TEMPORAL AND GEOGRAPHICAL VARIATION IN THE ATLANTIC USE OF INTRAVENOUS IMMUNOGLOBULIN: AN ECOLOGICAL STUDY FROM 2006-2007 TO 2013-2014.

by

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ABSTRACT

BACKGROUND: The use of intravenous immunoglobulin (IVIG) has been increasing worldwide and in Canada. The high use of IVIG can partially be explained by the publically funded health care system in Canada, higher sensitivity for diagnosing immunodeficiency disease, absence of supply demand issues of blood products, and the use of IVIG for unlabeled indications. There are other causes for high use, and non-random variations point towards the presence of modifiable underlying explanations influencing utilization. Although variation studies have been used to explore the utilization practices in other health disciplines, this type of research has never been done to study variations in the use of IVIG. This study measures the extent of geographical and temporal variations in the provincial age- and sex-adjusted rates of use of IVIG/1,000 (provincial rate) in the Atlantic provinces from 2006-2007 to 2013-2014, stratified by indications.

METHODS: Geographical and temporal variations are examined on the indirectly standardized rates using descriptive analyses, followed by statistical testing.

RESULTS: There are significant effects of each province and each fiscal year on the provincial rates (repeated measures analysis of variance, all $p<0.0001$). There are statistically significant increases in provincial rate, rates stratified by indications over time in each Atlantic province (Poisson regression, all $p<0.0001$). NL has the largest number of users of IVIG/1,000 and the largest mean annual usage of IVIG per patient. NL has the largest per capita number of hematologists (21/1,000,000) when compared with the other three Atlantic provinces. The rate of use in autoimmunity is the primary driver of provincial rates (ecologic graphic analysis).

CONCLUSION: There is significant temporal and geographical variation in provincial rates of IVIG use in the Atlantic provinces during 2006-2007 to 2013-2014. The emphasis of future research should be at reducing variations in the use of IVIG across Atlantic provinces by minimizing variations in physician related factors.

LIST OF ABBREVIATIONS USED

Canadian Blood Services (CBS)

Coefficients of variation (CV)

Department of Health and Wellness (DHW)

Intravenous immunoglobulin (IVIG)

Health Card Number (HCN)

National Advisory Committee (NAC)

New Brunswick (NB)

Newfoundland and Labrador (NL)

Nova Scotia (NS)

Nova Scotia Provincial Blood Coordinating Program (NSPBCP)

Primary Immune Deficiency (PID)

Prince Edward Island (PEI)

Provincial age- and sex-adjusted rates of use of IVIG/1,000 (provincial rate)

Provincial age- and sex-adjusted rate of use of IVIG/1,000 in autoimmunity indications (rate of use in autoimmunity)

Provincial age- and sex-adjusted rate of use of IVIG/1,000 in immunodeficiency indications (rate of use in immunodeficiency)

Subcutaneous immunoglobulin (SCIG)

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CHAPTER 1: INTRODUCTION

The human body has an innate capacity to defend itself from an attack by foreign antigens carried in bacteria, viruses, toxins, and cancer cells. Immunoglobulins, also called immune globulin or antibodies, are an important component of the natural immune system of the human body (39). Antibodies bind to the antigens and either neutralize them or recruit other cells of the body to eliminate them. Immune globulins are produced by the plasma cells in response to the presence of antigens. Plasma cells are activated B-Lymphocytes, a type of white blood cells. Each Y-shaped immunoglobulin protein is made up of two heavy, long chains and two light, short chains of amino acids. The tips of the short chains have variable sections, which define the antigens or targets to which the antibody can bind. There are five types of immune globulins (based on the long chain): IgA, IgD, IgE, IgG and IgM. The most abundant form is IgG.

Sometimes there is an intrinsic defect in the natural immune system, characterized by poor or absent function in one or more of its components; this condition is called Primary Immune Deficiency (PID) (4). Affected patients cannot fight infections, and commonly present with recurrent upper respiratory tract infections. While the infections usually get treated, a high index of suspicion is required to diagnose underlying PID. If left untreated, patients with PID continue to get repeated infections. Early diagnosis of PID and treatment with replacement therapy using intravenous immunoglobulin (IVIG) prevents further morbidity in such patients (4). Another defect in the natural immune system is called autoimmunity disorder, characterized by an inability of the natural immune system to distinguish between healthy tissues and antigens, thus initiating immune response against auto-antigens or the constituents of the body's own tissues. There are numerous autoimmunity disorders, some of which respond to immune modulation by IVIG. For these conditions, IVIG down-regulates the production of pathogenous antibodies and enhances their catabolism and destruction while maintaining the body’s ability to fight disease (31, 39).

Immunoglobulin concentrate was first used in 1952 by Colonel Bruton to

treat agammaglobulinemia, a type of immunodeficiency (25); the syndrome is called Bruton's syndrome or X-linked agammaglobulinemia. Initial products were of low purity and had to be administered intramuscularly to avoid anaphylactic reactions. The commercial products of IVIG contain a highly purified plasma protein extract of IgG (18) that is obtained from the pooled plasma (8) of 3,000 to 10,000 healthy blood donors (19, 25). Pooling of plasma ensures the presence of a wide range of antigen-binding sites (25) and enhances the ability of transfused IVIG to fight against a wide variety of antigens, just like normal human serum.

Based on the route of administration, there are actually two types of products, intravenous and subcutaneous immunoglobulin (SCIG). Both products are safe and effective in raising the serum immunoglobulin levels to physiologic concentrations (16). The main difference is that health care providers usually administer IVIG in a health care facility on inpatient or medical day units, whereas SCIG can be self-administered in the convenience of the home, after initial training by health care providers (21), making SCIG a less labor-intensive option. Although the initial transfusion by Colonel Bruton was intramuscular, this route of infusion did not gain popularity initially because it was considered slow and time consuming. The use of SCIG became popular in the 1990s, particularly in Scandinavian countries. A few years ago SCIG was available in Canada for urgent medical use only (47). Since 2009, it has been licensed in Canada as a regular blood product to be distributed by Canadian Blood Services (CBS) for immunodeficiency indications (47). This has resulted in a shift in the use of immunoglobulin from IVIG to SCIG among eligible immunodeficiency patients (46). Given that SCIG is used interchangeably with IVIG for immunodeficiency indications, in the following sections the term "IVIG" will be used to refer to both IVIG and SCIG.

IVIG is dispensed by CBS, to all the provinces and Territories in Canada except Quebec, where Hema-Quebec assumes this responsibility. CBS is an organization funded by the provincial and territorial ministries of heath. CBS is responsible for price negotiations, procuring and providing safe blood products

to the Canadians. Just like all other blood products, the total cost of IVIG for a province is paid to the CBS from the provincial blood budget. There is no direct cost of prescribing IVIG - to the physicians, to the health care facilities, or to the patients receiving it. Therefore, it may be perceived as a free product when compared with other competing treatment options. All physicians of Canada are licensed to prescribe all blood products, including IVIG. There are no barriers for prescribing IVIG.

CHAPTER 2: BACKGROUND

IVIG is an effective treatment if used appropriately. The appropriateness of the use of IVIG is measured in terms of the indication for which it is used and the dose used. In Canada IVIG is licensed for use in six indications: primary and secondary immunodeficiencies; allogeneic bone marrow transplantation; chronic lymphocytic leukemia; primary immune thrombocytopenia; and pediatric human immunodeficiency virus infection (10). However, it is also used for indications that are unlabeled but considered appropriate due to evolving scientific evidence. Conversely, the indication is considered inappropriate if IVIG is used for a diagnosis for which there is no evidence of benefit of use (46). The dose is considered appropriate when it is in compliance with recommendations in the literature. The recommendations of dose differ between indications (1, 18 and 44). The replacement dose of IVIG used in immunodeficiency indications is typically lower than the doses used for immune modulation (31). The recommended dose of IVIG for immunodeficiency is 0.4 to 0.6 g/kg patient weight every 3 to 4 weeks (44). The recommended dose of IVIG for immune modulation is 1 to 2g/kg every four weeks (1, 18). The recommended frequency of transfusion is every three to four weeks. The frequency is based on the half-life of IVIG when it is transfused in an immunocompetent person (39). The patient's weight has a fundamental role in the utilization of the IVIG because the dose is calculated in grams per kilogram patient weight. Being a blood product, it does carry transfusion-related risks, such as headache, chills, nausea, fatigue, muscle pain, joint pain, and back pain (39). However, it is considered a relatively safe preparation with minimal long-term serious adverse reactions, including infections (39).

The burden of illness of autoimmunity disorders and PID is high worldwide. Women are more prone to autoimmunity disorders; the estimated incidence rate of autoimmunity disorders in United States during 1996 was 1.3 per 1,000 females and 0.5 per 1,000 males (28). The prevalence of immunodeficiency indications was estimated and reported as six million people worldwide in 2013 (5); 1 in 1,200 people in the United States during 2007 (4),

and approximately 5,500 patients in Canada for 2012, based on the actual number of treated immunodeficiency patients in British Columbia during 2008-2009 (22).

The use of IVIG is increasing worldwide (16). The use of IVIG in Canada increased several fold from 47 grams per 1,000 population in 1998 to 123 grams per 1,000 in 2009 (44). It further increased to 157 grams per 1,000 population in 2012/2013 (48).

The high cost of IVIG, along with the increasing volumes of use, results in an escalating cost for the health care system. The mean cost of IVIG is $50 to $80 per gram (31). In Canada, a single dose of 1 gram/kg for a 75-kg person costs approximately $5000 (44). The total IVIG budget of Canada was $244.2 million for the fiscal year 2008-2009 (44). Although somewhat out dated, these numbers provide a sense of the financial burden of IVIG on the Canadian blood budget. While we are unaware of recent reports of the Canadian IVIG budget, it can be estimated for 2013-2014 from the provincial utilization report (48) as approximately $300 million dollars for Canada overall, and approximately $18 million for the Atlantic provinces.

The need to optimize use of IVIG has been recognized by the Canadian provinces (14, 39). This led to the development of Canadian guidelines for the use of IVIG in common hematology (1) and neurology indications by an expert panel of the Canadian National Advisory Committee (NAC) on Blood and Blood Products in 2007 (18). These publications were followed by guidelines for the use of IVIG in PID and solid organ transplant by the Canadian NAC in 2010 (44). Some Canadian provinces have implemented an IVIG request approval process in order to enhance compliance with the guidelines, and to avoid or reduce inappropriate utilization of the product (42). Other provinces have begun to use ideal or adjusted body weight of the patient instead of the actual weight for the IVIG dose calculations (10). Despite these interventions, Canada was the highest per capita user of IVIG in 2010 and the second highest user in 2012 among the most economically stable and developed countries of the world (44).

Although increasing use may partially be explained by rising rates of

disease (6) requiring the product for treatment, the easy procurement process for blood products, and the misperception of IVIG being a free product (44) when compared with treatment alternatives, suggest that increasing use may also be attributable to these causes. There is a need to explore other factors contributing to the rise in the use of IVIG. An aspect that needs to be explored is the 'variation' in the use of IVIG in Canada.

Variation analyses have been used in the past to describe the variation in the utilization of health related processes, procedures, medications and other resources in different geographical areas (49) and to identify the reasons or the potential factors associated with these variations (49). Geographical variations are the large differences in the rates of utilization between small geographical areas (11). Geographical variation studies have an underlying assumption that geographical areas with similar conditions should not exhibit variation beyond chance. If evidence-based clinical practice and universally fair distribution of health care facilities and resources are implemented, then all health care processes, procedures, and clinical practice should be similar and the variation random.

An early geographic variation study was conducted in1938 when the population-based rates of tonsillectomy were calculated, the age and sex distribution of this procedure described, variations in the rates based on geography noted and their association with poverty, housing, climate, social class, schooling, availability of health care facilities studied (23). That study identified not only a lack of association of poor quality of health with the underutilization of tonsillectomy, (23) but actually pointed out the parallelism between high rates of procedure and high mortality rates (23). A latest systematic review of 836 studies in 2014 reveals large geographical and physician practice variations across the Organization of Economic Co-operation and Development (OECD) countries in most of the medical and surgical conditions studied (12). A population-based study to examine the temporal trends of the incidence of Primary immune deficiencies has been conducted in Minnesota from 1996 to 2006 (30).

Research in health services has been used in a wide variety of health related fields in the past in order to find areas where the rate of use of medications, surgical procedures, or health care products and services could be altered to improve quality of care and patient outcomes. In the past, evidence has shown significant geographical variations in the hospitalization rates for many medical conditions like pneumonia and COPD (49). A study in United Kingdom (UK) found regional variation in the admission rates of alcohol-related diseases among similar ethnic groups (34). Past research has shown significant geographical variations for rates of many surgical procedures like tonsillectomy, hemorrhoidectomy, hysterectomy, and prostatectomy (43, 61). Although the breast cancer guidelines in England recommend immediate reconstruction surgeries after mastectomy, significant regional variation in the utilization rates of breast reconstruction surgeries, unexplained by patient characteristics, was found in a study of women who had mastectomy during 2006-2009 in the national health system of England (29).

Geographical variation has been exhibited in the use of blood products and medication use. During 2008, an observational study was conducted on 102,470 patients in the United States of America (USA) that revealed statistically significant variations in the rates of blood transfusions by geography among 798 hospitals during coronary artery bypass graft surgeries (3). Another study in Europe compared the non-hospital antibiotic sales in 1997 for 15 member countries to reveal 4-fold variation in their use among the member countries (9). Variation was also found in use between different classes of antibiotics in the same study (9). Presence of variation was also observed in the prescribing pattern of antipsychotic medications among nursing homes in Ontario (7). Geographic variation was also studied in the use of psychotropic medication to control behavioral issues of children in the U.S. child welfare system; there were 40-fold variations in the rates of use between geographies (36).

Historically, associations of these variations have been studied in search of potential causal factors influencing utilization. Older age, male sex, insurance and emotional and behavioral problems were found to be significantly

associated with the use of the psychotropic medications (36). In a study conducted in the UK during 1995-2006, socioeconomic status was significantly related with the lower odds of both prostate surgery as well as treatment with radiotherapy (38). In another study conducted on the Medicare data of Michigan, race, gender, and socioeconomic status were found to be statistically significantly associated with the rates of use of diagnostic procedures during 1986 to 1989 (41). By contrast, minimum regional variation was found in the utilization rates of imaging in a study on USA health referral regions from 2007 to 2011 (51). All these studies have not only helped to understand the presence of disparities in the utilization of procedures between geographic regions, communities, population groups, health systems and health care provider practices, but they have also helped to explain the relationship of variations with patient characteristics (36, 41), race and socio demographic factors (33).

Although desirable, the estimation of optimal rates of use might be a challenge. It may only be theoretically possible to obtain optimal rates by strict compliance with the evidence-based practice, fair distribution of health care resources and adherence with ethical practice patterns. Optimal use is difficult to achieve in real life due to factors like lack of availability of scientific evidence for clinical practice, especially in light of rare diseases, physician's personal preferences in clinical practice, and patient-related factors (11). The presence of these difficulties must be acknowledged, but they do not justify non-random geographical variations. Hence, research to help understand such variation remains important.

This type of research leads the direction of reform (24). Significant variations point towards modifiable causes that require exploration. Some causes may be beyond control, but the identification of controllable causal factors and their modification without compromising the quality of care is the ultimate goal of geographic variation studies (23). In the presence of significant variations, this can be done by: 1) local area root cause analysis to list the potential causes, 2) research to find which of the listed causes are related with the variation, 3) comparison of the details of the data with the neighboring

areas, and 4) formulating and implementing strategies to influence and impact the areas of huge differences in practice and health care access without compromising the personal style of clinical practice or care provided.

There are two potential contributors to variation for the use of any medication, procedure or product, which may be relevant to IVIG in particular: 1) variation in the number of users of IVIG and 2) variation in the mean usage of IVIG per patient.

The variation in the number of users of IVIG and the mean usage of IVIG per patient may stem from variations in any of the following three factors (refer to Figure 2.1) 1) variation in patient related factors, 2) variation in physician related factors (17) (variation in their practice styles and geographical mal distribution of clinical experts to diagnose and treat immunodeficiency and autoimmunity diseases) and 3) variation in the provision of health services (like access to care and funding systems) (27, 50).

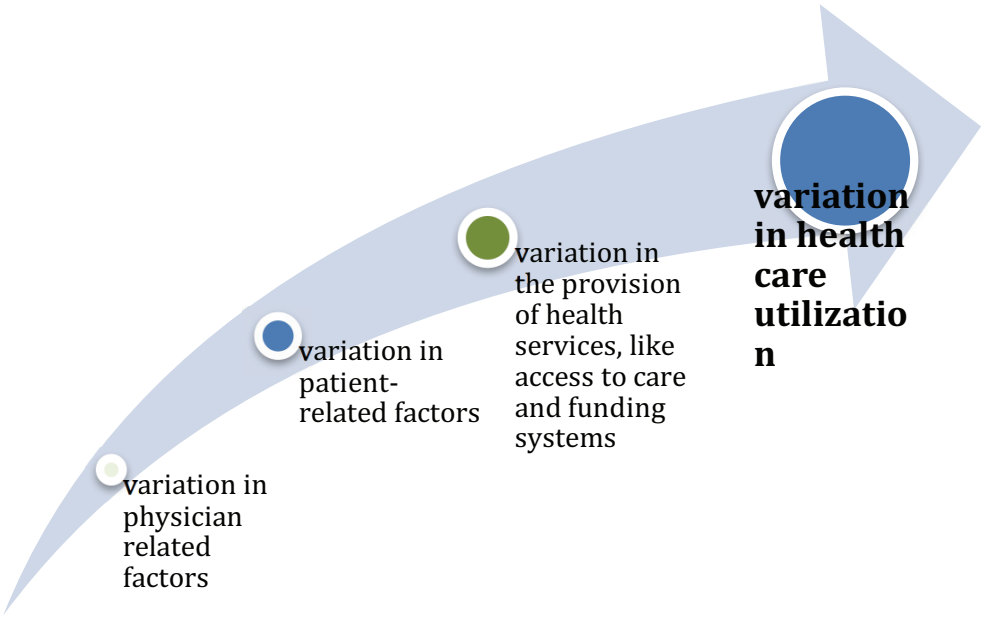

Figure 2.1 Factors known to be associated with variation in health care utilization.

Variation in age and sex distribution of the users of IVIG between Atlantic provinces may be a contributor to the variation of provincial rates. As the dose

of IVIG is patient weight dependent, the rising prevalence of obesity (20) in Canada (2, 55) may affect the overall utilization of provincial IVIG. Another factor contributing to variation could be varying individual requirements of IVIG, depending on the severity of the disease and the metabolic state of the patient. While there is a recommended range of the dose of IVIG for immune modulation, within this appropriate range, some patients have a higher IVIG requirement than others to control a similar degree of illness (32).

Variation in the prescribing practices among physicians could also contribute to variation of use. The physician's practice style, in turn, is influenced by a variety of other factors, including lack of availability of scientific evidence for standard practice, ease of obtaining the product or resource under study, income-seeking behavior, age of the physician, level of training and number of years of training, preference for certain style of practice or surgery, and the role of a physician as a patient's clinical advocate (17). The demand and the convenience of the patient may also influence a physician's practice (17). According to the results of a survey of US allergists and immunologists by the Primary Immunodeficiency Committee of the American Academy of Allergy Asthma and Immunology in 2009, the sensitivity of diagnosing and treating immunodeficiency indications varies by clinical expertise (63). Out of the 405 respondents, 18% were sub-specialty immunologists who devoted 10% of their clinical practice to care for PID, and 82% were general immunologists. The sub-specialty immunologists prescribed IVIG more frequently, used higher starting doses of IVIG, targeted higher trough levels of serum IgG, and used more premedication to prevent and treat adverse events of IVIG. This leads to an assumption that non-uniform distribution of clinical experts in any country could contribute to differential provincial use of IVIG. Inappropriate use could be another contributor to variation in use. Although IVIG is licensed for only six indications in Canada (26), it has been widely used for unlabeled or inappropriate indications in the past (19). Approximately 53% of total adult use of IVIG and 38% of total pediatric use of IVIG was off-label in Canada in 2003 (26). Physician related factors are also influenced by the category of care provided to the patients (58). These

include 1) Effective treatment: there are established benefits of the treatment in this category; therefore, variation in physician practice style is minimum. This is comparable to the use of IVIG in labeled indications; 2) Preference sensitive care: there is more than one option of treatment; therefore, there is highest variation in physician practice style in this category of care. This is comparable to the use of IVIG in unlabeled but appropriate indications for which there is evolving evidence based on the case reports. Variation in practice style can be minimized in this category by decreasing scientific uncertainty; 3) Supply sensitive care: the utilization rates are high because of greater availability of resources like hospital beds, physicians, and intensive care units (58).

Although the Canada Health Act ensures a publically administered, comprehensive, universal, portable, equitable and accessible health care system, there are documented examples where Canada has observed geographical variations in surgical procedures within its provinces (50). A study was done in the rural hospital areas of Manitoba, which revealed variation in surgical rates. Some jurisdictions in Manitoba exhibited one and half times as many surgeries as other areas (50).

Rate variation research has never been conducted for the utilization of IVIG; this study is a novel use of this type of research. It is known that statistically significant variations may be a result of modifiable underlying factors that influence the utilization practice in one direction or the other (9). However, no action can be taken to eliminate variation when it is not scientifically established. This project is designed to provide scientific evidence on the extent of geographical and temporal variation in the population-based rate of IVIG utilization among Atlantic Canadian provinces. This research also seeks to determine if variation in the utilization of IVIG in the Atlantic provinces during 2006-2007 to 2013-2014 is because of any of the following variables 1) number of users of IVIG/1,000, 2) mean annual usage of IVIG per patient or 3) distribution of hematologists and neurologists per million.

CHAPTER 3: OBJECTIVES

This thesis is undertaken in order to assess the geographical and temporal variations in the use of IVIG across Atlantic provinces. As indicated previously, the thesis is based on the utilization data of IVIG from 2006-2007 to 2013-2014, retrieved from NSPBCP.

The objective of this thesis is:

- to determine the extent of geographical and temporal variation in the rate of use of IVIG across Atlantic provinces of Canada from 2006/2007 to 2013/2014, stratified by indications (autoimmunity and immunodeficiency) and adjusting for age and sex.

This objective is achieved by answering the following question:

- Are there significant geographical and temporal variations in the rate of use of IVIG across Atlantic provinces of Canada from 2006/2007 to 2013/2014, stratified by indications (autoimmunity and immunodeficiency) and adjusted for age and sex?

CHAPTER 4: DATA SOURCES:

A secondary analysis of IVIG and SCIG utilization data from 2006/2007 to 2013/2014 is conducted using the data obtained from the Nova Scotia Department of Health and Wellness (DHW). In 2003, an Atlantic collaborative regional strategy created a registry of the use of IVIG in the Atlantic provinces of Canada (16). The Provincial Blood Coordinating Program of Nova Scotia was chosen as its secretariat. This provincial program, which was established for the utilization monitoring of blood and blood products, started collecting the dose-by-dose utilization data of IVIG from the four Atlantic provinces in 2006. In addition to the utilization data, the program also obtains and stores the distribution data of IVIG from the CBS on a regular basis. IVIG data can be divided into two categories, 1) the distribution data and 2) the utilization data. CBS distributes IVIG and SCIG to all the provinces and Territories of Canada except Quebec; Hema-Quebec distributes it to the health care facilities in Quebec (44). The distribution data is the total amount of IVIG for which payments are made from the provincial and territorial blood budget to the CBS. Utilization data are the data on dispensed IVIG that are routinely submitted from the blood transfusion laboratories of all four Atlantic provinces to the central registry at the Nova Scotia Provincial Blood Coordinating Program (NSPBCP). These data are transcribed and electronically transferred to the NSPBCP by the data submitters of the blood transfusion laboratories (obtained from the IVIG order forms). The IVIG order forms are Atlantic wide standardized physician requisition forms used for the procurement of IVIG for patients. A subset of this dataset is used for this study. The population data are obtained from Statistics Canada (53). The data on the provincial number of hematologists and the number of neurologists is obtained from the websites of the respective provincial colleges of physicians and surgeons (13, 14, 15, 54).

The IVIG utilization data elements are related with a unique identifier for each patient in each province. These data elements include names of the province and health care facility, the health card number (HCN) of the patient,

date of birth, sex, weight, height, and indication for use, date of dispensing, license number of the prescribing physician, total daily-dispensed amount of IVIG, and serum IgG levels for immunodeficiency patients. The program assigns the appropriateness of indications using national advisory committee guidelines, literature search and clinical expert opinions. The NSPBCP takes the responsibility of quarterly data review for quality checks and validation in terms of completeness, accuracy and reliability. The data are used for the generation of an annual Atlantic IVIG utilization report which is vetted through the Atlantic Blood Utilization Strategy (ABUS) before being made public on the website of NSPBCP. These data have not previously been used for any scientific research.

Because utilization data are stored using patient identifiers, permission to access the data has been obtained from the DHW of Nova Scotia (NS), Provincial Blood Programs (or their equivalents) of Prince Edward Island (PEI), New Brunswick (NB) and Newfoundland and Labrador (NL). Ethical approval of the study has also been obtained from the Dalhousie University Research Ethics Board. The HCNs are anonymized by the NSPBCP before providing access to the data for research.

CHAPTER 5: METHODOLOGY

To answer the study question, all amounts of IVIG distributed and utilized in the Atlantic provinces of Canada during 2006-2007 to 2013-2014 are examined. The database includes administrative information on the patients and the health care facilities in addition to the use of IVIG. The population data obtained from Stats Canada are used for the calculation of rates and are presented per 1,000 population for these analyses:

- The unadjusted rate of use of IVIG/1,000 population for each province for each fiscal year
- The provincial rate of use of IVIG/1000 for each province for each fiscal year
- The rate of use in autoimmunity and rate of use in immunodeficiency for each province for each fiscal year
- The number of users of IVIG/1,000 for each province for each fiscal year.
- The number of hematologists and the number of neurologists/1,000,000 for each province.

After the calculations of the unadjusted provincial rates of IVIG use/1,000 for each province for each fiscal year, the utilization data are divided into two separate indication groups for the calculations of the indication-specific provincial rates of use of IVIG/1,000. The provincial rates of use of IVIG/1,000 and the indication-specific rates of use of IVIG/1,000 are then age- and sex-standardized to reduce the effect of provincial differences in sex and age distributions, using the indirect method of standardization.

Descriptive analyses of the trends of the provincial rates, rate of use in autoimmunity and rate of use in immunodeficiency for each province are studied to examine variations in the use by geography and time in the Atlantic provinces during 2006-2007 to 2013-2014. Further statistical tests are conducted to support the findings of the descriptive analysis. These statistical tests include 1) Coefficient of Variation (CV) in provincial rate, rate of use in autoimmunity and rate of use in immunodeficiency for 2013-2014, 2) Kruskal

Wallis Rank Sum Tests, 3) Wilcoxon Signed Rank Test 4) total percentage change in the provincial rate, as well as rate of use in autoimmunity and rate of use in immunodeficiency over time, using Poisson regression, and 5) repeated measures analysis of variance.

Comparisons between provinces are made in the trends of the provincial number of users of IVIG/1,000. Comparisons between provinces are also made in the trends of the provincial mean annual usage of IVIG per patient for each fiscal year along with calculation of the provincial number of hematologists and neurologists (per million in each province), to analyze how variation in provincial rates may be because of these factors. The provincial number of hematologists and neurologists is used to calculate the number of hematologists and neurologists per million population.

Ecological graphic analysis is conducted to show which indication appears to be the primary driver of the provincial rate.

5.1 Study Population

The unit of analysis in the ecological study is the population rather than the individuals. Therefore, the provinces are the units of analysis. The provincial rate of each Atlantic province is the outcome of the analysis in this study. The study population includes the four Atlantic provinces of Canada, namely, NB, NS, PEI and NL.

The distribution data reflect the actual amounts of IVIG consumed by a province. This is important information for resource allocation and planning purposes. By contrast, the utilization data reflect the amount of IVIG that is dispensed from the transfusion laboratories of each province and reported as utilized. In this study, 96% of the distributed IVIG is accounted for in the utilization data. The utilization data are inspected and reviewed for incomplete entries. Records for nine out of 6,548 patients are eliminated due to missing values of age. This is equivalent to 2,706 grams being excluded from analysis, out of the total of 2,262,908 grams of utilized IVIG. The following analyses are conducted on the remaining 6,539 records, for 2,260,202 grams of IVIG.

5.2 Variables of Interest

As this is an ecological study, all the variables are population-based. The outcome of interest (dependent variable) is provincial rate. The independent variables of interest for the repeated measures analysis of variance are province and time. The independent variable of interest for the Poisson regression is time. The individual level variables that are used to generate population based numbers include age and sex. These are used for the computation of standardized provincial rates and standardized indication specific rates. The age- and sex-standardized provincial rates, rate of use in autoimmunity, and rate of use in immunodeficiency are used for the repeated measures analysis, Poisson regression, CV, rank sum tests and ecologic graphic analysis.

Other variables of interest (potentially related to the provincial rates) include the provincial number of users of IVIG; mean annual usage of IVIG per patient and the number of hematologists and neurologists per million provincial population. They are calculated as follows: 1) total provincial number of users in each province and each fiscal year as a numerator and corresponding provincial population as the denominator in the formula for the number of users of IVIG/1,000; 2) total amount of usage of IVIG in each province and each fiscal year as a numerator and total number of patients for the corresponding province and fiscal year as a denominator in the mean annual usage of IVIG per patient and, 3) most recent provincial total number of hematologists and total number of neurologists from the websites of the corresponding colleges of physicians and surgeons as the numerator and corresponding provincial population as the denominator in the number of hematologists and neurologists/1,000,000.

5.3 Data Analysis

All descriptive analyses are performed using Excel spreadsheets. The statistical analyses are performed using STATA 13.1 statistics package.

Unadjusted provincial rates of utilization of IVIG are calculated for each province and for each fiscal year per 1,000 population. The numerators used to calculate these rates are the utilized amount of IVIG in grams for each province and for each fiscal year. The denominators are the total populations for the corresponding provinces and years.

All the rates in this data are standardized for age and sex groups using the indirect method of standardization. This is done to minimize the effects of variation in the age and sex structures of the provincial populations being compared. Because the utilization data are highly representative (96%) of the distribution data in this study and can be linked to the age and sex of individual users, utilization data are used for the calculation of the standardized rates. Indirect standardization is computed using the following steps.

The IVIG use in grams is divided for men and women separately and for twenty-one five-year age groups in each province for each fiscal year, resulting in 42 sub-groups of the annual provincial utilization data. The selection of five-year age groups is designed to minimize confounding in the standardized rates. Age-specific use of IVIG is not available for some age groups of the populations of interest; therefore, indirect standardization is used. Age- and sex-specific rates are calculated for the standard population and applied to each provincial population under study to yield the expected rates. The observed rate is divided by the expected rate to get a standardized use ratio. In order to obtain the provincial adjusted rates per 1,000 population, each standardized use ratio thus obtained is multiplied by the crude rate of the standard population.

Currently, there are no proposed 'benchmarks' for the rates of use. Therefore, the Atlantic rates of use of IVIG for the fiscal year 2006/2007 are considered as the standard rates in this study. The Atlantic population is used as the standard population because it is larger and provides more stable age- and sex-specific rates than the individual provinces. Fiscal year 2006/2007 is chosen because this was the first year of monitoring of the IVIG utilization data. Data from Statistics Canada is used to provide the age- and sex-specific populations

for each Atlantic province for 2006 and their sum is used for the calculation of standard Atlantic rates of total use and indication-specific use.

Using the data set under study, there are several steps taken to accomplish standardization, as described below, 1) Crude Atlantic rates (Cs) of IVIG use per 1,000 population are calculated for 2006-2007. The numerator is the total Atlantic IVIG use in grams and the denominator is the total population of the Atlantic region in 2006. 2) Standard age- and sex--specific rates for the Atlantic region for 2006-2007 are calculated. The numerators are the age- and sex-specific Atlantic IVIG use in grams and the denominators are the age- and sex-specific population sizes of the Atlantic region in 2006. 3) These standard rates are applied to each age- and sex-specific provincial population for each year. 4) The sum of the products of age- and sex-specific standard rates and the age- and sex-specific population groups in each province for each fiscal year is determined as the "expected amount of IVIG use." 5) The observed amount of IVIG is simply extracted from the utilization data under study for each province for each fiscal year. 6) The standardized ratio of the use of IVIG per province per fiscal year is calculated as a quotient, where the numerator is the observed amount of IVIG for each province and each fiscal year and the denominator is the expected amount for the respective province and fiscal year, as follows:

Age- and sex-standardized Ratio (O/E) =

$$\frac{\text{Observed amount of IVIG in province i for fiscal year j}}{\text{Expected amount of IVIG in province i for fiscal year j}}$$

7) Age- and sex-standardized IVIG rates for each province for each fiscal year are then calculated as a product of the crude standard Atlantic rate for 2006-2007 and the age- and sex-standardized ratio of IVIG use for each province for each fiscal year.

In equation form:

Age- and sex-standardized IVIG rate/1,000 for each province each year = Cs (O/E)

Likewise, rate of use in autoimmunity and rate of use in immunodeficiency are computed after separating the utilization data into two

categories of use by indications, namely, autoimmunity indications and immunodeficiency indications.

The adjusted rates are used for all of the following analyses. The data are further described in detail using medians and inter-quartile ranges (IQR) of the provincial rates, rates of use in autoimmunity and rate of use in immunodeficiency. Median rates provide the primary summary measures of provincial use over time.

The extent of geographical variation in the Atlantic region for 2013-2014 is determined by computing the CV of provincial rates. CV is a unit free number and is used for comparing the rates. CV is the standard deviation of the provincial rates divided by the mean provincial rate for 2013-2014 x 100.

The Kruskal Wallis Rank Sum Test is a nonparametric test used when there are no assumptions about the probability distribution of the sample. This test is conducted to test the hypothesis that at least one province's provincial rates stochastically dominate one other province's provincial rates. However, because it does not have the capacity to identify the dominant province, the Wilcoxon Signed Rank Test is conducted to compare the median provincial rate of each province with the median provincial rates of the others. The test is repeated six times to accommodate all possible two-member comparator pairs of the four provinces.

To determine if there is a significant temporal variation, total percentage change of each province's provincial rate from 2006/2007 to 2013/2014 is computed. The magnitude of this number represents the rate of change relative to the change in the size of the populations across a time period for each province. In this study, Poisson regression is used to model the provincial rate as a function of fiscal year. Poisson regression is also used to model the rate of use in autoimmunity and rate of use in immunodeficiency as a function of fiscal year. The exponents of the regression coefficients for fiscal year (β_i) from each of the Poisson models is used as an estimate of the annual change in the provincial rate. A smoothed estimate of the total percentage change in the provincial rate over the eight years of study is calculated using the following formula: (100 * [{

exp [8*β_i]} - 1]). Where i indicate the *ith* province for provincial rate. Using the same formula, smoothed estimates of the total percentage change for the rate of use in autoimmunity and rate of use in immunodeficiency over the eight years of study are also calculated.

The IVIG data of provincial rates are correlated, and that condition violates the assumption of independence required for standard analysis of variance. Application of the standard regression in correlated data may produce invalid results. In this study, this limitation of standard regression modeling is overcome by the use of repeated measures analysis of variance, which has an inherent capacity to model correlation between the repeated measures. In this study the equality of PRs are tested for four Atlantic provinces of Canada in eight different fiscal years (where fiscal year is the condition that changes in this study). As the four Atlantic provinces are exposed to each fiscal year, the measurement of the provincial rate (dependent variable) is repeated. Time (eight fiscal years) and group (four Atlantic provinces in this study) are the two factors under study.

Comparisons are made to show how the variation in provincial rates may be because of variation in the provincial number of users of IVIG/1,000 or mean annual usage of IVIG in grams per patient, or provincial population based number of hematologists and neurologists. The following computations are made for comparison between provinces, 1) the total number of IVIG users in each province for each fiscal year is divided by the population of the corresponding province and fiscal year to obtain provincial number of users of IVIG and presented per thousand population, 2) the total amount of IVIG used in each province for each fiscal year is divided by the total number of users of IVIG in the corresponding province and fiscal year to obtain the mean annual usage per patient and 3) the total number of hematologists and neurologists in each Atlantic province as obtained from the corresponding websites of the provincial colleges of physicians and surgeons on January 2016 is divided by the respective population and presented per million population.

Ecological temporal trends in the provincial rates are compared with temporal trends of rate of use in autoimmunity and rate of use in immunodeficiency for each province in the Atlantic region over the study period, to identify the primary driver of the provincial rates.

CHAPTER 6: RESULTS

6.1 Description of the IVIG data

The utilization dataset is composed of 6,539 patients, of whom 3,314 are females and 3,225 are males. The ratio of females to males is 1:0.97. Females are more prone to the disease requiring IVIG, similar to that reported in literature (28). Table 6.1 shows the distribution of used amount of IVIG in grams by age and sex. Fifty four percent (1,216,413 grams) of total Atlantic amount of IVIG is used for men and forty six percent (1,043,789 grams) is used for women. Table 6.2 shows the amount of IVIG in grams used in each Atlantic province by fiscal year. Thirty eight percent of the total Atlantic amount is used in NS, twenty nine percent in NB, twenty seven percent in NL and about six percent in PEI.

The median rates with the respective 25^{th} and 75^{th} quartiles (Q1- Q3) and IQR are exhibited in Table 6.3. NL has the highest median provincial rate, rate of use in autoimmunity and rate of use in immunodeficiency at 143.9, 115.5 and 6.9 grams/1,000 respectively. NS has the lowest median provincial rate and rate of use in autoimmunity at 103.7 and 85.2 grams/1,000 respectively and NB has the lowest median rate of use in immunodeficiency at 5.3 grams/1,000.

6.2 Geographical variations in the provincial rates

Table 6.4 shows the unadjusted provincial rates of use of IVIG/1,000 for each province. These unadjusted provincial rates are plotted against time (fiscal years) in Figure 6.1. The profile plot in Figure 6.1 reveals four distinct lines, each representing a province. The provincial lines for NB, NS and NL do not intersect at any point in any of the fiscal years, exhibiting geographical variations in the provincial rates. The extent of variation measured between the Atlantic provinces by computing CV in 2013-2014 is 15%.

Table 6.5 shows the provincial age- and sex-adjusted rates of use of IVIG/1,000 (provincial rate) for each province and each fiscal year from 2006-2007 to 2013-2014. The profile plot of the provincial rates against fiscal years 2006-2007 to 2013-2014 is presented in Figure 6.2. This figure exhibits

negligible differences from Figure 6.1, although the effect of individual provincial age and sex distribution is minimized by indirect standardization in Figure 6.2. The similarity of the pattern of standardized rates to the unadjusted rate pattern indicates that there is actually little confounding by age and sex when comparing crude rates across the Atlantic provinces.

In Figure 6.2, the dotted line representing NL remains consistently higher than the other three lines of the Atlantic provinces for all fiscal years throughout the study period (except the provincial rate of use of IVIG/1,000 for PEI in 2012-2013). The dashed line representing PEI intersects all other lines at different points and shows the greatest variability in its position among the four Atlantic provinces. The solid line of NS shows a rising trend during 2011-2012 and 2013-2014, after exhibiting an initial decline from 2006-2007 until 2010-2011. The long dashed line of NB is relatively level in fiscal years 2011-2012 and 2012-2013, after exhibiting a rising trend.

Table 6.6 and Table 6.7 show the results of nonparametric tests. The Kruskal Wallis test (Table 6.6), reveals that at least one sample stochastically dominates one other ($p=0.02$). This means that at least one of the four provinces is consistently ranked higher than one other province in its provincial rates. The median provincial rate of NL is significantly distinct from the median provincial rates of NB, NS and PEI ($p=0.01$, 0.01 and 0.012, respectively), when the six comparator groups, NL and NS, NL and NB, NL and PEI, NS and NB, NS and PEI, NB and PEI are examined by the Wilcoxon signed rank sum test for equality of the median provincial rates (Table 6.7).

6.3 Temporal variations in the provincial rates

There are significant increases in the provincial rates of use of IVIG over time in each Atlantic province, as exhibited by the upward trending provincial lines in Figure 6.2. The results of the statistical analysis using Poisson regression are shown in Table 6.8 and reveal significant increases in the provincial rates of each Atlantic province ($p<0.0001$ each) over time from 2006-2007 to 2013-

2014. Although significant, the total percentage increase for NL over time is smallest at 41% when compared with the other three provinces. The largest increase in the provincial rates over time is observed in PEI at 81%; relatively modest increases in provincial rates are observed in NB and NS, at 65% and 72%, respectively.

Table 6.9 shows the results of repeated measures analysis of variance, exhibiting statistically significant effects of province (Atlantic provinces) and time (fiscal years) on the provincial rates ($p<0.0001$ for both).

6.4 Variations in indication specific rates

The age- and sex-adjusted rates stratified by indications are presented in Table 6.10. This table reveals relatively higher rates of use in autoimmunity as compared to rates of use in immunodeficiency for all provinces.

Figure 6.3 shows the rates of use in autoimmunity against fiscal years. This figure is similar in appearance to Figure 6.2 of the provincial rates. The dotted line representing NL's rate of use in autoimmunity in Figure 6.3 remains consistently higher than the other three lines of the Atlantic provinces for all fiscal years throughout the study period (except the provincial rate of use of IVIG/1,000 for PEI in 2012-2013). The extent of geographical variations between Atlantic provinces during 2013-2014 for rate of use in autoimmunity is 24%, as measured by CV. Table 6.8 shows the total percentage increase in rate of use in autoimmunity over time using Poisson regression. There are significant increases over time for each Atlantic province ($p<0.0001$ each). The total percent increases for NB, NS, PEI and NL are 47%, 57%, 53% and 40%, respectively. Although statistically significant, the total percentage increases over time for rates of use in autoimmunity are lower in magnitude than the total percent increases for rates of use in immunodeficiency of the corresponding provinces.

The extent of geographical variations for the rates of use in immunodeficiency as measured by CV between provinces during 2013-2014 is 12%. This is half in magnitude as compared to the CV between provincial rates

of use in autoimmunity for the same year. Figure 6.4 shows the rates of use in immunodeficiency plotted against fiscal years. This figure is unique in appearance. The dotted line representing NL is almost level. The long dashed line of NB shows a steady increase. The straight line of NS exhibit a steady decline till the fiscal year ending in 2011 followed by a sharp rise in the rates of use in immunodeficiency for the fiscal years ending in 2012, 2013 and 2014. The total percentage increase in the rates of use in immunodeficiency (Table 6.8) exhibit significant increases over time for each Atlantic province ($p<0.0001$ each). Total percent increases for rate of use in immunodeficiency is smallest for NL at 40%, and 3 to 5-fold higher for NB, NS and PEI at 167%, 127% and 235% respectively.

In order to show how variations in provincial rates may be because of 1) number of users of IVIG/1,000, 2) mean annual usage of IVIG per patient and, 3) distribution of population based hematologists and neurologists, comparisons between provinces are made in these three variables, (Figures 6.5 and 6.8 and Table 6.13, respectively).

6.5 Variations in population based number of users of IVIG

Figure 6.5 shows the comparison of overall provincial number of users of IVIG/1,000 by fiscal years. The provincial trends in Figure 6.5 are minimally different from trends in Figure 6.2, exhibiting that provincial rate of use of IVIG/1,000 follows the population-based number of users of IVIG in each Atlantic province. These lines exhibit an increasing trend in the number of users of IVIG over time in each province. The dotted line representing NL's number of users of IVIG/1,000 remains consistently higher than the other three lines of the Atlantic provinces for all fiscal years throughout the study period. The analysis is repeated for each indication. Figure 6.6 shows the comparison between provinces in their number of users of IVIG per 1,000 for autoimmunity indications over time. The dotted line representing NL's number of users of IVIG in autoimmunity indications remains consistently higher than the other three lines of the Atlantic provinces for all fiscal years throughout the study period.

Figure 6.7 exhibiting provincial number of users of IVIG per 1,000 for immunodeficiency show minimal geographical variations between Atlantic provinces during study period.

6.6 Variations in mean annual usage of IVIG per patient

Table 6.12 and Figure 6.8 show the mean usage of IVIG in grams per patient for autoimmunity indications, immunodeficiency indications, and overall by province by fiscal year. In each fiscal year, NL has the highest mean usage of IVIG per patient when compared with NB and NS. There are four distinct lines in Figure 6.8, each representing a province. The dotted line representing NL remains consistently higher than the lines representing NB and NS for all fiscal years throughout the study period. When stratified by indications in the same figure, the dotted line representing NL's provincial mean annual usage of IVIG in grams per patient for autoimmunity indications and immunodeficiency indications remains consistently higher than the other lines of NB and NS for all fiscal years throughout the study period in both indications.

6.7 Variations in the distribution of hematologists and neurologists

Table 6.11 shows the distribution of hematologists and neurologists per 1,000,000 population in each Atlantic province. NL has the highest number of hematologists at 21/1,000,000 and highest number of neurologists at 30/1,000,000 population, among all Atlantic provinces; NB, NS and PEI have 12, 9 and 0 hematologists, and 29, 28 and 21 neurologists per million population, respectively.

Figure 6.9 shows the ecological graphic analysis of the data under study. After stratifying for indications, rate of use in autoimmunity is the primary driver of the provincial rate, with trends in provincial rates closely resembling trends of rate of use in autoimmunity most of the time and in most of the geographies, except perhaps fiscal years 2011-12 and 2013-14 in NB and 2012-13 in NS.

In summary, there is significant geographical variation between Atlantic provinces from 2006-2007 to 2013-2014 (Figure 6.1). The extent of geographical variation between provinces in 2013-2014 as measured by CV is 15% in the provincial rates, and higher for rates of use in autoimmunity (21%) as compared to rate of use in immunodeficiency (12%). Age and sex adjustment makes little difference in the provincial rates (Figure 6.1 and 6.2). Provincial rates and indication specific rates are highest for NL in each fiscal year. There are significant increases in provincial rates over time in each Atlantic province ($p<0.0001$ each) (Table 6.8). When stratified by indications, each indication exhibits significant increases in rates over time for each Atlantic province ($p<0.0001$ each) (Table 6.8). Although significant, the total percentage change is smaller in NL for their provincial rates, rates of use in autoimmunity and rates of use in immunodeficiency (Table 6.8). For each province the total percentage increases for rates of use in autoimmunity are 3 to 5-fold smaller than corresponding rates of use in immunodeficiency (Table 6.8). Analysis shows that there are geographical variations in the number of users of IVIG/1,000, the mean usage per patient and the number of hematologists and neurologists/1,000,000. NL has highest number of IVIG users/1,000 population among all Atlantic provinces in each fiscal year (Figure 6.5), and also has the highest mean annual usage of IVIG per patient in each year (Table 6.12 and Figure 6.8). NL has the highest number of hematologists/1,000,000 and the highest number of neurologists/1,000,000 population when compared to all other Atlantic provinces. When stratified by indications, rate of use in autoimmunity is the primary driver of provincial rate (Figure 6.9).

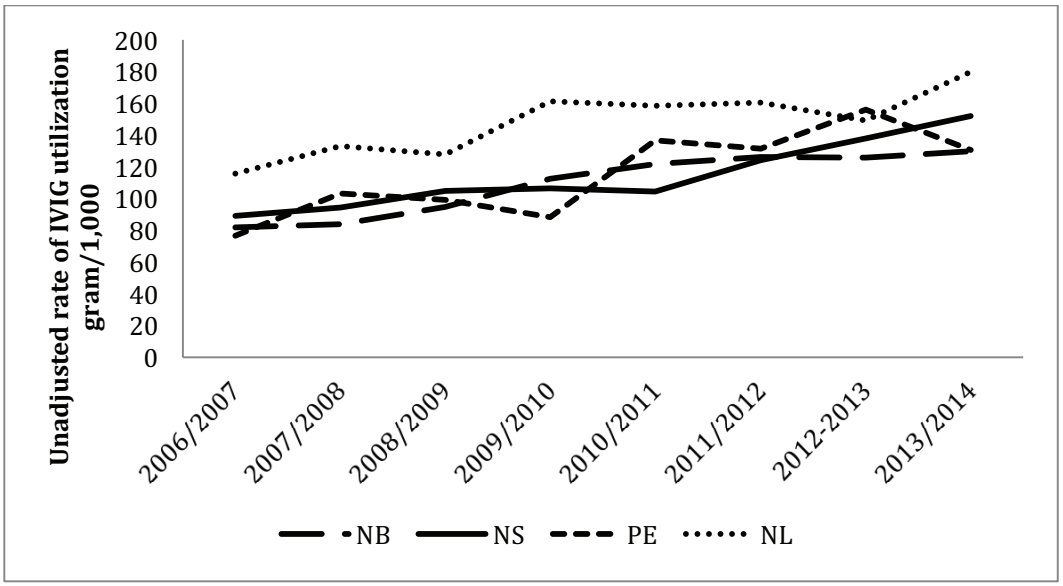

Figure 6.1: Comparison of the unadjusted provincial rates of use of IVIG grams/1,000 population, Atlantic provinces, 2006-2007 to 2013-2014.

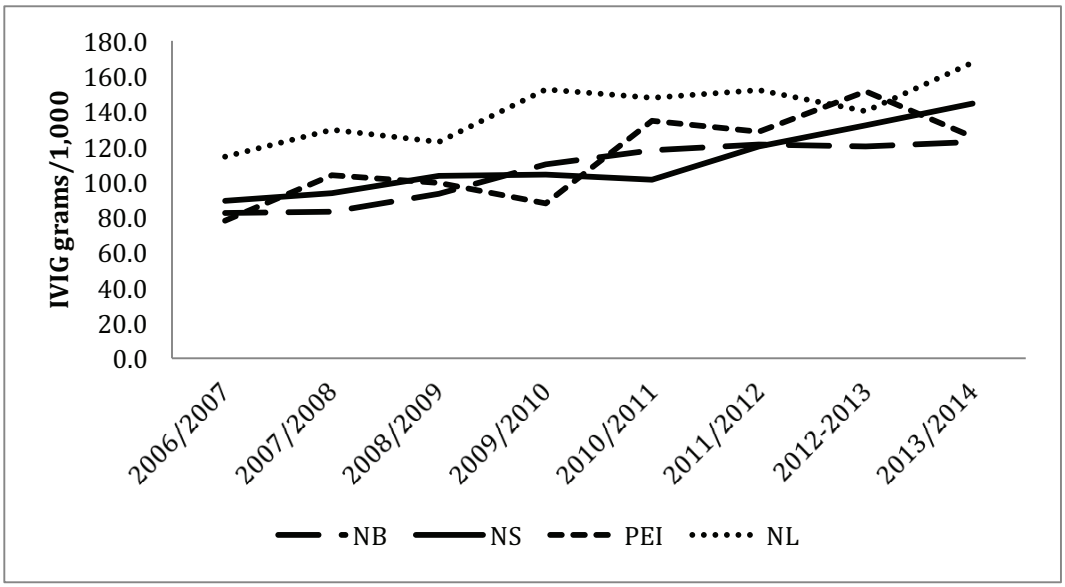

Figure 6.2: Comparison of the provincial age- and sex-adjusted rate of use of IVIG/1,000 (provincial rate), Atlantic provinces, 2006-2007 to 2013-2014.

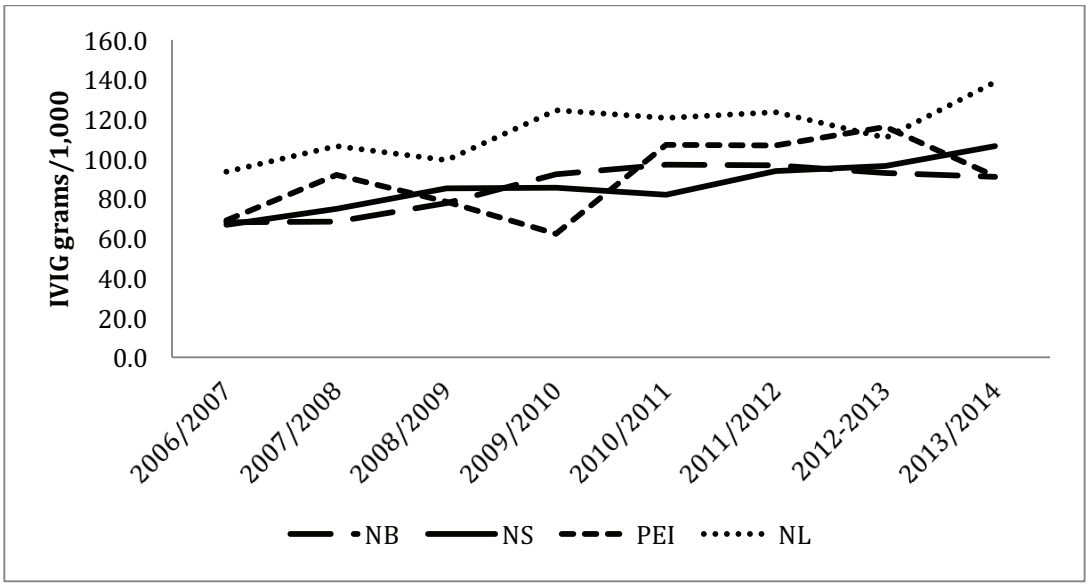

Figure 6.3: Comparison of the provincial age- and sex-adjusted rate of use of IVIG/1,000 in autoimmunity indications (rate of use in autoimmunity), Atlantic provinces, 2006-2007 to 2013-2014.

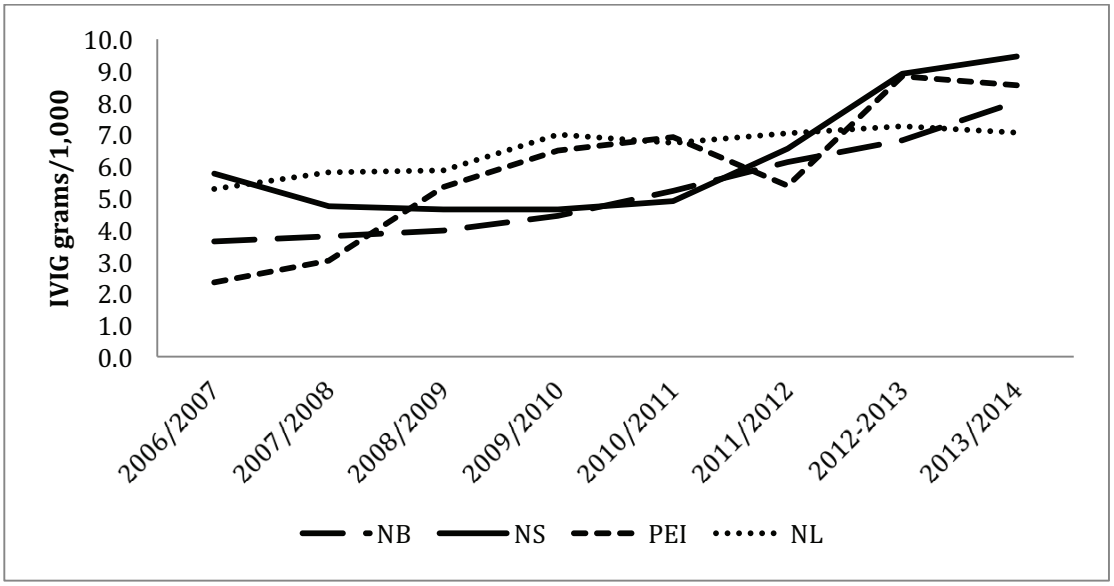

Figure 6.4: Comparison of the provincial age- and sex-adjusted rate of use of IVIG/1,000 in immunodeficiency indications (rate of use in Immunodeficiency), Atlantic provinces, 2006-2007 to 2013-2014.

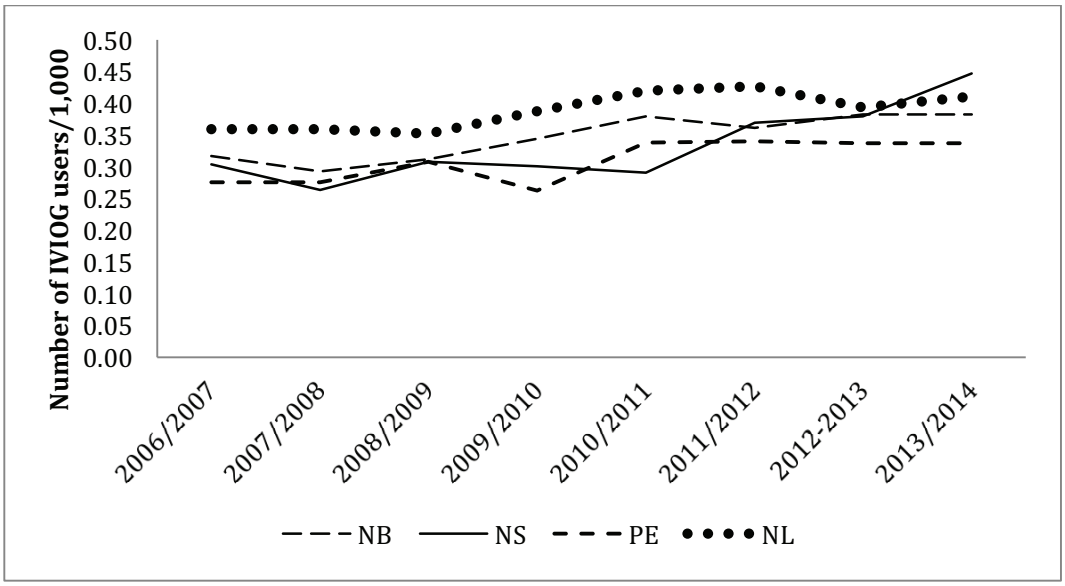

Figure 6.5: Comparison of number of users of IVIG/1,000, Atlantic provinces, 2006-2007 to 2013-2014.

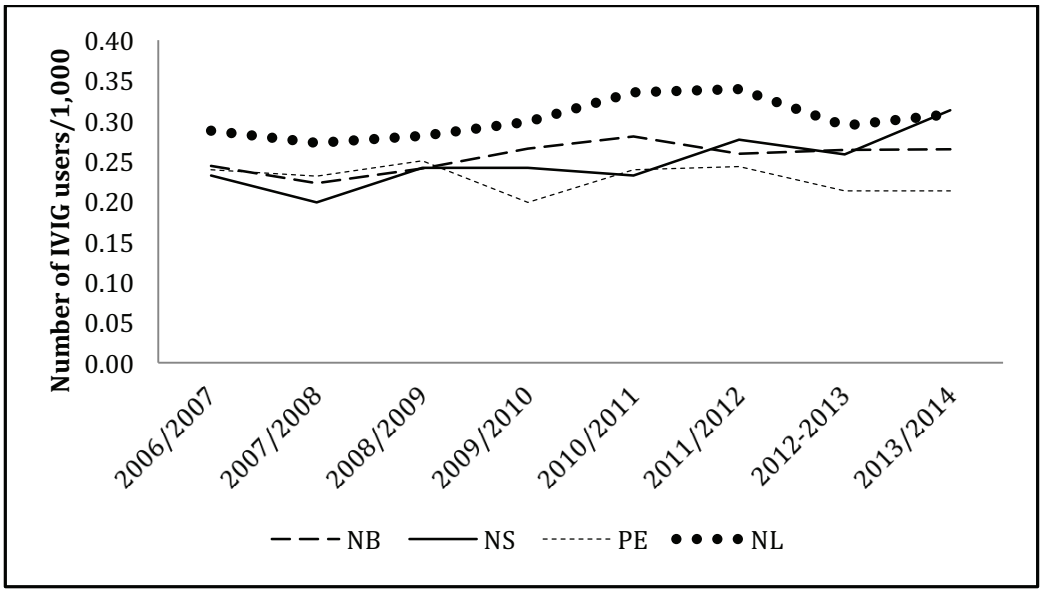

Figure 6.6: Comparison of number of users of IVIG/1,000 in autoimmunity indications, Atlantic provinces, 2006-2007 to 2013-2014.

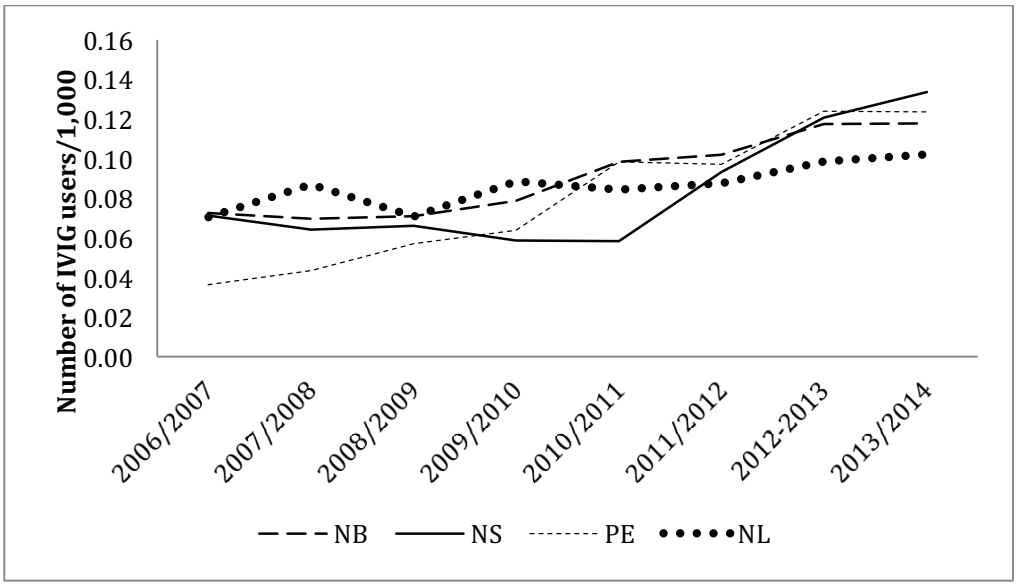

Figure 6.7: Comparison of number of users of IVIG/1,000 in immunodeficiency indications, Atlantic provinces, 2006-2007 to 2013-2014.

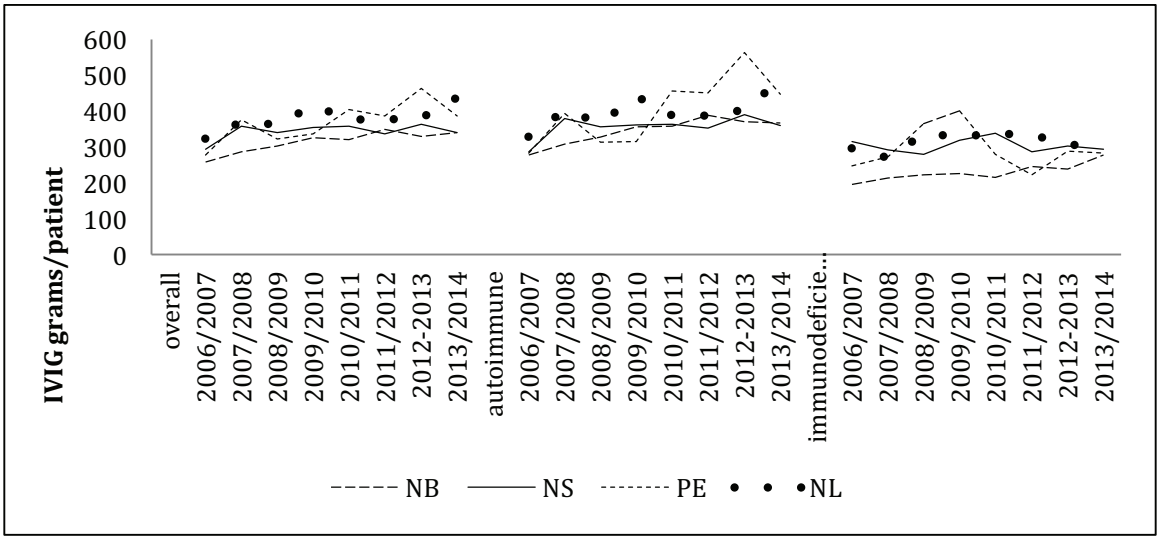

Figure 6.8: Mean annual usage of IVIG/patient, overall, autoimmunity and immunodeficiency, Atlantic provinces, 2006-2007 to 2013-2014.

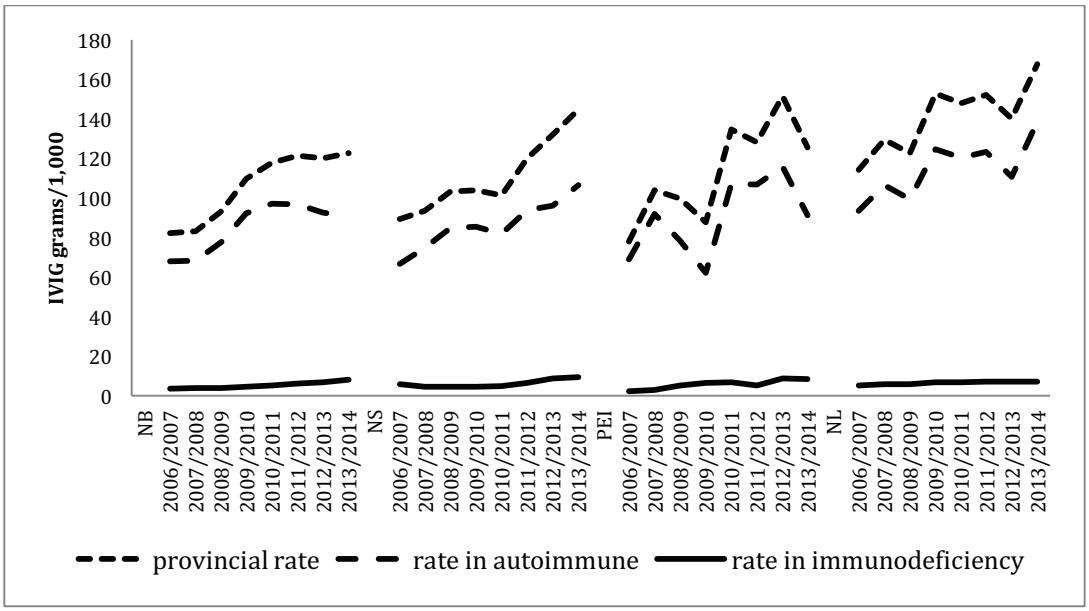

Figure 6.9: Ecological temporal trend in the provincial age- and sex-adjusted rate of use of IVIG/1,000 (provincial rate) compared with the ecological temporal trend of provincial age- and sex-adjusted rate of use of IVIG/1,000 in autoimmunity indications (rate of use in autoimmunity) and provincial age- and sex-adjusted rate of use of IVIG/1,000 in immunodeficiency indications (rate of use in immunodeficiency), Atlantic provinces, 2006-2007 to 2013-2014.

Table 6.1: Distribution of used amount of IVIG in grams by age and sex, Atlantic provinces, 2006-2007 to 2013-2014.

Age group	Male (n=3225)	% Of total use in males by age group	Female (n=3314)	% Of total use in females by age group	Total (n=6539)
01 to 04	7597	0.6	11423	1.1	19020
05 to 09	23194	1.9	25578	2.5	48772
10 to 14	30442	2.5	27422	2.6	57864
15 to 19	45746	3.8	21917	2.1	67663
20 to 24	17977	1.5	27974	2.7	45951
25 to 29	22060	1.8	23777	2.3	45837
30 to 34	17328	1.4	57778	5.5	75106
35 to 39	35226	2.9	50241	4.8	85467
40 to 44	68363	5.6	71787	6.9	140150
45 to 49	151118	12.4	110369	10.6	261487
50 to 54	133072	10.9	117494	11.3	250566
55 to 59	153040	12.6	119473	11.4	272513
60 to 64	129152	10.6	115898	11.1	245050
65 to 69	128760	10.6	82467	7.9	211227
70 to 74	110155	9.1	84301	8.1	194456
75 to 79	93242	7.7	57563	5.5	150805
80 to 84	34335	2.8	25125	2.4	59460
85 to 89	13512	1.1	9911	0.9	23423
90 to 94	1139	0.1	3191	0.3	4330
95 to 99	955	0.1	100	0.0	1055
All ages	1216413 g	100.0	1043789 g	100.0	2260202g

Table 6.2: Amount of provincial use of IVIG in grams, Atlantic provinces, 2006-2007 to 2013-2014.

Fiscal Year	NB	% Of Atlantic use	NS	% Of Atlantic use	PEI	% Of Atlantic use	NL	% Of Atlantic use	Atlantic
'06/07	61090	28.5	83676	39.0	10568	4.9	59027	27.5	214361
'07/08	62321	26.8	88198	38.0	14255	6.1	67403	29.0	232177
'08/09	70718	28.6	98223	39.7	13875	5.6	64831	26.2	247647
'09/10	84168	30.2	99777	35.8	12445	4.5	81939	29.4	278329
'10/11	91545	31.6	98192	33.9	19420	6.7	80730	27.8	289887
'11/12	95240	30.2	117329	37.2	18930	6.0	84252	26.7	315751
'12/13	95240	29.2	130034	39.8	22670	6.9	78610	24.1	326554
'13/14	98104	27.6	143401	40.3	18985	5.3	95006	26.7	355496
Total	658426	29.1	858830	38.0	131148	5.8	611798	27.1	2260202

Table 6.3: Medians of provincial age- and sex-adjusted rate of use of IVIG/1,000 (provincial rate), provincial age- and sex-adjusted rate of use of IVIG/1,000 in autoimmunity indications (rate of use in autoimmunity) and provincial age- and sex-adjusted rate of use of IVIG/1,000 in immunodeficiency indications (rate of use in immunodeficiency), Atlantic provinces, 2006-2007 to 2013-2014.

	Provincial rate Median (Q1-Q3, IQR	Rate of use in immunodeficiency Median (Q1-Q3, IQR)	Rate of use in autoimmunity Median (Q1-Q3, IQR)
NB	113.9 (88.2-120.7, 32.5)	4.8 (3.9-6.5, 2.6)	91.6(72.9-94.7, 21.8)
NS	103.7 (97.5-126.0, 28.5)	5.3 (4.7-7.7, 3.0)	85.2 (78.3-95.0,16.7)
PEI	114.6 (93.7-131.4, 37.7)	5.9 (4.2-7.7, 3.5)	91.6 (73.7-106.9, 33.2)
NL	143.9 (126.1-152.3, 26.2)	6.9 (5.8-7.1, 1.3)	115.5 (102.9-123.9, 21.0)

Table 6.4: Unadjusted rate of provincial use of IVIG in grams/1,000 population, Atlantic provinces, 2006-2007 to 2013-2014.

Fiscal year	NB	NS	PEI	NL
'06/07	81.9	89.2	76.6	115.7
'07/08	83.6	94.3	103.1	133.1
'08/09	94.6	104.7	99.2	127.6
'09/10	112.3	106.3	88.3	161.0
'10/11	121.8	104.2	136.5	158.4
'11/12	126.1	124.2	131.5	160.5
'12/13	125.8	137.6	156.0	149.2
'13/14	129.8	152.1	130.5	179.9

Table 6.5: Provincial age- and sex-adjusted rate of use of IVIG/1,000 (provincial rate), Atlantic provinces, 2006-2007 to 2013-2014.

Fiscal year	NB	NS	PEI	NL
'06/07	82.3	89.3	77.9	114.3
'07/08	83.1	93.6	103.9	129.4
'08/09	93.4	103.3	99.5	122.8
'09/10	109.8	104.0	87.8	152.6
'10/11	117.9	101.4	134.5	147.7
'11/12	121.3	120.0	128.3	151.9
'12/13	120.0	132.0	151.3	140.1
'13/14	122.6	144.5	125.4	167.5

Table 6.6: Results of Kruskal Wallis rank sum test exhibiting the geographical variation in the distributions of the samples of the provincial age- and sex-adjusted rate of use of IVIG/1,000 (provincial rate), Atlantic Canada, 2006-2007 to 2013-2014.

Province	Rank Sum
NB	93
NS	110
PEI	121
NL	204

p-value=0.0156

Table 6.7: Results of Wilcoxon signed rank tests exhibiting that median provincial age- and sex-adjusted rate of use of IVIG/1,000 (provincial rate) of NL is significantly distinct from the median provincial rates of NS, PEI and NB, Atlantic Canada, 2006-2007 to 2013-2014.

Null hypothesis	P-value
RateNL = RateNS	0.0117
RateNL = RateNB	0.0117
RateNL = RatePEI	0.0173
RateNS = RateNB	0.2626
RatePEI = RateNS	0.7794
RatePEI = RateNB	0.2076

Table 6.8: Total percentage increase in the provincial age- and sex-adjusted rate of use of IVIG/1,000 (provincial rate) over 8 years compared with the total percentage changes in the provincial age- and sex-adjusted rate of use of IVIG/1,000 in autoimmunity indications (rate of use in autoimmunity) and provincial age- and sex-adjusted rate of use of IVIG/1,000 in immunodeficiency indications (rate of use in immunodeficiency) over 8 years, Atlantic provinces, 2006-2007 to 2013-2014.

	Total percentage increase (provincial rate)	CI (95%)	Total percentage increase (rate of use in autoimmunity)	CI (95%)	Total percentage increase (rate of use in immunodeficiency)	CI (95%)
NB	65	64 to 66	47	46 to 48	167	163 to 171
NS	72	71 to 72	57	56 to 58	127	124 to 130
PEI	81	79 to 83	53	51 to 56	235	227 to 244
NL	41	40 to 42	40	39 to 41	40	36 to 44

p<0.0001 for all

Table 6.9: The effect of 'Province' and 'Time' on the provincial age- and sex-adjusted rate of use of IVIG/1,000 (provincial rate), Atlantic provinces, 2006-2007 to 2013-2014, using repeated measures analysis of variance.

Source	**Partial SS**	**MS**	**Prob>F**
Model	14509.7783	1450.97783	<0.0001
Province	5793.291	1931.097	<0.0001
Time	8716.48734	1245.21248	<0.0001

Number of observations 32.

Table 6.10: Provincial age- and sex-adjusted rate of use of IVIG/1,000 in autoimmunity indications (rate of use in autoimmunity) and provincial age- and sex-adjusted rate of use of IVIG/1,000 in immunodeficiency indications (rate of use in immunodeficiency), Atlantic provinces, 2006-2007 and 2013-2014.

Fiscal year	Rate of use in autoimmunity				Rate of use in immunodeficiency			
	NB	NS	PEI	NL	NB	NS	PEI	NL
'06/07	68.1	66.7	68.9	93.5	3.6	5.8	2.3	5.3
'07/08	68.2	74.8	92.0	106.3	3.8	4.7	3.0	5.8
'08/09	77.6	84.9	78.5	99.4	4.0	4.6	5.3	5.9
'09/10	92.1	85.5	62.2	124.5	4.4	4.6	6.5	7.0
'10/11	97.1	81.8	107.0	120.5	5.2	4.9	6.9	6.7
'11/12	96.7	93.8	106.7	123.3	6.1	6.5	5.4	7.0
'12/13	92.7	96.3	115.9	110.6	6.8	8.9	8.8	7.3
'13/14	91.0	106.5	91.2	138.5	8.0	9.5	8.6	7.1

Table 6.11: Number of users of IVIG/1,000 overall, autoimmunity and immunodeficiency, Atlantic provinces, 2006-2007 to 2013-2014.

	Overall				Autoimmune				Immunodeficiency			
	NB	NS	PE	NL	NB	NS	PE	NL	NB	NS	PE	NL
06/07	0.32	0.30	0.28	0.36	0.24	0.23	0.24	0.29	0.07	0.07	0.04	0.07
07/08	0.29	0.26	0.27	0.36	0.22	0.20	0.23	0.27	0.07	0.06	0.04	0.09
08/09	0.31	0.31	0.31	0.35	0.24	0.24	0.25	0.28	0.07	0.07	0.06	0.07
09/10	0.34	0.30	0.26	0.39	0.27	0.24	0.20	0.30	0.08	0.06	0.06	0.09
10/11	0.38	0.29	0.34	0.42	0.28	0.23	0.24	0.34	0.10	0.06	0.10	0.08
11/12	0.36	0.37	0.34	0.43	0.26	0.28	0.24	0.34	0.10	0.09	0.10	0.09
12/13	0.38	0.38	0.34	0.39	0.26	0.26	0.21	0.29	0.12	0.12	0.12	0.10
13/14	0.38	0.45	0.34	0.41	0.26	0.31	0.21	0.31	0.12	0.13	0.12	0.10

Table 6.12: Mean annual usage of IVIG/patient, autoimmunity, immunodeficiency, and overall, Atlantic provinces, 2006-2014

	Autoimmunity				Immunodeficiency				Overall			
	NB	NS	PE	NL	NB	NS	PE	NL	NB	NS	PE	NL
'06/07	278	287	283	329	195	316	248	297	259	294	278	323
'07/08	308	380	395	402	214	292	272	270	286	359	375	370
'08/09	327	357	313	368	223	279	365	338	304	340	323	362
'09/10	356	362	316	442	226	318	401	328	326	354	336	416
'10/11	358	363	456	387	215	339	280	337	321	358	405	377
'11/12	389	353	452	387	246	286	223	335	349	336	386	376
'12/13	370	391	563	403	239	304	289	309	330	363	463	380
'13/14	367	361	448	486	278	294	283	293	339	341	387	438

Table 6.13: Number of haematologists/1,000,000 and neurologists/1,000,000, Atlantic provinces, January 2016.

	NB	NS	PE	NL
Number of haematologists	11.9	8.5	0.0	20.8
Number of neurologists	29.2	27.6	20.5	30.3
Total	41.1	36.1	20.5	51.2

CHAPTER 7: DISCUSSION

In the past, numerous methods have been used to exhibit epidemiologic evidence of the extent of variation in utilization of health services and products: CV (23); extremal quotients and relative variability in terms of low, moderate, high (57); degree of multiples of the lowest rates (50, 62); Poisson regression (37); ecological trend analysis over time (33); and correlation and regression analyses to find the significant relevant factors influencing utilization rates (7, 8, 40, and 60). The current study uses a range of such methods to examine a new area of variation research, namely the utilization of IVIG. This study uses repeated measures analysis of variance for the existence of geographical and temporal variations, Poisson regression to determine the extent of temporal variations (37) and CV to determine the extent of geographical variation. Ecological trend analysis over time is used to describe and compare provincial rate over time with the temporal and geographical trends of rates of use in autoimmunity and rate of use in immunodeficiency, in order to find which of the two indications is the primary driver of provincial rate (33). The study also make use of descriptive analyses of the trends of number of users of IVIG/1,000 and mean annual usage of the amount of IVIG per patient, and compares the provincial number of hematologists/1,000,000 and neurologists/1,000,000 in order to discover how the provincial rates may be because of these variables.

The findings of the current study indicate that there is statistically significant geographical and temporal variation in the use of IVIG in the Atlantic provinces from 2006-2007 to 2013-2014. For 2013-2014, the estimates of geographical variation (as measured by the CV) among the four provinces for the provincial rates, rate of use in autoimmunity and rate of use in immunodeficiency are 15%, 21% and 12%, respectively. Throughout the study period, the provincial rate in NL remains consistently higher than the other three Atlantic provinces. There are significant temporal variations in all four provinces for provincial rates, rate of use in autoimmunity and rate of use in immunodeficiency. When stratified by indications, the rates of use in autoimmunity are higher than the rates of use in immunodeficiency. NL shows

higher rates of use in autoimmunity than the other three provinces, throughout the study period. Although significant, the total increases in the rate of use in autoimmunity over time is 2 to 5-fold lower than the rate of use in immunodeficiency for NB, NS and PEI. NL shows the least variability for both indication specific rates over time.

Variations in provincial rates are likely because of a higher number of users of IVIG/1,000 as well as a higher mean usage of IVIG per patient. The trends in provincial rates and rates of use in autoimmunity follow the trends in the number of users of IVIG/1,000, as well as the trends in mean annual usage of IVIG per patient. NL, which has the highest provincial rates, has the highest number of users of IVIG/1,000, as well as the highest mean annual usage of IVIG per patient in each fiscal year throughout the study period.

Rate of use in autoimmunity is the primary driver of provincial rate. This finding is not surprising, as approximately 80% of the total Atlantic use of IVIG during 2006-2007 to 2013-2014 is for autoimmunity indications. The relevance of examining the two indications separately is that these indications differ clinically and diagnostically. Therefore, the results can be used to define a focus of future research and strategies to optimize the use of IVIG.

Within autoimmunity indications, as reported in the Atlantic IVIG annual utilization report (46), the two main disease categories are hematology and neurology. The use of IVIG in hematological and neurological autoimmunity disorders accounts for 83% of the total Atlantic IVIG use in autoimmunity for 2013-2014 (48). This prompted investigations to show how variations in the provincial rates may be because of the number of hematologists and neurologists per million population. In this study, NL has the highest number of hematologists per million population when compared to the other three Atlantic provinces. The relatively higher number of population based hematologists in NL may be a reason why NL has a relatively higher number of users of IVIG/1,000. Variation in their practice style may be a reason why NL has the higher mean usage of IVIG per patient.

In general, the presence of excessive and unwarranted variation (by geography) is unhealthy and unwanted. Comparison of neighboring geographical areas has an underlying assumption of negligible demographic variations (58). If all patient-related factors due to race, genetic composition, dietary habits, and type of disease are similar in the neighboring areas being compared, then there is little allowance of variation in disease burden between areas under comparison (11). Similarly, if the physician practice styles and the provision of health care, access and funding systems are alike, then there should be no significant geographical variation in the utilization of IVIG.

The potential disadvantages of living in the areas with high rates of utilization include disproportionate use of resources, unnecessary exposure to the risks of side effects of procedures and products, as well as a higher risk of exposure to iatrogenic infections and disease with resultant morbidity and mortality (11, 23). Overutilization without significant improvement in health and its determinants also reflects an unnecessary financial burden on the health care system (11). In relation to this study, it can be hypothesized that areas with higher rates of blood product (IVIG) transfusion have the potential to expose the inhabitants to an unnecessary higher risk of transfusion-related morbidity. On the other hand, residents of areas with low utilization rates of health care resources, procedures, transfusions, medications, and health care facilities, are at risk of living with an undiagnosed and/or untreated disease (11). This underutilization may be a result of poor access, due to lack of funding, lack of resources, or lack of clinical expertise. Therefore, based on the findings of this study, further research is recommended to explore the reasons for geographical and temporal differences in IVIG use in Atlantic Canada.

Recommendations for future research:

There are several factors or variables known to be associated with variation in health care utilization. Their detailed analysis has potential to provide insight into the utilization practice of IVIG and to identify the areas where practice can be modified to minimize variation in the provincial rates between geographies and over time. These variables can be categorized as

follows: 1) variation in clinical practice (17); 2) variation in patient-related factors; and 3) variation in the provision of health services, including access to care and funding systems (27, 50). Each of these broad categories may be influenced by more specific factors.

Physician practice is influenced by availability of the scientific evidence for a standard practice, ease of obtaining the product or resource, income-seeking behavior, age of the physician, level of training and the number of years of training, preference for certain style of practice, and the role of the physician as a patient's clinical advocate (17). Patient demands and convenience may also influence physician practice (17). Dramatic evidence of the importance of physician practice factors (not specifically related to IVIG) comes from a study conducted in New Haven and Boston, two demographically similar areas. There were differences in per capita and overall expenditures (by $300 million), due to the higher use of beds by some Boston physicians, for diseases with debatable clinical need for admission (59). The same study also found variation in the rates of some surgeries between these geographical areas (59). The degree of training of health care providers was associated with variation in a study conducted in 44 counties of Ontario, Canada from 1973 to 1977 (56). This study found a considerable variation in the rates of eight surgical procedures, including hysterectomy, tonsillectomy/adenoidectomy, cholecystectomy, prostatectomy, appendectomy, mastectomy, colectomy and caesarean section (56). Although no association was found between these variations and the number of beds or the number of surgeons (56), lower rates of surgeries such as cholecystectomy, appendectomy, mastectomy and tonsillectomy/adenoidectomy were seen in the five teaching hospitals (56), suggesting that degree of training and clinical expertise were potential factors contributing to the variation in use (56).

The geographical variations found in the population based number of hematologists between Atlantic provinces in this study merits a recommendation for a detailed analysis of the reasons of differential distribution and their practice styles. A Manitoba study found inconsistent associations of access, in terms of seeing a doctor and having a regular doctor, with high

surgical rates (50); however, our study shows that the availability of a higher number of clinical experts in NL may have resulted in higher provincial rates of IVIG. It is possible that some physicians use IVIG as a first line treatment, or at a higher than recommended dose. Use of IVIG for inappropriate indications should be studied as a source of variation, particularly in light of the fact that IVIG has been used inappropriately in the past in Canada (26). In general, variation studies have found that appropriateness categorization varies with clinical expertise (45) and between geographies (8). Other studies have found the lack of consensus on diagnostic criteria (57) to be a cause of variation in use. In Canada, guidelines have been developed and published on the use of IVIG for common neurologic and hematologic indications (1), for primary immunodeficiency indications, as well as for solid organ transplantation. However, the level of compliance with these guidelines needs to be researched. There are situations when IVIG is used for a new indication that is not identified in the guidelines, but the use is considered "appropriate," based on evolving literature, case reports (in rare conditions) and clinical expert opinions. There is evidence that Canadians with lower incomes have higher rates of disease and death (11). It is possible that the diseases requiring IVIG may be related with lower levels of income. Given the current funding system in Canada, IVIG can be wrongly perceived as a free drug when compared with other treatment options, because neither the physicians nor the patients are directly billed for IVIG in Canada. This fact could influence physicians' decisions (as patients' advocates) regarding choice of treatment when medical insurance is a consideration. Thus, research should be done to examine physician-related factors as a cause of variation in the use of IVIG.

Patient-related factors include variation in age, sex, genetics, height, weight and predisposition to (as well as severity of) disease requiring IVIG. Many conditions for which IVIG is indicated require long-term use. Assessing the prevalence of such "chronic" IVIG use, as well as analysis of chronic use as a predictor of provincial rate are recommended future research activities. In this study, age and sex do not vary between provinces, making them unlikely causes

of variations. The study of other patient related factors is beyond the scope of this study.

Finally, another potential source of variation is variation in access to the health care system, including access to resources and to clinical experts (35, 62). Since health care access and funding system are similar in Canada, they may be less likely contributor of geographical or temporal variations. Although a survey conducted on 1049 participants in NL found under-utilization of health services to be related with poor access to family doctors and specialist services (27), this survey did not specifically focus on IVIG use.

Figure 2.1 in the background (Chapter 2) has been modified to reflect the findings of this study and is now presented as Figure 7.1. Possible sources of geographical and temporal variations are observed in the numbers of users of IVIG/1,000 and the mean annual usage of IVIG per patient between provinces. In turn, these differences may be related to the geographical variations found in the population-based number of hematologists between Atlantic provinces. Therefore, a detailed analysis of reasons of their differential distribution and practice style and other physician related factors should be studied as a predictor of IVIG utilization, and to optimize the use of IVIG.

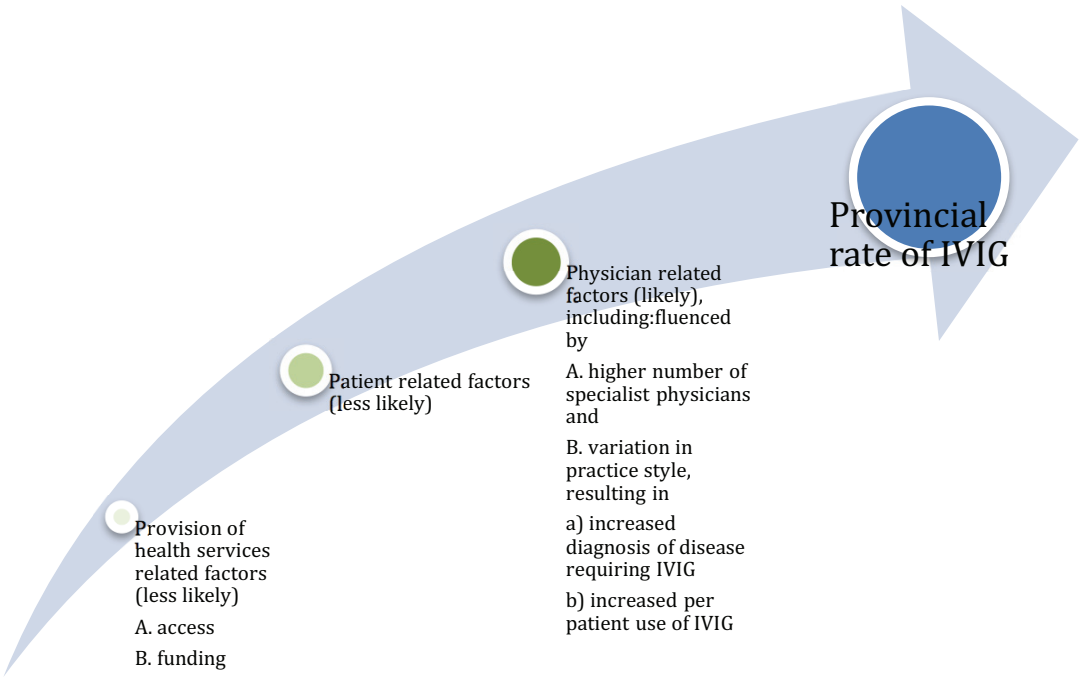

Figure 7.1: Potential factors associated with variation in the provincial rate of use of IVIG.

Strengths:

This study is the first to document and analyze the variation of IVIG use. The presence of statistically significant variation is a prerequisite (11) for action to redefine strategies and policies. In the past, some studies have only reported the differences in the magnitude of comparator rates (50), but this study has used multiple statistical analyses to illustrate the presence of statistically significant variations in the provincial rates.

While analysis of multiple factors causing variation in the provincial rate is beyond the scope of this research, the two variables rate of use in autoimmunity and rate of use in immunodeficiency are studied here in some detail. The results of this study provide immediately useful information as well as direction for the focus of future research.

Limitations:

Measurement bias due to manual data entry is a limitation of this study. This limitation is minimized by several layers of data tally and electronic data cleanup steps, done at NSPBCP in order to identify and rectify any incomplete

submissions, duplications, errors, or discrepancies in the data. Reporting of incorrect indications, in order to procure IVIG, is also a possible source of measurement bias. In this study, under-reporting of the utilization data or missing information is not a strong limitation because 96% of all distributed IVIG is included in this research.

The presence of unstable rates in PEI, the smallest province of Canada by population, is a limitation. This problem is recognized in the literature as a limitation of small area variation analysis (11). Variations may be exaggerated in areas with small populations because a small change in the numerator (utilized grams of IVIG) or a small change in the denominator (population) can result in unduly variable and statistically unstable rates (11).

Area-specific rate variation studies are not a true reflection of disease incidence and prevalence in the population. Therefore, this study should not be used to estimate the incidence of disease requiring IVIG. There may be diseased individuals who have not been diagnosed, or who are not receiving required IVIG treatment due to lack of access to health services (52).

Conclusion:

In conclusion, using a combination of descriptive and statistical analysis for determining the extent of geographical and temporal variation, stratified by indication and adjusted for age and sex, this study is successful in giving a detailed picture of the presence of significant effects of time and province on the provincial rates in the Atlantic provinces from 2006-2007 to 2013-2014. NL has the highest provincial rates, highest number of users of IVIG/1,000, highest mean annual usage of IVIG per patient, and highest number of hematologists and neurologists per million population.

Using ecologic graphic analysis, this study finds rate of use in autoimmunity as the primary driver of provincial rates. The results of this study contribute to the overall literature on variance, and particularly variance in the utilization of IVIG in the Atlantic provinces. Although the study is performed in the Atlantic region, the target population is Canada and all those countries where the escalating use of this valuable blood product is a source of concern.

Understanding the reasons for variability is crucial for designing utilization strategies, so that the utilization can be optimized and unnecessary transfusions prevented - making IVIG available for situations where it is most beneficial. Research in health services has demonstrated the usefulness of variation studies, in providing scientific evidence of areas where the rate of the use of procedures or health care products and services can be decreased without compromising quality of care and patient outcomes (3, 9). A multidisciplinary research approach is needed with a defined focus for physician related factors in autoimmunity indications of hematology before it will be possible to untangle the complex relationships among disease epidemiology, access, clinical practice and the provincial use of IVIG.

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