Chronic diseases and compliance with provincial guidelines for outpatient antibiotic prescription in cases of otitis media and respiratory infections: a population-based study of linked data in Quebec, Canada, 2010–2017

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Abstract

Background: In Quebec, antibiotic use is higher among outpatients with chronic diseases. We sought to measure compliance with provincial guidelines for the treatment of otitis media and common respiratory infections, and to measure variations in compliance according to the presence of certain chronic diseases.

Methods: We conducted a population-based study of linked data on antibiotic dispensing covered by the public drug insurance plan between April 2010 and March 2017. We included patients who had consulted a primary care physician within 2 days before being dispensed an antibiotic for an infection targeted by provincial guidelines, including bronchitis in patients with chronic obstructive pulmonary disease, otitis media, pharyngitis, pneumonia and sinusitis. We computed proportions of prescriptions compliant with guidelines (use of recommended antibiotic for children, and use of recommended antibiotic and dosage for adults) by age group (children or adults) and chronic disease (respiratory, cardiovascular, diabetes, mental disorder or none). We measured the impact of chronic diseases on compliance using robust Poisson regression.

Results: We analyzed between 14 677 and 198 902 prescriptions for each infection under study. Compliance was greater than 87% among children, but was lower among children with asthma (proportion ratios between 0.97 and 1.00). In adults, the chosen antibiotic was compliant for at least 73% of prescriptions, except for pharyngitis (≤ 61%). Accounting for dosage lowered compliance to between 31% and 61%. Compliance was lower in the presence of chronic diseases (proportion ratios between 0.94 and 0.98).

Interpretation: It is possible that prescribing noncompliant prescriptions was sometimes appropriate, but the high frequency of noncompliance suggests room for improvement. Given that variations associated with chronic diseases were small, disease-specific guidelines for antibiotic prescriptions are likely to have a limited impact on compliance.

Antimicrobial resistance is of concern to public health authorities worldwide.[1–5] As the frequency of multidrug resistant bacteria increases, with very few new antimicrobials developed, therapeutic options become more limited. This has led the World Health Organization to place antimicrobial resistance among its top 10 list of global health issues.[6] Antimicrobial use, especially inappropriate use, is the main modifiable determinant of resistance because of how it selects resistant strains.[6] Although exposure to antibiotics is higher in hospitals, most antimicrobial prescriptions are provided in the community.[7] In Quebec, hospitals are expected to have an antimicrobial stewardship program;[8,9] however, in the community, the main tools to support adequate use of antimicrobials are the provincial

clinical guidelines developed by the Institut national d'excellence en santé et services sociaux (INESSS) for the treatment of the most common infections.[10]

Quebec's rates of antimicrobial use in the community are among the lowest in Canada and are lower than those of most European countries.[7,11] It is unclear whether antibiotic use

may be further reduced. We have observed higher rates of antibiotic use in outpatients with chronic diseases than in patients without these diseases, between April 2014 and March 2017.[12] As this might present an opportunity for intervention, we aimed to measure the proportion of antibiotic prescriptions compliant with provincial guidelines for the treatment of otitis media and common respiratory infections, and to quantify variations in this proportion in the presence of certain chronic diseases.

Methods

Study design and population

We conducted a retrospective, population-based study of antibiotic prescriptions delivered to individuals covered by the province of Quebec's public drug insurance plan (the Régie de l'assurance maladie du Québec) for at least 1 day between Apr. 1, 2010, and Mar. 31, 2017. Although coverage is offered to all people aged 65 years or older, it is restricted to those without access to private insurance among younger people (i.e., those who are self-employed or benefitting from social assistance).

We included children and adults (≥ 18 yr) who visited a primary care physician in the 2 days before receiving antibiotics, and who had been consulted for otitis media (children only), chronic obstructive pulmonary disease (COPD) exacerbations and bronchitis (only adults with COPD), pharyngitis, pneumonia, sinusitis or other upper respiratory tract infections (URTIs). These infections are covered by the INESSS guidelines for common infections, except likely viral URTI, which should not be treated with antibiotics. We used this very short delay between medical visits and antibiotic delivery to minimize the risk of imputing the wrong treatment indication if antibiotics were actually prescribed for another indication that was not reported. We excluded medical visits occurring less than 90 days after a visit for a similar infection as they were considered recurrent infections or treatment failures; these situations are more complex and could justify noncompliance with guidelines. We also excluded other URTIs when a medical visit for a bacterial infection had also occurred in the previous or following week.

Only antibacterials for systemic use (class J01 of the ATC classification system) were included in the study.[13] We used the 2009 guidelines as a reference in the analysis, although new guidelines were issued in March 2016 for pediatric infections and pharyngitis in adults, and in November 2016 for sinusitis in adults. Historically, uptake of guidelines has not been immediate and this was confirmed by the absence of sudden changes in 2016 in our data, following exploratory analyses. Moreover, changes in recommendations were limited, as presented in Appendix 1, available at www.cmajopen.ca/content/10/3/E841/suppl/DC1.

Data sources and variables

The Québec Integrated Chronic Disease Surveillance System (QICDSS) links information from the 5 following administrative health databases: the health insurance registry (Fichier d'inscription des personnes assurées), the hospital admission and discharge database (Maintenance et exploitation des données pour l'étude de la clientèle hospitalière), the vital statistics death database, the physician claims database and the pharmaceutical services database.[14] We used data from the QICDSS to identify people covered by the public drug insurance plan and their medical visits for otitis media or respiratory infections, based on the *International Classification of Diseases, Ninth Revision* (see detailed codes in Appendix 2, available at www.cmajopen.ca/content/10/3/E841/suppl/DC1). We also used the QICDSS to identify this population's antibiotic prescriptions (antibiotic chosen and, for oral prescriptions delivered to adults, the total dosage), and individuals with chronic diseases. We included only prescriptions delivered within 2 days after an outpatient consultation for an infection to increase the probability that the indication for a prescription was indeed the diagnosis indicated in the medical claim. As pediatric dosages are defined according to the patient's weight, which was unavailable to us, we did not evaluate compliance of dosages for children.

We selected the most frequent chronic diseases that are the subject of surveillance in the QICDSS, and grouped them into 5 categories based on diagnostic codes in medical claims and hospital admissions data, and on drugs served in pharmaceutical claims data: chronic respiratory diseases (i.e., asthma or COPD), diabetes, cardiovascular diseases (i.e., hypertension, heart failure and ischemic heart disease), mental disorders (e.g., attention-deficit/hyperactivity disorder, schizophrenia, anxiety disorders, Alzheimer disease) or none of these chronic diseases. We also collected year of prescription (financial years, starting in April and ending in March), patient age group (1–4 yr, 5–9 yr, 10–17 yr, 18–29 yr, 30–39 yr, 40–49 yr, 50–64 yr, 65–69 yr, 70–79 yr, ≥ 80 yr), sex, geographical zone (in a 4-category gradient from urban to rural) and quintiles of social and material deprivation indices.

For prescriptions after a visit for otitis media or a respiratory infection, we assessed compliance with INESSS' 2009 clinical guideline based on the type of infection, the antibiotic prescribed and, for adults, the total dosage delivered at the pharmacy.[10] We considered any treatment corresponding to a recommendation described in the guidelines as compliant, even second-line treatments or treatments in cases of allergies, because the necessary clinical information for a more detailed analysis was not available. The total dosage had to be within the minimal and maximal limits recommended in the guideline to be considered compliant (Appendix 1). Other URTIs are usually viral and no antibiotic prescription is recommended for their treatment and, therefore, no provincial guideline exists. We considered any antibiotic prescription discordant with recommendations; this is why we excluded medical visits for other URTIs when a visit for a bacterial infection was also reported in the same week, to minimize the risk of imputing the wrong treatment indication. We measured compliance of prescriptions with the guideline, not patients' compliance with prescribed treatments.

Statistical analysis

We computed the proportion of compliant prescriptions for each infection and chronic disease category, by age group.

We measured the impact of the presence of chronic diseases on the proportion of compliant prescriptions using 1 robust Poisson regression model per infection group, adjusting all regressions for year, age group, sex, geographical zone and quintiles of deprivation.[15] We used generalized estimating equations to account for correlation between prescriptions for a given patient or prescriptions issued by the same prescriber. A separate analysis was performed for each of the 10 groups. Categories of chronic diseases are not mutually exclusive, so "unadjusted" proportion ratios were actually obtained from a model that adjusted for the presence of other chronic diseases. We used SAS Enterprise version 7.1 for all analyses, and regression analyses were done using the GENMOD procedure.

Ethics approval

The use of QICDSS for surveillance purposes has been approved by the government bodies, the Public Heath Ethics Committee and the Commission d'accès à l'information du Québec.[14]

Results

Between April 2010 and March 2017, a total of 424 148 prescriptions were delivered to children covered by the public drug insurance plan for otitis, pharyngitis, pneumonia, sinusitis or another URTI. These prescriptions are described in Table 1. Prescribed antibiotics were usually among the recommended options for infections targeted by a guideline (i.e., excluding those prescribed for other URTIs that are likely viral), as compliance was at least 87% for all infections and categories of chronic diseases. Of note, clarithromycin, azithromycin or cefprozil were used in 32% of cases of otitis media, despite being recommended only in case of an allergy to penicillin.

Regarding the association of chronic diseases with compliance, the presence of asthma was always associated with lower compliance; however, this variation was small (relative decrease of compliance by 3% or less, for the treatment of sinusitis in patients with a respiratory disease). Mental health disorders were also associated with a 2% relative reduction of compliance in the treatment of pharyngitis. A total of 70 064 antibiotic prescriptions delivered for a likely viral URTI were identified, but no compliance proportion could be computed given the lack of a denominator.

A total of 697 543 prescriptions were delivered to adults covered by the public drug insurance plan for COPD exacerbation or bronchitis, pharyngitis, pneumonia, sinusitis or another URTI (Table 2). Throughout the study period, 175 107 antibiotics were prescribed following a medical visit for a likely viral URTI (excluded from proportion of compliance computations). In patients with none of the studied

Table 1: Impact of the presence of chronic diseases on compliance of antibiotic prescriptions with the provincial clinical guideline for the treatment of otitis media or respiratory infections in children, April 2010 to March 2017

Infection	Chronic disease category*	No. of prescriptions	Recommended antibiotic, %	Proportion ratio* (95% CI) Unadjusted	Proportion ratio* (95% CI) Adjusted
Otitis	None	167 066	97.9	Ref.	Ref.
	Diabetes	265	97.7	1.00 (0.98–1.02)	1.00 (0.98–1.02)
	Mental health disorder	14 995	97.7	1.00 (1.00–1.00)	1.00 (1.00–1.00)
	Respiratory disease	19 300	97.4	1.00 (0.99–1.00)	1.00 (0.99–1.00)
Pharyngitis	None	86 131	90.6	Ref.	Ref.
	Diabetes	180	89.4	1.00 (0.95–1.05)	0.99 (0.95–1.04)
	Mental health disorder	9497	88.7	0.98 (0.98–0.99)	0.99 (0.98–0.99)
	Respiratory disease	14 558	88.4	0.98 (0.97–0.99)	0.98 (0.97–0.99)
Pneumonia	None	25 240	90.1	Ref.	Ref.
	Diabetes	55	87.3	0.97 (0.87–1.07)	0.97 (0.87–1.07)
	Mental health disorder	2771	89.8	1.00 (0.98–1.01)	0.99 (0.98–1.01)
	Respiratory disease	5132	88.9	0.98 (0.97–0.99)	0.98 (0.97–0.99)
Sinusitis	None	10 410	93.6	Ref.	Ref.
	Diabetes	41	97.6	1.05 (1.00–1.11)	1.06 (1.00–1.11)
	Mental health disorder	1958	92.5	1.00 (0.99–1.01)	1.00 (0.99–1.01)
	Respiratory disease	2814	90.2	0.96 (0.95–0.98)	0.97 (0.96–0.98)

Note: CI = confidence interval, Ref. = reference category.
*Categories of chronic diseases are not mutually exclusive, so the total number of prescriptions is not equal to the sum of prescriptions for each chronic disease category, and unadjusted proportion ratios are adjusted for the other categories of chronic diseases. The adjusted regressions were also adjusted for year, age group, sex, geographical zone and quintiles of deprivation.

Table 2: Impact of the presence of chronic diseases on compliance of antibiotic prescriptions with the provincial clinical guideline for the treatment of respiratory infections in adults, April 2010 to March 2017

Infection	Chronic disease category	No. of prescriptions*	Recommended antibiotic, %	No. of prescriptions with a dosage	Recommended antibiotic and dosage, %	Proportion ratio* (95% CI)	
						Unadjusted	Adjusted
COPD exacerbations and bronchitis	COPD only	24 576	94.5	24 564	33.3	Ref.	Ref.
	Diabetes	38 398	91.9	38 355	31.4	0.96 (0.94–0.98)	0.95 (0.93–0.97)
	Mental health disorder	31 629	92.1	31 596	32.8	1.02 (1.00–1.04)	1.01 (0.99–1.03)
	Cardiovascular disease	101 208	92.1	101 097	32.2	0.99 (0.97–1.01)	0.99 (0.97–1.01)
Pharyngitis	None	74 188	63.5	74 123	50.6	Ref.	Ref.
	Diabetes	8736	53.1	8725	42.0	0.94 (0.92–0.97)	0.98 (0.95–1.01)
	Mental health disorder	21 273	60.5	21 241	47.0	0.98 (0.96–0.99)	0.98 (0.96–0.99)
	Cardiovascular disease	21 719	52.8	21 699	41.3	0.85 (0.84–0.87)	0.96 (0.93–0.98)
	Respiratory disease	22 563	59.2	22 536	44.7	0.93 (0.92–0.95)	0.94 (0.92–0.96)
Pneumonia	None	23 971	83.9	23 933	40.3	Ref.	Ref.
	Diabetes	26 245	73.4	26 112	37.6	0.97 (0.95–0.99)	0.96 (0.95–0.98)
	Mental health disorder	26 515	73.4	26 429	36.5	0.94 (0.92–0.95)	0.94 (0.92–0.96)
	Cardiovascular disease	71 019	74.0	70 731	38.5	0.99 (0.98–1.01)	0.96 (0.94–0.98)
	Respiratory disease	51 273	74.2	50 992	37.5	0.94 (0.92–0.95)	0.94 (0.92–0.95)
Sinusitis	None	53 750	86.4	53 728	60.8	Ref.	Ref.
	Diabetes	15 959	82.4	15 941	52.3	0.96 (0.94–0.98)	0.97 (0.95–0.98)
	Mental health disorder	27 540	83.2	27 522	55.0	0.96 (0.95–0.97)	0.95 (0.94–0.97)
	Cardiovascular disease	50 174	82.7	50 139	52.5	0.90 (0.89–0.91)	0.94 (0.93–0.96)
	Respiratory disease	36 744	83.5	36 716	54.3	0.96 (0.95–0.97)	0.96 (0.95–0.97)

Note: CI = confidence interval, COPD = chronic obstructive pulmonary disease.
*Categories of chronic diseases are not mutually exclusive, so the total number of prescriptions is not equal to the sum of prescriptions for each chronic disease category and unadjusted proportion ratios are adjusted for the other categories of chronic diseases. The adjusted regressions were also adjusted for year, age group, sex, geographical zone and quintiles of deprivation.

chronic diseases, the antibiotic choice was compliant with the 2009 guideline in 64% of prescriptions for a pharyngitis, 84% of prescriptions for pneumonia and 86% of prescriptions for sinusitis. The lower compliance for pharyngitis was owing to the frequent use of amoxicillin, which was not recommended until the 2016 guideline, but was prescribed in 24% of cases nonetheless (Appendix 1, Appendix 3, available at www.cmajopen.ca/content/10/3/E841/suppl/DC1). Compliance was excellent for

patients with COPD exacerbations and bronchitis at 95%. For all infections, when we accounted for the total dose served to patients, compliance decreased markedly, particularly in cases of more severe infections such as COPD exacerbations (33%) and pneumonia (40%).

Regarding the presence of chronic diseases, we observed a relative decrease in compliance by 6% or less for almost all infections and chronic disease categories, with the exception

of pharyngitis treatments in patients with diabetes. Treatment of COPD exacerbations and bronchitis was only evaluated in patients with COPD; the presence of most chronic diseases did not decrease compliance, except for diabetes. Most noncompliant dosages were higher than what was recommended in the guideline (up to 59% of prescriptions against COPD exacerbations and bronchitis for which the chosen antibiotic was compliant), except for the treatment of pneumonia, for which dosages were too low or too high in similar proportions.

Interpretation

Between April 2010 and March 2017, antibiotic prescriptions issued to people covered by the public drug insurance plan were compliant with the antibiotics recommended by the provincial guideline at least 87% of the time among children, but much less frequently among adults, reaching a low of 53% for the choice of antibiotic for pharyngitis in people with diabetes. Compliance was lower when we accounted for dosage, with estimates varying between 31% and 61% depending on the infection and the presence of certain chronic diseases. Most discordant dosages were higher than recommended. Chronic diseases were systematically associated with lower compliance in both children and adults, but more so in adults, for whom dosage was also considered. The lower compliance associated with any single chronic disease was, however, very limited (relative reduction of 6% or less), revealing that the overall low levels of compliance in adults were not driven by prescribing for patients with chronic diseases.

A higher risk of exposure to inappropriate antibiotic use in the presence of certain chronic diseases has also been observed in a British study.[16] In children, a Charlson Comorbidity Index of 3 or 4 was associated with more inappropriate use (odds ratio [OR] 1.34); in adults, the presence of comorbidities increased the odds of inappropriate prescriptions against URTIs, lower respiratory tract infections and sinusitis (ORs of 1.20, 1.19 and 1.12, respectively). The QICDSS uses sensitive algorithms to identify chronic diseases without distinguishing between early and advanced stages, which might contribute to the lower associations between chronic diseases and antibiotic use in our study. For instance, based on our data, mental disorders were quite frequent among children, but the definition includes attention-deficit/hyperactivity disorder, which is very different from adults' Alzheimer disease in terms of medication and vulnerability. The need to add an antibiotic to regular medications taken for the management of a chronic illness may make the choice of antibiotic more challenging, given the risk of drug interactions; this complexity is likely to increase with the number of diseases.[17] Indeed, in another study on the treatment of urinary tract infections, the cumulation of chronic diseases in an individual increased the risk of receiving a noncompliant prescription by up to 12% for patients with 4 chronic conditions.[18] In these cases, not following guidelines can be the appropriate line of conduct to prevent drug interactions, but resources should be available to support primary care physicians.

Limitations

With our methodology, we do not know whether noncompliance was appropriate or justifiable, especially as chronic diseases seem to explain only a small fraction of discordances. We have not looked at the potential impact of obesity, which could explain at least some of the excessive dosages, given the high prevalence of obesity in Quebec (25% of the adult population in 2018).[19] The absence of a reliable indicator of treatment duration in our data sources makes it impossible to identify suboptimal doses for long treatment durations or large doses given over a short period. Considering antimicrobial resistance, suboptimal doses and longer treatment durations are more problematic as they could lead to selection of resistant strains.[20,21] This would have to be investigated with another methodology. Antibiotics that are not recommended were frequently prescribed (especially in adults), which is more difficult to understand than a noncompliant dosage. The probability of selecting 1 of the recommended agents was proportional to the number of antibiotics recommended in the guideline for a given condition (5 for pharyngitis treatment v. 10 for bronchitis and COPD exacerbations treatment, with sinusitis and pneumonia in the middle).[10] In the specific case of pharyngitis, however, practices may have been influenced by American guidelines, which have included amoxicillin since 1997.[22,23] Substantial levels of inappropriate use are reported in the literature, according to different methodologies.[24–26] A 2007 Quebec study, similar to our study, reported that the proportion of viral respiratory infections treated with antibiotics varied between 22% and 43%, depending on the infection; 2 decades later, we still found thousands of antibiotic prescriptions against URTIs that are likely viral.[26] We thus believe that our measures, even if imperfect, remain meaningful.

On average, people covered by the public drug insurance plan are older and poorer than the provincial average owing to eligibility criteria.[27] It seems unlikely that this would bias the association we found between chronic diseases and compliant antibiotic use because recommended antibiotics are basic medications that are covered, regardless of insurance plans, and the province offers publicly funded health care to all its citizens. Our regressions, adjusting for age and deprivation indices, gave results similar to bivariate regressions, suggesting little impact on our results.

We measured compliance with the provincial guideline when a diagnosis was available, but we were unable to determine if antibiotics were necessary in the treatment of infections; however, a study from the neighbouring province, Ontario, estimated rates of unnecessary prescribing between 37% and 48% for sinusitis, otitis media and pharyngitis.[28] High proportions of infections treated with antibiotics are sometimes used as a signal of overuse; however, diagnostic codes are not mandatory in medical claims and we could not assume that all patients had an infection of interest, especially as untreated infections may have been coded less frequently. Indeed, a previous study reported good validity of diagnostic codes for acute respiratory infections in Quebec's medical claims database, but a sensitivity of less than 50%.[29] For similar

reasons, we could not measure the frequency of patients who should have received antimicrobials but did not. However, we could still measure compliance with the guideline (molecule and total dosage) when antimicrobials were prescribed after one of the selected diagnostic codes was reported.

Finally, we may have overestimated the association between chronic diseases and noncompliant use if diagnostic codes related to chronic diseases were reported preferentially over codes for minor infections. Another study reported fewer influenza-like illnesses among patients with chronic diseases, who nonetheless received more antibiotics.[30] We did not observe this trend in our data; data preparation for this project rather showed more infections per patient in the presence of chronic diseases.

Conclusion

People with chronic diseases were slightly more exposed to antibiotic prescriptions that are not compliant with the provincial clinical guideline and they also used more antimicrobials than the rest of the population. We could not determine whether discordance was actually appropriate or not; it could be attributable to an avoidance of certain drug interactions or an increased fear of complications in more vulnerable patients. However, the high frequency of noncompliant prescriptions overall suggests that there is room for improvement. Circumstances justifying a derogation to guidelines for primary care should be investigated, as should the impact of more recent guidelines and of COVID-19 on circulating respiratory viruses and consultation or prescribing habits. Further work should focus on the number of comorbidities, on comorbidities that were not studied here and comorbidities that could explain extreme dosages, such as obesity and kidney failure.

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Data sharing: Data used for this study cannot be shared.

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