the College of Pharmacists of British Columbia, for collaborating to arrange this analysis; the BC Ministry of Health, for assisting with initial data compilation; and Rick White, for statistical and analytic assistance.

Financial support. Pfizer Canada and the University of British Columbia Centre for Disease Control.

References

