Estimating Rheumatoid Arthritis Prevalence and Care Quality in a Large Sample from the Quebec Population

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Preface

"We owe all the great advances in knowledge to those who endeavor to find out how much there is of anything." -James Maxwell (1831-1879)

"If you can measure that of which you speak, and can express it by a number, you know something of your subject, but if you cannot measure it, your knowledge is meager and unsatisfactory." -William Thomson, (1824-1907)

Starting with these two quotes, one can clearly appreciate that the most central aspect of understanding a disease is through accurate measurement. To address any chronic disease problem, we must first define the extent of the problem. This can be achieved by several measures such as, incidence rates, prevalence rates and other measures (1). Large amounts of resources may be invested to gather and house data to characterize the incidence, prevalence, and impact of chronic diseases; however, it is important to realize that all data are imperfect. Our efforts to characterize and understand chronic diseases must take this into account. Some pioneers in epidemiology and public health have shed light on this issue long ago; the first recorded example of correction of misclassification error was done by John Graunt (1620-1674). Graunt is known as the world's first epidemiologist and demographer. From his work on the classification of deaths in Britain's Bills of Mortality, Graunt was concerned about the possible misclassification of causes of death. He deduced that about 20% of plague deaths were incorrectly classified as deaths due to other causes, and hence he worked on producing a more accurate estimate of mortality from the plague (2).

Chronic disease epidemiologists should have the knowledge and skills to produce accurate estimates of disease prevalence. The current thesis is a humble endeavor to report a

refined estimate of the prevalence of rheumatoid arthritis (RA), a potentially debilitating chronic disease which may affect the quality of life of patients and their families. Up until recently, RA has not been on the radar screen of Canadian surveillance teams (unlike diabetes or renal disease) (3). This is being challenged; and recent authors have stated that "Never has there been a more urgent need for a coordinated, multi-partnered approach, to integrate RA into a broad chronic disease management strategy" (3). Therefore, in my thesis, I focused on characterizing the burden of RA. First, I characterize Quebec RA prevalence estimates derived from a combination of population-based data sources, adjusted for misclassification error. Second, I examine the quality of care received by RA patients in Quebec. My goal is to provide an evidence base to help public health leaders identify RA as a priority for efforts to improve care and outcomes.

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Abstracts

Study # 1: Estimating Rheumatoid Arthritis Prevalence with a Combination of Administrative and Health-Report Data

In the absence of a gold standard, studies of disease prevalence face methodological challenges related to misclassification of disease status. We present this issue in the context of rheumatoid arthritis (RA), the most common inflammatory arthritis in the developed world. A Bayesian approach was implemented to estimate RA prevalence, adjusted for misclassification, using three data sources (self-reported RA diagnoses, disease-modifying anti-rheumatic drug use, and RA physician billing codes) in Quebec, Canada. Our methods estimated RA prevalence in 2010 among adults aged 40- 69 to be 1.1% (95% credible interval: 0.9, 1.3%) combining all three ascertainment approaches, under the conditional independence assumption and using uninformative prior distributions. Gains in sensitivities were found when combining two or three methods. This is the first RA prevalence study to adjust for misclassification error inherent in each data source, when combing self-report and administrative data. Unbiased prevalence estimates are essential to understand the burden of RA and to plan health services. The methods used respond to the needs of public health researchers working on surveillance of chronic diseases like RA.

Study # 2: Capture of Rheumatoid Arthritis Cases within RAMQ Database

The Régie de l'assurance maladie du Québec (RAMQ) health services administrative databases, which are widely used for surveillance of chronic disease, may be limited in capturing the full spectrum of prevalent RA cases. Additional studies are needed to elucidate the effect of both the observation period and the use of self-reported information on the completeness of RA

numerator data within administrative databases. This study's specific objective is to calculate, using eleven different observation periods, unadjusted and adjusted RA prevalence estimates, as well as estimates of sensitivity and specificity of RAMQ ascertainment approach, using administrative data (alone or combined with self-report data). We studied CARTaGENE participants. CARTaGENE is a large established population-based study which recruited 19,995 participants (aged 40 to 69 years old) from August 2009 to October 2010 from four metropolitan regions in Québec (Montréal, Sherbrooke, Québec City, and Saguenay). RA prevalence estimates both unadjusted and adjusted for misclassification error were derived using Bayesian methods. The three-year 2010 prevalence estimate among adults aged 40 to 69 years old using the three ascertainment methods, assuming conditional dependence between self-report information, and adjusting for misclassification error in each method was 0.9% (95% CrI: 0.7, 1.2). Our results show variations in the prevalence point estimates related to the length of observation period within administrative data, the inclusion of self-reported information on RA, and adjustment for misclassification error in administrative data. There was negligible change in the sensitivity estimates for RA ascertainment using administrative data with more years of observation, but a noticeable increase in sensitivity when self-reported information on RA diagnosis and current disease-modifying anti-rheumatic drug use were added. Our study illustrates that, when using administrative data, RA point prevalence estimates are lower if few years of data are observed, and that multiple data sources can help capture more RA cases.

Study # 3: Care Quality of Rheumatoid Arthritis Patients

In 2004, the Arthritis Foundation Quality Indicator (QI) Project established, for the first time, a set of measures for assessing process of care provided to RA patients. To date, no study in Quebec has assessed these quality indicators at the population level. The objectives of this

study were to determine whether some quality indicators could be assessed from self-reported data using CARTaGENE linked with the Quebec health administrative databases administered by Régie de l'assurance maladie du Québec (RAMQ) administrative data. A cohort of RA patients was constructed. An individual was said to have RA if he/she self-reported a RA diagnosis by a health professional in the CARTaGENE survey and had two or more RA diagnosis by any physician at least two months apart but within a two-year span or at least one RA diagnosis by a rheumatologist in the RAMQ database .We assessed six QIs, four pertained to RA management and treatment received (use of Disease Modifying Anti-Rheumatic Drug DMARD therapy, annual medical visits, use of folate supplementation with methotrexate therapy, and use of calcium and vitamin D in steroid-exposed patients) and two pertained to lifestyle factors (physical activity and smoking cessation). QIs were reported in terms of proportion of patients fulfilling them. Bayesian logistic regression analyses were preformed to investigate potential variation with DMARD use which was our outcome of interest defined as a binary variable of current use/non-use. Our cohort included 142 RA patients. The QIs that pertain to RA pharmacotherapy and medical management (i.e. DMARDs, annual medical check-ups, folate, calcium and vitamin D) ranged from 60% to 80%. Regarding the QIs focusing on lifestyle factors, 55% patient reported performing moderate physical activity and only 16.6 % reported current smoking. Results from the Bayesian logistic regression showed no definite associations between DMARD use and patient characteristics (age, education, income, and sex). Our findings suggest a seemingly modest performance of Quebec's health care system for RA patients, with respect to these QIs.

Résumé

Étude # 1: Estimation de la prévalence de la polyarthrite rhumatoïde avec une combinaison de données administratives et de données sur la santé

En l'absence d'un étalon, les études sur la prévalence de la maladie font face à des défis méthodologiques liés aux erreurs de classification de l'état de la maladie. Nous présentons ce problème dans le contexte de la polyarthrite rhumatoïde, l'arthrite inflammatoire la plus courante dans le monde. Une analyse statistique bayésienne a été mise en œuvre pour estimer la prévalence de la polyarthrite rhumatoïde, ajustée pour la classification biaisée, en utilisant trois sources de données dont les diagnostics autodéclarés de polyarthrite rhumatoïde ainsi que l'utilisation de médicaments antirhumatismaux modificateurs de la maladie et finalement des codes de facturation des médecins au Québec, Canada. Nos méthodes ont estimé que la prévalence de la polyarthrite rhumatoïde en 2010 chez les adultes âgés de 40 à 69 ans était de 1.1% (intervalle crédible 95%: 0.9, 1.3%) combinant les trois approches de vérification, sous l'hypothèse d'indépendance conditionnelle et utilisant des distributions a priori non informatives. Des gains dans les sensibilités ont été observés en combinant deux ou trois méthodes. Il s'agit de la première étude de prévalence de la polyarthrite rhumatoïde à corriger les erreurs de classification inhérentes à chaque source de données, lors de la combinaison des données auto-déclarées et administratives. Des estimations de prévalence non biaisées sont essentielles pour comprendre le fardeau de la polyarthrite rhumatoïde et planifier les services de santé en conséquence. Les méthodes utilisées répondent aux besoins des chercheurs en santé publique travaillant sur la surveillance des maladies chroniques comme la polyarthrite rhumatoïde.

Étude # 2: Étude de cas de polyarthrite rhumatoïde dans la base de données de la RAMQ

Les données médico-administratives de la Régie de l'assurance maladie du Québec (RAMQ), qui sont largement utilisées pour la surveillance des maladies chroniques, peuvent être limitées quant à l'identification de l'ensemble des cas de polyarthrite rhumatoïde prévalents. Des études supplémentaires sont nécessaires pour élucider l'effet de la période d'observation et de l'utilisation d'informations auto-déclarées sur l'exhaustivité du nombre total de cas de la polyarthrite rhumatoïde dans les bases de données administratives. L'objectif spécifique de cette étude est de calculer, en utilisant onze périodes d'observation, des estimations non ajustées et ajustées de la prévalence de la polyarthrite rhumatoïde, ainsi que des estimations de sensibilité et de spécificité de l'approche de calcul utilisant les données administratives de la RAMQ seules ou combinées avec des données auto-déclarées. Nous avons étudié les participants à CARTAGÈNE. CARTAGÈNE est une vaste étude de population qui a recruté 19 995 participants (âgés de 40 à 69 ans) d'août 2009 à octobre 2010 dans quatre régions métropolitaines du Québec (Montréal, Sherbrooke, Québec et Saguenay). Les estimations de la prévalence de la polyarthrite rhumatoïde, non corrigées et corrigées pour les erreurs de classification, ont été calculées à l'aide de méthodes d'analyses bayésiennes. En utilisant trois méthodes de détermination ainsi qu'en supposant une dépendance conditionnelle entre les données autodéclarées et une erreur de classification pour chaque méthode, la prévalence sur trois ans chez les adultes âgés de 40 à 69 ans a été estimée à 0.9% (95% intervalle crédible: 0,7; 1.2%). Nos résultats montrent des variations dans les estimations de la prévalence liées à la durée de la période d'observation dans les données administratives et à l'inclusion d'informations auto-déclarées sur la polyarthrite rhumatoïde ainsi qu'à l'ajustement pour l'erreur de classification dans les données administratives. Les changements dans les estimations de sensibilité liées à la durée de la période d'observation dans les données

administratives étaient négligeables, mais une augmentation notable a été observée dans la sensibilité lorsque des informations auto-déclarées sur le diagnostic de polyarthrite rhumatoïde et l'utilisation actuelle de médicaments antirhumatismaux modificateurs de la maladie ont été ajoutées. Notre étude montre que, lors de l'utilisation de données administratives, les estimations ponctuelles de la prévalencede polyarthrite rhumatoïde sont plus faibles si l'on se limite à quelques années de données et que plusieurs sources de données peuvent aider à saisir plus de cas de polyarthrite rhumatoïde.

Étude # 3: Qualité des soins des patients atteints de polyarthrite rhumatoïde

En 2004, le projet Indicateurs de qualité de la Fondation de l'Arthrite a établi, pour la première fois, un ensemble de mesures pour évaluer le processus de soins dispensé aux patients atteints de polyarthrite rhumatoïde. À ce jour, aucune étude au Québec n'a évalué ces indicateurs de qualité au niveau de la population. Les objectifs de cette étude étaient de déterminer si certains indicateurs de qualité pouvaient être évalués à partir des données auto-déclarées de CARTAGÈNE liées avec les données des bases de données médico-administratives de la Régie de l'assurance maladie du Québec. Une cohorte de patients atteints de polyarthrite rhumatoïde a été construite. Cette cohorte incluait toutes les personnes qui avaient auto-déclarée ayant été diagnostiquées avec une polyarthrite rhumatoïde dans le sondage CARTAGENE et avaient aussi reçu deux diagnostics de polyarthrite rhumatoïde ou plus à au moins deux mois d'intervalle, mais en dedans de deux ans ou un diagnostic ou plus de polyarthrite rhumatoïde fait par un rhumatologue dans les données médico-administratives de la Régie de l'assurance maladie du Québec. Nous avons évalué six Indicateurs de qualité, dont quatre concernaient la prise en charge de la polyarthrite rhumatoïde et le traitement reçu (traitement antirhumatismal modificateur de la maladie, visites médicales annuelles, supplémentation en folate chez les utilisateurs de méthotrexate et utilisation du calcium

et de la vitamine D chez les patients exposés aux stéroïdes) et deux ont trait à des facteurs liés au mode de vie (activité physique et renoncement au tabac). Les Indicateurs de qualité ont été rapportés en termes de proportion de patients les remplissant. Des analyses de régression logistique bayésienne ont été conduites d'abord pour étudier la variation potentielle de l'utilisation d'un agent antirhumatismal modificateur de la maladie qui était notre issue clinique d'intérêt représentée par une variable binaire (utilisation oui/non). Notre cohorte comprenait 142 patients atteints de polyarthrite rhumatoïde. Les Indicateurs de qualité se rapportant à la pharmacothérapie et à la prise en charge médicale de la polyarthrite rhumatoïde variaient de 60% à 80%. En ce qui concerne les indicateurs de qualité axés sur les facteurs liés au mode de vie, 55% des patients ont déclaré avoir fait de l'activité physique modérée et seulement 17% ont déclaré fumer présentement. Les résultats de la régression logistique bayésienne n'ont montré aucune association précise entre l'utilisation des antirhumatismaux modificateurs de la maladie et les caractéristiques des patients (âge, niveau de scolarité, revenu et sexe). Nos résultats suggèrent une performance apparemment modeste du système de santé du Québec pour les patients atteints de polyarthrite rhumatoïde, en ce qui concerne ces Indicateurs de qualité analysés.

Contribution of Authors

My supervisors and I were jointly responsible for the conception and design of the three studies included in my thesis. For every study, I have been involved in all stages starting from identifying the research questions, conducting literature reviews, designing the studies, identifying the suitable methods and analytical techniques, analyzing the data, interpreting the results and writing all thesis chapters. My supervisors critically contributed to reviewing all thesis chapters for the intellectual content and they provided important suggestions to improve my work.

Statement of Originality

The first study in this thesis is the first study to date to enhance self-reported ascertainment methods for RA combining Canadian provincial administrative data with large population health surveys. Thus, my work is novel and will fill this knowledge gap. Moreover, no published study to date has investigated how RA prevalence estimates may be affected by the length of the observation window used within administrative health databases, adjustment for misclassification error and combining administrative database with self-reported data. Finally, the third study is the first Canadian study to attempt to describe QIs in a large RA sample obtained from self-reported data.

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Though my PhD degree would thrill me, it will certainly not define me. My identity rests profoundly and contentedly on one fact: the person I became by the end of the PhD journey which can be summarized in three words: faith, patience, and courage.

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To my parents
whose love and discipline
gave me the insight, wisdom and courage
to live happily in such a challenging world

Feryal and Nasser,
you will always be my pride and my glory…

List of Abbreviations

RA	Rheumatoid Arthritis
DMARD	Disease Modifying Anti-Rheumatic Drug
RAMQ	Régie de l'assurance maladie du Québec
ACR	American College of Rheumatology
Anti-CCP	Anti-Cyclic Citrullinated Proteins
COPCORD	Community Oriented Program for Control of Rheumatic Diseases
ICD	International Classification of Disease
PPV	Positive Predictive Value
NPV	Negative Predictive Value
CrI	Credible Interval
CANRAD	Canadian Rheumatology Administrative Data Network
QI	Quality Indicator
RISE	Rheumatology Informatics System for Effectiveness
OR	Odds Ratio

CHAPTER ONE

INTRODUCTION

Due to the ageing of the world's population, the prevalence of chronic and disabling diseases has been increasing in both developed and developing countries, and the global burden of disease has shifted from communicable diseases to chronic diseases (1-3). For example, conditions like arthritis affect nearly 4 million Canadians aged 15 years and older, and this number is estimated to increase to 6 million by the year 2026. Additionally, the economic burden of rheumatoid arthritis (RA) as direct medical costs and its associated indirect costs due to work-related disability has been estimated in some countries such as Canada, Germany and United States to exceed 8 billion dollars; with an average direct medical cost exceeding $11,200 (per patient per year) (4, 5) and indirect costs of work disability with lost wages of more than $19,150 (per patient per year) (6, 7).

In response to the escalating number of people with chronic diseases, public health departments need to develop initiatives, implement and evaluate them for successful treatment of chronic diseases (8, 9). The first step towards chronic diseases control is through an accurate and robust surveillance (9). Such surveillance provides information which can act as an early wake up call for policy makers to properly allocate resources, plan and implement public health strategies. In their article "Public Health Surveillance for Chronic Conditions: A Scientific Basis for Decisions", Thacker et al. nicely address the usefulness of surveillance data for chronic diseases and discuss the importance of using many data sources such as epidemiologic studies, health surveys, and administrative systems for better surveillance, and eventually for improved decisions in public health (10). Table 1.1 is reproduced from Thacker et al. (1995) and reports the uses of

surveillance data (10). An important application of surveillance information is its contribution to determining, for example, the number of clinics or types of rehabilitation services needed. Additionally, prevalence data derived from surveillance assist in making future projections and predicting the changes that are likely to take place in chronic diseases' burden. For example, time trends and geographic variations of hard to diagnose diseases like RA can be derived through using prevalence data (11).

Rheumatoid arthritis (RA) is one type of chronic autoimmune disease, and like most chronic diseases (10), it is caused by a constellation of potential factors, including environmental and genetic risk factors. Surveillance data can provide insights into the epidemiology of RA. For instance, estimates of RA prevalence can be monitored to track the development of this chronic disease, to identify groups at high risk, and to plan strategies for treatment. Having unbiased prevalence estimates is essential to understand the burden of RA and to plan health services for RA patients. Some jurisdictions have either self-report data or health administrative databases, or both, as potential sources for population-based surveillance of RA. However, due to their inherent misclassification errors, these types of data sources are imperfect. Furthermore, there is no perfect reference standard readily available to validate self-report or health administrative data sources. Current surveillance methods are not always optimal because they rarely compile multiple data sources. Existing methods may provide prevalence figures that are either overestimated or underestimated because they are unadjusted for misclassification error.

There are different methods used to estimate the prevalence of a chronic disease, and as I explain in chapters two and three, there are potential advantages of Bayesian methods in this regard. Concerning examples of possible data sources, these include both secondary repositories (particularly administrative datasets, e.g. physician billing, drug dispensation) and cohorts

constructed with clinical data (including CARTaGENE, a rather unique research resource with self-reported diagnoses and drug exposures). In chapter three, I describe what kinds of variables these sources have, and the relative benefits or drawbacks in terms of potential misclassification of RA status.

RA is a chronic disease and patients require specific medical attention and continuous management. Besides prevalence estimates, evaluating treatment of RA in a population-based sample could be an important step in efforts to reduce the burden of this disease on the individuals and the community, and thus the last part of my thesis focusses on quality of RA care.

The current thesis is a modest endeavor to fill in a knowledge gap within RA surveillance studies and care quality. The main research questions of this thesis are: In the absence of gold standard, what is the RA prevalence estimate and what are the accuracy properties of combinations of imperfect ascertainment methods in population-based studies adjusting for the inherent misclassification error? Additionally, how does the number of years of data in health administrative databases affect prevalence estimates (both unadjusted and adjusted for misclassification error)? Finally, what is the quality of care provided to RA patients?

In the first study of this thesis, I report prevalence estimates of RA from the imperfect self-report and health administrative data as unadjusted or naive estimates. Two ascertainment methods are based on self reported data and these are, RA diagnosis and current disease-modifying anti-rheumatic drug (DMARD) use. DMARDs are recommended for all RA patients with active disease. Therefore, I used it as an indicative method of the presence of RA. The third method is RA ascertainment from physician billings in the Régie de l'assurance maladie du Québec (RAMQ) administrative data. To adjust for misclassification error related to these

imperfect ascertainment methods, I developed several Bayesian latent class models and compared the prevalence as well as accuracy properties of the three ascertainment approaches. Additionally, I considered the scenario when information from one ascertainment method is used alone, as well as when information from two or all the methods are used in combination. I performed sensitivity analyses to assess the impact of choice of prior distribution on the final results and to examine the effect of conditional dependence between ascertainment methods. All these analyses used data from the very large CARTaGENE general population research cohort, which has been linked to the RAMQ administrative data.

The second study in this thesis entails two projects. First, I applied RA billing code definitions to RAMQ data to estimate the unadjusted RA prevalence for eleven observation periods from 1998 till 2010. I compared these prevalence estimates across all periods to determine the effect of using short observation periods on RA prevalence estimates within RAMQ databases. Second, I derived the adjusted prevalence estimates for every observation period using RAMQ data alone or when combining them with self-reported RA diagnosis, and self-reported DMARD use. With this approach, I compared the unadjusted and adjusted prevalence estimates to investigate if the adjustment method removed the time-window bias from prevalence estimates across all time-periods.

In the third study, I identified RA patients from the CARTaGENE cohort using self-reported diagnoses and RAMQ billing codes. I then explored several variables (i.e. DMARD use, physician visits, use of folate supplementation, use of vitamin D and calcium, exercise and smoking status) in this sample for assessing management and care of RA.

List of Tables

Table 1.1. Uses of public health surveillance data (10)

- Providing quantitative estimates of the magnitude of a health problem
- Detecting emergent health problems and epidemics
- Documenting the distribution and spread of a health event geographically or among defined populations
- Testing hypotheses
- Facilitating planning
- Facilitating epidemiologic and laboratory research
- Monitoring change in risk factors for health-event occurrence
- Detecting changes in health practices
- Assessing control and prevention activities

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CHAPTER TWO
LITERATURE REVIEW

Burden of Rheumatoid Arthritis (RA)

RA is the most common inflammatory joint disease, with a prevalence ranging between 0.5% and 1.6% in North America (1, 2). It is often considered a difficult disease to diagnose, and cure is nowhere near due to lack of knowledge of its etiology, incomplete understanding of its pathogenesis, disease heterogeneity, and inability to make an early clinical diagnosis (3). RA can occur at any age, although it often manifests in people of work-force age and older. RA prevalence increases with age and is about 2% in seniors (4); unfortunately many patients become disabled as a result of this lifelong disease (5), when uncontrolled inflammation (6) leads to severe joint damage (3).

The impact of RA on affected individuals, caregivers, employers and health care system is significant. RA is responsible for disability, lost productivity and a significant consumption of health and social resources in a large proportion of patients. Patients with RA often require life-long treatment to control disease activity. RA is associated with co-morbidities such as increased risk of infections, cancer, cardiovascular disease, gastrointestinal dysfunction, respiratory diseases, and depression (1, 7). Moreover, patients with RA have increased mortality compared with the general population, possibly due to the increased incidence of cardiovascular disease (8).

Prevalence studies on RA

Some of what is known about RA prevalence estimates comes from provincial administrative health databases which contain patient demographic data and information on physician billings, prescribed medications and hospitalization records (2, 9). Prevalence

estimates of RA obtained from administrative health databases have varied depending on case definitions (10). Using a single billing code for RA over a certain period within administrative data may not by itself be a very sensitive means for RA case ascertainment, since generally only one diagnostic code per physician visit is allowed. RA patients often have multiple morbidities; therefore, RA patients with comorbidities may escape detection based on physician billings if the diagnostic code reported by the physician is for comorbidity and not RA. In addition to missing some true cases, any ascertainment method will also misclassify some persons. And what is more, previous prevalence studies in administrative databases have shown that not just the case definition, but also the length of the observation period has a strong effect on prevalence estimates of rheumatic diseases like Systemic Lupus Erythematosus (SLE), an autoimmune disease similar in nature to RA (11, 12). In these studies, a phenomenon has been noted where falsely low prevalence rates of SLE were estimated, using short observation periods in health administrative data. This artefact is due to the relapsing-remitting nature of the disease, which may not be captured if the observation period is short.

An additional source of data for RA surveillance is self-reported data collected from questionnaires (13-16). These surveys often use broad and colloquial terms such as “arthritis” and “rheumatism” in their questions and ask about physicians’ diagnosis of specific rheumatic diseases. Ascertainment of RA based on the patient’s self-reported data should be done with caution since misclassification is a concern. RA is frequently considered by lay people to be synonymous with other types of rheumatic diseases, and individuals often do not know the specific rheumatic condition they have. In a study on the role of health knowledge in self-reported musculoskeletal disorders, authors noted that low health literacy influence the responses to self-reported questions, and eventually impacts the inferences on population estimates of

rheumatic diseases (17). Furthermore, self-reported questions are usually subject to poor recall, particularly for mild cases (18). Inaccuracy of self-report may be also influenced by factors such as lack of communication between physicians and patients regarding their diagnosis (19). Other demographic, clinical and functional factors that can increase and/or decrease the accuracy of self-reported physician diagnosis of specific rheumatic conditions include comorbidities, age, functional status, and education level (18).

Previous studies on self-reported RA have shown a positive predictive value (PPV) ranging between 20%-35.8% (5, 20-24). Kvien et al showed in their 1996 study that patient self-report was inaccurate with a PPV ranging between 20% and 25% when compared to clinical examination (22). While the accuracy of self-reported RA was low in some studies, supplementing this ascertainment method with medication information improved its accuracy in other studies. For example, in a survey of postmenopausal women aged 50-79 years, the PPV of self-reported RA diagnosis increased from 14.7% to 62.2% when disease-modifying anti-rheumatic drugs (DMARDs) use was added to the RA ascertainment method (20). Similarly, self-reported RA along with the use of DMARDs demonstrated a high PPV for RA in African American women aged 27 to 73 years (25). Another study that combined self-reported information including diagnosis and medications with serological testing of anti-cyclic citrullinated proteins (anti-CCP) anti-bodies, yielded a 100% PPV for physician-validated RA (21).

Imperfect standards for RA ascertainment

One challenge in population-based surveillance for RA is that often there is no perfect "gold standard" readily available. The 1987 revised American College of Rheumatology (ACR) criteria for RA (26) and the 2010 ACR/European Union League Against Rheumatism

classification criteria for RA (27) may be considered a reference standard for RA definition and they can be of use for clinical and research practices. However, clinical variables required to score the ACR RA criteria are generally lacking in both administrative and self-reported data. Also, subjects with a single swollen joint and anti-CCP positivity may well have RA, but fail to meet recognized classification criteria (28). The ACR classification criteria were designed to ensure enrolment of homogeneous phenotypes in clinical trials and may not be suitable to identify all RA cases with various disease duration, activity, progression and associated-disability. Therefore, physician misdiagnosis can still arise when using the ACR criteria. Also, diagnoses of RA evolve over time. For example, patients fulfilling RA criteria at first diagnosis, may then fulfil clinical criteria for SLE or another disease later (29).

Methods to adjust for misclassification in the absence of a gold standard

A variety of methods have been proposed to adjust for misclassification of diseases status in the absence of a gold standard. Some methods depend on multiple information sources to construct a reference standard outcome. In these methods, the results of several imperfect case definitions are combined through either a consensus or a composite reference standard. Expertise from a group of clinicians is usually required to conduct a case-per case ascertainment which is not practical in a large prevalence estimate study.

Alternatively, several imperfect ascertainment methods can be combined using latent class analysis (30, 31) which is the method considered for this thesis. The basic idea of latent class analysis is that there is a "latent" disease status which is existing but not currently apparent. This "unobservable" status is linked to the "observed" results of imperfect ascertainment methods in a latent class model in an effort to adjust for misclassification of disease status (32, 33). Latent class analysis can be conducted through the usual frequentist maximum likelihood

approach (34-36); alternatively, Bayesian latent class analysis can be applied (37). Frequentist methods impose constraints on certain parameters such as the sensitivities and specificities to allow the remaining latent class model parameters to be estimated freely. However, this approach has some limitations. First, it does not always yield meaningful parameter estimates and it does not take into account the uncertainty in the assumed values. Second, the true values of sensitivities, specificities and the prevalence of any disease, are rarely exactly known in advance. Finally, constrained parameters are not estimated. Bayesian latent class models provide a way for prior information to be incorporated to correct for misclassification of imperfect RA case definitions. Therefore, a Bayesian approach eliminates the need to place constraints on the prevalence as well as accuracy properties, draws inferences on all parameters of interest simultaneously, and accounts better for the uncertainty around the parameters of interest. Using the Bayesian approach, posterior distributions of the unknown parameters of interest i.e. prevalence of RA and accuracy properties (sensitivity and specificity) of several ascertainment methods can be estimated by combining the likelihood of the observed data with a prior distribution on the unknown parameters. In this case, computing the posterior distribution analytically is complicated, but researchers have developed analytical methods based on Gibbs sampling (38-40).

Treatment and Care in RA

Understanding the burden of RA and planning health services to address the needs of RA patients require not just accurate prevalence estimates, but also means of measuring quality of health care to prevent RA-related disability and for tracking progress in treatment and management. Self-reported data often have variables on pharmacotherapy of patients. They also include variables on nonpharmacologic management of RA such as exercise and tobacco

abstinence (14). These variables can provide opportunities to assess the quality of care and management provided to RA patients and to compare these data to others such as those obtained from administrative health databases.

Twenty-seven indicators to measure the quality of care for patients with RA have been established by the Arthritis Foundation Quality Indicator (QI) Project. These indicators have been based on evidence as well as expert opinion (41). Other quality measures have been proposed by the Rheumatology Informatics System for Effectiveness (RISE) (42). QIs are often considered the minimal requirement of care and their assessment can lead to information about what elements of RA care may need to be improved.

RA is a treatable (albeit not curable) disease and results are best if RA is treated very early after disease onset (43). Even before RA becomes clinically apparent, immune system over-activity (including the presence of auto-antibodies which are antibodies against normal "self" proteins) can be documented. The reason for the breakdown in immune tolerance towards self-antigens is still unidentified (6). In a recent systematic review that I published, auto-antibodies particularly anti-CCP, can be found in the serum of patients with undifferentiated arthritis and healthy subjects, thus predicting future onset of RA (44). Furthermore, several studies have shown that joint damage occurs within the first two years after RA onset (45), which may represent a "window of opportunity" to stop irreversible structural damage and prevent long-term physical disability (46).

Patients with RA need chronic and uninterrupted therapy to halt the manifestations of disease (3). Treatments to reduce pain and inflammation include nonsteroidal anti-inflammatory drugs, corticosteroids, DMARDs and biological agents that include pro-inflammatory cytokine tumour necrosis factor-α (47). Additionally, encouraging a healthier lifestyle such as exercise

(48) and smoking cessation (28) has been suggested (49, 50). Despite recommendations on RA management, some patients do not receive adequate care (51-53). A population based study in British Columbia on gaps of care showed that RA treatment was not consistent with current treatment guidelines. Particularly, DMARDs were not used constantly and combination therapy i.e. using two medications or three, was uncommon (51). Another study in Quebec suggested that access of RA patients to rheumatology care is very poor (52).

PhD Objectives

The objectives of this thesis are:

1- Within the CARTaGENE cohort, to assess and compare the unadjusted and adjusted prevalence estimates of RA as well as the sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) of one, two, and three combinations of imperfect ascertainment methods for RA identification.

2-Within the RAMQ health administrative databases, to determine how the observation period affects unadjusted and adjusted RA prevalence estimates as well as estimates of sensitivity and specificity of RAMQ ascertainment approach using administrative data (alone or combined with self-report data).

3- Using CARTaGENE data, to assess selected care quality indicators for RA patients, and to identify if subsets of the RA population are at particular risks of not obtaining quality care, according to these indicators.

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CHAPTER THREE

ESTIMATING RHEUMATOID ARTHRITIS PREVALENCE WITH A COMBINATION OF ADMINISTRATIVE AND HEALTH-REPORT DATA

Introduction

Prevalence estimates of RA range between 0.4% and 8% worldwide (1, 2). These estimates come from either provincial administrative health databases or self-reported questions on RA diagnosis in population-health surveys. Ascertainment methods from these databases are imperfect and their reported estimates do not account for misclassification in RA status. It is possible that subjects may be false positives or false negatives using these data sources. Furthermore, some studies assumed that a gold standard exists such as medical records to evaluate the validity of self-reported questions (3) as well as administrative health databases (4). However, this method of validation is often lacking in large population-based studies because of its costs and impracticality.

Few RA prevalence estimates are available in Quebec or even in Canada (5). One estimate of RA prevalence exists for Quebec (0.483%; 95% credible interval 0.480,0.486) , using only physician billing and hospitalization diagnostic codes for the period 1992–2008, this accounted for misclassification error in administrative data (6). We were thus motivated to produce an updated RA prevalence estimate, using more data sources from health report data. Besides administrative data, surveys and general-population cohorts may be a valuable source of data to estimate RA prevalence. Examples of large survey databases include the Community Oriented Program for Control of Rheumatic Diseases (COPCORD) in developing countries (7),

the Canadian Partnership for Tomorrow Cohort (of which CARTaGENE is a part) (8), and Canadian Community Health Survey (CHSS, Canada, 2002)(9).

The current study applies state-of-the-art Bayesian latent class methods to generate estimates about the unknown parameters of interest i.e. RA prevalence, accuracy properties including sensitivity, specificity, PPV and NPV of imperfect RA ascertainment methods in the absence of gold standard. The objective of my study was to compare the adjusted RA prevalence as well as accuracy properties of combinations of ascertainment approaches from self-report and physician billing administrative data of a population-based sample aged 40 to 69 years old from four Quebec regions.

Methods

A. Study setting and the Sources of Data

This study took place in the context of a large established population-based study entitled CARTaGENE which recruited 19,995 participants (aged 40 to 69 years old) from August 2009 to October 2010 from four metropolitan regions in Québec (Montréal, Sherbrooke, Québec City, and Saguenay). Data on population density from the 2006 Census was used to select and proportionately distribute participants across the different regions. Participants were randomly selected from the provincial health insurance FIPA files (fichier administratif des inscriptions des personnes assurées). Individuals who were not registered in the FIPA files, who resided outside the selected regions in 2009, and who lived in First Nations Reserves or long-term health care facilities or were in prison, were excluded. Recruitment efforts targeted a sample with an age and sex distribution proportionate to that of the general population with participation rate of 25.6%. Participants completed a self-administered socio-demographic and lifestyle questionnaire as well as an interviewer-administered health questionnaire. These questionnaires contain variables on

demographic and socio-economic factors, lifestyle habits, mental health, environment, individual and family history of disease, medical care history such as visits to a doctor or a nurse, and medications. Drug exposures were captured by a trained research assistant who noted details of all drugs in use at the time of the interview (prescribed and non-prescribed) including drug name, and last time used (in the past three days before the assessment) (10).

In my work, I used CARTaGENE cohort data, which is linked to the RAMQ databases using patients' unique provincial health insurance number. The RAMQ medical service database has information on physician outpatient and inpatient visits and procedures, including diagnoses coded according to the International Classification of Diseases, ninth revision (ICD-9) during the time interval of data collection. RAMQ data are available on CARTaGENE participants for the period from January 1, 1998 until December 31, 2012.

Approval for the study was obtained from McGill University Ethics Review Board, CARTaGENE as well as Commission d'accès à l'information du Québec (CAI).

B. Ascertainment of RA cases using CARTaGENE and RAMQ

I ascertained RA cases from the CARTaGENE database using the participants' answers to the screening questions in the baseline health assessment questionnaire: "Has a doctor ever told you that you had arthritis?". I identified possible RA cases if they indicated RA for the next question: "What kind of arthritis is it?".

Another ascertainment method for a possible RA case in the CARTGENE data was from self-reported data on current drug exposures. These drug exposures include doses and drug identification numbers for all prescribed drugs, including DMARDs as well as over the counter medications. DMARDs are the cornerstone of RA treatment and, according to national and international guidelines, all RA patients with active disease should be offered DMARD therapies.

Of course, a small number of RA patients may not take these drugs (if their RA is in remission- a relatively rare event- or for other reasons). In CARTaGENE data, DMARD exposure was assessed by noting whether the participant was taking conventional DMARDs (hydroxychloroquine, sulfasalazine, methotrexate, leflunomide, azathioprine, cyclosporine, gold, and cyclophosphamide), and/or the biologic DMARDs (infliximab, adalimumab, etanercept, abatacept, and rituximab).

The third RA ascertainment method was based on RAMQ administrative billing codes linked to the CARTaGENE database. Possible RA cases in RAMQ were those who have two or more RA diagnosis (ICD-9 code 714) by any physician at least two months apart but within a two-year span or at least one RA diagnosis by a rheumatologist. This case definition was chosen because it was used previously by the Public Health Agency of Canada for estimating the prevalence of RA as well as in many surveillance studies (6, 11). Additionally, this case definition was validated using primary care records as reference standard (4).

C. Statistical Methods

1. Prevalence estimates assuming perfect ascertainment methods

I calculated the unadjusted (naïve) estimates of RA prevalence based on each single ascertainment method (i.e. self-reported RA diagnosis, DMARD use and RAMQ billing codes) as if that ascertainment method had no misclassification error.

2. Prevalence estimates after adjusting for misclassification error in the absence of gold standard

To estimate the prevalence of RA adjusted for misclassification error, the sensitivity and specificity of every ascertainment method should be known in advance; however, this is rarely available in the absence of a gold standard. In this case, the true disease status of each individual

is “latent” or “unobservable”. However, the results of the imperfect ascertainment methods are observable. The number of subjects who are categorized as having RA according to each method, is a mix of true positive and false positive individuals. Similarly, among the subjects who are categorized as non-RA cases, there is both true negative and false negative results. A Bayesian latent class model can be used to link the observed results of several ascertainment methods to the “unobserved truth”, and the number of positives on certain RA ascertainment method can be written in terms of its sensitivity and specificity i.e. (total sample size)*[(prevalence of RA*sensitivity of the ascertainment method)+(1- prevalence)(1-specificity of the ascertainment method)]. Then, a priori information i.e. prior beliefs/assumptions about the probability distribution of the sensitivity and specificity can be incorporated in order to estimate the sensitivity and specificity of all ascertainment methods along with the prevalence of RA by the model (12). Estimates generated from these Bayesian methods summarise the state of knowledge about the unknown parameters, conditional on prior beliefs about the parameters and the present data (13).

When using one or two ascertainment methods, there are fewer degrees of freedom than the number of parameters (sensitivity and specificity of each method as well as the prevalence of RA) to be estimated. In that case, the desired parameters are non-identifiable unless informative prior distributions are specified on at least two parameters. When using three ascertainment methods, there are seven degrees of freedom and seven parameters to estimate assuming the methods are independent conditional on the true disease status. The sensitivity and specificity of the three methods, as well as the prevalence of RA can be estimated from the data alone (12).

For each ascertainment approach, I estimated the adjusted RA prevalence and accuracy properties using a Bayesian Latent Class model. I also estimated and compared the adjusted

prevalence of RA and accuracy properties of various combinations, assuming conditional independence between the methods.

3. Prior Distributions

For all parameters, I used a beta prior distribution as this distribution is the conjugate prior for the binomial likelihood, with parameters α and β. I matched the end points of a chosen prior range to beta distributions with similar 95 percent probability intervals (12). To calculate α and β from the prior information I have, I used a software available at: http://www.medicine.mcgill.ca/epidemiology/Joseph/PBelisle/BetaParmsFromQuantiles.html#example. Tables 3.1 and 3.2 show the equally tailed 95% probability ranges and coefficients of the beta prior densities for RA prevalence as well as the sensitivity and specificity of each ascertainment method.

I aimed to elicit prior information on the different parameters based on the literature which was reviewed for constructing the priors. In the literature, the sensitivity estimates of self-reported RA diagnoses ranged between 59% and 97%, with specificity ranging between 66% and 99% (14). Therefore, I chose the priors for the sensitivity and specificity of self-reported RA diagnosis as (59%-97%) and (66%-99%), respectively. For DMARD use, several studies have reported that the DMARD use among RA patients may range from 30% to 77% (15, 16). DMARDs are also used to treat some rare autoimmune diseases. Therefore, it is uncommon, but possible that some non-RA individuals report using DMARDs. Given this, I constructed the priors for the sensitivity and specificity for DAMRD use to be (30%-77%) and (95%-99%), respectively. Finally, based on a validation study using primary care records as reference standard (25), I chose the sensitivity of RAMQ billing codes to be between 60%-93% and its specificity between 90%-99%. As for the prevalence of RA, knowledge accumulated from

previous studies suggests a range between 0.4% and 8% (1, 2). I conducted a sensitivity analysis to compare two ranges of prior distributions over the prevalence: (0%-10%) and (0%-8%). The results from these sensitivity analyses were very similar; therefore, I used informative prior distributions with a range between 0%-8% throughout all analyses for the prevalence.

Since prior distributions have an impact on the posterior estimates in the setting of one and two ascertainment methods, I elicited another set of prior distributions over parameters of the accuracy properties of all ascertainment methods from experts who are members of the Canadian Rheumatology Administrative Data Network (CANRAD). I developed a short questionnaire, pilot tested it, and I sent it to nine experts via email. The questionnaire is presented in appendix-1 of this chapter. The range in which researchers were 95% confident that the true value of the parameters would be, were obtained from the experts (17, 18). All experts were blinded to the other experts' opinions. From these responses, lower and upper limits of 95% intervals were generated to construct the prior distributions for the accuracy properties of all three ascertainment methods. I compared results from these analyses to the other results using prior distributions from the literature. In the setting of three ascertainment methods, I used uninformative prior distributions over all parameters as a third set of priors. In this case, the data mainly contributes to the final inferences which are expected to be numerically similar to the frequentist methods.

The unadjusted prevalence estimates were calculated using Bayesian method for single proportions with uninformative priors.

4. Conditional Independence Assumption

Conditional independence occurs when ascertainment methods' results are statistically independent of each other, given the true disease status of each subject. This may not always be

the case. For example, there might be some dependence between the billing codes and the self-reported DMARDs which are presumably prescribed by the same diagnosing physician or between the billing codes and self-reported RA or between the two self-reported data sources. Therefore, I considered additional models as sensitivity analyses to account for conditional dependence in the setting of two and three ascertainment methods.

I modeled conditional dependence by incorporating the covariance between the ascertainment methods in RA subjects (covp) and in non-RA subjects (covn). It has been shown that (19):

$P(\text{Ascertainment method}_1=1,\text{Ascertainment method}_2=1/RA=1)=\text{Sensitivity}_1\ \text{Sensitivity}_2+covp_{12}$

$P(\text{Ascertainment method}_1=1,\text{Ascertainment method}_2=0/RA=1)= \text{Sensitivity}_1(1-\text{Sensitivity}_2)-covp_{12}$

Assuming positive conditional dependence, $P(\text{Ascertainment method}_1=1,\text{Ascertainment method}_2=1)$ is increased by an amount $covp_{12}$ when the two ascertainment methods are correlated compared with the conditionally independent case. The feasible range of the covariance is determined by the sensitivities (Se) among the diseased and the specificities (Sp) among the non-diseased.

covp ~ dunif(minp,maxp)

covn ~ dunif(minn,maxn), with the minimum and maximum as follows:

$minp <- (1-Se_{\text{Ascertainment method1}}) * (Se_{\text{Ascertainment method2}}-1)$

$minn <- (Sp_{\text{Ascertainment method1}}-1) * (1-Sp_{\text{Ascertainment method2}})$

$maxp <- \min (Se_{\text{Ascertainment method1}}, Se_{\text{Ascertainment method2}}) - Se_{\text{Ascertainment method1}} * Se_{\text{Ascertainment method2}}$

$maxn <- \min (Sp_{\text{Ascertainment method1}}, Sp_{\text{Ascertainment method2}}) - Sp_{\text{Ascertainment method1}} * Sp_{\text{Ascertainment method2}}$

Since the lower bound is always negative and the situation assumed in this study is positive correlation between the ascertainment methods, the lower bound was fixed at zero:

$Covp \sim U(0, \min(Se_{Ascertainment\ method1}, Se_{Ascertainment\ method2}) - Se_{Ascertainment\ method1} * Se_{Ascertainment\ method2})$

$Covn \sim U(0, \min(Sp_{Ascertainmentmethod1}, Sp_{Ascertainmentmethod2}) - Sp_{Ascertainmentmethod1} * Sp_{Ascertainmentmethod2})$(19)

5. Likelihood

The likelihood function relating the observed and latent data to the unknown parameters for one ascertainment method is as follows:

$L(a,b,X,Y/\ \pi, Se, Sp) = [\pi Se]^X\ [\pi(1-Se)]^Y\ [(1-\pi)(1-Sp)]^{a-X}\ [(1-\pi)(Sp)]^{b-Y}$; Where a is the observed number of positives, b is the observed number of negatives, X and Y are the latent truly positive subjects, π is the prevalence of RA, Se and Sp are the sensitivity and specificity of the ascertainment method, respectively.

In the case of two and three ascertainment methods, the likelihood contributions of all possible combinations of observed and latent data are shown in Tables 3.3 and 3.4. The likelihood is proportional to the product of each entry in the last column raised to the power of the corresponding entry in the first column of the table.

I used contingency tables of self-reported RA diagnosis (either positive or negative), self-reported DMARDs utilization (either positive or negative) and RAMQ billing codes (either positive or negative) to summarize the observed data from the different ascertainment methods.

6. Posterior distributions

Posterior estimates for each parameter were determined based on a sample from the posterior distribution using Gibbs sampling with the WinBUGS statistical freeware (version 1.4.3, MRC Biostatistics unit, Cambridge, UK). Each model was assessed after a burn in of 5000

iterations and 30,000 iterations for use in inferences (20). I extracted the mean and 2.5-97.5 percentile values (95% Credible Intervals) for each parameter. I used a total of three chains with different initial values and I checked the convergence of the models by visual inspection of the densities and trace plots.

Results

The CARTaGENE data included 19,704 persons with unknown (latent) RA status that is to be classified. Using only self-reported RA diagnosis without any adjustment for misclassification, the prevalence estimate was 2.9% (564 out of 19,704) with 95% CrI: 2.6, 3.1. In comparison, the naïve estimate from DMARD use was lower at 0.9% (182 out of 19,704) with 95% CrI: 0.8, 1.1. The unadjusted prevalence estimate from RAMQ billing codes 1.9% (372 out of 19,704) with 95% CrI: 1.7, 2.1.

The adjusted RA prevalence estimate for the self-report point estimate was 1.3% (95% CrI: 0.07, 3.2) and the sensitivity, and specificity of self-reported data, derived from the Bayesian Latent Class model, were 81.7% (95% CrI: 57.2, 96.8), and 98.1% (95% CrI: 97.1, 99.6), respectively. The PPV and NPV of self-reported RA diagnosis were 35.1% (95% CrI: 1.9, 86.8) and 99.8% (95% CrI: 99.0, 100.0), respectively. The adjusted prevalence estimate of RA using self-reported DMARD alone was 0.4% (95% CrI: 0.02, 1.1), with a sensitivity of 50.8 % (95% CrI: 26.6, 74.8). The PPV and NPV of self-reported current DMARD use were 18.2% (95% CrI: 0.9, 51.8) and 99.8% (95% CrI: 99.3,100.0), respectively. The adjusted prevalence estimate using RAMQ billing codes alone was 0.7 % (95% CrI: 0.04, 1.8), with a sensitivity of 78.1% (95% CrI: 58.5, 92.6). The PPV and NPV for RAMQ billing codes were 27.8% (95% CrI: 1.5, 72.7) and 99.8 (95% CrI: 99.4, 100.0), respectively.

To benefit from the availability of several sources of information about RA status, and ultimately enhance the accuracy of the methods in correctly classifying RA patients, self-reported RA diagnosis was combined with either self-reported DAMRD use, or RAMQ billing codes, or both. Observed data of the two and three ascertainment methods are presented in tables 3.5, 3.6, and 3.7.

When combining self-reported RA diagnosis with DMARD use and assuming conditional independence, the posterior RA prevalence estimate was 1.1% (95% CrI: 0.7, 1.9). In further sensitivity analysis, conditional dependence between self-reported RA diagnosis and DMARD use was accounted for and the resulting RA prevalence estimate was 0.4% (95% CrI: 0.02, 1.1).

Self-reported RA diagnosis was combined with RAMQ billing codes in a different model under conditional independence. The resulting posterior RA prevalence estimate was 1.1% (95% CrI: 0.8, 1.7). In the sensitivity analysis accounting for the potential correlation between self-reported RA diagnosis and RAMQ billing codes, the prevalence estimate was 0.5% (95% CrI: 0.04, 1.2).

When all three ascertainment methods under conditional independence assumption are combined in one model and using informative prior distributions from the literature, the RA prevalence estimate was 1.1% (95% CrI: 0.9, 1.3). When uninformative prior distributions were used over all parameters, there was no change in the prevalence estimate (1.1%, 95% CrI: 0.9, 1.3). In addition, higher values of sensitivities for RAMQ billing codes and self-reported DMARD use were generated when using data from all three ascertainment methods together. The credible intervals obtained from using uninformative prior distributions overlapped with those derived from using the diffuse informative prior distributions from the literature.

Accounting for conditional dependence between the two self-reported sources of information had very little impact on RA prevalence estimate (1.2%, 95% CrI: 0.9, 1.7).

Table 3.8 displays estimates and credible intervals from all analyses i.e. one, two and three ascertainment methods as well as all sensitivity analyses. All posterior estimates appear reasonably close to the corresponding values of their parameters obtained from the literature and all latent class models converged.

The PPVs and NPVs of all possible combinations of the data from each analysis under conditional independence assumption are reported in table 3.9. Higher values of PPVs for RAMQ billing codes and self-reported DMARD use were generated when combining these data with self-reported RA diagnosis compared to when using each method alone.

Robustness of the results were tested in sensitivity analysis where different prior information was obtained from eight experts in the field of rheumatic diseases surveillance. Results are shown in Table 3.10. The RA prevalence estimates combining all three ascertainment methods, assuming conditional independence, were robust to changes in the prior distributions (i.e. uninformative priors, diffuse priors based on the literature and narrow priors from experts), of accuracy parameters.

Discussion

In this study, a series of Bayesian latent class models were developed to estimate the prevalence of RA in a large population-based sample and to assess the accuracy of self-reported RA diagnosis, self-reported DMARD use and RAMQ billing codes for RA identification in the absence of gold standard. This study showed differences between the unadjusted and adjusted prevalence estimates of RA using either of the three methods alone. Furthermore, gains in sensitivities to classify RA patients was found when combining two or three ascertainment

methods together. Using the three ascertainment methods together, our adjusted RA prevalence estimates in 2010 among adults aged 40 to 69 years old resemble the "one percent prevalence" for RA that is characteristically though often informally quoted (6).

To the authors' knowledge, this is the first study to date to combine self-report data and Canadian provincial health administrative data to estimate RA prevalence, adjusting for the error inherent in each data source, in the absence of gold standard. Previous research reported RA prevalence estimates without adjusting for misclassification errors which are unavoidable in health surveys and health administrative databases. Other studies validated self-reported questions against medical charts (21) or administrative data (22). However, previous research on chronic diseases have shown that using medical charts to validate population-based data may overlook some cases if one care provider is the single source of charts (23). Furthermore, conducting a validation study across many participants in large prevalence studies is cumbersome. Other researchers used self-reported surveys as the gold standard to validate case definitions for RA in health administrative databases (24). This is not the ideal way to derive unbiased population prevalence estimates of RA because self-reported data is imperfect (i.e. not truly a gold standard). RA is not a well-defined disease from the perspective of a lay person; therefore, under-reporting and/or over-reporting are very possible in health surveys (25).

In the 2005 Canadian Community Health Survey (CCHS), 18% of adult participants aged 18 years and over reported having been diagnosed with arthritis. Among these, 20.9% reported having RA, suggesting an RA prevalence in that sample of about 3.8% (18% x 20.9%), which clearly seems inflated (9). Our prevalence figure (1.1%), combining two self-reported data sources with RAMQ billing codes, is higher than the rather low RA estimate (0.48%) in Quebec in 2008, using only health administrative data, and adjusting for inherent error (6). On the other

hand, a study using the Ontario RA administrative database without adjustment for imperfect case definitions estimated RA prevalence at 0.9%, similar to some of our results (5). It may be that our study, by including an additional source of data, was able to better balance both false negatives and false positives. In fact, a key potential message from our study is that the ability to correctly classify RA cases is enhanced through combining self-report data and health administrative data.

These findings have important implications for monitoring the prevalence of RA and other chronic diseases. However, in developing countries, self-report may be the only way to assess the chronic disease burden. The World Health Organization and the International League of Associations for Rheumatology have established the Community Oriented Program for Control of Rheumatic Diseases in 1983 as a low cost -low infrastructure local resources community program to determine the burden of rheumatic conditions using health surveys (7). In light of our findings, investigators who have access only to self-report data might choose to combine self-report RA diagnosis with the use of DMARD therapy, and apply Bayesian latent class methods to adjust for the inherent misclassification error in each method to obtain reliable prevalence estimates.

Accuracy properties (i.e. sensitivities, specificities and predictive values) estimates from our study have implications for future etiological and/or analytical research on RA. Depending on the objectives of future studies, RA ascertainment methods can be selected based on high sensitivity to increase identification of positive cases, high specificity to reduce false positive cases, or the maximum combination of sensitivity and specificity (22). For example, quality indicators of RA care or RA outcomes can be studied in a cohort of patients that are positive on

all three ascertainment methods. This optimizes cohort homogeneity and helps lessen false positive cases.

Our study has several strengths. First, a number of useful data sources, including self-report and comprehensive health administrative data, were used. Therefore, within population level surveillance studies, this study fills an important knowledge gap in that it provides a way to combine different data sources, while accounting for misclassification in each.

Although the participation rate in CARTaGENE was low (25.6%), the non-participation by itself is not a good prognosticator of the magnitude of bias on RA prevalence estimate. More important than the participation rate is the extent to which non-participation is associated with factors that could relate to RA, which is widely associated with age, sex and other demographics. A comparison of the participants with the general population of Quebec, suggests that our results are generalizable with respect to demographics.

In our analyses, posterior estimates derived from models using one and two ascertainment methods were highly dependent on the choice of priors. However, we used diffuse informative priors to allow equal contribution from the data and priors on the final inferences. Moreover, we performed sensitivity analysis to assess the impact of prior distributions on the final estimates. There were some differences in prevalence estimates derived from the two types of priors in the setting of one and two ascertainment methods. This can be explained by the narrow informative priors based on the experts' subjective opinion. On the other hand, estimates from models combining all three ascertainment methods were robust to changes in prior distributions.

Conclusion

The methods used in this study respond to the needs of researchers and public agents working in the field of public health for tracking chronic diseases like RA. Combining data from various sources is a powerful approach from the public health perspective (10). Given recent initiatives to develop surveillance system for chronic diseases on the part of organizations like the Public Health Agency of Canada (26), the Institut national de santé publique du Québec, the Community Oriented Program for Control of Rheumatic Diseases (7), the Bone and Joint Decade group (27), the World Health Organization, and the International League of Associations for Rheumatology, the methods used in this study are timely and relevant. The findings highlight the importance of combining more than one source of data to improve the classification of chronic diseases like RA.

List of Tables

Table 3.1. Equally tailed 95% probability ranges and coefficients of the beta prior densities for the prevalence of RA as well as the sensitivity and specificity of each ascertainment method based on the literature

	Range (%)	α	β
Prevalence of RA	0, 8	1.183362	48.6518
Sensitivity $_{\text{Self-RA diagnosis}}$	59, 97	11.02576	2.337667
Specificity $_{\text{Self-RA diagnosis}}$	66, 99	11.12959	1.529257
Sensitivity $_{\text{DMARD use}}$	30, 77	8.50477	7.251135
Specificity $_{\text{DMARD use}}$	95, 99	231.9531	6.258926
Sensitivity $_{\text{RAMQ billing codes}}$	60, 93	17.02904	4.517471
Specificity $_{\text{RAMQ billing codes}}$	90, 99	71.08486	3.242059

Table 3.2. Equally tailed 95% probability ranges and coefficients of the beta prior densities for the prevalence of RA as well as the sensitivity and specificity of each ascertainment method based on experts' beliefs

	Range (%)	α	β
Sensitivity $_{\text{Self-RA diagnosis}}$	78.1, 93.1	67.09662	10.48296
Specificity $_{\text{Self-RA diagnosis}}$	45.8, 61.5	82.45528	71.1053
Sensitivity $_{\text{DMARD use}}$	68.9, 86.5	64.53928	17.83246
Specificity $_{\text{DMARD use}}$	76.0, 88.5	114.758	24.01331
Sensitivity $_{\text{RAMQ billing codes}}$	77.6, 93.0	64.48967	10.31262
Specificity $_{\text{RAMQ billing codes}}$	82.5, 92.1	155.655	21.82744

Table 3.3. Likelihood contribution of observed and latent data for the case of two ascertainment methods

Number of subjects	**Truth**	**Ascertainment method$_1$ result**	**Ascertainment method$_2$ result**	**Likelihood contribution**
Y1	+	+	+	$\pi Se1Se2$
Y2	+	+	-	$\pi Se1(1-Se2)$
Y3	+	-	+	$\pi (1-Se1)Se2$
Y4	+	-	-	$\pi(1-Se1)(1-Se2)$
a-Y1	-	+	+	$(1-\pi)(1-Sp1)(1-Sp2)$
b-Y2	-	+	-	$(1-\pi)(1-Sp1)Sp2$
c-Y3	-	-	+	$(1-\pi)Sp1(1-Sp2)$
d-Y4	-	-	-	$(1-\pi)Sp1Sp2$

Where a, b, c, d are the observed cells in a 2x2 table of two ascertainment methods. Y1, Y2, Y3, Y4 are the latent truly positive subjects in each cell. π is the prevalence of RA. Se1, Se2, Sp1, and Sp2 are the sensitivity and specificity of two ascertainment methods.

Table 3.4. Likelihood contribution of observed and latent data for the case of three ascertainment methods

Number of subjects	**Truth**	**Ascertain-ment method$_1$ result**	**Ascertain-ment method$_2$ result**	**Ascertain-ment method$_3$ result**	**Likelihood contribution**
Y1	+	+	+	+	$\pi Se1Se2Se3$
Y2	+	+	+	-	$\pi Se1Se2(1-Se3)$
Y3	+	+	-	+	$\pi Se1(1-Se2)Se3$
Y4	+	+	-	-	$\pi Se1(1-Se2)(1-Se3)$
Y5	+	-	+	+	$\pi(1-Se1)Se2Se3$
Y6	+	-	+	-	$\pi(1-Se1)Se2(1-Se3)$
Y7	+	-	-	+	$\pi(1-Se1)(1-Se2)Se3$
Y8	+	-	-	-	$\pi(1-Se1)(1-Se2)(1-Se3)$
a-Y1	-	+	+	+	$(1-\pi)(1-Sp1)(1-Sp2)(1-Sp3)$
b-Y2	-	+	+	-	$(1-\pi)(1-Sp1)(1-Sp2)Sp3$
c-Y3	-	+	-	+	$(1-\pi)(1-Sp1)Sp2(1-Sp3)$
d-Y4	-	+	-	-	$(1-\pi)(1-Sp1)Sp2Sp3$
e-Y5	-	-	+	+	$(1-\pi)\ Sp1(1-Sp2)(1-Sp3)$
f-Y6	-	-	+	-	$(1-\pi)\ Sp1(1-Sp2)Sp3$
g-Y7	-	-	-	+	$(1-\pi)\ Sp1Sp2(1-Sp3)$
h-Y8	-	-	-	-	$(1-\pi)Sp1Sp2Sp3$

Where a, b, c, d, e, f, g, h are the observed results of three ascertainment methods. Y1, Y2, Y3, Y4, Y5, Y6, Y7, Y8 are the latent truly positive subjects. π is the prevalence of RA. Se1, Se2, Se3, Sp1, Sp2, and Sp3 are the sensitivity and specificity of three ascertainment methods.

Table 3.5. Results of observed data from self-reported rheumatoid arthritis (RA) diagnosis and self-reported DMARD use among CARTaGENE participants

Self-reported RA diagnosis	DMARD use	Number of subjects
+	+	100
+	-	464
-	+	82
-	-	19,058

Abbreviations: RA, Rheumatoid Arthritis; DMARD, disease modifying anti-rheumatic drug

Table 3.6. Results of observed data from self-reported RA diagnosis and RAMQ billing codes among CARTaGENE participants

Self-reported RA diagnosis	RAMQ codes	Number of subjects
+	+	147
+	-	417
-	+	225
-	-	18,915

Abbreviations: RA, Rheumatoid Arthritis; RAMQ, Régie de l'assurance maladie du Québec

Table 3.7. Results of observed data from the three ascertainment methods among CARTaGENE participants

Self-reported RA diagnosis	DMARD use	RAMQ codes	Number of subjects
+	+	+	83
+	+	-	17
+	-	+	64
+	-	-	400
-	+	+	21
-	+	-	61
-	-	+	204
-	-	-	18,797

Abbreviations: RA, Rheumatoid Arthritis; DMARD, disease modifying anti-rheumatic drug; RAMQ, Régie de l'assurance maladie du Québec

Table 3.8. Posterior means (upper entry of each cell) and lower and upper limits of the posterior equal tailed 95% CrI (lower entry of each cell) for the prevalence of RA (π), the sensitivities (Se), and the specificities (Sp) from each analysis based on prior distributions from the literature, under conditional independence and dependence.

	π	Se $_{\text{self-reported RA}}$	Se $_{\text{DMARD use}}$	Se $_{\text{RAMQ}}$	Sp $_{\text{self-reported RA}}$	Sp $_{\text{DMARD use}}$	Sp $_{\text{RAMQ}}$
One ascertainment method							
Self-reported RA alone	1.3 0.07, 3.2	81.7 57.2, 96.8			98.1 97.1, 99.6		
Self-reported DMARD use alone	0.4 0.02, 1.1		50.8 26.6, 74.8			99.2 99.0, 99.5	
RAMQ billing codes alone	0.7 0.04, 1.8			78.1 58.5, 92.6			98.6 98.1, 99.5
Two ascertainment methods							
Self-reported RA and DMARD use, with conditional independence	1.1 0.7, 1.9	88.6 74.1, 98.0	53.2 30.6, 75.8		98.1 97.7, 98.8	99.6 99.5, 99.7	
Self-reported RA and DMARD use, with conditional dependence	0.4 0.02, 1.1	82.5 59.2, 96.9	51.1 26.6, 75.3		97.4 97.0, 98.0	99.2 99.0, 99.5	
Self-reported RA and RAMQ, with conditional independence	1.1 0.8, 1.7	83.7 62.9, 97.1		78.6 59.3, 92.8	98.0 97.8, 98.4		99.0 98.7, 99.3
Self-reported RA and RAMQ, with conditional dependence	0.5 0.04, 1.2	81.6 57.4, 96.8		78.3 58.7, 92.8	97.5 97.1, 98.1		98.5 98.1, 99.0
Three ascertainment methods							
Three methods using uninformative priors, with conditional independence	1.1 0.9, 1.3	79.4 71.1, 86.7	57.4 49.1, 65.6	83.1 75.0, 90.1	98.0 97.8, 98.2	99.7 99.6, 99.8	99.0 98.9, 99.2
Three methods using	1.1 0.9, 1.3	80.6 72.9, 87.4	57.6 49.7, 65.2	83.4 76.1, 89.6	98.0 97.8, 98.2	99.7 99.6, 99.8	99.0 98.8, 99.1

informative priors from literature, with conditional independence							
Three methods using informative priors from literature, with conditional dependence between the two self-reported data	1.2 0.9, 1.7	69.9 49.9, 83.7	50.0 35.0, 62.1	86.5 77.9, 94.4	97.9 97.7, 98.2	99.7 99.6, 99.8	99.1 98.9, 99.6

Abbreviations: CrI, Credible Interval; RA, Rheumatoid Arthritis; DMARD, disease modifying anti-rheumatic drug; RAMQ, Régie de l'assurance maladie du Québec

Table 3.9. Posterior means, and lower and upper limits of the posterior equal tailed 95% CrI for the PPV and NPV of all possible combinations of the data from self-reported RA diagnosis, self-reported current DMARD use and RAMQ billing codes under conditional independence assumption.

	$PPV_{\text{self-reported RA}}$	$NPV_{\text{self-reported RA}}$	$PPV_{\text{DMARD use}}$	$NPV_{\text{DMARD use}}$	PPV_{RAMQ}	NPV_{RAMQ}
Self-reported RA alone	35.1 1.9, 86.8	99.8 99.0, 100.0				
Self-reported DMARD use alone			18.2 0.9, 51.8	99.8 99.3,100.0		
RAMQ billing codes alone					27.8 1.5, 72.7	99.8 99.4, 100.0
Self-reported RA and DMARD use, with conditional independence	34.5 21.7, 57.7	99.9 99.6, 100.0	59.3 49.2, 72.0	99.4 98.7, 100.0		
Self-reported RA and RAMQ, with conditional independence	32.7 25.5, 44.1	99.8 99.4, 100.0			46.3 36.7, 62.1	99.7 99.4, 100.0
Three methods using uninformative priors, with conditional independence	30.4 26.1, 34.8	99.7 99.6, 99.9	67.6 59.9, 75.0	99.5 99.4, 99.7	48.1 42.1, 54.4	99.8 99.7, 99.9

Abbreviations: CrI, Credible Interval; RA, Rheumatoid Arthritis; DMARD, disease modifying anti-rheumatic drug; PPV, Positive Predictive Value; NPV; Negative Predictive Value

Table 3.10. Posterior means (upper entry of each cell) and lower and upper limits of the posterior equal tailed 95% CrI (lower entry of each cell) for the prevalence of RA (π), the sensitivities (Se), and the specificities (Sp) from each analysis based on prior distributions from experts, under conditional independence assumption*

	π	Se $_{\text{self-reported RA}}$	Se $_{\text{DMARD use}}$	Se $_{\text{RAMQ}}$	Sp $_{\text{self-reported RA}}$	Sp $_{\text{DMARD use}}$	Sp $_{\text{RAMQ}}$
One ascertainment method							
Self-reported RA alone	0.06 0.003, 0.2	86.3 77.8, 93.0			96.9 96.6, 97.1		
Self-reported DMARD use alone	0.06 0.003 0.2		78.1 68.6, 86.3			99.0 98.9, 99.2	
RAMQ billing codes alone	0.1 0.006, 0.4			86.0 77.3, 92.9			98.1 97.9, 98.4
Two ascertainment methods							
Self-reported RA and DMARD use, with conditional independence	0.6 0.5, 0.8	89.7 83.2, 94.7	81.5 73.4, 88.4		97.4 97.1, 97.6	99.5 99.4, 99.6	
Self-reported RA and RAMQ, with conditional independence	0.9 0.7, 1.1	88.3 81.2, 94.0		89.3 82.5, 94.5	97.6 97.3, 97.8		98.8 98.6, 99.0
Three ascertainment methods							
Three methods using experts' informative priors, with conditional independence	1.0 0.8, 1.1	84.8 79.8, 89.5	67.2 60.9, 73.3	87.3 82.1, 91.7	97.6 97.4, 97.8	99.6 99.5, 99.7	98.9 98.7, 99.0

Abbreviations: CrI, Credible Interval; RA, Rheumatoid Arthritis; DMARD, disease modifying anti-rheumatic drug; RAMQ, Régie de l'assurance maladie du Québec

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Appendix

Experts' Questionnaire

Elicitation of Prior Distributions on sensitivity and specificity of Rheumatoid Arthritis Case Ascertainment Methods from experts

The purpose of this exercise is to assess your beliefs about the sensitivity and specificity of selected case ascertainment methods for RA identification in different data sources.

These ascertainment methods are:

-Self-reported RA diagnosis through survey questions completed by members of the general population: "Has a doctor ever told you that you had arthritis?" and then indicated RA for the next question: "What kind of arthritis is it?".

-Self-reported DMARD use through survey questions completed by the general population. This method would ask patients to list all medications that they **currently** take.

-Provincial physician billing code algorithm: Two or more RA billing code diagnosis codes (ICD-9 code 714) by any physician at least two months apart but within a two-year span, or at least one RA diagnosis by a rheumatologist.

Sensitivity is the true positive rate i.e. The proportion of RA patients correctly identified by the ascertainment methods as having RA; specificity is the true negative rate i.e. the proportion of healthy people correctly identified by the ascertainment methods as not having RA.

For example, say that out of 100 people, 10 of them have RA (RA prevalence being about 1% of the population). How many RA patients do you think that a given ascertainment method will correctly identify as RA and non-RA? If you think that of 10 patients with RA, that 9 of them will be positive by that case ascertainment method, then that ascertainment method would be

90% sensitive. If you think that of 90 people without RA, 10 of them will be falsely identified as RA, and 80 will be correctly identified as not having RA, then the specificity is 80/90=89%.

For sensitivity and specificity, please provide the 95% credible interval (the Bayesian counterpart of the frequentist confidence interval) i.e. an upper number and a lower number, within which you think the sensitivity or specificity lies. The interval should be such that there is a 95% probability the sensitivity or specificity will lie in the interval.

	Self-reported RA diagnosis on survey	**Self-reported DMARD use on survey**	**RAMQ billing code algorithm**
95% interval around the sensitivity			
95% interval around the specificity			

CHAPTER FOUR

CAPTURE OF RHEUMATOID ARTHRITIS CASES WITHIN RAMQ DATABASE

Background and Rationale

Due to reasons of practicality, cost-effectiveness and comprehensiveness, health administrative databases represent an important resource for the surveillance of chronic diseases, both rheumatic (e.g. Rheumatoid Arthritis, RA, (1), Systemic Lupus Erythematosus, SLE (2)), and non-rheumatic (e.g. diabetes, hypertension, asthma (3), chronic obstructive pulmonary disease) (4). Health administrative databases include data on various elements of health care including physician visits, hospitalizations, and other information. Since these data are not collected specifically for research purposes (5), the use of these data for chronic disease surveillance requires not only an understanding of the nature of the chronic disease being studied but also knowledge of how the data are recorded and their potential limitations (4, 6).

Regarding potential limitations, there are two elements that determine the accuracy of these databases. The first element is validity, which is related to the probability that a patient with a RA diagnosis in a database truly has the disease. The other element is completeness of the database or the sensitivity (7).

Several studies have investigated the usefulness of administrative databases for identifying cases of various chronic diseases. In one study, Quebec's universal health administrative databases were used to estimate SLE prevalence. Results pointed to an effect of the length of observation period on the estimates (2), with underestimation of the prevalence when short observation periods were used. Another study by Powell et al found such a phenomenon in some rheumatic diseases including RA, using the Kaiser Permanente Georgia

Region and the Georgia Medicaid administrative databases, in which up to ten diagnoses are allowed with any single visit (8).

Since Canadian provincial government health insurance is nearly universal, administrative databases like those collected by the Régie de l'assurance maladie du Québec (RAMQ) have been also an attractive resource for prevalence studies on RA (1). Methods for estimating RA prevalence in these databases rely on physician billing and/or hospitalization International Classification of Diseases (ICD) codes (9). Only one diagnostic code is allowed per physician visit in Quebec. Also, RA may be a difficult diagnosis for physicians who are not rheumatologists. RA patients are heterogeneous, differing in clinical, pathological and immunological characteristics (10), thus diagnosing RA often requires a very alert general practitioner. For example, a preliminary diagnosis of RA by non-specialists may later turn out to be merely a self-limiting synovitis (11). Additionally, RA is a dynamic chronic disease, characterized by unpredictable flares and remissions of disease activity (12). During periods of remission, patients may not seek medical treatment, at least for RA. Short observation periods of RAMQ data may miss some cases, particularly for patients in remission or with mild disease activity, who may not receive care for their disease in the years under observation.

It has been suggested that ascertainment of chronic diseases cases (9, 13) particularly those that are hard-to-diagnose (4) like RA can be enhanced if a number of sources is used. To optimize ascertainment of the full spectrum of RA cases, specifically in very short observation periods, it is possible to complement health administrative databases with other data sources (5). Alternatively, investigators can use longer observation periods to capture missed RA cases in shorter observation periods (2, 5). This method has some drawbacks. Some investigators need more recent estimates because temporal changes such as diagnostic drift can occur over time (5).

For example, the American College of Rheumatology (ACR) criteria for RA have changed three times (14). The most recent are 2010 ACR/European Union League Against Rheumatism classification criteria (15). These changes in diagnostic criteria over long observation periods could alter RA prevalence estimates. Moreover, disease control is more common than it used to be, due to more aggressive therapy (16). Identifying RA cases through billing data may potentially miss patients whose disease is controlled, if those patients do not seek care frequently. This could also result in variations of RA prevalence estimates with observation periods. Other ways to ascertain RA cases may be through self-reported diagnosis and/or use of Disease Modifying Anti-Rheumatic Drugs (DMARDs). DMARDs are an essential part of RA treatment.

One prior study estimated RA prevalence for Quebec, using only physician billing and hospitalization diagnostic codes for the period 1992–2008, this accounted for misclassification error in administrative data (1). However, additional studies may be helpful to elucidate the effect of both the observation period and the use of self-reported information on the completeness of RA numerator data within administrative databases.

This study's specific objective is to calculate, within eleven different observation periods, unadjusted and adjusted RA prevalence estimates, as well as estimates of sensitivity and specificity of RAMQ ascertainment approach, using administrative data (alone or combined with self-report data).

Methods

A. CARTaGENE cohort

I studied CARTaGENE participants; this cohort enrolled subjects aged 40 to 69 years old who had been randomly selected from four metropolitan regions in Québec (Montréal,

Sherbrooke, Québec City, and Saguenay). Approval for the study was obtained from McGill University Ethics Review Board, CARTaGENE as well as Commission d'accès à l'information du Québec (CAI).

B. Data sources and RA ascertainment methods

The CARTaGENE research cohort has been linked to RAMQ data from 1998 to 2010. For physicians' claims data, I defined RA cases according to an algorithm requiring two or more RA diagnoses by any physician at least two months apart but within a two-year span or at least one RA diagnosis by a rheumatologist. I also defined RA cases from the self-reported information on RA diagnosis and current use of DMARD in CARTaGENE questionnaire.

C. Time frame

RAMQ data on the cohort are available from January 1, 1998 to December 31, 2010. The observation period is the time for which data is available for analysis. I constructed eleven observation periods, ranging from a minimum of three years (2008-2010) to as long as thirteen years (1998-2010). I created successive longer periods by adding one earlier year to the year under observation. For example, one earlier year was added to the shortest observation period i.e. (2008-2010) to yield four-years observation period (2007-2010).

I estimated the unadjusted and adjusted 2010 RA prevalence for every observation period. I also estimated the adjusted prevalence using RAMQ ascertainment method alone as well as combining it with self-reported information. For every observation period, I generated three different 2010 prevalence estimates i.e. an unadjusted prevalence estimate using the imperfect RAMQ method, an adjusted estimate using RAMQ method alone, and an adjusted estimate combining RAMQ with the self-reported data. Additionally, in every observation period, I generated two estimates for sensitivity and specificity of using RAMQ data (one

estimate derived from using RAMQ alone and another from combining it with self-reported information).

D. Statistical Analysis

For each observation period, the unadjusted estimates using RAMQ ascertainment method were generated using Bayesian methods which account for the uncertainty about the unknown parameters. A Bayesian analysis starts with a prior probability distribution over all unknown parameters of interest. The prior distribution is then updated by new data, through the likelihood function, to give posterior distributions using Bayes' theorem (17). The likelihood function of the data from the imperfect RAMQ ascertainment method is the binomial probability formula: Pr(*x* successes in *N* trials)= (N!/N-x! x!) * θ^{x} *1- $\theta^{(N-x)}$ (where *x* is the number of successes, N is the number of trials, θ is the true but unknown probability of success). Since there are enough degrees of freedom to estimate one parameter (i.e. RA prevalence), I used 'uninformative' prior distribution where all values are equally likely with beta distribution parameters (α=1, β=1).

I generated alternative estimates of prevalence using Bayesian statistical approaches, which accounts for misclassification error in all the data sources. Using this approach, I derived adjusted prevalence estimates as well as the sensitivity and specificity of RAMQ ascertainment method.

When using RAMQ alone or with the two other data sources, if we do not assume conditional independence between the self-reported information sources, there are more parameters to estimate than the number of degrees of freedom. In this setting, the data alone must be supported by informative priors. I constructed informative prior distributions over the sensitivity and specificity of RAMQ based on a published validation study of provincial

administrative data, which used primary care records as reference standard (18) as well as based on the subjective opinions of eight experts in the field. I chose prior distributions over the sensitivity and specificity of RAMQ ranging from 60% to 90% and 82% to 99%, respectively. I also used informative prior distributions over the prevalence ranging from 0% to 8% based on the literature. For the sensitivity and specificity of self-reported data, I used 'uninformative' prior distributions.

To address the potential issue of conditional dependence, I incorporated into my model the conditional correlation between the two CARTaGENE self-reported sources of information (RA diagnosis and DMARD use) in RA subjects and in non-RA subjects (19).

Posterior estimates for each parameter were determined based on a sample from the posterior distribution using Gibbs sampling with the WinBUGS statistical freeware (version 1.4.3, MRC Biostatistics unit, Cambridge, UK). Each model was assessed after a burn in of 5000 iterations and a further 30,000 iterations for use in inferences (20). I extracted the mean and 2.5-97.5 percentile values (95% Credible Intervals) for each parameter. I used a total of three chains with different initial values and I checked the convergence of the models by visual inspection of the densities and trace plots.

For each observation period, I used contingency tables of RAMQ billing codes (either positive or negative), self-reported RA diagnosis (either positive or negative), and self-reported DMARDs use (either positive or negative) to summarize the observed data. Table 4.1 presents the different combinations of the observed data when supplementing RAMQ ascertainment method with self-reported RA diagnosis and self-reported DMARD use. In each observation period, the number of RA cases identified by RAMQ method only can be extracted by adding the number of positive subjects using RAMQ in all the combinations reported in the table.

Results

Over the three-year period, 197 RA cases were identified using only the RAMQ data, unadjusted for misclassification error. When longer time windows were used, the number of RA cases continued to increase, up to 321 in the thirteen-year period.

The unadjusted 2010 RA prevalence point estimate based on three-years of RAMQ data alone was 1.0% (i.e. 1 in 100 people) with a 95% credible interval (CrI) of 0.9, 1.2. Using five-years of data, the prevalence point estimate increased by 20%. When using thirteen years of RAMQ data, there was a 60% increase in the unadjusted prevalence point estimate (1.6%; 95% CrI 1.5, 1.8) compared to the estimate from using three years of data (Table 4.2).

Adjusting for misclassification error, using a Bayesian latent class model, decreased the unadjusted RA prevalence point estimate to 0.4% (95% CrI 0.03, 1.1) for the shortest period. Additionally, the adjusted prevalence was lower than the unadjusted prevalence estimate for all observation periods. The adjusted estimates across all periods showed an increasing trend but less than when administrative data was used without adjustment for misclassification error. The credible intervals around the adjusted point estimate using RAMQ alone were much wider than the credible intervals around the unadjusted estimates, which is expected since adjustment accounts for misclassification error.

For all observation periods, the adjusted point estimates derived from combining RAMQ with self-reported data were lower than the unadjusted estimates and higher than the adjusted estimates using RAMQ alone. When combining administrative and self-report data, adding more years of administrative data increased the adjusted point estimates (Table 4.2) in a similar fashion to when administrative data were used alone. The credible intervals were all overlapping.

Figure 1 shows the increasing trends in the point estimates (unadjusted and adjusted, with administrative data alone and then adding self-report).

The results for the sensitivity estimates of case ascertainment across varying time windows (with administrative data alone, and combining with self-reported data) are shown in Table 4.3. The sensitivity of case ascertainment using RAMQ data alone was unchanged (78%) for all observation periods. However, complementing RAMQ billing codes case ascertainment method with self-reported data sources on RA diagnosis and current DMARD use increased the point estimate for sensitivity from 78.1% (95% CrI: 58.3, 92.6) to 84.0% (95% CrI: 74.0, 93.7) for the shortest observation period. Our estimates of the sensitivity of RAMQ data combined with self-reported data remained relatively steady over time. The specificity of RAMQ ascertainment method alone as well as combining it with self-reported data was high (99%) and stable throughout all time windows.

Discussion

With these data, we found RA prevalence point estimates close to 1%, which is the commonly quoted prevalence figure in North America. The strengths of our study were the use of a very large cohort of individuals with both self-reported and administrative data on RA. Both data sources were adjusted for misclassification error in the absence of gold standard, which reflects a real-life challenge since few RA ascertainment approaches are considered to be 100 percent accurate.

The current study explicitly quantified the effects on RA prevalence estimates of three factors i.e. the length of observation period within administrative data, inclusion of self-reported information on RA, and adjustment for misclassification error in administrative data. Our results show variations in the prevalence point estimates related to all the three factors. There was

negligible change in the sensitivity estimates for case ascertainment using administrative data with more years of observation, but a noticeable increase in sensitivity when self-reported information on RA diagnosis and current DMARD use were added. The three-year 2010 prevalence estimate among adults aged 40 to 69 years old using the three ascertainment methods, assuming conditional dependence between self-report information, and adjusting for misclassification error in each method was 0.9% (95% CrI: 0.7, 1.2).

Previous studies of the effect of increasing years of administrative data on rheumatic diseases prevalence estimates found trends similar to ours, i.e. higher prevalence estimates with more years of data (2, 3, 8, 21, 22). However, ours is the only one that adjusted for the imperfect data sources. As evident from our study, the inclusion of self-reported RA data reduced the trend for incomplete ascertainment with few years of administrative data. Ng et al studied the effect of the number of years of administrative data observed on estimates of SLE prevalence, and recommended the use of long observation periods to avoid under-ascertainment (2). However, using longer observation periods could lead to overestimation of RA prevalence if misclassification error is not accounted for. This highlights the importance of carefully thinking about both sensitivity and specificity. Using the thirteen-year period as an example from our study, the unadjusted prevalence estimate was 1.6 % while the adjusted prevalence estimate using RAMQ alone was 0.7%.

The sensitivity of case ascertainment using administrative data alone was about 78%, and remained steady throughout all periods in our study. Supplementing administrative data with patient self-reported RA diagnosis and current use of DMARD increased the point estimate for sensitivity to about 85% (although credible intervals overlapped). This finding may be important for investigators who may have access to only a few years of administrative data, if they have

additional sources of information on RA status. The importance of using multiple data sources is corroborated by recommendations from other researchers working on chronic disease surveillance (4, 5, 23). In the absence of other data sources, lengthening the number of years of RAMQ data increases RA prevalence point estimates, but with overlapping credible intervals across all observation periods.

One potential limitation of this study is that participants had to consent to be enrolled, even though they were randomly sampled from four regions in Quebec. These four regions include both the two most populated areas, and two rural areas that are of interest given their Quebecois heritage. However, it is possible that our sample does differ from the rest of Quebec in terms of health services delivery (e.g. access to specialists) or other important factors (24). These could limit the generalizability of the estimates in this study. However, the CARTaGENE sample does appear to reflect the Quebec general population in terms of demographics and other comorbidities (25). Additionally, our adjusted results using health administrative data alone were not that precise even with such a large sample size. However, the precision was improved with additional information on RA status from self-reported data.

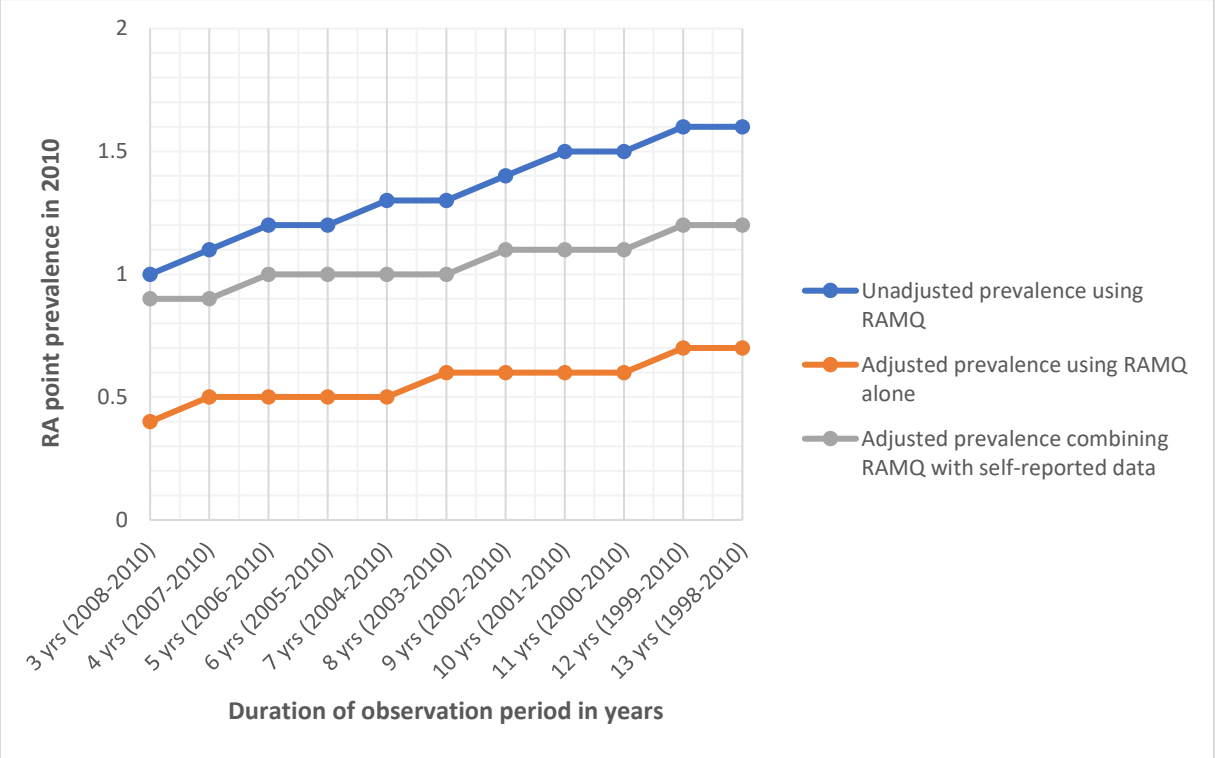
In our study, we did not use hospitalization RA codes. In fact, the Canadian working group on rheumatic disease definitions for surveillance using administrative data has done analyses of billing data with or without hospitalization data, and their consensus (based on analyses from each province) was that hospitalization data does not increase sensitivity of RA ascertainment. Additionally, we did not use administrative drug data because not all Quebec residents have RAMQ drug insurance and two-thirds of our sample will be lost if RAMQ drug data was used. However, this information was available from CARTaGENE health questionnaire.

Conclusion

Our study illustrates that, when using administrative data, RA point prevalence estimates are lower if few years of data are observed, and that multiple data sources can help capture more RA cases. To identify RA cases within RAMQ data, we recommend the use of at least ten years of administrative data and adjusting for misclassification error in administrative case definition.

List of Figures

Figure 1. RA point prevalence estimates by the duration of observation period within RAMQ



Abbreviations: RA, Rheumatoid Arthritis; RAMQ, Régie de l'assurance maladie du Québec

List of Tables

Table 4.1. Observed data for the combinations of the three ascertainment methods for the eleven observation periods

Three-year period (Jan 1, 2008-Dec 31, 2010)	Self-reported RA diagnosis	Self-reported DMARDs use	RAMQ billing codes	Number of subjects
	+	+	+	78
	+	+	-	22
	+	-	+	40
	+	-	-	424
	-	+	+	14
	-	+	-	68
	-	-	+	65
	-	-	-	18993
Four-year period (Jan 1, 2007-Dec 31, 2010)	Self-reported RA diagnosis	Self-reported DMARDs use	RAMQ billing codes	Number of subjects
	+	+	+	78
	+	+	-	22
	+	-	+	41
	+	-	-	423
	-	+	+	16
	-	+	-	66
	-	-	+	79
	-	-	-	18979
Five-year period (Jan 1, 2006 -Dec 31, 2010)	Self-reported RA diagnosis	Self-reported DMARDs use	RAMQ billing codes	Number of subjects
	+	+	+	81
	+	+	-	19

	+	-	+	43
	+	-	-	421
	-	+	+	17
	-	+	-	65
	-	-	+	85
	-	-	-	18973

Six-year period (Jan 1, 2005 - Dec 31,2010)	Self-reported RA diagnosis	Self-reported DMARDs use	RAMQ billing codes	Number of subjects
	+	+	+	81
	+	+	-	19
	+	-	+	44
	+	-	-	420
	-	+	+	17
	-	+	-	65
	-	-	+	96
	-	-	-	18962

Seven-year period (Jan 1, 2004 - Dec 31,2010)	Self-reported RA diagnosis	Self-reported DMARDs use	RAMQ billing codes	Number of subjects
	+	+	+	80
	+	+	-	20
	+	-	+	47
	+	-	-	417
	-	+	+	16
	-	+	-	66
	-	-	+	104
	-	-	-	18954

Eight-year period (Jan 1, 2003 - Dec 31,2010)	Self-reported RA diagnosis	Self-reported DMARDs use	RAMQ billing codes	Number of subjects
	+	+	+	80
	+	+	-	20
	+	-	+	49
	+	-	-	415
	-	+	+	16
	-	+	-	66
	-	-	+	115
	-	-	-	18943

Nine-year period (Jan 1, 2002 - Dec 31,2010)	Self-reported RA diagnosis	Self-reported DMARDs use	RAMQ billing codes	Number of subjects
	+	+	+	80
	+	+	-	20
	+	-	+	53
	+	-	-	411
	-	+	+	17
	-	+	-	65
	-	-	+	123
	-	-	-	18935

Ten-year period (Jan 1, 2001 - Dec 31,2010)	Self-reported RA diagnosis	Self-reported DMARDs use	RAMQ billing codes	Number of subjects
	+	+	+	81
	+	+	-	19
	+	-	+	53

	+	-	-	411
	-	+	+	17
	-	+	-	65
	-	-	+	134
	-	-	-	18924

Eleven-year period (Jan 1, 2000 - Dec 31,2010)	Self-reported RA diagnosis	Self-reported DMARDs use	RAMQ billing codes	Number of subjects
	+	+	+	81
	+	+	-	19
	+	-	+	56
	+	-	-	408
	-	+	+	18
	-	+	-	64
	-	-	+	142
	-	-	-	18916

Twelve-year period (Jan 1, 1999 - Dec 31,2010)	Self-reported RA diagnosis	Self-reported DMARDs use	RAMQ billing codes	Number of subjects
	+	+	+	81
	+	+	-	19
	+	-	+	59
	+	-	-	405
	-	+	+	20
	-	+	-	62
	-	-	+	152
	-	-	-	18906

Thirteen-year period (Jan 1, 1998 - Dec 31,2010)	Self-reported RA diagnosis	Self-reported DMARDs use	RAMQ billing codes	Number of subjects
	+	+	+	81
	+	+	-	19
	+	-	+	61
	+	-	-	403
	-	+	+	19
	-	+	-	63
	-	-	+	160
	-	-	-	18898

Abbreviations: RA, Rheumatoid Arthritis; DMARD, disease modifying anti-rheumatic drug; RAMQ, Régie de l'assurance maladie du Québec

Table 4.2. Posterior means (upper entry of each cell) and lower and upper limits of the posterior equal tailed 95% CrI (lower entry of each cell) for the prevalence of RA of the different combinations of ascertainment methods for the eleven observation periods

	Unadjusted prevalence using RAMQ data alone	**Adjusted prevalence using RAMQ alone**	**Adjusted prevalence using RAMQ and the self-reported data**
Three-year period	1.0	0.4	0.9
(Jan 1, 2008-Dec 31, 2010)	0.9, 1.2	0.03, 1.1	0.7, 1.2
Four-year period	1.1	0.5	0.9
(Jan 1, 2007-Dec 31, 2010)	1.0, 1.2	0.03, 1.2	0.7, 1.2
Five-year period	1.2	0.5	1.0
(Jan 1, 2006 -Dec 31, 2010)	1.0, 1.3	0.03, 1.3	0.8, 1.3
Six-year period	1.2	0.5	1.0
(Jan 1, 2005 - Dec 31, 2010)	1.1, 1.4	0.03, 1.3	0.8, 1.3
Seven-year period	1.3	0.5	1.0
(Jan 1, 2004 - Dec 31, 2010)	1.1, 1.4	0.03, 1.4	0.8, 1.4
Eight-year period	1.3	0.6	1.0
(Jan 1, 2003 - Dec 31, 2010)	1.2, 1.5	0.03, 1.5	0.8, 1.4
Nine-year period	1.4	0.6	1.1
(Jan 1, 2002 - Dec 31, 2010)	1.2, 1.6	0.03, 1.5	0.8, 1.5
Ten-year period	1.5	0.6	1.1
(Jan 1, 2001 - Dec 31, 2010)	1.3, 1.6	0.04, 1.6	0.8, 1.5

Eleven-year period	1.5	0.6	1.1
(Jan 1, 2000 - Dec 31, 2010)	1.3, 1.7	0.04, 1.6	0.9, 1.5
Twelve-year period	1.6	0.7	1.2
(Jan 1, 1999 - Dec 31, 2010)	1.4, 1.8	0.04, 1.7	0.9, 1.6
Thirteen-year period	1.6	0.7	1.2
(Jan 1, 1998 - Dec 31, 2010)	1.5, 1.8	0.04, 1.7	0.9, 1.6

Abbreviations: CrI, Credible Interval; RAMQ, Régie de l'assurance maladie du Québec

Table 4.3. Posterior means (upper entry of each cell) and lower and upper limits of the posterior equal tailed 95% CrI (lower entry of each cell) of the sensitivity and specificity of RAMQ ascertainment method alone as well as combining it with self-reported data for the eleven observation periods

	RAMQ alone		**RAMQ combined with self-reported data**	
	Sensitivity %	Specificity %	Sensitivity %	Specificity %
Three-year period	78.1	99.3	84.0	99.8
(Jan 1, 2008- Dec 31, 2010)	58.3, 92.6	99.0, 99.8	74.0, 93.7	99.6, 100.0
Four-year period	78.0	99.3	84.0	99.7
(Jan 1, 2007- Dec 31, 2010)	58.5, 92.5	98.9, 99.8	74.1, 93.6	99.5, 99.9
Five-year period	78.1	99.2	85.4	99.7
(Jan 1, 2006 -Dec 31, 2010)	58.5, 92.7	98.8, 99.8	76.3, 94.1	99.5, 99.9
Six-year period	78.1	99.2	85.5	99.6
(Jan 1, 2005 - Dec 31,2010)	58.4, 92.7	98.8, 99.8	76.3, 94.2	99.5, 99.9
Seven-year period	78.1	99.2	85.0	99.6
(Jan 1, 2004 - Dec 31,2010)	58.4, 92.6	98.7, 99.8	75.7, 93.9	99.5, 99.7
Eight-year period	78.1	99.2	85.0	99.5
(Jan 1, 2003 - Dec 31,2010)	58.6, 92.6	98.9, 99.6	75.7, 93.9	99.4, 99.8
Nine-year period	78.1	99.1	85.0	99.5
(Jan 1, 2002 - Dec 31,2010)	58.4, 92.7	98.6, 99.7	75.6, 94.0	99.3, 99.8
Ten-year period	78.1	99.0	85.0	99.5

(Jan 1, 2001 - Dec 31,2010)	58.4, 92.7	98.5, 99.7	76.3, 94.1	99.3, 99.8
Eleven-year period	78.2	99.0	85.4	99.4
(Jan 1, 2000 - Dec 31,2010)	58.7, 92.7	98.5, 99.7	76.3, 94.1	99.2, 99.8
Twelve-year period	78.1	98.9	85.4	99.4
(Jan 1, 1999 - Dec 31,2010)	58.5, 92.7	98.4, 99.7	76.2, 94.0	99.2, 99.8
Thirteen-year period	78.2	98.9	85.5	99.4
(Jan 1, 1998 - Dec 31,2010)	58.8, 92.7	98.3, 99.7	76.3, 94.1	99.1, 99.8

Abbreviations: CrI, Credible Interval; RA, RAMQ, Régie de l'assurance maladie du Québec

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CHAPTER FIVE

CARE QUALITY FOR RA PATIENTS IN QUEBEC

Background and Rationale

Rheumatoid Arthritis (RA) is often challenging for primary health practitioners to manage; reasons for this include the relatively few number of patients in a given primary practice, the limited rheumatology training for primary care physicians, and hurdles related to rheumatology access (1-3). One description of quality of care is the "degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge"(4). Furthermore, quality assurance efforts have been directed by a classical model composed of three domains. The first domain is structure which refers to organisational factors such as resources, tools, management, team-work and financing. The second domain is process of care which involves the concrete delivery and receipt of care (e.g. physical examination, medication prescription). The third domain relates to outcomes such as improvement of symptoms, cure, death, and complications. Eventually, the first two elements i.e. structure and delivery of care processes, may influence outcome either positively or negatively (5, 6).

Until recently, there were no specific measures to assess quality of health care in RA. A landmark study was published in 2004 as part of the Arthritis Foundation Quality Indicator (QI) Project to establish measures to comprehensively review RA management (7). These measures span the spectrum of RA care (and thus relate to the second domain mentioned above) including diagnosis, assessment of disease activity, treatment with pharmacologic, nonpharmacologic, and surgical approaches, and patients education (6). Twenty-seven validated indicators were

developed, based on evidence as well as expert opinions (7). The American College of Rheumatology, ACR (8) and the Canadian Rheumatology Association, CRA have recognised several of the Arthritis Foundation quality indicators (9, 10). Additional quality measures for RA care (e.g. addressing cigarette smoking) have been proposed by the Rheumatology Informatics System for Effectiveness (RISE). This is an electronic health record registry aimed at measuring health care quality and improvement in the United States (11).

Since there is no cure for RA, proper management can greatly reduce disability, pain and functional losses associated with this disease (12). Disease Modifying Anti-Rheumatic Drugs (DMARDs) have played a key role in RA management for decades, resulting in a growing literature on the benefits of early treatment with these drugs. There is a "window of therapeutic opportunity" during which initiation of a DMARD may promote disease remission and prevent joint damage and disability (6). Consequently, research on monitoring DMARD use is an important part of the literature on RA care (2).

A few studies in Canada have applied some of the Arthritis Foundation project indicators to assess RA quality of care using health administrative databases (13, 14). However, RA patients were selected in these studies based on physician billing codes, an approach which suffers from misclassification of disease status. In fact, the first study in this thesis showed a low positive predictive value (PPV) of RAMQ physician billing codes for RA (27.8%; 95% CrI: 1.5, 72.7). Therefore, studies of care quality that identify RA patients from administrative data may not provide a valid picture of the care quality.

Another study was conducted at McGill University Health Centre, to assess quality indicators in a group of clinically confirmed RA patients. This study was based on a small

convenience sample of RA patients from a tertiary center, and the results may not be generalizable to the general population (15).

Furthermore, rarely is compliance with QIs assessed using self-reported surveys. By surveying patients, one can have first-hand information about variables that do not exist in health administrative databases (and which are often missing from medical records) such as physical activity and smoking status. These measures are an important part of the recommended comprehensive RA managing strategy and should be evaluated (3).

To date, no study in Quebec has assessed the QIs at the population level. The current study addresses this knowledge gap, using self-reported data from RA patients. The specific objectives of this study were to first, measure the proportion of CARTaGENE RA patients fulfilling pre-specified quality indicators (i.e. DMARD use, regular follow-up, use of folate supplementation, use of vitamin D and calcium, exercise and smoking status) and second to examine variation in DMARD use with respect to patient age, sex, education, and income.

Methods

A. Data sources and study sample

I used the linked CARTaGENE-RAMQ data to select RA patients from among CARTaGENE participants. Based on the results of the first study in this thesis, we considered a patient to have RA when their self-reported RA diagnosis was confirmed on RAMQ billing codes (i.e. those with two or more RA diagnosis (ICD-9 code 714) by any physician at least two months apart but within a two-year span or at least one RA diagnosis by a rheumatologist). The positive predictive value of this approach was shown to be very high with precise credible intervals (CrI) (97.3%; 95% CrI: 96.3, 98.3). Here the RAMQ billing data which I used was for

the period between January 1, 1998 and October 2010. CARTaGENE self-reported data was collected between August 2009 and October 2010.

B. Assessment of selected quality care indicators

I analyzed six QIs. Four QIs were centered on RA management (i.e. use of DMARD therapy, routine medical check-up, use of folate supplementation, and use of calcium and vitamin D). The other two QIs were centered on lifestyle factors (i.e. smoking status and physical activity).

As mentioned earlier, DMARDs can modify RA progression including improvement of functional status as well as reduction of bony erosions, inflammation, and long-term structural damage (6). The first QI, related to DMARD therapy, states that if a patient has an established RA diagnosis, then the patient should be treated with a DMARD unless refusal or contraindication is documented (7). I defined DMARD QI as a binary variable with or without any current use of hydroxychloroquine, sulfasalazine, methotrexate, leflunomide, azathioprine, as well as biological agents (which are also disease-modifying) including etanercept, infliximab, adalimumab, abatacept, and rituximab (newer biologics were not on the formulary at the time of the study).

The second QI I evaluated is related to regular follow-up of patients. If a patient has an established diagnosis of RA, then the patient's RA should be evaluated by a physician at least annually (7). RA is a longstanding disease and regular follow-up of patients is needed to monitor disease activity, pain, and functional disability, which in turn is important to guide therapy for enhanced outcomes (6). I used two questions in the baseline CARTaGENE questionnaire to operationalize and measure this QI. The first question pertains to whether the patient usually has a routine medical check-up undertaken by a doctor or a nurse (i.e. it involves a series of general

health related questions and a physical examination). The second question relates to the last time the patient had a routine medical check-up. Using these two questions, I operationalized the physician visit QI as the proportion of CARTaGENE RA patients who reported having had any medical check-up in the last year. I also used the linked CARTaGENE-RAMQ billing data to explore patients' consultations with rheumatologists, internists and general practitioners in the year after their baseline CARTaGENE survey.

The third QI is the use of folate supplementation. If a patient is being treated with methotrexate, then folate supplementation should be given. Folate supplementation may help reduce side effects caused by folate depletion including mucositis, mild alopecia, gastrointestinal disturbances (6). I operationalized this quality indicator as the proportion, among methotrexate users, who reported folate use in CARTaGENE survey.

The fourth QI pertains to the use of vitamin D and calcium. RA is associated with an increased risk of osteoporosis regardless of whether the patients is taking steroids (3). If a patient with RA is started on prednisone and continued on prednisone for more than 3 months, then 1,500 mg/day of calcium and 400 IU/day of vitamin D should be prescribed in order to prevent steroid-induced osteoporosis. Among prednisone users, I accepted any dose of calcium or vitamin D as fulfilling this QI given the imperfect nature of self-reported data.

Since optimal RA management involves more than pharmacologic therapy, the final two indicators pertain to lifestyle factors. The fifth indicator is physical exercise; if a patient has a diagnosis of RA and has no contraindications to exercise and is physically and mentally able to exercise, then a directed or supervised muscle strengthening or aerobic exercise program should be prescribed (7). Muscle-strengthening exercise programs reduce patient-reported functional disability as well as pain, and the ACR recommends exercise for RA management (6). For this

indicator, I explored, in the baseline CARTaGENE self-reported survey, the proportion of RA patients who currently do moderate physical activities.

The final indicator was proposed in RISE (11) and it pertains to smoking status of RA patients. Rheumatologists should play important roles in educating the RA patient on adopting a healthier lifestyle (16). Studies have shown a reduced clinical response to some medications (17, 18) if RA patients smoked. For this indicator, I explored the proportion of RA patients who are currently smoking (daily or occasional).

C. Variation in DMARD use

To explore variations in DMARD use (the outcome variable), I chose several relevant explanatory variables including age, sex, income, and educational level, which were all determined form CARTaGENE self-reported questionnaire.

D. Statistical analysis

1. Descriptive statistics

I evaluated the baseline characteristics of the study cohort, including demographics (age and sex), social (income, work, education, social support) and other characteristics (e.g. health perception).

2. Estimates of proportions fulfilling QIs

For all of the above indicators, I estimated proportions of patients fulfilling these indicators (and 95% credible intervals) using Bayesian methods for single proportions with uninformative priors. The number of patients fulfilling the QIs follow a binomial distribution. The likelihood function is the binomial probability formula: $Pr(x \text{ successes in } N \text{ trials }) = N!/((N-x)!\, x!) * \theta^{x} * (1-\theta)^{(N-x)}$ (where x is the number of successes, N is the number of trials, θ is the true but unknown probability of success).

3. Estimates of odds ratios from logistic regression

I identified correlates of DMARD use through Bayesian logistic regression analysis and I reported odds ratios (ORs) along with their corresponding 95% credible intervals. In logistic regression, the likelihood contribution from the ith subject is:

$\text{Likelihood}_i = \pi(x_i)^{yi}\,(1-\pi\,(x_i))^{(1-yi)}$; where $\pi\,(x_i)$ represents the probability of the event for subject i who has covariate vector x_i and is equal to:

$e^{\beta 0+\beta 1X1+\ldots+\beta pXp}/(1+ e^{\beta 0+\beta 1X1+\ldots+\beta pXp})$, and yi indicates the presence, $y_i= 1$, or absence $y_i= 0$ of the event for that subject. Since individual subjects are assumed independent from each other, the likelihood function over a data set of N subjects is then the product of Likelihood_i,

$$\prod_{i=1}^{n} \text{Likelihood}_i$$

I chose non-informative priors for the parameters of interest for the logistic regression i.e. intercept and the slopes for the covariates. These distributions are in the form of: $\beta \sim N(\mu, \sigma^2)$. For a non-informative prior, I chose zero for μ and 10 for σ.

The posterior distributions for each parameter were determined using Gibbs sampling with the WinBUGS freeware.

Results

A. Profile of participants

The ascertainment approach in this study (i.e. being positive on both self-reported RA diagnosis and RAMQ billing codes) identified 142 RA patients. Their ages ranged from 40 to 70 years old (mean 57.28 ± standard deviation 7.18). More than two thirds of the sample were females (69.7%) as is expected for RA, and the overwhelming majority lived in Montreal or Quebec City. Regarding current work status, 41.5% reported currently working at the time of the survey, 35.9% reported being retired, and 12.7% were unable to work.

Only 10% of the sample perceived their general health as poor, and more than 85% felt that they were socially supported i.e. they had someone to share their worries with and trust their advice. The full profile of the participants is presented in table 5.1.

B. Quality Indicators

QIs are presented in Table 5.2. Specifically, 59.7% (95% CrI: 51.5, 67.7) of the 142 patients were taking DMARD therapy and 79.9% of the patients reported having a routine medical check-up in the past year.

Among methotrexate users, 78.3% were using folate and among prednisone users, 66.7% were taking calcium or vitamin D. Based on RAMQ data, in the year after the interview visit, 79.2% (95% CrI: 72.2, 85.5) saw a rheumatologist and 90% saw a general practitioner, with 10.6% seeing an internist.

Regarding the QIs focusing on lifestyle factors (i.e. physical activity and smoking status), 55% of our subjects reported performing moderate physical activity. Most (83.4 %) reported no current smoking. Less than half (44.4%) of the 142 patients reported that they were past smokers.

C. Variations in DMARD use

The OR for age, sex, income, and education are presented in Table 5.3. All our estimates are associated with wide credible intervals, which precludes strong conclusions.

Discussion

In this study, six QIs combining both pharmacologic and non-pharmacologic management of RA were assessed using CARTaGENE self-reported survey. Performance across most QIs was relatively modest, with the exception of yearly medical exams, which was found in 80% of patients by self-report (with 90% seeing a general practitioner in the following year). Only two-thirds of patients were on DMARDs, and we did not find any definite independent

associations with the considered variables i.e. age, education, income and sex. Perhaps on the bright side, the vast majority of patients were non-smokers and over half engaged in moderate physical exercise.

In one study using only Ontario administrative data to identify RA cases, the rate of DMARD prescription was 58% among a cohort of RA patients aged 65 years or older for the period 1997-2001 (14), which was similar to the percentage of DMARD self-reported use (59.7%) in our study, although the Ontario study did not use an external source to confirm the RA diagnosis of patients, and the study was limited to seniors. Using administrative billing data in British Columbia between 1996 and 2000, DMARD therapy among prevalent RA patients (not limited to seniors) was lower (43%) than that found in our study (13); this study also used administrative data to identify RA patients, with no external validation. Very frequent DMARD use (96%) was seen at two teaching hospitals affiliated with the McGill University Health Center, based on review of clinic records between 2004 and 2008 (15); since the study focussed on an academic centre, generalizability may be limited. Clearly, divergent study results may be explained by differences in the data, case definitions used to select RA patients, and the degree of misclassification of disease status. Moreover, using different time intervals obviously could lead to different results in reporting the prevalence of DMARD use, as demonstrated by Angew-Blais et al (8). That may explain the higher prevalence of DMARD use in other RA studies, which simply assessed ever use of DMARDs during a four-year period (19).

In the study conducted at McGill University Health Center, the use of folate with methotrexate (83%) was similar to our study, and the use of calcium and vitamin D was higher (81%) than in our study (15). Some differences in the methodology of studies of RA care quality exist and may explain some of the discrepancies in their results regarding the QIs of DMARD,

folic acid, calcium and vitamin D use. One difference noted among these studies is the way the RA cohort was constructed. In some studies RA patients were selected from a hospital setting that may have followed a pre-specified protocol for medication prescribing, while others including ours were population-based, and therefore more heterogenous with respect to prescribing patterns of DMARD, folic acid, calcium and vitamin D that may have varied according to the prescriber's preferences. Indeed, a study by Carli et al. has shown that a hospital setting can influence DMARD prescribing trends in early RA (20). Folic acid, calcium and vitamin D use may also be difficult to identify if using pharmacy claims (since patients might buy these over the counter) as well as by self-report (since patients may consider these agents as 'dietary supplements' and not as medications.

Over half of our sample reported doing moderate physical activity, and a very high proportion of our sample were non-smokers. This is an indication that patients in our sample are health conscious who are aware of the benefits of adopting good lifestyle habits. This may also be the reason for the high proportion of patients who sought regular medical check-up. Still, patients who saw their physician for a medical check-up may not have had their RA assessed, especially if it was a visit to a non-rheumatologist. Studies have shown that differences in the way a QI is measured may affect the score on a certain indicator for RA management (8). A study by Kahn et al. found inconsistency regarding scoring to some RA QIs when data was collected from medical records compared to when data was collected from patient self-report (19). To overcome this challenge, I used an additional source of information to measure physician visits using administrative data.

Of course, our RA diagnosis required confirmation by a physician, so by definition our RA population had to have had access to physician; from our perspective this is logical as one can hardly measure RA care quality in patients who do not have contact with physicians.

A large proportion of patients saw a general practitioner on an annual basis, which potentially suggests that the primary health care physicians could have a role in monitoring RA. The level of training and experience in managing RA differs among primary care physicians (3), and hence the collaboration between both rheumatologists and primary care physicians is essential; the care of a RA patient should be shared between family doctors and other health professionals more familiar with RA, such as internists and rheumatologists. Nurses, physical therapists, occupational therapists, social workers, psychologists, and other allied care professionals all have potential roles in RA care, (3) although we were unable to evaluate these in our study.

Of note, patient-reported general health status is used in some studies to assess the quality of services received by patients. In our study, the reported health status was generally good (21).

To our knowledge, this is the first study to use both self-report and administrative health data to assess quality indicators for RA patients in a population-based Quebec sample. This population-based sample included diverse backgrounds, socioeconomic status, and geographic locations. Moreover, RA cases were ascertained using a combination of ascertainment methods from self-reported and administrative databases which insured excellent accuracy of RA status. We enhanced the data obtained from CATRaGENE survey by complementing it with data from administrative billing records.

Our study has some potential limitations. First, we did not assess all QIs established by the Arthritis Foundation Quality Indicator Project. Second, CARTaGENE was designed to

investigate determinants of multiple chronic disorders and not specifically to assess the quality of care received by RA patients. Moreover, the QI on DMARD use requires patient information on contraindication or refusal to enhance its accuracy (22). This type of data does not exist in the self-reported CARTaGENE nor in the administrative billing data. The cross-sectional nature of our study lacked the ability to measure the QIs in a longitudinal way. For example, the QI which necessitates monitoring drug toxicity as well as the QI requiring medication adjustment if RA worsens cannot be assessed without a more complex longitudinal design. We did not use RAMQ pharmacy data to assess ever use of DMARD therapy, because a very small group of the 142 subjects was covered by provincial drug plans during the study period. Though the CARTaGENE cohort was meant to represent the general population, there may have been selection bias (as suggested by the relatively healthy life habits of many subjects).

Conclusions

Our study illustrates that patterns of RA care are modestly consistent with current treatment guidelines, although some of our QIs estimates may have been underestimated because of the cross-sectional nature of our study design.

List of Tables

Table 5.1 Demographic, social and health characteristics of the RA sample (n=142) among CARTaGENE participants

Variables	**Total (N=142)**
Age in years, mean ± SD	57.28 ± 7.18
Sex (N)%	
Male	(99) 30.3
Female	(43) 69.7
Region (N)%	
Montreal	(108) 76.1
Quebec	(19) 13.4
Saguenay	(7) 4.9
Sherbrooke	(8) 5.6
Average total annual income (N)%	
Lowest (Less than 10,000 – 24,999)	(30) 21.1
Lowest-middle (25,000 – 49,000)	(34) 23.9
Middle (50,000 – 74,000)	(33) 23.2
Upper-middle (75,000 – 149,000)	(30) 21.2
Highest (150,000 – more than 200,000)	(7) 4.9
Education (N)%	
High school and less	(53) 37.3
College	(47) 33.1
University	(40) 28.1
Marital status (N)%	
Single	(25) 17.6
Married	(86) 60.6
Widowed	(7) 4.9
Divorced	(23) 16.2
Working status (N)%	
Currently working	(59) 41.5
Retired	(51) 35.9
Unable to work	(18) 12.7
Unemployed	(6) 4.2
Care giving at home	(6) 4.2

General health perception (N)%	
Poor	(15) 10.6
Fair	(44) 31.0
Good	(62) 43.7
Very good	(16) 11.3
Excellent	(4) 2.8

Table 5.2 Percentages along with the Credible Interval (CrI) of QIs for the RA cohort using CARTaGENE self-reported questionnaire

QIs	**Adherence, % (95% CrI)**
DMARD use	59.7% (51.5, 67.7)
Routine medical check-up	79.9% (72.8, 86.1)
Folate use	78.3% (67.1, 78.6)
Vitamin D or calcium	66.7% (45.8, 84.7)
Performing physical activity	54.9% (46.6, 63.0)
Currently smoking	16.6% (10.9, 23.1)

Table 5.3 Results from the logistic regression of the association between DAMRD use and some correlates including age, education, income, and sex

Variables	**Odds ratios (95% CrI)**
Age	1.01 (0.96, 1.07)
Education	
High school and less	1.27 (0.46, 2.89)
College	1.17 (0.42, 2.68)
University	Ref
Income	
Lowest (Less than 10,000 – 24,999)	1.67 (0.33, 5.06)
Lowest-middle (25,000 – 49,000)	1.22 (0.26, 3.69)
Middle (50,000 – 74,000)	0.86 (0.19, 2.51)
Upper-middle (75,000 – 149,000)	3.59 (0.72, 10.96)
Highest (150,000 – more than 200,000)	Ref
Sex	
Female	1.54 (0.64, 3.11)
Male	Ref

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CHAPTER SIX

CONCLUSION AND FUTURE PROJECTIONS

RA is a potentially debilitating inflammatory rheumatic condition affecting about 1% of Canadians, and is thus an important chronic disease for the clinical and research community, as well as for policy makers. The methodologies used in this thesis research to estimate RA prevalence can be applied to other chronic diseases of similar disease development and unpredictable periods of relapse and remissions.

In study # 1 and # 2, we have highlighted the importance of combining more than one source of population-based data to improve the classification of RA patients for further etiological research as well as analytical studies on outcomes and evaluation of quality of care. Moreover, the second study showed that the span of years in health administrative data affects prevalence estimates of RA.

In study # 3, data from our population-based RA cohort indicate that patterns of RA care are modestly consistent with current treatment guidelines. More data need to be collected to confirm the results from our cross-sectional design. Particularly, longitudinal data is needed to study the QIs that require follow-up and to improve the operationalizing of the QIs used in our study. For example, the QI pertaining to DMARD therapy requires documentation of contraindications to the use of these drugs as well as worsening of symptoms in order to modify the DMARD treatment (1). These additional data can explain the scoring on DMARD QI. Furthermore, CARTaGENE plans future cycles of questionnaires which might be improved by adding variables to assess both physician and patient-level data for a better refinement of the QI measures. For instance, the QI relating to exercise requires more details from the patient and/or

physician including contraindications to exercise, whether the patient is physically and mentally able to exercise, and if the muscle strengthening or aerobic exercise program is directed or supervised and reviewed at least once per year (1).

Linkage to more comprehensive pharmacy data (i.e. prescriptions dispensed for individuals covered by private insurance) is also important in order to assess use of DMARDs and other medications in this population.

Another line of future research could use qualitative efforts (for example, focus groups) to determine barriers and facilitators of optimal health care delivery in RA, from the perspective of patients, health care providers, and other decision-makers. Bringing the patient perspective in is always essential to understanding how processes of care may fail or succeed. It would be very important to understand if unmet educational needs for patients are part of the problem, in terms of the importance of compliance to RA medications, and how to access the correct level of care at the right time to receive the appropriate treatment (2).

In summary, existing information from population-based cohorts and health administrative databases offer great opportunities to accurately estimate parameters like disease prevalence and QIs measures, not only for RA but potentially for other chronic diseases as well. Data from these sources are likely to remain of great interest to researchers, patient groups, health care providers, and other decision makers interested in enhancing clinical and public health strategies that will optimize the health of Canadians.

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