Chronic respiratory disease should be considered when interpreting indicators of community antimicrobial use in people over 65 years old

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Abstract

Objectives Chronic respiratory diseases (CRD) put patients at increased risk of respiratory infection and antimicrobial use, but surveillance results on community antimicrobial use are generally not adjusted for this risk factor. The objective of this study was to demonstrate the importance of accounting for CRD when interpreting indicators of community antimicrobial use in people over 65 years old, in Québec, Canada.

Methods Retrospective cohort study of antimicrobial use according to CRD status in individuals over 65 years old covered by Québec's public drug insurance plan between 2010 and 2015. Defined daily doses per 1000 person-days (DID) were computed per antimicrobial class and were further stratified according to chronic disease group, fiscal year, gender and age group.

Results Antimicrobial use was 2.3 times higher in the CRD group (29.7 DID) compared with the other chronic disease group (13.1 DID) and 3.1 times higher than in the no chronic disease group (9.6 DID). The same gradient was reflected as well in use per antimicrobial class, per age group, per gender, and in time. Antimicrobial use increased throughout the study period and was higher in older age groups and in women.

Conclusions Interpretation of results of antimicrobial use surveillance should consider the prevalence of CRD in populations. In order to identify opportunities for adapted interventions targeting inappropriate use, finer analyses are necessary.

Résumé

Objectifs Les maladies respiratoires chroniques (MRC) accroissent le risque d'infection respiratoire des patients ainsi que leur utilisation d'antibiotiques, mais les résultats de surveillance de l'utilisation communautaire d'antibiotiques ne sont généralement pas ajustés pour ce facteur. L'objectif était de démontrer l'importance de prendre les MRC en compte lors de l'interprétation des indicateurs d'utilisation communautaire d'antibiotiques chez les personnes de plus de 65 ans au Québec, Canada.

Méthodologie Étude de cohorte rétrospective portant sur l'utilisation d'antibiotiques selon la présence de MRC chez les individus de plus de 65 ans qui étaient couverts par le régime public d'assurance médicament du Québec, entre 2010 et 2015. Les doses journalières définies par 1000 individus-jours (DIJ) ont été calculées selon la classe d'antibiotiques, le groupe de maladie chronique, l'année financière, le genre et le groupe d'âge.

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Résultats L'utilisation d'antibiotiques était 2,3 fois plus élevée chez les individus ayant une MRC (29,7 DIJ) que chez ceux ayant une autre maladie chronique (13,1 DIJ) et 3,1 fois plus élevée que chez les individus n'ayant pas de maladie chronique (9,6 DIJ). Le même gradient était observable par classe d'antibiotiques, groupe d'âge, genre et année. L'utilisation d'antibiotiques a augmenté tout au long de la période à l'étude et elle était plus élevée chez les personnes plus âgées et chez les femmes.

Conclusions La prévalence des MRC devrait être prise en compte lors de l'interprétation des résultats de surveillance de l'utilisation d'antibiotiques. Des analyses plus fines sont nécessaires afin d'identifier des opportunités d'interventions adaptées ciblant l'usage inapproprié des antibiotiques.

Keywords Surveillance · Public health · Antimicrobial use · Chronic respiratory diseases · COPD

Mots-clés Surveillance · Santé publique · Utilisation des antibiotiques · Maladies respiratoires chroniques · MPOC

Introduction

With the rise of antimicrobial resistance, quantifying antimicrobial use and identifying its determinants are essential to direct interventions aiming to protect the effectiveness of existing antimicrobials (Transatlantic Taskforce on Antimicrobial Resistance 2014; Institut national de santé publique du Québec 2015; The White House 2014). Chronic respiratory diseases (CRD) put patients at increased risk of respiratory infection and antimicrobial use (Santos et al. 2016). A meta-analysis has estimated world prevalence of chronic obstructive pulmonary disease (COPD) at 11.7% in 2010, the prevalence being highest in the Americas at 15.2% (Adeloye et al. 2015). Typically, surveillance results on community antimicrobial use focus on the total use of systemic antimicrobials, following a methodology promoted by the World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology in order to facilitate external comparisons (WHO Collaborating Centre for Drug Statistics Methodology 2019; Agence de la santé publique du Canada 2017; ECDC 2019; BCCDC 2014; Statens Serum Institute 2017; Public Health England 2017). Despite this important advantage, results do not account for CRD prevalence, which prevents the identification of truly avoidable or improvable antimicrobial use. The Québec Integrated Chronic Disease Surveillance System (QICDSS) performs surveillance of chronic diseases and of associated community drug use in individuals over 65 years old (Blais et al. 2014). The aim of this study was to demonstrate the importance of accounting for CRD when interpreting indicators of community antimicrobial use in people over 65 years old, using QICDSS data.

Methods

The QICDSS has been described in detail elsewhere (Blais et al. 2014). Using an anonymized unique identifier, this system integrates information from five administrative health databases: the health insurance registry, hospital discharges, vital

statistics death registry, physician claims, and pharmaceutical services. At the time of the study, data on pharmaceutical services was only available for individuals over 65 years old.

Our retrospective cohort study followed antimicrobial use according to CRD status in individuals over 65 years old covered by Québec's public drug insurance plan between April 1, 2010 and March 31, 2015. To be included, these individuals had to fulfill at least one criterion based on diagnostics, physician visits, hospital procedures, or pharmaceutical dispensations related to chronic diseases under surveillance in the QICDSS (diabetes, cardiovascular diseases, CRD, osteoarticular diseases, osteoporosis, mental disorders, Alzheimer's disease, and related disorders) (Blais et al. 2014). Individuals not covered by the public drug insurance plan for an entire fiscal year (i.e., private insurance or dweller in long-term care) were excluded from the cohort for that given year. No formal consent was necessary for this type of study.

Previously validated case definition algorithms referring to the International Classification of Diseases (ICD) codes were used to identify individuals with COPD (≥ 1 outpatient consultation or 1 hospitalization; ICD-9 codes 491, 492, or 496 or ICD-10 codes J41 to J44) or asthma (≥ 2 outpatient consultations within 2 years or 1 hospitalization; ICD-9 code 493 or ICD-10 codes J45 or J46) (Gershon et al. 2009a, b). These individuals were classed in the CRD group. Individuals who met a case definition related to at least one chronic disease monitored by the QICDSS but who did not respect the one related to CRD were in the other chronic disease group. Individuals fulfilling some diagnosis criteria without fulfilling a case definition for any given chronic disease were classed in a third and last group of no chronic disease. The study focused on antibacterials for systemic use, according to the Anatomical Therapeutic Chemical classification (class J01) (WHO Collaborating Centre for Drug Statistics Methodology 2019). Antibiotics from this class that were prescribed in our population are listed in an [online supplement](#).

Antimicrobial use was measured in defined daily doses (DDD) per 1000 person-days (DID), the indicator recommended by the WHO; guidelines define a DDD as “the assumed average maintenance dose per day for a drug used for

its main indication in adults.” (WHO Collaborating Centre for Drug Statistics Methodology 2019). Results were stratified according to chronic disease group, before further stratifying them according to other variables (gender, age group, fiscal year or antimicrobial class). Due to the very large number of observations, providing very precise estimates, no confidence intervals are presented.

Results

Between April 1, 2010 and March 31, 2015, 1,945,656,590 person-days were followed, of which 25.0% had a CRD (Table 1). Fifty-three different antimicrobials were dispensed, reaching totals of 4,025,706 prescriptions, 32,671,774 DDD, and a global rate of 16.8 DID.

Antimicrobial use was 2.3 times higher in the CRD group (29.7 DID) compared with the other chronic disease group (13.1 DID) and 3.1 times higher than in the no chronic disease group (9.6 DID; Table 1). Observed for all antimicrobial classes, this gradient is particularly obvious in aminoglycosides, for which use was 67 times higher in the CRD group (0.260 DID) compared with the other chronic disease group (0.002 DID; Table 2). Both the proportion of person-days with CRD and antimicrobial use increased with age: 20.7% and 16.1 DID in those 66–69 years old, 24.6% and 17.0 DID in those 70–79 years old, and 29.6% and 17.1 DID in those ≥ 80 years old (Table 1). However, within chronic disease groups, antimicrobial use decreased with increasing age. The association between age and antimicrobial use was thus confounded by CRD prevalence.

Annual antimicrobial use increased from 16.0 DID in 2010–2011 to 17.7 DID in 2014–2015, and it increased in all chronic disease groups (Table 1). Both the absolute and relative increases were more important in individuals with CRD (+ 3.6 DID and + 12.8%) than in the two other groups (other chronic diseases + 1.0 DID and + 8.2%; no chronic disease + 1.0 DID and + 11.7%). Of note, in the CRD group, clarithromycin use decreased from 3.9 DID to 3.1 DID during the study period (– 20%), while azithromycin use more than doubled (from 1.8 DID to 3.9 DID, + 120%); such important variations were not observed in the other chronic disease group (– 11% and + 10%, respectively) nor in the no chronic disease group (+ 1% and + 17%, respectively).

Discussion

This study describes community antimicrobial use in Quebecers over 65 years old over a 5-year period, while accounting for the presence of CRD. The presence of CRD was systematically associated with increased rates of antimicrobial use. This was reflected as well in use per antimicrobial class,

Table 1 Distribution of person-days and defined daily doses, and rates of antimicrobial use according to demographic characteristics

Demographic characteristics	Chronic respiratory disease			Other chronic disease			No chronic disease			Total		
	Person-days	DDD	DID	Person-days	DDD	DID	Person-days	DDD	DID	Person-days	DDD	DID
Gender												
Male	219,543,120	6,396,457	29.1	497,020,135	6,278,691	12.6	125,497,220	1,144,547	9.1	842,060,475	13,819,695	16.4
Female	266,625,565	8,044,376	30.2	719,068,980	9,627,299	13.4	117,901,570	1,180,403	10.0	1,103,596,115	18,852,079	17.1
Age (years old)												
66–69	106,309,535	3,247,515	30.5	300,463,985	3,971,705	13.2	106,346,035	1,052,963	9.9	513,119,555	8,272,183	16.1
70–79	218,771,875	6,762,794	30.9	560,659,710	7,320,818	13.1	109,340,130	1,031,982	9.4	888,771,715	15,115,594	17.0
≥ 80	161,087,275	4,430,525	27.5	354,965,420	4,613,468	13.0	27,712,625	240,006	8.7	543,765,320	9,283,999	17.1
Fiscal year												
2010–2011	90,099,155	2,526,758	28.0	226,500,385	2,854,416	12.6	45,893,640	416,194	9.1	362,493,180	5,797,368	16.0
2011–2012	93,312,980	2,686,985	28.8	234,205,170	3,055,348	13.0	46,782,050	441,046	9.4	374,300,200	6,183,379	16.5
2012–2013	97,171,760	2,882,560	29.7	243,114,090	3,192,634	13.1	48,429,295	466,213	9.6	388,715,145	6,541,407	16.8
2013–2014	100,721,020	3,026,068	30.0	252,035,785	3,256,020	12.9	50,173,995	473,740	9.4	402,930,800	6,755,828	16.8
2014–2015	104,863,770	3,318,462	31.6	260,233,685	3,547,573	13.6	52,119,810	527,757	10.1	417,217,265	7,393,792	17.7
Total	486,168,685	14,440,833	29.7	1,216,089,115	15,905,991	13.1	243,398,790	2,324,950	9.6	1,945,656,590	32,671,774	16.8

DDD defined daily doses, DID DDD per 1000 person-days. Other chronic disease: diabetes, cardiovascular diseases, osteoarthritis, osteoporosis, mental disorders, Alzheimer's disease, and related disorders

Table 2 Antimicrobial use per chronic disease group and per antimicrobial class (defined daily doses per 1000 person-days [DID])

Antimicrobial class	Chronic respiratory disease	Other chronic disease	No chronic disease	Total
Fluoroquinolones	8.3	3.3	2.3	4.4
Penicillins	6.4	3.4	2.5	4.0
Macrolides	6.4	1.9	2.0	3.0
Cephalosporins	3.5	1.4	0.8	1.9
Tetracyclines	1.8	1.1	0.9	1.2
Sulfonamides and trimethoprim	1.2	0.6	0.3	0.7
Lincosamides	0.4	0.2	0.2	0.3
Aminoglycosides	0.3	0.0	0.0	0.1
Carbapenems	0.1	0.1	0.0	0.1
Glycopeptides	0.1	0.1	0.0	0.1
Monobactams	0.0	0.0	0.0	0.0
Other	1.3	1.0	0.4	1.0
Total	29.7	13.1	9.6	16.8

Other chronic disease: diabetes, cardiovascular diseases, osteoarticular diseases, osteoporosis, mental disorders, Alzheimer's disease, and related disorders

per age group, per gender, and in time. Increasing age was associated with higher antimicrobial use, a trend completely reversed when stratifying antimicrobial use per chronic disease group: this result puts emphasis on CRD, a modifiable factor, rather than on aging.

With a rate of antimicrobial use of 16.8 DID, our cohort used less antimicrobials than other populations above 65 years old. In 2010, Danish estimates of 25 DID and 40 DID were published for individuals between 65 and 79 years old and for those 80 years old or over, respectively (Gaardbo Kuhn et al. 2014). Rates between 25 and 30 DID were reported for individuals 65 years old or over in a Polish province (Dziurda et al. 2008). The Canadian rate of antimicrobial use (17.4 DID, also including individuals below 65 years old) is relatively close to the rate obtained in this study, despite differing data sources (Agence de la santé publique du Canada 2017). Yet, without the combined prevalence of COPD and asthma in these populations, comparisons are complicated. For instance, in this study, prevalence of CRD was 25%. Had it been 5% lower (and the prevalence of “other chronic diseases” 5% higher), with similar rates of antimicrobial use per chronic disease group, total antimicrobial use would have been 16.0 DID instead of 16.8 DID.

These results constitute a reminder of the importance of a good knowledge of monitored populations for a correct interpretation of results (age, gender, prevalence of antimicrobial resistances and of CRD, incidence of infections), especially for external comparisons and for trend analyses. The reality of community antimicrobial use surveillance is such that data will usually not include readily available information on risk factors like pre-existing CRD. This reinforces the rationale for a qualitative surveillance of antimicrobial use, based on

treatment indication, as not all antimicrobial use can be prevented and high use does not necessarily indicate inappropriate use (Fleming-Dutra et al. 2016; Cadieux et al. 2007). In this case, higher antimicrobial use is expected in individuals with CRD, given their higher risk of infection, but concerns regarding the consequences of infections might lead to unnecessary prescribing; ensuring an appropriate use of antimicrobials would be relevant given quantities used in this group. A surveillance system such as the QICDSS, linking health administrative data on millions of individuals, allows clinicians and standard-setting bodies to establish standard patterns of antimicrobial use and to better understand diverging uses.

Our study has limitations. The cohort excluded person-days of individuals without any signs of a chronic disease, who most probably use less antimicrobials than the average; however, with over 80% of all person-days 65 years old or over (based on Québec's 2014 demographics), we can reasonably expect our estimates to be representative of all Quebecers 65 years old or over living in the community (Institut de la statistique du Québec 2014). The identification of CRD in health administrative data is a challenge, but QICDSS' algorithms to define COPD and asthma have been validated in the neighbouring Canadian province, Ontario, and had sensitivities of 85% and 84%, and specificities of 78% and 77%; trends in antimicrobial use that were observed are consistent with current knowledge on CRD, and it is unlikely that any misclassification would be large and biased enough to create the gradient observed in this study (Gershon et al. 2009a, b). Nonetheless, individuals with CRDs other than COPD or asthma were misclassified as not having a CRD, which likely underestimates the difference in antibiotic use between CRD and non-CRD groups; as no validated case definition exists

for these other CRDs in health administrative data, they are not monitored by the QICDSS. Finally, the study design does not allow causal inference, as no association measure perfectly adjusted for all confounders was computed; the association between CRD and infections is already known, so our objective was rather to demonstrate how the prevalence of CRD should influence the interpretation of surveillance indicators of antimicrobial use.

Conclusion

Our study quantifies the impact of CRD on highly aggregated indicators of antimicrobial use frequently used as the basis for surveillance activities. These indicators are useful for external comparisons and trend analyses and to measure the impact of interventions on total antimicrobial use, but a certain general knowledge of populations under surveillance is necessary for their interpretation. In addition, a finer analysis of data is necessary to develop adapted interventions aiming to improve antimicrobial use and preserve antimicrobials' effectiveness, in the general population as well as in subgroups at higher risk of exposure to antimicrobials. This analysis should focus on the appropriateness of antimicrobial use, by using linking techniques to impute a therapeutic indication to prescriptions and by taking into account chronic diseases and conditions leading to immunosuppression. Prevention of these chronic diseases should also be considered in efforts to reduce antimicrobial use.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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