QUality of ASthma Treatment in Children and Adolescents (QUAST-CA)

by

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A thesis submitted to the Faculty of Graduate Studies of
The University of Manitoba
in partial fulfillment of the requirements of the degree of

MASTER OF SCIENCE

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ABSTRACT

Asthma is a chronic heterogeneous condition of the airway and is prevalent in large number of Canadian children and adolescents. Despite the existence of evidence-based treatment guidelines, the management of asthma remains suboptimal, and many patients continue to experience 'uncontrolled' asthma. The aim of this study was to describe the prescribing pattern of asthma-related drugs (anti-asthmatic medications, inhalational devices, antibiotics, vaccines) among children and adolescents and examine the clinical consequences of inappropriate prescribing and lack of prescribers' adherence to expert treatment recommendations (Global Initiative for Asthma (GINA) guidelines). A retrospective longitudinal descriptive cohort study spanning 2013-2017 was conducted using health administrative data from Manitoba Centre for Health Policy (MCHP). Out of 25,732 patients receiving anti-asthmatic prescriptions with a physician confirmed asthma diagnosis, 7140 constituted the cohort of newly treated persistent asthma patients. Two-year treatment follow-up from their index date revealed that 45.53% of them failed to take any anti-asthmatic medications in their second year. Antibiotic prescriptions, particularly broad-spectrum antibiotics was common among patients with asthma as compared to non-asthmatic matched controls and were mainly prescribed for Upper Respiratory Tract Infections (URTI). Multivariate logistic regression analysis indicated that non-compliant prescriptions defined against the expert treatment recommendations from GINA were not associated with any risk of exacerbation in two years, however patients with notable overuse of Short-Acting β-Agonist (SABA) [adjusted Odds Ratio (aOR) : 1.25 (1.07-1.46) -first year; 1.57 (1.19-2.06)-second year] and lower (<50%) Inhaled Cortico Steroids to total asthma drug ratio (ICS/R03) [aOR: 2.10 (1.73-2.52)-first year; 2.50 (1.84-3.39)- second year] in both the follow-up years had higher likelihood of experiencing asthma exacerbations.

ACKNOWLEDGEMENT

First and foremost, I am deeply grateful to my supervisor Dr. Geert W ‘t Jong and co-supervisor, Dr. Lauren E Kelly, for providing me with the opportunity to be part of the Clinical Pharmacology Lab. Beginning from the first day and throughout my study, I have received invaluable guidance and relentless support from them that helped me steer in the right direction. Supervision by Dr. ‘t Jong was helpful in building a solid foundation and robust research environment in pediatric clinical pharmacoepidemiology by facilitating active participation in activities undertaken by the Children’s Hospital Research Institute of Manitoba (CHRIM). Working with Dr. Kelly was fundamental in nurturing my knowledge of real prospective interventional research or clinical trials and extending my insights and expertise into medical cannabinoid research by being part of a living systematic review. In addition, her support also enabled me to be involved with the Centre for Healthcare Innovation (CHI) that offered biostatistical assistance during various stages of my study and research training programmes through the Society of Clinical Research Associates (SOCRA). Without their supervisory support, moral advice and benevolence at all times when needed, I would have neither achieved my goals nor been able to accomplish this endeavour. I am thankful to the whole Clinical Pharmacology Lab for helping me polish my skills in presentation, critical appraisals, and moreover growing mutually. I would like to specially thank my advisory committee members, Dr. Grant Hatch and Dr. Christine Leong, for their timely instructions, advice and critiques, which were pivotal in refining my thesis.

I acknowledge with heartfelt gratitude the nonpareil role of Dr. Florentia Kaguelidou in developing this project from a conceptual status to what it is now through her timely advice. I would also like to extend my gratitude to Heather Prior, Lead data analyst at the Manitoba Centre for Health Policy (MCHP), for the remarkable support she provided me in understanding the SAS program and the administrative data. I am grateful to Kun Liu, a graduate student with the Department of Community Health Sciences, for her immense help and support in framing the SAS codes and understanding regression analysis, which were the pivotal components of this project and its progression. I would also like to sincerely thank my

colleagues Manik Chhabra, Omaymah Abulannaz (Ph.D. students in our lab), Uma Yakandawala (master's student), Zina Zaslawski (Research Coordinator) other students and all members of our lab for their invaluable support. Additionally, I would like to recognize all the help I received from Janelle Metcalfe, office assistant and Karen Donald, administrative secretary at the Department of Pharmacology & Therapeutics, during my programme.

I am extremely thankful to my family, especially my father Paulose N.P, mother Valsa Paulose, sister Anu Paul and brother-in-law Manu M.T for their unswerving love, encouragement and mental support that backed me on all important times and crucial decisions I made. I am also happy to have had my cousin brother Allan James who stayed with me and helped, especially in getting adapted to a new country and environment. Although I did miss the physical presence of my family, I am fortunate to have friends like Abin Chandrakumar, Anjana Abin, Alen Paiva and Vignesh Krishnamoorthy who helped me throughout my student life.

The author acknowledges the Manitoba Centre for Health Policy for use of data contained in the Manitoba Population Research Data Repository under project # 2021-006 (HIPC# 2020/2021– 49). The results and conclusions are those of the authors, and no official endorsement by the Manitoba Centre for Health Policy, Manitoba Health, or other data providers is intended or should be inferred. Data used in this study are from the Manitoba Population Research Data Repository housed at the Manitoba Centre for Health Policy, University of Manitoba and were derived from data provided by Manitoba Health, Winnipeg Regional Health Authority and Department of Families.

Finally, but most importantly, I would like to express my sincere gratitude to all the funding agencies who believed in my competencies and provided me scholarships during my master's program. I want to thank Research Manitoba, Children's Hospital Research Institute of Manitoba, BREATHE (The Lung Association, Manitoba) and Mitacs for full-time scholarships, stipend and generous support for furthering my research.

Dedicated to my family for their relentless love and support….

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ABBREVIATIONS

AAP	American Academy of Pediatrics
ADAM33	A Disintegrin And Metalloprotease 33
ADT	Admissions, Discharge & Transfer
aOR	Adjusted Odds Ratio
ASM	Airway Smooth Muscle
ATC	Anatomical Therapeutic Chemical
cAMP	Cyclic Adenosine Mono Phosphate
CFC	ChloroFluoroCarbon
CI	Confidence Interval
CRP	C-Reactive Protein
CTAS	Canadian Triage & Acuity Scale
CTC	Canadian Thoracic Society
DALY	Disability Adjusted Life Years
DPIN	Drug Program Information Network
DPIs	Dry Powder Inhalers
DPP10	Di Peptidyl Peptidase 10
ED	Emergency Department
EDIS	Emergency Department Information System
EIA	Employment, and Income Assistance
FEV_1	Forced Expiratory Volume in 1 second
FSA	Forward Sortation Area
GERD	GastroEsophageal Reflux Disease
GINA	Global Initiative for Asthma
GPR154	G-Protein Coupled Receptor 154
GWAS	Genome Wide Association Studies
HIPC	Health Information Privacy Committee
HL	Hosmer-Lemeshow
HREB	Health Research Ethics Board
HRV	Human Rhino Virus
ICD	International Classification of Diseases
ICS	Inhaled Cortico Steroids
ICS/R03	Inhaled Cortico Steroids to total asthma drug ratio
IgE	Immunoglobulin E
LABA	Long- Acting β-Agonist
LRTI	Lower Respiratory Tract Infection
LTM	Leukotriene receptor Modifiers
LTRA	Leukotriene Receptor Antagonists
MCHP	Manitoba Centre for Health Policy
MDI	Metered Dose Inhalers
MIMS	Manitoba Immunization Monitoring System
NHLBI	National Heart, Lung and Blood Institute
OCS	Oral Corticosteroid
OR	Odds Ratio

ORMDL3	ORM1 (yeast)–like protein 3
PEF	Peak Expiratory Flow
PHIN	Personal Health Identification Numbers
PIN	Product Identification Number
pMDIs	Pressurized Metered Dose Inhalers
PY	Person Years
RR	Rate Ratio
RSV	Respiratory Syncytial Virus
SABA	Short-Acting β-Agonist
SAMIN	Social Allowances Management Information Network
SEFI	Socio Economic Factor Index
SES	Socioeconomic Status
SMART	Salmeterol Multicenter Asthma Research Trial
Th	T helper cells
URTI	Upper Respiratory Tract Infection
UTI	Urinary Tract Infection
WHO	World Health Organization
WRHA	Winnipeg Regional Health Authority

Chapter 1: INTRODUCTION

Asthma is a chronic, heterogeneous respiratory disease affecting around 262 [1] million people worldwide or 1-18% of the population across various geographical regions [2]. It is a real public health concern having an estimated loss of 21.6 million disability-adjusted life years in 2019 and represents 20.8% of the total global burden from all chronic respiratory diseases [3]. In Canada, asthma affects 3.8 million people [4], with over 300 new cases being diagnosed every day and has an annual mortality rate of 250 patients [5].

The definition and classification of asthma has been the subject of multiple approaches and controversies over decades. However, considering variable airway obstruction as a key characteristic of the disease, a description of its clinical features was proposed by Global Initiative for Asthma (GINA) as "a heterogeneous disease, usually characterized by chronic airway inflammation. Asthma is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation" [2].

1.1 Asthma in children and adolescents

The morbidity of childhood asthma is a major health concern that witnessed an exponential rise in prevalence over the last 20 years affecting approximately 14% of children globally [6] [7]: 6% in children under six years of age, 5 to 10% in children between 6 and 12 years of age and between 10 and 15% in adolescents [8, 9]. Health resource utilization is substantial for children with asthma, and hospital admissions are frequent (approx. 30.1 / 10,000 children) with seasonal peaks [10].

The characteristics of asthma and its symptoms fluctuate across childhood. In younger children (<6 years of age), especially during the first years of their life, infection-induced asthma is quite common. It often appears episodic, presenting difficulty in determining whether

wheezing in younger children is due to asthma or not [11]. Hence, unlike adult asthma, considerable variability in the severity, natural history of the disease, clinical phenotype and drug response has been observed in pediatric asthma, establishing it as highly heterogeneous[12].

1.2 Factors underlying asthma development/expression

Numerous heterogeneous phenotypes expressing variability in clinical presentation, pathophysiology and etiology of asthma have been identified for which the risk factors could either attribute to environmental or host origin [13]. However, the ambiguity in explaining their underlying mechanisms prevails, given the heterogeneity and lack of a 'gold standard' biomarker for the disease.

Table 1: Factors affecting asthma development and expression [13]

Host factors	Environmental factors

• Genetic (e.g., genes predisposing to atopy, airway hyperresponsiveness, airway inflammation and innate immunity
• Obesity
• Sex
• Preterm birth or small size for gestational age (SGA)
	• Allergens
	  ○ Indoor: domestic mites, furred animals (e.g., dogs, cats, mice), cockroaches, fungi
	  ○ Outdoor: pollen, moulds
	• Occupational sanitizers and allergens (e.g. Flour, laboratory rodents, paints)
	• Infections (primarily viral)
	• Microbiome
	• Exposure to tobacco smoke
	Passive smoking
	Active smoking
	• Outdoor or indoor air pollution
	• Diet
	• Stress

1.2.1. Host factors

The hosts' genetic make-up can be linked to the development of asthma in several ways, ranging from attenuating the pathways regulating the production of allergen-specific IgE (Immunoglobulin E) antibodies, inflammatory mediator generation (e.g.: cytokines), expression of the airway hyper responsiveness and maintenance of T helper cells Type 1/Type 2 (Th1/Th2) immune balance [14, 15]. Linkage analysis and genome wide association studies (GWAS) have recognized the role of genes such as ADAM33, DPP10, GPR154, ORMDL3[16, 17] to be incurring asthma susceptibility. Despite the unclarity in the pathogenesis, sex is also a risk factor for asthma in which males have more vulnerability to the disease in childhood as compared to females who develop risk in adulthood. The dysynaptic growth of airways in boys and varying sex hormone levels in females after puberty are some potential explanations for this [18, 19]. Several other factors including obesity, preterm birth also influences asthma expression in children and adolescents [13].

1.2.2. Environment factors

Allergic sensitization induced by the exposure to indoor, outdoor, occupational allergens can precipitate asthma exacerbations [20, 21]; however, their initial causal relationship to the development of the disease is uncertain [13]. Respiratory viral infections account for 70% of the exacerbations in individuals with established asthma [22]. Nevertheless, infections from respiratory syncytial virus (RSV), influenza virus, parainfluenza virus, human rhinovirus (HRV), and metapneumovirus infections that develop wheezing episodes during infancy and normally diminish with age, may persist for longer and marks asthma inception in some individuals[23]. Contrary to these findings which connect early life infections to asthma morbidity, the 'hygiene hypothesis' that postulated the development of T helper cells Type 1 (Th1) mediated immunity in the 'non-allergic pathway after infection exposures leave controversy for discussions. Besides these factors, the effect of stress, diet, exposure to smoke, pollution on the development or prolapse of asthma are also not negligible.

1.3 Asthma severity classification based on clinical features and treatment

Clinical assessment of asthma severity includes evaluation of the level and frequency of clinical symptoms, airway limitations, and variability in lung function. These parameters categorize patients into intermittent asthma, mild, moderate, or severe persistent asthma. However, in light of the recognition that severity is not static or is alternatively influenced by patients' responsiveness to the treatment has brought to a deviation from this predictive categorization to a newer paradigm of treatment-related classification. It is usually assessed when the patient is settled on a controller or maintenance treatment of asthma for several months and is appropriately modified into a 'step up' or 'step down' phase as needed [24].

Table 2: Classification of asthma severity based on clinical symptoms and treatment [24]

Based on clinical symptoms	Based on treatment
Intermittent	
Symptoms less than once a week Brief exacerbations Nocturnal symptoms not more than twice a month FEV_1 or PEF ≥ 80% predicted FEV_1 or PEF variability < 20%	Step 1: As needed SABA, consider low dose ICS
Mild Persistent	
Symptoms more than once a week but less than once a day Exacerbations may affect activity and sleep Nocturnal symptoms more than twice a month FEV_1 or PEF ≥ 80% predicted FEV_1 or PEF variability < 20 - 30%	Step 2: As needed SABA with low dose ICS or LTRA
Moderate Persistent	
Daily symptoms Exacerbations may affect activity and sleep Nocturnal symptoms more than once a week Daily use of inhaled short-acting β2-agonist FEV_1 or PEF 60- 80% predicted FEV_1 or PEF variability > 30%	Step 3: Asthma controlled by as needed SABA and using low dose ICS+LABA

Severe Persistent	
Symptoms daily Frequent exacerbations Frequent nocturnal asthma symptoms Limitation of physical activities FEV_1 or PEF ≤ 60% predicted FEV_1 or PEF variability > 30%	Requiring Step 4 or Step 5 therapy advised by GINA with as needed SABA plus medium to high dose ICS +LABA to prevent uncontrollable asthma

$FEV_{1:}$ Forced expiratory volume in 1 second, PEF: Peak expiratory flow, GINA: The Global Initiative for Asthma, SABA: Short-acting β-agonist, LABA: Long-acting β-agonist, ICS: Inhaled corticosteroids, LTRA: Leukotriene receptor antagonists

1.4 Pharmacotherapy of asthma

1.4.1 Achievement of asthma control

The pharmacotherapy of asthma typically aims at achieving symptom control marked by the Canadian Thoracic Society guidelines as [25]:

Table 3: Indicator of symptom control in asthma as reported in the Canadian Thoracic Society Asthma Management Continuum: 2010 Consensus Summary [25]

Characteristic	**Frequency**
Daytime symptoms	<4 days/week
Nighttime symptoms	<1 night/week
Physical activity	Normal
Exacerbations	Mild, infrequent
Absence from work or school due to asthma	None
Need for a fast-acting beta2-agonist	<4 doses/week
FEV1 or PEF	≥90% personal best
PEF diurnal variation*	<10% to 15%

* Diurnal variation is calculated as the highest peak expiratory flow (PEF) minus the lowest PEF divided by the highest PEF multiplied by 100 for morning and night (determined over a two-week period). FEV1: Forced expiratory volume in 1 s

1.4.2 Medications for asthma management

Pharmacologically, the drugs used in the treatment of asthma can broadly be classified into bronchodilators and anti-inflammatory agents.

I. Bronchodilators: This class of drug remains central to the management of symptomatic asthma as they directly affect smooth muscle cell relaxation in the airway [26]. Bronchodilators can further be classified as,

i) β2-agonists: They represent one of the oldest bronchodilator classes and are known as the frontline treatment in asthma care. The broncho-dilatory effect is observed when the activation of β2 receptors present on the airway smooth muscle (ASM) leads to its relaxation. Drugs discovered early on such as ephedrine, epinephrine in this class were nonselective to α and β receptors and exhibited cardiotoxicity, which was later resolved by the development of selective β2-agonists while preserving its efficacy[27]. The β2-agonists are of two types: short-acting beta-agonists (SABA) that perform their function between 4 to 6 hours and long-acting beta-agonists (LABA) with 12 hours of activity depending upon their affinity to the receptors. Rapid onset SABAs are typically recommended for use 'pro re nata (as needed)' for relieving acute asthma symptoms and do not exhibit any anti-inflammatory properties. Salbutamol (albuterol), levalbuterol, and terbutaline are widely used SABAs and have been observed to precipitate tremors at normal therapeutic doses or tachycardia and palpitations at higher doses as potential adverse events. Unlike SABAs, LABAs including salmeterol, formoterol are preferred as long-term controllers due to the longer duration of action [28, 29].

ii) Methylxanthines: Methylxanthines act by the non-selective inhibition of the phosphodiesterase enzyme that leads to intracellular elevation of the cyclic adenosine monophosphate (cAMP) resulting in bronchodilation [30]. The most commonly used methylxanthine: theophylline, was an actively prescribed drug for

a while, but the use was later restricted due to its narrow therapeutic index that induces adverse events when plasma concentrations are above 20mg/ml [31]. Nonetheless, it has marked efficacy in mitigating three cardinal attributes pertaining to asthma: reversible airway obstruction, inflammation, and hyperresponsiveness of the airway [32].

iii) Anticholinergics: Anticholinergics exert their action by the reversible competitive inhibition of muscarinic receptors, predominantly M2 and M3, that are present on the airway smooth muscles and submucosal glands. This results in bronchodilation and a reduction in mucous secretion [33]. Among the existing licensed anticholinergics, only two drugs are currently approved to be used in asthma therapy, short-acting ipratropium, and long-acting tiotropium. Ipratropium is indicated for the treatment of reversible airway obstruction in acute and chronic asthma in conjunction with β2-agonists. In contrast, tiotropium, which has a greater selectivity to M3 receptors and a longer duration of action (9hrs), is generally preferred as add-on therapy with LABA and inhaled corticosteroids (ICS) [28, 34].

II. Anti-inflammatory agents

As the inflammatory nature of asthma is demonstrated, anti-inflammatory drugs remain the mainstay in long-term asthma control. Various drug types used in this class include:

i) Corticosteroids: The use of corticosteroids in the resolution of asthmatic symptoms has become widespread. They are one of the most used classes of medications in the treatment of asthma as they exhibit broad effects of anti-inflammatory action and properties of immunosuppression. The systemic steroids are generally reserved for emergency/rescue therapies or conditions with severe refractoriness, whereas the administration of topical inhaled corticosteroids is particularly deemed as first-line agents of controller treatment for persistent asthmatic patients [35, 36]. Inhaled

corticosteroids are considered as the most effective medications for producing long-term asthma control across all ages despite the common apprehension about the systemic side effects, and are potent in minimizing airway hyperresponsiveness along with significant improvement asthma symptoms, pulmonary function, [37] and morbidity rate reduction. In comparison to oral corticosteroid therapy, ICSs precipitate only fewer side effects due to minimal systemic absorption. Nonetheless, the usage of inhaled corticosteroids still comes with its risks. Dose-dependent adrenal suppression secondary to the use of ICSs has been noted in children and asthma patients when daily doses exceeded 1000μg [28, 37].

ii) Mast cell stabilizers: This class of anti-inflammatory agents functions by inhibiting the release of inflammatory mediators, such as histamines, that are released by mast cells when triggered by immunoglobulin E (IgE). A commonly used mast cell stabilizer is Cromolyn [28]. Known for its potent anti-inflammatory properties and having few side effects, Cromolyn is valuable in the treatment of asthma [38].

iii) Leukotriene receptor modifiers (LTMs): Discovered in the late 1900s, the mechanism of leukotriene receptor modifiers is observed to have a combined effect of both bronchodilation and anti-inflammatory properties [39]. They work blocking the cysteinyl leukotrienes from binding to their receptors that are found on the proinflammatory cells as well as smooth muscles, resulting in decreased bronchoconstriction, edema, and inflammation [40]. Although not as popular as ICSs, due to their risk of causing hepatotoxicity, LTMs are used as an alternate therapy in mild to severe persistent asthma [28].

iv) IgE binding antibodies: IgE binding antibodies such as Omalizumab work by forming complexes with free IgE circulating found in the plasma, ultimately inhibiting the IgE from binding to surface receptors that would otherwise trigger the release of inflammatory mediators. The usage of this therapy has shown a decrease in the number of IgE receptors on mast cells and basophils over time.

Although this drug class shows potential in airway remodeling, one of its major drawbacks is its risk for anaphylaxis [28].

In addition to the pharmacologic classification, drugs for asthma management can also be categorized as relievers and controllers. Relievers or otherwise termed as 'rescue' medications that open the airway quickly and relieve acute symptoms are typically used during sudden asthma attacks with noticeable symptoms or prior to the exposure to triggers such as physical exercise. Short-acting beta-agonists, anticholinergics, and systemic corticosteroids are major relievers used in this regard. They are normally delivered with a metered-dose inhaler, however, may also be administered as injection or intravenous drip in state of emergency with acute asthma attacks where airways are constricted by mucous deposition [41].

Controllers, in contrast, do not cease 'flare ups', but are preventers or 'maintenance' medications that acts on the underlying pathology by reducing inflammatory responses and thus preventing symptoms and exacerbations over long term. Commonly used controller medications include drug classes such as inhaled corticosteroids, leukotriene modifiers, long-acting B2 agonists, methylxanthines, and monoclonal antibodies [42].

1.5 Inhaler use in asthma

Appropriate delivery of anti-asthmatic drugs by inhalation is as important as its efficacy in treating patients, given the clinical characteristics of asthma. An exponential growth in the market for inhaled therapy has taken place over the past three decades with increased use by over ninety billion doses even prescribed for patients in a single year [43]. Inhaled medications unlike the systemic therapy are rapidly released and directly absorbed in the lungs avoiding first pass metabolism, therefore their effective doses used are lower and adjusted to minimize side effects. The abundance of different types of drug-device combinations (approximately 230 types), variable in design and characteristics of the device can be challenging for clinician to make an appropriate selection among them [43]. The most commonly used among the device types are pressurized metered-dose inhalers (pMDIs or MDIs) and dry powder inhalers (DPIs).

Pressurized metered-dose inhalers (pMDIs): It is widely used considering its compatibility over a large spectrum of medications and low cost. The risk of environmental and health hazards induced by chlorofluorocarbon (CFC); a propellant used in pMDIs has recently resulted in a shift into the use of hydrofluoroalkane (HFA) type of pMDI. Use of extra fine particles in pMDI formulations are helpful in minimizing oropharyngeal deposition and promoting enhanced delivery of drugs into the lungs. Many ICS formulations in this regard have achieved lower risk of pneumonia, exacerbations, and other adverse respiratory events among patients. However, patient-related mis practices such as rapid inhalation, improper positioning of inhaler, failure in emptying the lungs before and holding breath after inhalation may result in inadequate effect from inhalers [43].

Dry powder inhalers (DPIs): These types of inhalers were introduced into the clinical practice as an alternative to CFC and HFA pMDIs to mitigate the difficulties associated in synchronizing their actuation with inspiration. DPIs offering higher stability as compared to liquid formulations, however, are more prone to environmental moisture [44]. DPIs are mainly of 3 main types: capsule-based pre-metered single dose devices; preloaded multi- dose inhalers; and multiple-dose inhalers on reservoir-based design [45, 46]. As DPIs use the forceful inspiratory flow of the patients as their energy source for emptying the drug system, a failure to this can be a critical error in drug delivery occurring in 26-38% of the cases [47]. Conversely, extremely forceful inspiration may result in increased particle velocity, oropharyngeal deposition, and systemic side effects. Furthermore, improper positioning of the device and failure to empty lungs before inspiration can also be other instances of mishandling of the device [48].

The drug disposition and its kinetics in lungs is largely dependent on several parameters such as inspiratory flow rate, aerosolized drug release rate, and particle size of the inhaled drug [49]. Therefore, patient’s ability for synchronizing their inhalation in concordance with aerosol release in pMDI or produce required airflow to deagglomerate particles in case of DPIs is

pivotal in determining the drug disposition into the lungs and obtaining improved response from the use of device.

1.6 Professional guidelines for asthma management

Clinical practice guidelines are systematically developed scientific statements that are designed to help the practitioners and patients in making appropriate health care decisions to deal with specific circumstances. A burgeoning rise in the development of guidelines over the years has inundated clinicians with conflicting advice in making therapeutic decisions. The history of asthma guidelines incepts 30 years ago with the publication of the first guideline by Thoracic Society of Australia and New Zealand in 1989 [50]. Recognition of asthma as an epidemic or public health concern resulting from the spike in asthma mortality between 1970 and 1985 in New Zealand led to the public interest in adopting measures to reduce morbidity and mortality [51]. The tides of this necessity further reverberated to other initial guidelines from the British Thoracic Society [52] and a Canadian practical guideline report in 1990 [53]. However, as stated in the Canadian report, these guidelines were not regarded as ‘an absolute or definitive statement on assessment and treatment’ for asthma due to the dearth of ‘definitive information and a lack of agreement among experts on several questions’ [53]. In fact, they were consensus-based documents or expert opinions generated on population-based demand and continued producing over the next two decades in many countries.

1.6.1 Canadian Guidelines

The Asthma Committee of the Canadian Thoracic Society (CTC) in 1995 invited a meeting for reviewing the existing guideline report and assimilating recent recommendations on emergency asthma management evolved from the Canadian Association of Emergency Physicians [54] and published a consensus statement. Subsequent review to this report was later made in 1999 by the asthma committee of CTC and a group of other asthma specialists and debated it across various regional meetings. The goal was to compare similar parallel national and international recommendations to arrive at a consistent document that entails

asthma management strategies among all patient populations in both ambulatory and in-patient settings [55].

1.6.2 International asthma consensus and the Global Initiative for Asthma (GINA) guidelines

Despite the existence of national guidelines, the necessity of a global guideline to cascade health education to professionals was pivotal given the increasing prevalence of asthma. In this regard, the US's National Heart, Lung and Blood Institute (NHLBI) commenced an International Asthma project under the supervision of Dr. Claude Lenfant and released their first 'International consensus report on the diagnosis and management of Asthma' in 1992 [56]. The report was globally accepted, disseminated, and reproduced in many languages across countries.

Nevertheless, the realization that mere existence of such discrete reports are less likely to ameliorate the global asthma burden, led to initiation of 'The Global Initiative on Asthma (GINA)' in 1993 through the collaborative efforts of the NHLBI and World Health Organization (WHO) [51]. Its mission was to improve asthma care by developing recommendations from the best accessible scientific evidence and could be adapted to other regional healthcare systems. They published their first report 'The global strategy for asthma management and prevention' in 1995 which reflected the most up-to-date, evidence-based clinical recommendations on asthma and incorporated discrete chapters on epidemiology, pathogenesis, prevention, and treatment [57]. It has dramatically metamorphosized over the years and has been updated annually since 2002, by collating scientific evidence synthesized through a twice-yearly review of the existing published literature [51].

1.6.3 GINA: Stepwise asthma management

The stepwise management of asthma as recommended by GINA guidelines entails a 5-step treatment strategy as follows:

Step1: As-needed reliever

This step involving 'as-needed' (pro re nata) reliever medication is reserved for patients who are untreated, having occasional daytime symptoms (appearing twice or less/ week), or infrequent nocturnal symptoms of short duration. Patients in this stage are usually asymptomatic and exhibit normal lung function between their episodes. However, progressive deterioration of symptoms requires further initiation into controller therapy in addition to the relievers. SABA has been a preferred reliever option in most situations due to the potential for rapid relief of asthma symptoms, albeit there are inconsistencies in data regarding its long-term safety.

The risk of exacerbations and mortality has gradationally perpetuated among potential asthma patients with persistent long-term higher use of SABA [58]. A long-term study by *Haahtela et al* among newly diagnosed asthmatic patients receiving regular SABA has reported worse outcomes and impaired lung functions as compared to patients treated with low dose of ICS from inception [59]. Recently, in response to the accumulating evidence of asthma-related deaths and hospitalizations among such patients receiving SABA monotherapy, GINA has introduced an amendment that no longer recommends the use of SABA-only treatment for asthma in adults and adolescents. Instead, they warrants the use of ICS-formoterol (ICS-fast onset LABA) taken as needed as preferred reliever for asthma [60].

Step2: Reliever medication and a single controller

Treatment steps starting from 2 to 5 involves combination therapy of relievers and controllers. In Step 2, administration of low dose ICS are considered as preferred controller option among patients across all ages along with as-needed SABA or ICS-formoterol reliever based on newest recommendations. Nonetheless, alternative options such as LTRAs are also advised for patients with either concurrent allergic rhinitis, intolerable to glucocorticoids or having adverse events such as persistent hoarseness from ICS. A few more parallel options including

sustained-release theophylline and cromones [61] are also available but are not recommended given their subtherapeutic effects and susceptibility to adverse events [61-63].

Step 3: As needed reliever with one or two controllers

In this step, a combination therapy of low dose ICS and LABA either in single discrete forms or combination inhalers, with as-needed SABA (or ICS-formoterol) are recommended for relieving symptoms in adolescents/adults. As this combination therapy exhibits additive effects, low dose of ICS are typically sufficient in efficacy response but may also be increased if 3-4 months treatment of this regimen fails to achieve symptom control. This therapy consisting of the drug formoterol (LABA) in particular, has been found to be efficacious as both reliever and controller even at lower doses and are also tried as an alternate regimen in adults and adolescents [64, 65]. Mechanistically, formoterol is as efficacious as SABA and has rapid onset of action either in independent or fixed-dose combinations. It itself vindicates its potential for being used as widely preferred LABA in the combination therapy. Nevertheless, its monotherapy as a reliever is strictly dissuaded considering the development of tolerance, insensitivity, and downregulation of β2-adrenoceptors subjecting patients to increased risk of mortality [66]. It is therefore critical that LABA should be used in association with inhaled corticosteroids.

In children aged 6-11 years, the recommended option for achieving symptom control is by stepping up the dose of inhaled corticosteroid to a medium dose since the combination therapy has neither been well studied in this population nor found to be efficacious than dose escalation of ICS [67] [68]. Use of an inhalation chamber or spacer to improve drug delivery into the airways is also recommended across patients of all ages on medium to high dose of ICS if they are using a pressurized metered-dose inhaler. Alternatively, other therapeutic options such as combining leukotriene modifiers (LTRAs) or sustained-release theophylline to the low dose ICS may also be used as controller options with as-needed SABA if the preferred therapy is ineffective.

Step 4: As needed reliever with two or more controllers

Selection of treatment approach in step 4 is typically guided by prior options in step 2 and 3 albeit the basis or order of these selections would be highly relied on clinical efficacy assessed from available scientific evidence. Prior to considering a step up, patients requiring step 4 are generally requested for an evaluation of their inhaler technique, adherence to medications, or alternate diagnosis or cause of noncompliance by referring to a health care professional. Preferred treatment option in adolescents and adults are either using a combination of low dose ICS/formoterol as both maintenance and reliever regimen, or a combination of medium-dose ICS/LABA along with as-needed SABA. In children aged 6-11 years, the decision should be guided from an expert opinion.

Trials on increasing dose of ICS to high dose in ICS/LABA combination have also been tried among adolescents and adults nonresponsive to the standard preferred options, but with little additional benefits. High dose is not a regular recommendation and can only be tried on an experimental basis for three to six months in patients with uncontrolled symptoms even after medium ICS/LABA and/or a third controller. Given the potential for risk of systemic side effects such as impaired growth in children, risk of adrenal suppression, reduction in bone mineral density, skin thinning, and bruising resulting from the long-term use, it is therefore not advisable to receive long term treatment with high dose of inhaled corticosteroids on most cases [69]. Addition of tiotropium (by mist inhaler) or LTRA or low dose theophylline can also be used as an add-on secondary controller option in addition to ICS/LABA among adolescents and adults with history of exacerbations.

Step 5: Reliever with additional controllers

Patients presenting with uncontrolled symptoms or exacerbations even after Step 4 are generally referred to a specialist for evaluation of the inhaler techniques, adherence, and requirement of add-on treatment. Accordingly add- on treatment with anticholinergic tiotropium can be initiated for adolescents and adults with history of exacerbations. Alternative

treatments with monoclonal antibodies such as omalizumab (anti-IgE) and mepolizumab (anti-IL5) or dupilumab (anti-IL4) in addition to previously described relievers are several other treatment options for patients with severe allergic asthma and eosinophilic asthma, respectively.

Add-on treatment with low dose oral corticosteroids (≤7.5mg/day prednisone equivalent) may also be used as an effective alternative, but the long-term exposure is coupled with dose-related severe side effects including infections, osteoporosis, diabetes as well as psychiatric disorders [70]. It is therefore considered only if patient's symptoms are uncontrollably high with inadequate response even after Step 4 therapy.

1.7 Professional recommendations for prescribing inhalational devices

Inappropriateness in prescribing and use of inhalational devices can be troublesome in achieving optimal treatment response, leading to poor efficacy of medications, uncontrolled exacerbations, and emergency visits [47]. Literature evidence reveal that the incorrect inhaler technique affects 60 to 92% [71, 72] asthmatic patients. The variability in patients' response across multiple inhaler types and ages should be addressed by the appropriate selection and individualization of the inhalers. A dearth of information about required lung dose with many pediatric drug formulations resulting in variable response needs to be considered whenever substitution to an inhaler is made. Additionally, efficacy, cost, ease of use, convenience, and safety are several other parameters that guide a selection.

The GINA recommends the use of pressurized MDIs along with the use of a dedicated spacer in children 4-6 years old. Spacers help to synchronize the inspiration with the device actuation and retain relatively large drug particles that normally get accumulated in the oropharynx, causing oropharyngeal side effects, reduced GI absorption, and systemic bioavailability. Drugs such as beclomethasone dipropionate, budesonide with first-pass metabolism administered through pMDI are highly benefited by this mechanism. In children older than 6 years, either a dry powder inhaler or a breath-actuated pMDI or a pMDI with a spacer and mouthpiece should

be used as preferred device based on the patient's condition. Nebulizer with a mouthpiece can also be used as an alternative and are typically reserved for children with difficulties in using inhalational devices. Finally, as improper switching to multiple devices or devices that requires varied inhalational techniques can confuse patients, GINA recommends avoiding the use of multiple inhalers whenever possible.

1.8 Trends in drug prescribing in asthmatic patients

Despite having established and evidence-based expert recommendations, the use of anti-asthmatic drugs still remains suboptimal.

1.8.1 Overuse of SABA

As the inflammatory nature of the asthma is demonstrated, the importance of early initiation of controller therapy has been emphasized by guidelines for many years. However, patients in cynicism towards the affordability, efficacy, and safety of controllers expressed more propensity towards the rescue medications which should otherwise be reserved only to relieve acute symptoms.

A large study conducted in 11 European countries with 8000 patients evinced that 45% of them had presented with uncontrolled asthma, and greater than 40% used SABAs at least three times or more every week [73]. Similarly, a study by *Stanford et al* using the Medicaid database reported 17.5% asthma patients,4-17 years, using ≥ 3 canisters/year, and every increase into an additional canister resulted in 8-14% of asthma-related exacerbation [74]. In concordance with these findings, *Belhassen et al* [75]and *Hull et al* [76], indicated the prevalence of SABA overuse (≥ 12 prescriptions/year) to be ranging from 2-6% among children and 6% (≥ 13 inhalers/year) among adolescents. Nevertheless, the annual trends across different countries varied inconsistently in which the use as reported by *Belhassen et al* increased from 8.6 to 10.5% between 2007 and 2013 in the UK but remained nearly stagnant in France (5.4% - 5.2%) [75]. In contrast, a considerable decline in the SABA overuse was noticed in Canada from 1.1 -0.4% between 2002 and 2013.

Although the definition of excessive use reported across studies has been transfiguring invariably by the terms overuse, high use, inappropriate use [75, 77, 78], it is relatively evident that this trend is associated with higher risk of exacerbations, [79] hospital admissions, mortality and visits to emergency department (ED) [78, 80]. Possible reasoning to this repercussion can be described as the masking of actual severity by the overuse resulting in undertreatment and triggering potential pro-inflammatory effects such as enhanced allergen response, insensitivity to SABA, or downregulation of the β receptors [81, 82].

1.8.2 Underuse and high dose of ICS

Unlike the overreliance noted with the case of SABA, ICS are commonly underused or used at a higher dose than the threshold and are variably referred by different terms across studies as, but not limited to 'suboptimal', 'underuse' and 'unlicensed use'. *Hull et al* [76] described the use of ICS less than 10 canisters/year as suboptimal, whereas a Japanese study categorized the frequency of use as: 'almost every day (≥ 4 d/week), "used occasionally" (1-3 days/week), 'used less than once/week' and 'not used' in a month before an exacerbation [83]. A better examination of the underutilization was made by *Laforest et al* by calculating the ratio of ICS used against the total dispensed anti-asthmatic medications (ICS/R03) and discovering that the patients with low ratio were more susceptible to asthma exacerbations [84]. In general, ICS underuse/no use is apparent and observed from 38% to 76% among asthma patients across various studies [76, 83].

Prolonged use of high dose of ICS has also been a major concern. The recommendation from GINA discourages its use above 500 µg/ day [2] (fluticasone propionate or equivalent) among patients with moderate to severe asthma unless it is essential, considering the risk or systemic side effects. Nonetheless, it has become more common and a report from Australia revealed that over 2/3rd of daily ICS doses were provided as high dose preparations [85]. *Turner et al* in a longitudinal study elicited similar findings showing the surge of ICS prescriptions (>800 mg/day) from 1.1% to 4.6% between 1992 and 2004 among children 5-11 years [86].

Comparable findings were also noted by *Elkout et al* and a Scottish study in varying proportions [77, 85].

1.8.3 Monotherapy of LABA

Despite the recommendations from GINA for using LABA concomitantly with ICS in the Step3 stage of the therapy, incidents with chronic exposure to monotherapy of LABA have been widely reported. A study by *Morales et al* using Scottish database identified LABA prescriptions in separate inhalers in 7.6% asthma patients among which 17.7% were on either sustained (5.8%) or episodic (11.9%) monotherapy [87] and the authors attributed sustained monotherapy to irrational prescribing whereas episodic to be caused by ICS non-adherence. ICS nonadherence occurring in up to 60% of asthma patients and risking to higher morbidity can be resulted due to multiple reasons ranging from complexity of treatment regimen, apprehensions on steroid side effects, and failure in identifying asthma symptoms [88]. Findings from *Morales et al* was consistent with a Dutch study by *de Vries et al* which reported LABA monotherapy in 9% [89] children and a similar US study reporting it in 11% users [90]. Even though LABA bronchodilators improve the lung function and overall quality of life, chronic exposure to monotherapy precipitates tolerance and insensitivity even to SABA leading to adverse outcomes. Premature termination of a randomized trial called SMART in 2006 that reported greater incidence of asthma-related deaths (RR-4.37) or life-threatening experiences (RR- 1.71) in patients receiving salmeterol (LABA) as compared to placebo[91], exemplifies the magnitude of possible adversities.

1.8.4 Antibiotic prescribing in asthmatic patients

Antimicrobial resistance is a major threat leading to increased medical costs, prolonged hospital stays, morbidity, and mortality. Professional guidelines [92, 93] do not recommend the unnecessary use of antibiotics in acute asthma as almost 80% [94] of the asthma exacerbations are identified to occur from respiratory viruses. Despite this, it is evaluated that 15-25% of children presenting with wheezing episodes or asthma receive antibiotics [95-97].

A recent study in the US reported nearly three-fold higher likelihood of antibiotic treatment among asthmatic children and adolescents hospitalized in general hospitals with minimum pediatric support as compared to specialized pediatric hospitals [98]. Comparable findings of antibiotic overprescribing was also noted in a Dutch study by *Baan et al* with 197/1000 PY (person-years) asthma patients reporting antibiotic usage as compared to non-asthmatics (126/100 PY), and 14% of them being reportedly given for an asthma exacerbation [99].

Not only the rate of antibiotic prescription but also the type of antibiotic has also been found to influence the resistance pattern. Broad-spectrum antibiotics or macrolides in particular are associated with greater risk of resistance [100]. However, despite the refractoriness a fifteen-fold rise in its use among preschool children was observed in a study by *Kozyrskyj et al* [101].

1.8.5 Use of multiple inhalers

Incorrect inhalation technique prevailing up to 94% [102] patients and its risk to poor asthma control has been widely investigated with regard to potential factors contributing to it. Few such factors include age, gender, diagnosis, emotional problems, education level, and type of device[103]. In addition to these, the use of multiple inhalers has now been accounted as a major determinant to improper technique due to the overabundance in the availability of various device types. A study by *J. Van der Palen et al* demonstrated that 35% of asthma patients receiving two types of inhalers had errors in using the device, which escalated to 64% with three devices[104]. Similar findings were also reported by *Rootmensen et al* with 50% inhalational errors among patients using multiple devices[105]. Furthermore, the clinical consequences of inconsistently switching to different inhalers was recently reported by *S. Principe et al* with significant correlation between the rate of switching and asthma exacerbations.

1.8.6 Role of vaccines

Patients with asthma have increased susceptibility to influenza, which is an acute respiratory illness caused by influenza virus. Chronic inflammation of the airway and type 2 immune

responses can impair antiviral immunity among asthma patients predisposing them to a higher risk of asthma attacks following infection with influenza virus [106]. The WHO recommends annual immunization with flu vaccine irrespective of age, however, the uptake in at-risk patients especially in asthma is below 75% [107]. Apprehension among patients and health care providers regarding the safety and efficacy of the vaccine might be some among the multifactorial reasons for this underuse [108]. A systematic review by *Vasileiou et al* concluded that the flu vaccine counteracts 59-78% of asthma attacks that requires emergency room visit or hospitalization [107]. Similarly, in another retrospective study in children 0 to 12 years old with asthma, a beneficial clinical effect was identified in vaccinated preschool children. While these results are of great interest, some major drawbacks like lack of adjustment for asthma severity and recall bias are to be noted [109].

Pneumococcal vaccines can also have effect on asthmatic patients in such a way that they prevent infections form *Streptococcus pneumonia* and tend to reduce the risk of developing associated morbidity from pneumonia among patients with asthma. Therefore, it has been routinely encouraged to use in patients with asthma. However, there is still uncertainty in evidence regarding the actual intake. A review by *Sheikh et al* explored the existence of any scientific evidence pertaining to the efficacy of the vaccine and found that in a subset of 30 children in a study, the vaccine was effective to reduce the incidence of exacerbations of asthma from 10 to 7 exacerbations/ child/year [110]. However, it still poses inconclusiveness in evidence and has to be subjected to further studies.

1.9. Rationale for the study

In recent years, several national and international guidelines have been published for the use of anti-asthmatic drugs to help clinicians improve the management of children and adolescents with asthma. However, despite having such high-quality guidelines, over half of the asthmatic patients are inadequately controlled [111]. Control of childhood asthma remains unacceptable in 33% of children and only 25% of children have optimal disease control [112]. Among children hospitalized for an asthma exacerbation, 2/3rd are undertreated or not effectively

managed [112]. Poor control of asthma results in adverse clinical and economic outcomes [113, 114]. Potential factors that have been attributed as indicators of inadequate asthma control could either be patient-related including patent/ parent errors, lower adherence to the treatment, or prescriber-related such as deviance from guideline-recommended care to the actual care [111]. The rates of patients' non-adherence have been reported ranging from 32 - 50% across various studies [115-117]. With regard to prescriber-related reasons, conflicting recommendations among available guidelines, ambiguities about their validity, robustness, and contemporaneity may result in such divergence and has been questionable over time [118]. In Canada, the guideline published by the Canadian Thoracic Society (CTS) were last updated in 2012 [119] and recently in 2021 [120]. Unlike this, international guidelines like GINA, which is evidence-based, globally relevant across regional jurisdictions get periodically updated with updates almost every year. Given a large number of children and adolescents with 'uncontrolled' asthma, regardless of the severity of the disease, the issue of physicians' nonadherence to expert recommendations has been a subject of concern in several studies [77, 89, 121-125]. However, many of these studies represented only practitioners from a specific discipline such as concerning either general practitioners or pediatricians, addressed only a specific therapeutic class of anti-asthmatic drugs or a type of inhalational device, and have studied relatively smaller number of children. Furthermore, longitudinal population studies are lacking, and very few studies have aimed to assess the association between prescriptions compliance with expert recommendations and their negative consequences on asthma control. In Canada, no study has evaluated the adherence to expert recommendations for the treatment of childhood and adolescent asthma, nor quantified the implications of this misuse.

Chapter 2: METHODOLOGY

2.1 Study design

This was a population-based, retrospective, longitudinal cohort study spanning 2013-2017, conducted using the health administrative data for children and adolescents housed at the Manitoba Centre for Health Policy (MCHP). Expert recommendations on asthma management in children and adolescents were defined according to major treatment recommendations produced by GINA over the study years and selected due to the obsoleteness of CTS guidelines after 2012.

2.2 General research objectives

This study aimed to describe the pattern of use of asthma-related drugs (anti-asthmatics, oral corticosteroids, antibiotics, vaccines) and medical devices in asthmatic children and adolescents, to evaluate non-compliance to expert recommendations with regards to anti-asthmatic drug prescribing and to evaluate the clinical consequences of this misuse.

2.2.1 Specific objectives

1. To describe the modalities of use of anti-asthmatic drugs (ATC R03), oral corticosteroids, and medical devices (inhalation chambers) regarding user profiles, characteristics of prescriptions and prescribers, and trends over time.

2. To quantify the use of prescriptions (anti-asthma drugs and medical devices) that do not comply with expert treatment recommendations.

3. To describe the modalities of use of antibiotics in asthmatic children and adolescents regarding quantification of use, the profile of users and prescribers, characteristics of prescriptions (types of antibiotics prescribed), and trends over time.

4. To compare the use of antibiotics within 2 years of the diagnosis of persistent asthma between asthmatic children and adolescents and non-asthmatic matched controls.

5. To describe the use of influenza vaccination among asthmatic children and adolescents.

6. To evaluate the consequences of noncompliant and suboptimal use of anti-asthma drugs and medical devices for inhalation, and vaccination on the number of asthma exacerbations.

2.3 Source of data

The following databases were used in the study: Drug Program Information Network (DPIN), Emergency Department Information System (EDIS), Hospital Abstracts, Manitoba Immunization Monitoring System (MIMS), Medical Claims / Medical Services, Employment, and Income Assistance Data (EIA) (SAMIN), Manitoba Health Insurance Registry, Provider Registry/Physician Master File as relevant, valid sources with quality assessment using MCHP's data quality framework [126] that explains the comprehensive evaluation of quality process performed at acquisition level and handling data [127, 128].

1) **Drug Program Information Network (DPIN):** It is an online, electronic drug database that connects Manitoba Health with all outpatient pharmacies present in Manitoba and is regularly updated. The DPIN records the complete drug profile of prescription medications for each client at the point of distribution. Information pertaining to the dispensed medications and non-drug products (eg: Drug Identification number (DIN), Therapeutic class, active ingredient, strength, dosage, route of administration, matric quantity claimed, days of supply), and prescription information (eg: prescriber ID number, dispensed date) are captured in DPIN at the point of sale, regardless of their age and insurance coverage. However, services delivered in hospital pharmacies, nursing stations, and outpatient visits are not recorded in this database.
2) **Medical/Physician Claims:** This database also known as physician billing claims, stores data in the large repository of the Medical Services Database, and it contains information about physician claims submitted to the provincial government by individual physicians for their services. It comprises ambulatory physician service information including the type of service, date, who sought the service, and tariff rates. Typically, physicians get paid either under the fee-for-service method based on the

claims submitted or by a surrogate payment plan (session rate, contracts, etc.) for which claims are submitted just for administrative purposes, otherwise called "shadow billing".

3) **Hospital Abstracts:** The database is managed by Manitoba Health and includes demographic data, summaries of administrative and clinical data submitted by the hospitals in Manitoba which are collected during in-patient admissions and completed during discharge of patients after their hospitalization for acute or chronic reasons. Diagnostic data are coded based on the International Statistical Classification of Diseases and Related Health Problems (ICD 9-CM till March 31, 2004, and ICD 10 from April 1, 2004). Records of both the residents and non-residents hospitalized in Manitoba health care facilities in addition to the abstracts of Manitobans admitted in out-of-province hospitals are submitted and documented in this database.
4) **Emergency Department Information System (EDIS):** The EDIS database contains detailed information about patients' emergency department (ED) visits from their point of entry in triage to their discharge. It contains two datasets: 1) Emergency - Admissions, Discharge & Transfer (ADT) and E-Triage data, 2) Emergency Department Information System (EDIS) data. Prior to 2009, the former captured ED data but was basically limited to patients' arrival, (date, time, method), discharge, duration, and computer-generated Canadian Triage & Acuity Scale (CTAS) scores that assess patients' urgency of treatment. The latter, in comparison to this, was established in 2009/2010 and maintains complete records of ED visits under Winnipeg Regional Health Authority (WRHA) including prior ED history, diagnosis, orders, and test results that were absent in the former.
5) **Manitoba Immunization Monitoring System (MIMS):** Maintained by Manitoba Health, it contains information on the immunization status, histories of Manitoba Health registrants, and provides reminders to ensure the receipt of recommended immunization at proper times. Captured data includes vaccine type, vaccine sequence schedule, provider information, service date, and some patient demographics obtained from the Manitoba Health Insurance Registry. However, vaccination details

of clients from First Nation communities and immunization provided by private companies are not recorded in this database.

6) **Employment and Income Assistance Data (EIA) (SAMIN):** The EIA data is captured by the Social Allowances Management Information Network (SAMIN) database maintained by the Department of Families and includes information about clients under the Employment and Income Assistance Program, who receive financial support. Only one record of an individual every month is stored, and it basically comprises patient or family level information about demographics, education, employment, and income.
7) **Manitoba Health Insurance Registry:** Maintained by Manitoba Health, it keeps a record of all clients registered with Manitoba Health since 1970. Client-level data constitutes demographics, family composition, postal codes, date of birth, and migration in/out of the province. Information about individuals such as federal inmates and military personnel who are federally insured is not recorded. Manitoba Health sends "snapshot files" of this data semiannually to MCHP.
8) **Provider Registry/Physician Master File:** This database is maintained by Manitoba Health and contains a snapshot of de-identified information specific to providers and their practice such as their specialty, date of birth, physical location, practice years, and payment methods. MCHP receives this data as quarterly updated by Manitoba Health.

MCHP provides de-identified data from the administrative records of Manitobans to protect personal privacy. De-identification is processed by removing any possible patient-specific identifiers such as names or addresses before the data is transferred to MCHP. Distinct personal health identification numbers (PHIN) are encrypted in the form of scrambled PHIN in MCHP that helped in linking the databases or their subsets and for detecting individual-level temporal associations. Ethics clearance for the study was received from the Health Research Ethics Board at the University of Manitoba (HREB) [#HS22203 (H2018:393)] and the Health Information Privacy Committee (HIPC) [# 2020/2021-49].

2.4 Cohort definition

2.4.1 Study population:

(1) All children and adolescents (5-17 years) included in the aforementioned databases under MCHP between 01/01/2013 and 31/12/2017. Children under the age of 5 were excluded because the clinical diagnosis of asthma in this age group is particularly difficult due to the difficulty in spirometric measurements and frequent occurrence of episodic respiratory symptoms in children without asthma that may lead to misdiagnosis [129, 130].

(2) are registered in the MCHP (having Manitoba provincial health insurance) at least two years before the first dispensing of an anti-asthmatic medication.

A. Asthma cohort: Children and adolescents from 01/01/2013 to 31/12/2017 who received at least one anti-asthma medication (ATC code: R03) * during the study period (first dispensing in the study period = date of entry in the cohort = index date). Asthma diagnoses were confirmed by one or more hospitalizations with a diagnosis of asthma: ICD–9 code 493; ICD–10 code J45, OR one or more physician visits with a diagnosis of asthma (same codes) during the study period. (*ATC codes in Appendix 1). Patients diagnosed with the following diseases were excluded: cystic fibrosis (ICD9: 277; ICD 10-E84.0), chronic obstructive pulmonary diseases (ICD–9: 491, 496; ICD 10- J44.0). This exclusion was based on the assumption of avoiding probable misclassification and overlapping resulting from the usage of the same medications across these conditions.

2.4.2 Predefined subgroups based on medication usage patterns:

a) The asthma cohort was mainly subdivided into two categories based on the history of asthma medication use: prevalent/existing users and incident/new users.

A prevalent drug user is defined as a child or adolescent who has received at least one anti-asthma medication in the period under review for analysis with its prior history in 24 months before the index date. A new user of an anti-asthmatic drug is defined as a child or adolescent who has received at least one anti-asthma medication in a specific year and without its receipt in 24 months before the first issue of the year in question. As irrationalities in prescribing is anticipated to be more prominent in new users, only new users were considered for the study.

b) The new anti-asthmatic medication users were then subclassified based on the type of drug user into three mutually exclusive classes:

   i) *Occasional users*: Patients receiving only one unique dispensing in the first 12 months from index date (first year follow up)

   ii) *Moderate users*: Patients with 2 time dispensing of anti-asthmatic drugs in the first 12 months or ≥ 3 dispensing of anti-asthma medications in <3 different trimesters of the year.

   iii) *Frequent users*: Patients with ≥3 times dispensing of anti-asthmatic drugs in the first 12 months with at least one dispensing in 3 different trimesters of year.

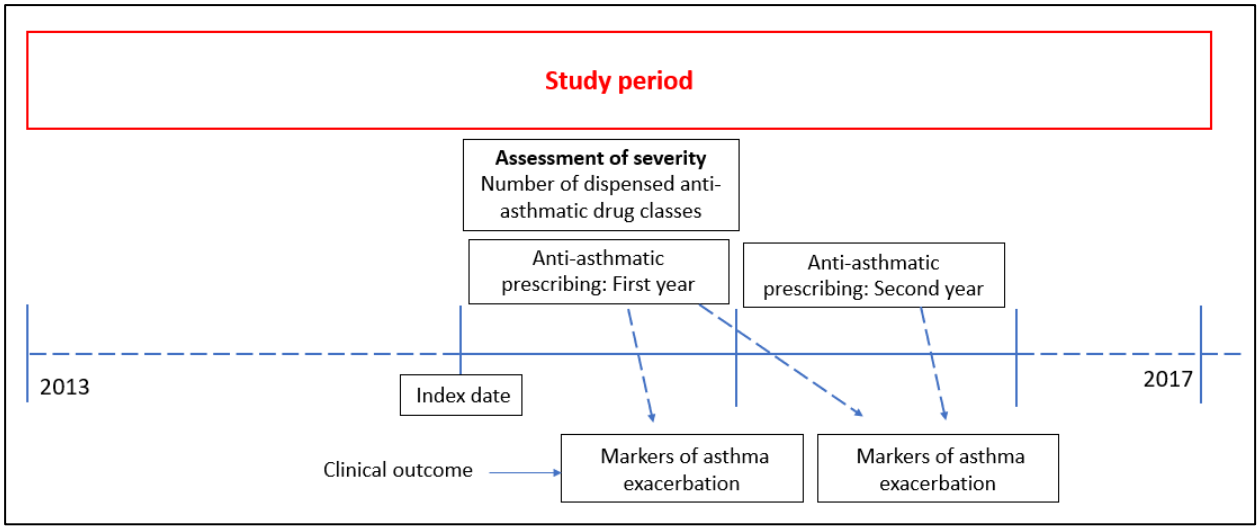
This definition was adapted from a study by *Bianchi et al* [131] and from expert opinion. The occasional users with confirmed asthma diagnosis were considered to be patients corresponding to either intermittent asthma or exercise-induced asthma [131] and hence considering the infrequent use of medications, they were not included in the analysis. Therefore, only moderate and frequent users anticipated having persistent asthma were selected for the study analysis.

2.4.3 Non-asthmatic matched control

The control group used for assessing the antibiotic use against the asthma cohort was matched by 3 participants for every 1 persistent asthmatic patient (moderate and frequent users) based

on the index date, birthdate (± 90 days), sex, and postal code (using first 3 digits of the postal code referred as forward sortation area (FSA). These parameters helped to minimize the confounding influences by the age group, sex, and geographic region. All children and adolescents other than the asthmatic cohort included in the Manitoba Health Insurance Registry database between 01/01/2013 and 31/12/2017 were eligible for control group.

Figure 1: Overview of the QUAST Study design



MCHP data collected at least two years before the first anti-asthma medication dispensing was used to verify the medical history, particularly the baseline comorbidities and prior exposure to anti-asthma medications. The potential new asthmatic children and adolescents except for the occasional users of the study were followed until 1) 2 years from the index date, 2) their death, or 3) move out of province.

2.5 Exposures of interest

Exposures of interest included all anti-asthma medications (ATC: R03), oral corticosteroids (ATC: H02), inhalational devices, antibiotic medications (ATC: J01), and vaccinations (influenza (J07AG, J07BB) and pneumococcal vaccine (J07AL)). To determine whether oral corticosteroids (OCS) were prescribed for asthma indication, patients having diagnosis of

several other overlapping conditions for which OCS are commonly administered were excluded (given in the order of ICD9; ICD 10 codes): Systemic lupus erythematosus (710; M32), Scleroderma (710.1; M34), Juvenile dermatomyositis (710.3; M33.0), Crohn's disease (555; K50), ulcerative colitis (556; K51), juvenile rheumatoid arthritis (714; M05), emphysema (492; J43), bronchiectasis (494; J47).

Users of the drugs and medical inhalation devices of interest were identified via the ATC codes (3rd level) corresponding to the pharmacological class and then the individual molecules (5th level) included in each class. Corresponding ATC codes of each class of drugs, vaccines, and inhalational devices are described in Appendix Tables 1-5.

2.6 Patient and prescriber characteristics

The reported characteristics of the study participants included demographics collected at the treatment baseline such as age, sex, geographical region (rural/urban), socioeconomic status, the severity of asthma, and comorbidities.

Socioeconomic status (SES) was measured by using a scale called socioeconomic factor index (SEFI) [132] in order to estimate the likelihood of receiving suboptimal asthma treatment among participants with low SES as noticed in previous literature [133, 134]. The SEFI is a factor score assigned to the residents based on the postal code and is derived from the Canadian Census data using four variables such as unemployment rate for people with age 15+, the proportion of single-parent households, proportion of 15+ aged people without high school graduation and average household income which categorizes people into SEFI <0 (ideal SES) and >0 (poor SES) [132].To determine the severity of asthma, children's prescribed asthma medications were used as a proxy and categorized them into 3 groups based on the number of classes of drugs dispensed (including oral corticosteroids): Mild (Patients receiving only 1 class of drug), Moderate (2 classes of drugs), Severe (3 or more classes of drugs where one is an inhaled anti-inflammatory). This definition is aligned with the medication-based asthma

index explained by *Wendy et al* [135], *Taylor et al* [136] and used in an administrative database study by *Laforest et al* [84, 135].

Comorbidities were assessed by the presence of ICD 9/ICD10 codes as a primary or secondary diagnosis in 2 years prior to the index date for the following conditions: Atopy {(Atopic dermatitis (691*; L20*), Allergic rhinitis (477*; J30*), Chronic rhinitis (472, J31), Chronic sinusitis (473, J32), Anxiety (300.0*; F40, F41), Depression (311; F32, F33) GERD (530.11, 530.81; K21*), Pneumonia (480-486; J12-J18). (* *Wild cards used*)

Characteristics of prescribers collected during the follow-up period primarily constituted the prescriber profile such as their type or specialty which included but not limited to pediatricians, allergists, general practitioners/physicians, and other specialists.

2.7 Prescribing quality indicators

The quality of prescriptions of anti-asthmatic drugs, antibiotics, inhalational devices, and their compliance to expert recommendations was measured with regard to the following indicators:

a) Overuse of SABA

The use of SABA was quantified based on the number of canisters/boxes dispensed per year. To account for multiple doses and different types of SABA canisters, a standardized canister unit was fixed as 200 doses, since it was most frequently distributed in our data. SABA overuse was calculated on an assumption that a patient with well-controlled asthma used 2 puffs on each occasion and not more than twice a week, which approximated to a maximum of 2 canisters per year as described in previous studies [137, 138]. Therefore, the collection of 3 or more canisters per year in practice was considered as overuse. Patients were grouped into classes based on this definition in the follow-up years as 0 [No SABA], 1-2 [appropriate use], ≥3 [overuse] {3-5, 6-10 and ≥11 (excessive use)} [138].

b) Inhaled corticosteroid to total asthma drug (ICS/R03) ratio

The ratio of the number of prescribed ICS units (either in a single inhaler or fixed-dose combinations with LABA) to the total units of asthma drugs dispensed (R03) per person per year in the follow-up period was computed and categorized as follows: 0% (no ICS), 0% to <50% (low ratio) and ≥ 50% (high ratio) [84]. Selection of this 50% ratio threshold was driven by evidence from previous studies [139]. For estimating units, we performed the following calculations [140]: a) 1U of oral medications was equivalent to 1 dispensing unit/pack estimated based on the pack size. b) 1U of inhalational solutions and suspensions was equivalent to 1 unit volume c) 1 unit claim of solutions for injections was counted as 1U d) In case of inhalers, 1U was 1 canister, and prescribed unit doses <1 were also counted as 1U. The number of units was calculated by diving the total dispensed dose by the actual product dose available in product monographs. While calculating final ICS/R03 ratios, decimals were also rounded off to the nearest whole number.

c) Non-compliant prescriptions.

The following situations of use of anti-asthmatics and inhalations devices were considered as not in conformity with the expert recommendations (GINA 2012-2017):

First-year dispensing data

a) Absence of short-acting β2-mimetics (SABA) dispensing
b) Dispensing of long-acting β2-mimetics (LABA) in monotherapy
c) Absence of dispensing of a medical inhalation device
d) Dispensing of several types of medical inhalation devices except those associated with SABA (measured from 01/Jan/2015)
e) Dispensing of dry powder inhaler in the first intention in children <8 years old
f) Dispensing of an anti-asthmatic metered-dose inhaler without an inhalation chamber except those in 'autohaler' form.

Second year dispensing data

a) The absence of inhaled corticosteroids (ICS) in patients of moderate and high severity (= use of ≥2 classes in the first year)
b) Duration of inhaled corticosteroid treatment <3 months in patients of moderate and high severity (= use of ≥ 2 classes in the first year)
c) Dispersion of LABA in monotherapy
d) Dispensing of several types of medical inhalation devices except those associated with SABA (measured from 01/Jan/2015)
e) Dispensing of an anti-asthmatic dry powder inhaler in new users <8 years old
f) Absence of SABA dispensing (measured till 01/Jan/2015)
g) Absence of dispensing of an inhaler
h) Dispensing of an inhaler without an inhalation chamber except those in 'autohaler' form.

The dispensing of multiple inhalers in both years was assessed in an assumption that multiple inhaler techniques lead to confusion among anti-asthma medication users. Therefore, they were considered as contributing to non-compliant prescriptions when they were prescribed as either: a) separate DPIs and MDIs b) Among DPIs, that require distinct actuation procedures such as Diskus, Turbuhaler, Ellipta, Twisthaler, Handihalers. Furthermore, this parameter was measured only from 01/Jan/2015 as this recommendation was introduced in May/2014 GINA guidelines, allowing for the prescribers to be acquainted with it in the following 7 months period. Similarly, the use of MDIs without a spacer device was only measured for children (5-11 years) as advised by the guidelines assuming adolescents being able to use it properly and also measured in both the follow-up years considering the need for replacement of spacers at least once a year. However, accounting for the possibility that spacers can also be purchased ‘over the counter’, it was not kept in the final analysis. With regard to the absence of SABA dispensing, this parameter was also measured in the second year considering the normal expiry of SABA canisters (prescribed in the first year) in 12 months and thus the expected need for another canister at least once in the second

year. However, as per the GINA recommendation introduced in May/2014, a low dose ICS/LABA was also alternatively preferred as a reliever other than SABA among adolescents adequately managed with ICS/LABA as controller. As we expected all new patients to be stabilized on their controller treatment by the end of first year, measuring this parameter post May/2014 (or 01/Jan/2015 considering dissemination time to the prescribers) in the second year would lead to overreporting and hence was only limited to this time frame. Patients were categorized as having non-compliance prescriptions (yes/no) after applying these recommendations.

d) High dose of ICS

The comparison of dose of ICS was achieved by calculating the daily dose of ICS and verifying it with the standard doses advised by the GINA. In the absence of prescribing instructions, the calculation of daily ICS dose was approached by using the total dispensed matrix quantity and days of supply [141]. In order to account for multiple types and doses of ICS among individual patients, their fluticasone equivalent doses were calculated based on their relative topical potency and expert opinions [142]. Fluticasone propionate was selected as the standard since it represented majority of the prescriptions in our study. Dose equivalencies used in the study were: Children (6-11 years): 50µg of Fluticasone propionate, 40µg of beclomethasone, 40µg of budesonide, 16µg of ciclesonide, 44µg of mometasone; Adolescents (12-17 years): 50µg of Fluticasone propionate, 100µg of beclomethasone, 80µg of budesonide, 32µg of ciclesonide, 44µg of mometasone , 20µg of fluticasone furoate [143]. Fluticasone equivalent doses of each product were converted into their daily ICS doses by using the following method: (1) Fluticasone equivalent dose (matrix quantity claimed) was multiplied by the strength of each product to get the total dose 2) Total dose/days of supply gives the daily ICS dose 3) Daily dose was classified as: Children: low (100-200 µg), medium (>200-500 µg), high (>500 µg); Adolescents : low (100-250µg), medium (>250-500 µg) and high (>500 µg [141, 143-145].

Table 4: Daily dose of inhaled corticosteroids in fluticasone equivalence [24]

Children				
Drug	**Daily dose (µg)**			**Fluticasone equivalent dose***
	Low	**Medium**	**High**	
Fluticasone propionate	100-200	>200-500	>500	1.0 (Reference)
Beclomethasone	100-200	>200-400	>400	1.25
dipropionate	100-200	>200-400	>400	1.25
Budesonide	80	>80-160	>160	3.125
Ciclesonide	110	≥220-<440	≥440	1.14
Mometasone furoate				
Adolescents				
Fluticasone propionate	100-250	>250-500	>500	1.0 (Reference)
Beclomethasone	200-500	>500-1000	>1000	0.5
dipropionate	200-400	>400-800	>800	0.63
Budesonide	80-160	>160-320	>320	1.56
Ciclesonide	110-220	>220-440	>440	1.14
Mometasone furoate	100	N/A	200	2.5
Fluticasone furoate				

*****Fluticasone equivalent dose calculated from the stated 'high dose' from the GINA guidelines

e) Antibiotic use

The description of antibiotic consumption across children and adolescents was reported with respect to the dispensed drug classes, individual drug molecules, and the number of courses of antibiotics used (0, 1-2, ≥3 courses) and was compared against non-asthmatic matched controls. Corresponding therapeutic indication for antibiotics use was described based on the ICD codes provided in Appendix table 6. The ratio between

the number of broad-spectrum and narrow-spectrum antibiotic users (B/N ratio) was computed to investigate the quality and balance between these prescriptions, in which a lower ratio implies the most appropriate prescribing [99].

2.8 Outcome definitions and covariates

2.8.1 Prescribing pattern

We described the prescribing pattern by reporting the number/proportion of patients prescribed with the drugs of interest and also based on the aforementioned quality indicators in 24 months follow-up period from their index date. Annual trends in prescribing stratified by age and sex over the study period was also reported.

2.8.2 Clinical outcome

The clinical outcome was the proportion of patients presenting with ≥ 1 exacerbation of asthma in first year and second year from the index date. Asthma exacerbation was defined as a composite outcome of one or more hospitalization(s) or emergency department (ED) visit(s) with a primary diagnostic code for asthma (ICD 10: J45) or receipt of OCS associated with asthma [146]. The following covariates were assessed:

<u>Demographic covariates</u>:

- Age (5-11, 12-17)
- Sex
- Location of residence: Rural, Urban
- Socioeconomic status: SEFI (<1 or >1)
- Baseline comorbidities: Atopy (Atopic dermatitis, Allergic rhinitis), Rhinosinusitis (Chronic rhinitis, Chronic sinusitis), Anxiety, Depression, GERD, Pneumonia

<u>Health related covariates</u>

- Asthma severity (based on the number of dispensed drug classes)

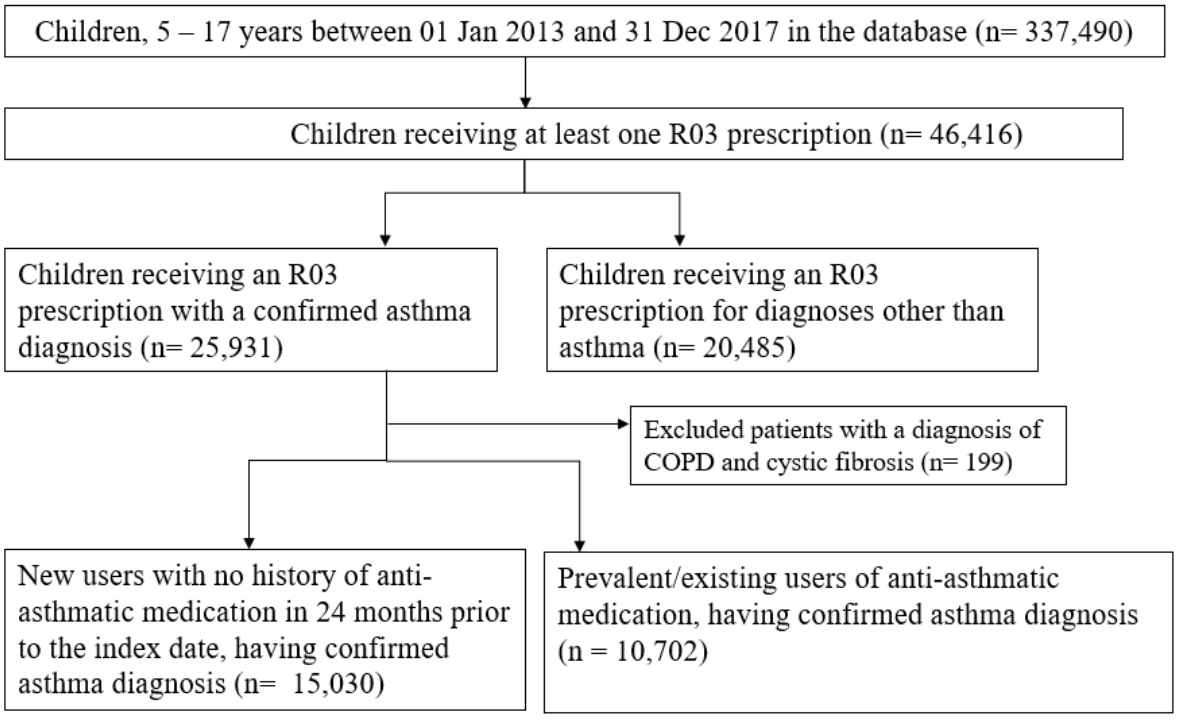
2.9 Statistical analysis

The annual prevalence of users of the drugs of interest (anti-asthmatic/antibiotics) with confirmed asthma as crude and by age, sex, type of drug (3rd level of the ATC code), was expressed as the number of people who have benefited from at least one drug delivery in a specific year, divided by the number of person-years of all individuals in the study population during the year in question. Similarly, the annual incidence of users of anti-asthmatic drugs, crude and by age, sex, type of drug (3rd level of the ATC code), was expressed as the number of patients starting treatment per 1000 affiliated person-years registered in the database. The characteristics of prescriptions, prescribers, and patients were described by absolute numbers (percentages) for categorical variables and means (± SD) or medians (1st quartile (Q1) - 3rd quartile (Q3)] for quantitative variables. 95% bilateral confidence intervals (CI) were used for reporting each estimate. Chi-square (χ^2) test was performed for comparisons between persistent asthma patients and matched control groups in order to assess the differences in the distribution of antibiotic use. Trends over time in the prevalence and incidence of asthma was estimated by using Poisson regression model. Crude prevalence/incidence rates and rates stratified by age and sex was further determined and expressed with rates and confidence intervals. Adjustments were made when potential interaction between age*sex was observed. Concerning the primary clinical outcome, confounders were priori defined (age, sex, socioeconomic status, region of residence, comorbidities, severity of asthma measured by the number of dispensed drug classes) and in addition, univariate logistic regression was run to test the additional relationship between the exposures of interest and outcome. Covariates that significantly affected the crude odds ratio (e.g. number of antibiotic courses) was also retained in the final model. Multivariate logistic regression model performed thereafter, evaluated the true relationship between the impact of the non-compliant prescriptions, ICS/ R03 ratio, overuse of SABA, high dose of ICS, and flu vaccines on the likelihood of having acute exacerbations of asthma after adjusting for confounders. A p-value < 0.05 was considered to be statistically significant for estimates of coefficients. Hosmer-Lemeshow (HL) test was used for testing model fit ($p > 0.05$ indicating good fit). All statistical analyses were performed using SAS software version 9.4.

Chapter 3: RESULTS

There were 337,490 children and adolescents, 5-17 years old in the province of Manitoba between 2013 and 2017. The population of interest, defined by children and adolescents receiving at least one anti-asthmatic drug prescription (R03) among the study population constituted a total of 46,416 for which 273,878 prescriptions were issued during the study period. Out of these users, 25,931 of them had a confirmed asthma diagnosis identified by the diagnostic codes with a physician claim or hospital visit during the study period. There were 20,485 children and adolescents who received anti-asthma medications for diagnoses other than asthma. Individuals with comorbid diagnostic codes for COPD (n=157) and/or cystic fibrosis (n=42) were excluded. A total of 25,732 asthmatic patients met inclusion criteria, among which 10,702 were existing users of anti-asthmatic drugs and 15,030 users were considered as new patients based on the absence of history of anti-asthmatic drugs in 24 months prior to their index date.

Figure 2: Flowchart illustrating the patient flow in the study



3.1 Patient demographics

The cohort comprised a greater proportion of males as new users and prevalent users, 7770 (51.70%) and 6392 (59.73%) respectively as compared to females. Similarly, children (5-11 years) occupied 59.60% and 60.45% of new and prevalent users respectively in comparison to adolescents. and the mean age at baseline observed among both the users (10.51±3.74 and 10.45±3.68) was consistent. The socioeconomic status of patients determined at the baseline using SEFI denoted more than half of the new (50.20%) and prevalent (52.94%) users as belonging to the 'high' category. For a mere proportion (7.97% and 5.8%) of new and prevalent users, the SEFI could not be assessed corresponding to the factors related to its determinants such as missing postal codes, suppressed census data (e.g.: First nation community). Region of residence categorized primarily into urban (includes cities: Winnipeg and Brandon) and rural (rest of the cities) also represented a considerable proportion of the new (66.45%) and prevalent users (67.45%) as living in urban cities.

Table 5: Patient demographics among new and existing users of anti-asthmatic medications

Baseline characteristics	**New users, n (%)**	**Prevalent users, n (%)**
Sex		
Male	7770 (51.70 %)	6392 (59.73%)
Female	7260 (48.30 %)	4310 (40.27%)
Age at entry		
Children (5-11 years)	8958 (59.60 %)	6469 (60.45%)
Adolescents (12- 17 years)	6072 (40.40 %)	4233 (39.55%)
Age, Mean ± SD	10.51±3.74	10.45±3.68
Socio economic status		
High (SEFI <0) *	7546 (50.20%)	5666 (52.94%)
Low (SEFI >0)	6285 (41.81%)	4408 (41.18%)
(Missing)	1199 (7.97%)	628 (5.8%)

Geographical region		
Rural	5043 (33.55%)	3483 (32.55%)
Urban	9987 (66.45%)	7219 (67.45%)
Comorbidities		
Atopy	1308 (8.70 %)	1435 (13.40 %)
Bronchitis	2360 (15.70 %)	1940 (18.12 %)
Chronic rhinosinusitis	475 (3.16 %)	443 (4.14 %)
Pneumonia	594 (3.95 %)	471 (4.40 %)
Anxiety	235 (1.56 %)	-
Depression	297 (1.97 %)	182 (1.70 %)
Gastroesophageal reflux disease (GERD)	49 (0.33 %)	-
Index year		
2013	3487 (23.20 %)	9539 (89.13%)
2014	4104 (27.31 %)	1163 (10.87%)
2015	3114 (20.72%)	-
2016	2603 (17.32%)	-
2017	1722 (11.46%)	-

Baseline comorbidities that may affect asthma control and assessed among the new and prevalent users in two years before their index date constituted atopy (atopic dermatitis, allergic rhinitis), rhinosinusitis (chronic rhinitis, chronic sinusitis), anxiety, depression, GERD, and pneumonia. A greater proportion of prevalent users had bronchitis compared with new users of asthma medications (new user vs prevalent user: 15.70 % and 18.12 %) in their history followed by atopy. Chronic sinusitis was seen in similar proportion among both the users, however, GERD and psychological conditions such as anxiety which are considered as common triggers for uncontrolled asthma were unseen among the prevalent users as compared to new users who had its history in minor proportions (1.56 % and 0.33 %). All index prescriptions received by prevalent users was in the first two years of the study period with a

greater proportion (89.13 %) noted in 2013. In contrast, the majority or more than a quarter (27.31 %) of the new users had their index prescription filled in 2014 followed 2013 (23.20 %), whereas only a mere proportion was dispensed in the final year of the study period.

3.2 Annual trends in prevalence and incidence of users of anti-asthmatic medications

The overall annual prevalence of anti-asthmatic medication users with confirmed asthma fluctuated over the study period with peaks of 58.50/1000 PY and 57.59/1000 PY noted in 2014 and 2016 and a descending trend in alternate years. However, the overall rate of change was insignificant. Incidence of users, in contrast, had a peak observed in 2014 (17.06/1000 PY) and then gradually declined to 7.28/1000 PY in 2017 (Fig:3a) which depicted a 15% reduction in incidence rate every year over the study period. The prevalence was lower in females than males (F: 0.823 (0.810- 0.835)) and their trend across years showed a mild reduction among males in contrast to a slight upward trend noticed among females. However, the incidence rate among both sexes remained consistent through the years with almost similar proportions and similar downward trends [M: 0.84 (0.83-0.85); F: 0.86 (0.85-0.87)]. The peak was observed in 2014 (M: 17.22; F:16.89 per 1000 PY) and the lowest value in 2017 (7.28/1000 PY for both males and females) (Fig 3b). Prevalence across age groups demonstrated highly observable distinctions between children and adolescents. Even though the prevalence rate in children increased to its peak in 2014 (64.01/1000 PY) and then reduced gradually, the relative change every year witnessed a consistent decline by 10%. In contrast, the prevalence in adolescents demonstrated a steady rise till 2016 with an overall 5% increase every year. Incidence in comparison was more consistent and comparable to the trend exhibited across sexes with peak and minimal vales observed in 2014 (Children:19.92; Adolescents:13.94 per 1000 PY) and 2017(Children:8.15; Adolesnts:6.23 per 1000 PY) respectively (Fig 3c). Additionally, it exhibited a downward trend among both children and adolescents at a reduced rate of 16% and 14 % respectively, every year over the study period.

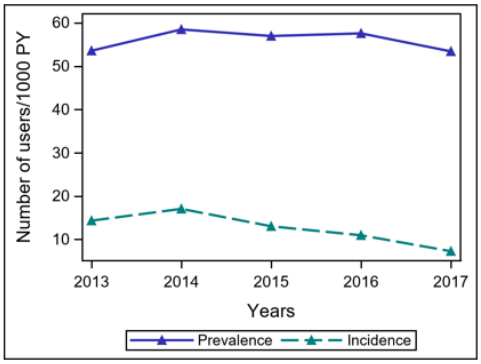
Table 6: Trends in prevalence and incidence of anti-asthma medication users (per 1000 PY)

	2013	2014	2015	2016	2017	Rate ratio (RR)
Crude prevalence and incidence						
Total person years	243114	240581	238852	237474	236496	
Prevalent users (per 1000)	13026 (53.58)	14073 (58.50)	13609 (56.98)	13676 (57.59)	12635 (53.43)	1.00 (0.99-1.00) p = 0.4718
Incident users (per 1000)	3487 (14.34)	4104 (17.06)	3114 (13.04)	2603 (10.96)	1722 (7.28)	0.85(0.84-0.86) p <0.0001
Prevalence and incidence by sex						
Person years: male	125588	124094	122895	121971	121390	
Prevalent users (per 1000)	7574 (60.31)	8024 (64.66)	7645 (62.21)	7555 (61.94)	6948 (57.24)	0.98 (0.97-0.99) p <0.0001
Incident users (per 1000)	1861 (14.82)	2137 (17.22)	1588 (12.92)	1300 (10.66)	884 (7.28)	0.84 (0.83-0.85) p <0.0001
Person years: female	117525	116486	115956	115502	115105	
Prevalent users (per 1000)	5452 (46.39)	6049 (51.93)	5964 (51.43)	6121 (52.99)	5687 (49.41)	1.01 (1.00-1.02) p = 0.0006
Incident users (per 1000)	1626 (13.84)	1967 (16.89)	1526 (13.16)	1303 (11.28)	838 (7.28)	0.86 (0.85-0.87) p <0.0001
Prevalence and incidence by age						
Person years: Children	124114	125338	126947	128305	129691	
Prevalent users (per 1000)	7677 (61.85)	8023 (64.01)	6979 (54.98)	6377 (49.70)	5273 (40.66)	0.90 (0.893-0.907) p <0.0001
Incident users (per 1000)	2016 (16.24)	2497 (19.92)	1831 (14.42)	1557 (12.14)	1057 (8.15)	0.84 (0.83-0.85) p <0.0001
Person years: Adolescents	119000	115243	111905	109169	106805	
Prevalent users (per 1000)	4885 (41.05)	5442 (47.22)	5705 (50.98)	5843 (53.52)	5451 (51.04)	1.05(1.04—1.07) p <0.0001
Incident users (per 1000)	1471 (12.36)	1607 (13.94)	1283 (11.47)	1046 (9.58)	665 (6.23)	0.86 (0.84-0.87) p <0.0001

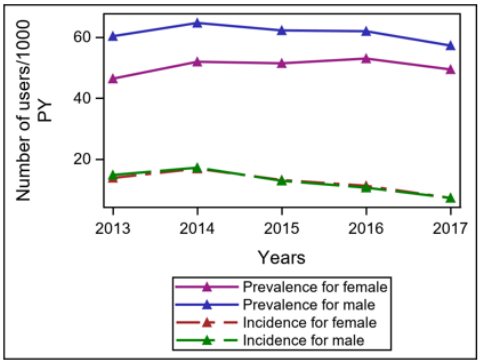
Prevalence and incidence by age and sex are adjusted for interaction between year and age/sex, RR- Rate ratio

Figure 3: Trends in prevalence and incidence rates of anti-asthmatic medication users with confirmed asthma

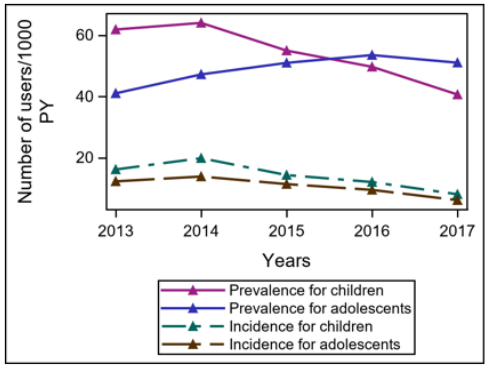
(a) Crude prevalence and incidence over the study period per 1000 person years



(b) Prevalence and incidence categorized by sex per 1000 person years



(c) Prevalence and incidence categorized by age group per 1000 person years

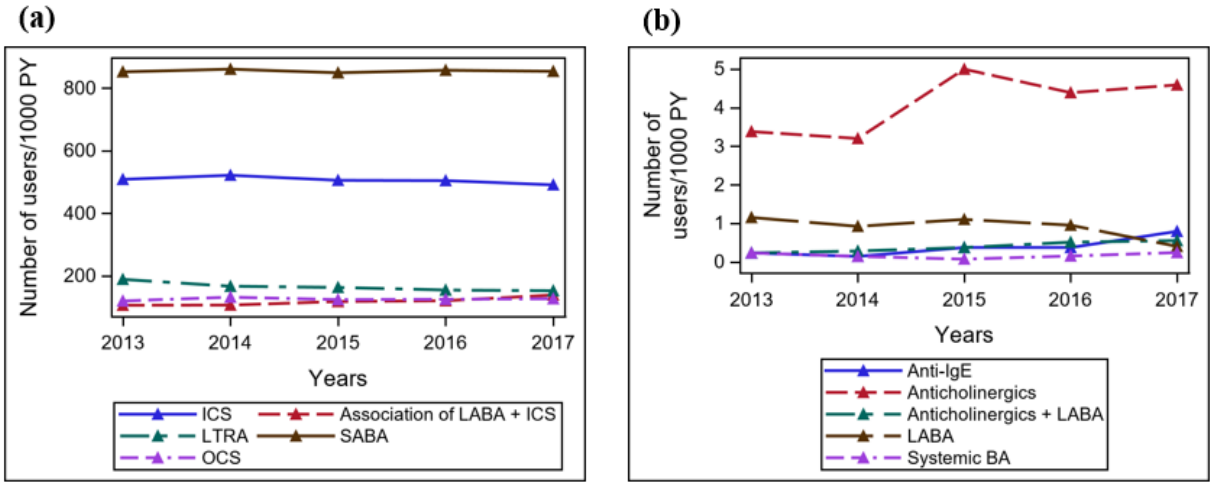


3.3 Prescribing pattern of drugs for asthma

3.3.1 Trends in user prevalence of individual drugs

The annual prescribing trends of asthma-related drugs among patients with asthma varied across various drug classes. SABA was used by the majority of children and adolescents in the index year (851.76 per 1000 PY) and remained consistent throughout the study period. Inhaled corticosteroids, being the mainstay of chronic asthma management were the second most commonly used drug with a proportion of 508.21 users/1000 PY in 2013. Despite having a marginal increase in 2014, a steady state in its use was noticed over the remaining study years. Whilst the use of LTRA declined gradually over the years, the use of a fixed-dose combination of ICS-LABA in contrast exhibited an upward trend with peak users observed in 2017 (138.58/1000 PY). Even though a majority of the study participants received ICS/LABA combination as controller, there were few patients who used LABA alone for which the trend over the years had declined from 1.15/1000 (2013) to 0.40/1000 (2017) PY. The trend in requirement of OCS among users had its peak observed in 2014 (131.88/1000 PY).

Figure 4: Proportion of children and adolescents using various anti asthmatic drugs over the study period expressed per 1000 PY



3.3.2 Classification of medication users based on the degree of consumption

The first-year dispensing data collected after the index date was used to assess the degree of drug consumption among the new asthmatic children and adolescents. Occasional users corresponding to the usage of anti-asthmatic medications only one time in the first year were 7890 (52.49%) and represented the majority among the new users. Moderate, 5851 (38.92 %) and frequent users, 1289 (8.57 %) who used anti-asthmatic medications more commonly constituted the remaining proportions.

SABA was the most commonly used drug class among all the user categories, particularly frequent users (92.47 %) followed by moderate and occasional users. The majority of the frequent (68.27 %) and moderate users (58.38 %) were identified as using ICS alone as their preferred controller therapy followed by LTRA. Non-fixed combination of ICS-SABA was more prominent among the frequent (66.4 %) and moderate users (55.52 %). Similarly, the use of a fixed-dose combination of ICS/LABA was also apparent among them as compared to occasional users. More importantly, drug classes such as LABA, xanthines, Anti-IgE, systemic BA, or fixed-dose anticholinergics + LABA combination unlike other user categories was neither used by the occasional users for managing asthma symptoms.

Table 7: Anti-asthmatic medication prescribing among the type of users

Drug class	**Occasional user, n (%)**	**Moderate user, n (%)**	**Frequent user, n (%)**	**Total users, N (%)**
	7890	**5851**	**1289**	**15030**
SABA	6833 (86.60)	5400 (92.29)	1192 (92.47)	13425 (89.32)
ICS	2638 (33.43)	3416 (58.38)	880 (68.27)	6934 (46.13)
LTRA	431 (5.46)	927 (15.84)	416 (32.27)	1774 (11.80)
Anticholinergics	10 (0.13)	20 (0.34)	10 (0.78)	40 (0.27)
LABA	0	2 (0.03)	1 (0.08)	3 (0.02)
Xanthines	0	1 (0.02)	1 (0.08)	2 (0.01)
Anti-IgE	0	0	1 (0.08)	1 (0.01)
Systemic BA	0	1 (0.02)	2 (0.16)	3 (0.02)
Combinations				
ICS+SABA (non-fixed)	2125 (26.93)	3249 (55.52)	856 (66.4)	6230 (41.45)
ICS+LABA (fixed dose)	311 (3.94)	404 (6.90)	174 (13.50)	889 (5.91)
Anticholinergics + SABA (fixed)	2 (0.03)	4 (0.07)	1 (0.08)	7 (0.05)
Anticholinergics + LABA (fixed)	0	1 (0.02)	0	1 (0.01)

Analysis of the degree of medication use for the occasional users at the prescription level in the follow-up period indicated that the mean dispensing for them in the first year was 1 followed by 0.420 in the second year as compared to 3.187 and 1.424 for the non-occasional users (both moderate and frequent users). This reduction further indicates that the occasional users might correspond to patients with intermittent or exercise-induced asthma and therefore were not selected for further analysis.

3.3.3 Prescriber profile of the types of prescriptions in the first year

In the first year, overall, a total of 39,056 prescriptions were dispensed for all the new asthmatic patients among which 10,236 were for occasional users, 19274 for moderate users, and the remaining 9546 prescriptions were received by frequent users. A majority of prescriptions among all study participants were prescribed by physicians, particularly general practitioners. These proportions were comparable and ranged from 44.38% across occasional users to 46.54% and 44.02% respectively among moderate and frequent users. Out of the total prescriptions filled in first year, 28 % were from pediatricians and frequent users were the most common (29.35%) recipient. Similarly, the number of prescriptions after consultation with an allergist/immunologist was also considerably higher among frequent users as compared to others. For a mere proportion of the patients, their prescriptions were either written by physicians from other departments including but not limited to internal medicine, gastroenterology, and otorhinolaryngology or from unknown specialties. Several patients had also received prescriptions from practitioners other than physicians: such as nurses and pharmacists. This accounted for 2.36% and 0.31% of the total prescriptions respectively, regardless of the type of users. Furthermore, prescriber profile was unavailable for 6555 (16.78%) prescriptions among all users.

Table 8: Prescriber profile based on dispensed prescriptions in the first year

Prescriber profile	**Number of prescriptions, n (%)**			
	Occasional user	Moderate user	Frequent user	Total prescriptions
Physicians	7571 (73.96)	15692 (81.41)	8195 (85.85)	31458
General practitioner	4543 (44.38)	8970 (46.54)	4202 (44.02)	17715
Pediatrician	2642 (25.81)	5489 (28.48)	2802 (29.35)	10933
Allergy/Immunologist	214 (2.09)	864 (4.48)	881 (9.23)	1959
Others /unknown	172 (1.68)	369 (1.91)	310 (3.25)	851
Nurse practitioners	186 (1.81)	482 (2.50)	253 (2.65)	921

Pharmacists	9 (0.09)	55 (0.28)	58 (0.61)	122
Unknown				6555
Total prescriptions	10236	19274	9546	**39056**
Pediatrician/immunologist: General physician prescription ratio	0.63	0.71	0.88	0.73

The ratio between the number of prescriptions from a pediatrician/immunologist to prescriptions from general physicians, among all the anti-asthmatic medication users indicated that most prescriptions received by children and adolescents were mainly from a general physician as compared to pediatrician/immunologist with an overall ratio of 0.73 among all asthma medication users in the first year.

3.3.4 Classification of users based on the number of dispensed drug classes in the first year

The number of drug dispensed classes during the first year among moderate and frequent users who were considered as persistent asthmatic patients was used as a proxy to determine the severity of asthma. Based on this criterion, less than one-third of the total subjects (27.86%) were determined in mild category, 3574 subjects into the moderate category, and the remaining 22.09 % individuals into the severe category.

Table 9: Classification of asthma severity based on dispensed medication classes

Asthma severity	**Number of study participants, n (%)**
Mild (1 class)	1989 (27.86%)
Moderate (2 classes)	3574 (50.06%)
Severe (≥ 3 classes)	1577 (22.09 %)

3.4 Drug prescribing among new persistent asthma patients

Table 10: Prescribing of anti-asthmatic drugs by drug class in 2 years follow up

Drug class	**Number of children and adolescents receiving anti-asthmatic drugs, n (%)**	
	First Year	**Second-year**
Total users	7140 (100 %)	3889 (54.47 %)
Relievers		
SABA	6593 (92.33)	3217 (45.06)
No SABA	547 (7.66)	672 (9.41)
Anticholinergics	30 (0.42)	12 (0.17)
Oral corticosteroids	891 (12.47)	436 (6.10)
Controllers		
ICS	4709 (65.95)	2349 (32.9)
ICS alone [a]	3537 (49.53)	1712 (23.98)
ICS+LABA	578 (8.09)	395 (5.53)
ICS+LTRA	118 (1.65)	265 (3.71)
No ICS	2431 (34.04)	1540 (21.57)
LABA alone	3 (0.04)	2 (0.028)
LTRA	1343 (18.80%)	627 (8.78%)
Treatment options		
SABA exclusively [b]	1787 (25.02)	1221 (17.1)
SABA + ICS [b]	3399 (47.60)	1421 (19.9)
SABA+ ICS+LABA [b]	369 (5.17)	204 (2.86)
SABA+ICS+LTRA [b]	536 (7.50)	200 (2.80)

[a] without any other controller either in fixed or non-fixed form; [b] without any other anti-asthmatic medication

In our study sample of 7140 new persistent asthmatic patients which consisted of 4417 (61.86) children and 2723 (38.14) adolescents, a vast majority of them were prescribed SABA as a reliever in their first year. Out of these, salbutamol occupied prescriptions among 91.01 % of

the SABA users. Exclusive use SABA without any other anti-asthmatic medications was notable in a quarter (25.02 %) of total users or 27.10% of the SABA users. On the contrary, in a mere proportion of 547 individuals, SABA was not all prescribed in the first intention of treatment. Oral corticosteroids (12.47%) and anticholinergics (0.42%) were other relievers used on-demand with varying severity. Requirement of controller therapy was observed in close to two-thirds of the patients in their first year out of which inhaled corticosteroids were the preferred controller of choice. The most frequently preferred ICS was fluticasone propionate (45.88 %) used in metered-dose inhalers. It was followed by beclomethasone (7.89%) and ciclesonide (7.27 %). Among the patients who required controllers, ICS was notably used alone without any other controller combinations in close to half (49.53%) of the patients or otherwise used along with SABA (47.60%). However, a step-up therapy requiring an additional controller was also noticed in 12.67% of individuals either as LABA or LTRA in addition to having a reliever SABA medication. Budesonide-formoterol (4.71%), Fluticasone-salmeterol (2.89%) were the most frequently prescribed fixed-dose ICS-LABA combinations. Montelukast and formoterol on the other hand were the only drugs used as single LABA and LTRA therapy respectively. Interestingly, prescriptions with monotherapy of LABA were seldom observed in patients (0.04%) and were always associated with ICS in fixed-dose combinations.

Less than half (45.53%) of those who received a prescription in their first year did not use any anti-asthmatic prescriptions in the subsequent year. Among the remaining 54.47 % of patients who took medications, 2484 (63.87%) were children and 1405 (36.13%) were adolescents. This was similar to the proportion noted in the first year and implies no change due to age groups. As noted with the overall trend, a reduction in the use of SABA and ICS was also apparent with a decrease from 92.33%, 65.95% to 45.06%, 32.9% respectively. Nevertheless, salbutamol and fluticasone propionate were still the major preferred drugs of choice in both classes. For the patients who used LTRA in combination with ICS (1.65%) in the first year, a slight increase in number was seen (3.71%) in the second year. The most frequently used dual-controller therapy (ICS+LABA and ICS+LTRA) with SABA in the first year was also reduced to half of its proportions among the second-year users. Among these patients, budesonide-

formoterol and montelukast were still the desired drug choices under respective drug classes such as ICS-LABA fixed combination and LTRA. The requirement of OCS which is generally initiated for severe asthma/exacerbations was also lower in the second year and might be an indication of the lessening severity or undertreatment. Prednisone, dexamethasone, and prednisolone were the most frequently used oral glucocorticoids for which a notable reduction was observed from 6.72 %, 3.97%, 2.25% in the first year to 3.17%, 1.97%, and 1.23% respectively in the second year.

Table 11: Prescribing of anti-asthmatic medication by individual drugs in 2 years follow up

Drug class	**Number of users of anti-asthmatic medications, n (%)**	
	First Year	**Second year**
Total users	7140 (100)	3889 (54.47)
SABA		
Salbutamol	6498 (91.01)	3173 (44.44)
Terbutaline	135 (1.89)	54 (0.75)
ICS		
Fluticasone propionate	3276 (45.88)	1449 (20.29)
Beclomethasone	564 (7.89)	269 (3.76)
Ciclesonide	519 (7.27)	288 (4.03)
LTRA		
Monteleukast	1343 (18.81)	627 (8.78)
ICS-LABA		
Budesonide-formoterol	336 (4.71)	223 (3.12)
Fluticasone-salmeterol	207 (2.89)	139 (1.94)
Mometasone-formoterol	40 (0.56)	36 (0.50)
Anticholinergics		
Ipratropium bromide	30 (0.42)	12 (0.16)
LABA		

Formoterol	3 (0.04)	2 (0.02)
Oral corticosteroids		
Prednisone	480 (6.72)	227 (3.17)
Dexamethasone	284 (3.97)	141 (1.97)
Prednisolone	161 (2.25)	88 (1.23)

Concerning the use of inhalational devices, a total of 937 patients were received at least one prescription for a dry powder inhaler among which a majority of 753 patients had it in the first year as compared to the second year. Among 6732 patients who used a metered-dose inhaler, 92.6% had taken it in the first year whereas only 52% of the first year MDI users took the device in second year. Two-fifths of the MDI users in the follow-up period had also used an inhalation chamber to optimize the drug delivery.

3.5 Prescriptions of non-compliance according to expert recommendations by GINA

Non-adherence to the expert recommendations from GINA was investigated for the parameters outlined in Table 12, separately among prescriptions dispensed in both follow-up years. Prescription of SABA, which is the preferred reliever for newly treated patients, was absent in 547 patients (7.66%) during first year. However, the remaining vast majority of 6593 patients exhibited prescribing compliance to this recommendation. In the first year, 581 children and adolescents had been prescribed LABA in any form, among which the lack of association with inhaled corticosteroid or otherwise termed as LABA monotherapy was only seen in a negligible patient proportion. In contrast to the majority of users in the first year who received their medication either in the form an MDI or DPI, 257 patients were not even prescribed an inhalation device. Conversely, among those prescribed with inhalers, multiple inhalers requiring dissimilar actuation procedures were noticed in 98 patients. Dispensing of DPIs in children less than 8 years is not recommended by the GINA guidelines, however, it was discerned in a negligible proportion of first-year users. Similarly, the guidelines recommend the incorporation of a spacer device with MDIs to get optimal delivery of the drug particles.

In less than one-third 2065 (28.28%) of the first-year medication users, this recommendation was appeared to be not followed.

Table 12: Patients with non-compliant prescriptions in follow up period

Principle	**Patients, n (%)**
First year	
a) Absence of SABA dispensing	547 (7.66)
b) Monotherapy of LABA	3 (0.04)
c) Absence of dispensing of an inhaler	257 (3.59)
d) Dispensing of multiple inhaler types except those associated with SABA	98 (1.37)
e) Dispensing of dry powder in children <8 years	18 (0.25)
f) Dispensing of an MDI without spacer	2065 (28.92)
Second year	
a) Absence of ICS in patients of moderate and high severity	843 (11.80)
b) Duration of ICS for <3 months in patients of moderate and high severity	1368 (19.15)
c) Monotherapy of LABA	2 (0.03)
d) Dispensing of multiple inhaler types except those associated with SABA	51 (0.71)
e) Dispensing of dry powder in children <8 years	3 (0.04)
f) Absence of SABA dispensing	99 (1.38)
g) Absence of dispensing of an inhaler	199 (2.78)
h) Dispensing of an MDI without spacer	1623 (22.73)

Assessment of parameters pertaining to non-compliance in the second year also exhibited similar results. Out of the study participants categorized into moderate and severe asthma based on the number of dispensed drug classes (≥2 classes), prescription for controller therapy with ICS was absent in 843 patients (11.80%). Correspondingly, a fraction (19.15%) of the patients who received ICS in the aforementioned severity categories did not receive prescriptions for a duration longer than 3 months evincing under prescribing. Similar negligible fraction of patients in second year had LABA monotherapy as seen from the first year. Whilst multiple inhaler device types were prescribed in 98 patients in the index year, it was declined to half in the following year. Comparable reduction was also apparent with the case of dispensing of DPIs in children<8 years and lack of incorporation of inhalation

chambers with MDIs. Whilst the former was reduced to 0.04% from 0.25 %, the latter had a decrease of 6.19% from the first year which might represent either an improved adherence or be resulting from the overall decline in drug consumption in the second year. Similarly, the proportion of patients without a reliever prescription and inhaler device also had a reduction noticed in the second year. Overall, after applying all the recommendations except the use of spacer devices it appeared that out of 7140 patients, 656 (9.18%) children and adolescents in the first year and 2364 (33.10 %) in the second year were not treated according to the expert recommendations.

3.6 Prescribing pattern of SABA inhalers

A total of 6593 patients were prescribed with SABA canisters during the first year, among which the majority of the users received 1-2 canisters/year that regarded as appropriate use. Overuse of SABA defined by the requirement of 3 or more canisters was observed in 2099 patients accounting for 29.40 % of the total first-year anti-asthmatic medication users. Among these patients, 1824 of them had 3-5 canisters, 240 with 6-10 canisters, and the remaining 0.49% received ≥11 canisters/year (excessive use). Overall, as the frequency of drug prescriptions in second year was declining, this trend was also reflected in SABA use with almost equal distribution among the patients. As compared to first-year users, only half of them,2437 (34.13%) received appropriate SABA prescriptions in second year. Comparably, the number of patients overusing SABA with 3-5 canisters was also noticed to be reducing in second year. In contrast, a slight increase in SABA prescriptions with excessive use was noted among patients using ≥11 from 0.49 % to 0.53% in second year.

Table 13: Dispensing of SABA canisters in first and second year

SABA use (canisters/year)	**Number of patients, n (%)**	
	First year	**Second year**
No SABA use	547 (7.66 %)	3923 (54.94 %)
1-2	4494 (62.94 %)	2437 (34.13 %)

3-5	1824 (25.55 %)	607 (8.50%)
6-10	240 (3.36 %)	135 (1.89 %)
≥11	35 (0.49 %)	38 (0.53 %)

3.7 Prescribing of inhaled corticosteroids

The ratio between the number of inhaled corticosteroid packs/canisters to total packs of asthma drugs (ICS/R03) prescribed for patients was investigated at an individual level. Among 4709 patients who were issued ICS in any form as single inhalers or fixed-dose combinations in first year, slightly less than one-third of them were prescribed with suboptimal ICS packs (<50 %) indicating under prescribing; however the remaining 35.78% received adequate therapy.

Table 14: Classification of users based on inhaled corticosteroid -total asthma drug ratio

ICS/R03 ratio	**Number of patients, n (%)**	
	First year	**Second year**
No ICS	2431 (34.05 %)	1540 (39.60 %)
<50 %	2154 (30.17 %)	752 (19.34 %)
≥50 %	2555 (35.78 %)	1597 (41.06 %)

Despite the absence of ICS prescriptions in 1540 children and adolescents, the use of this controller therapy was markedly improved in second year with a majority of patients belonging to the 'high ratio' (41.06%) category reflecting in optimal receipt of treatment. The percentage of patients regarded as receiving under treatment or 'low ratio' was also lower, implicating similar findings.

Table 15: Prescribing based on daily doses of inhaled corticosteroids

ICS daily dose *	**Number of patients, n (%)** ±	
	First year	**Second year**

Children		
Low (100-200 µg)	1650 (46.65 %)	738 (43.11 %)
Medium (>200-500 µg)	409 (11.56 %)	182 (10.63 %)
High (>500 µg)	371 (10.49 %)	197 (11.51 %)
Adolescents		
Low (100-250µg)	942 (26.63 %)	497 (29.03 %)
Medium (>250-500 µg)	129 (3.65 %)	76 (4.44 %)
High (>500 µg)	36 (1.02 %)	22 (1.29 %)

*ICS doses are expressed as fluticasone propionate equivalent. ± Percentages expressed out of total 3537 users prescribed with ICS alone

Evaluation of the proportion of patients issued with high dose prescriptions concerned 3537 patients who received ICS prescriptions without association with any other controllers. Among these, 2430 were children and the remaining 1107 users were adolescents. Conversion of prescribed doses to fluticasone equivalents revealed that the majority of children (46.65%) and adolescents (26.63%) were treated with low doses (children: 100-200 µg; adolescents: 100-250µg) in the first year. While slightly less than one-fifth of the first-year ICS users were issued medium-dose prescriptions, 11.51 % of the patients received a high dose defined as a daily dose greater than 500 µg. Among children, even though the number of ICS users (including low and medium dose) out of the total patients declined during the second year, a slight elevation was noted in the proportion of ICS users receiving high dose by an increase of 1.02 %. Unlike this, among adolescents, an increase was noted among all dose categories. However, despite this rise in proportion, the overall number of patients receiving low (497), medium (76), and high (22) doses of ICS had a substantial fall during the second year.

3.8 Antibiotic prescribing in asthma

3.8.1 Annual trends in antibiotic prescribing

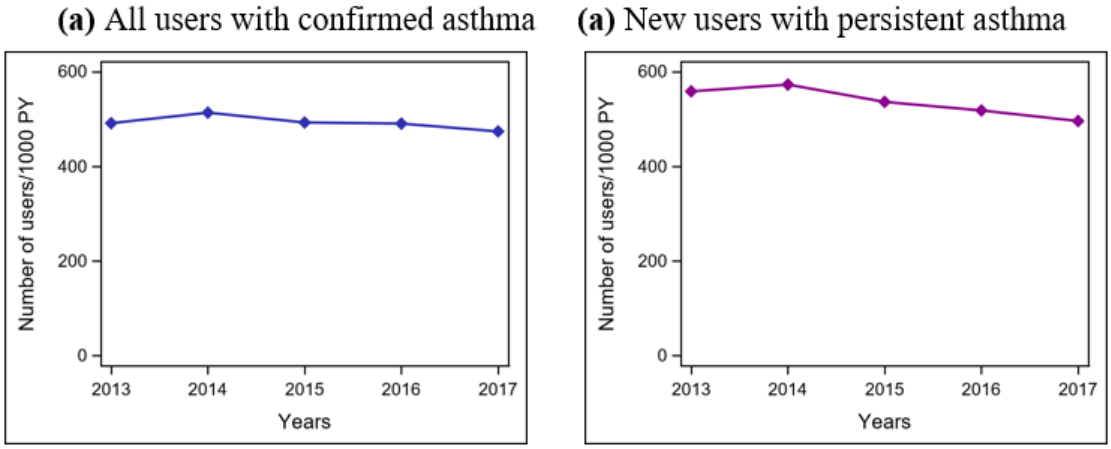
Trends in antibiotic prescribing among all anti-asthmatic medication users (n=25,732) exhibited a downward trend through 2015 to 2017 after having its peak observed in the year

2014 (513.82/1000 PY) and the prevalence rate showed a slight reduction by 1% every year. A comparable trend was also observed among anti-asthmatic medication users with persistent asthma (n=7140). From the index year (558.79/1000 PY), it showed an elevation in 2014 (573.18/1000 PY) and then gradually decreased over the rest of the years and exhibited a 4% decrease in prevalence rate every year.

Table 16: Annual trends in antibiotic prescribing among anti-asthmatic medication users

Anti-asthmatic medication users						Rate ratio
	2013	2014	2015	2016	2017	
Asthma	13026	14073	13609	13676	12635	
Antibiotics (per 1000 PY)	6403 (491.56)	7231 (513.82)	6709 (492.98)	6710 (490.64)	5990 (474.08)	0.99 (0.98-0.99) p=0.0025
New anti-asthma medication users with persistent asthma						
Persistent asthma	1582	3184	3795	4093	4032	
Antibiotics (Per 1000 PY)	884 (558.79)	1825 (573.18)	2036 (536.5)	2122 (518.45)	2000 (496.03)	0.96 (0.95-0.98) p<0.0001

Figure 5: Annual prevalence trends of antibiotic use among anti-asthma medication users (per 1000 PY) from 2013 to 2017



3.8.2 Characteristics of study participants and prescribers of antibiotic prescriptions

Evaluation of the prescription of antibiotics during the 2 years follow-up period indicated that a total of 14,595 antibiotic prescriptions were issued for 5038 study participants. Two third of them were issued to children, however, there was no variation observed among males/females. As noticed with the trend of anti-asthmatic medication prescribing, the use of antibiotics was also higher among participants from high affluent households and urban regions. Among 85.87% of the prescriptions by physicians, general practitioners issued majority of them, followed by pediatricians (Table 17).

Table 17: Patient and prescriber profile of anti-asthmatic medication users issued antibiotics

Patient profile	
Characteristics	**Number of antibiotic users, n (%)**
Sex	
Male	2509 (49.80 %)
Female	2529 (50.20 %)
Age at entry	
Children (5-11 years)	3127 (62.07 %)
Adolescents (12- 17 years)	1911 (37.93 %)
Age, Mean ± SD	10.23 ± 3.83
Socio economic status	
High (SEFI <0) *	2445 (48.53%)
Low (SEFI >0)	2198 (43.63%)
(Missing)	395 (7.84%)
Geographical region	
Rural	1722 (34.18%)
Urban	3316 (65.82%)
Prescriber profile	
Prescribers	**Number of prescriptions, n (%)**

Physicians	12,533 (85.87%)
General practitioner	9638 (66.04%)
Pediatrician	2415 (16.55%)
Others /unknown	480 (3.29%)
Dentists	502 (3.44%)
Nurse practitioners	497 (3.40%)
Pharmacists	16 (0.11%)
Unknown	1047 (7.17%)
Total prescriptions	**14595**

3.8.2 Antibiotic use during the follow-up period

Among the total patients issued with an antibiotics prescription 4135 (57.91%) in the first year, penicillin was the highly prescribed drug class in both children (26.18%) and adolescents (12.24%), followed by macrolides and trimethoprim-sulphonamides combinations. Prescriptions for tetracyclines and fluoroquinolones were higher in adolescents as compared to children.

Table 18: Antibiotic prescribing in 2 years follow up

Antibiotic use	**Number of patients, n (%)**			
	First year		**Second year**	
Total antibiotics	4135 (57.91)		3101 (43.43)	
Antibiotics by class				
	Children	Adolescents	Children	Adolescents
Penicillin	1869 (26.18)	874 (12.24)	1347 (18.87)	695 (9.73)
Macrolides	1069 (14.97)	758 (10.62)	565 (7.91)	429 (6.01)
Cephalosporins	481 (6.73)	258 (3.61)	394 (5.51)	236 (3.31)
Trimethoprim-sulphonamides	118 (1.65)	105 (1.47)	77 (1.07)	98 (1.37)
Other antibiotics*	50 (0.7)	98 (1.37)	44 (0.61)	106 (1.48)

Tetracyclines	6 (0.08)	104 (1.45)	11 (0.15)	89 (1.25)
Fluoroquinolones	8 (0.11)	84 (1.17)	2 (0.02)	64 (0.90)

*Other antibiotic classes include lincosamides, nitrofurans, and aminoglycosides

As compared to the first year, only 3101 patients received an antibiotic prescription in the second year. Findings pertaining to the use of penicillin and macrolides were comparable to first year with both of them being the highly prescribed antibiotic classes. Even though the issuance of penicillin was twice higher among children (18.87%) as compared to adolescents (9.73), only a minor difference in proportion was noted in the use of macrolides. As noted from the first year, the prescriptions for tetracyclines and fluoroquinolones were considerably higher among adolescents also in the second year. Concerning the reasons for the use of antibiotics, in addition to asthma, upper respiratory tract infections (20%), acute bronchitis (17%), and acute pharyngitis (16%) were found as some of the major indications.

3.8.3 Comparison of antibiotic prescriptions in asthma with matched control

Among 7118 new persistent asthma patients, a total of 5025 patients were prescribed at least one antibiotic during the 2 years follow-up period. In the control group that consisted of 21,354 subjects without asthma, antibiotic prescriptions were issued to 8370 (39.20%) of them. Majority of the prescriptions issued to asthma patients were penicillin antibiotics (51.32 % users) among which amoxicillin was heavily prescribed. Additionally the prescription rate was also substantially higher within asthma patients exemplified by the total prescription count and count of individual drug classes. As seen with penicillin ($p<0.0001$), the proportion of use of macrolides which was the next heavily prescribed antibiotic was also almost more than three times higher in asthma patients ($p<0.0001$). Among patients who were issued macrolide prescriptions, azithromycin was the most used drug. Comparably, prescriptions for other antibiotic classes such as cephalosporins (16.97%), trimethoprim-sulphonamides combinations (5.14%), tetracyclines (2.51 %), and fluoroquinolones (1.97%) were also higher in asthma patients as compared to subjects without asthma implicating the frequent use of antibiotics during asthma.

Table 19: Antibiotic prescribing among asthma patients and non-asthmatic controls

Characteristics	**Asthmatic patients, n (%)** (Total =7118) *	**Matched controls, n (%)** (Total = 21,354)	**P value**
Total antibiotics	5025 (70.60%)	8370 (39.20 %)	
Antibiotics by class			
Penicillin	3653 (51.32 %)	5844 (27.37 %)	<0.0001
Macrolides	2324 (32.65 %)	2029 (9.50 %)	<0.0001
Cephalosporins	1208 (16.97 %)	1935 (9.06 %)	<0.0001
Trimethoprim-sulphonamides	366 (5.14 %)	607 (2.84 %)	<0.0001
Other antibiotics	277 (3.89 %)	472 (2.21 %)	<0.0001
Tetracyclines	179 (2.51 %)	387 (1.81 %)	0.0002
Fluoroquinolones	140 (1.97 %)	168 (0.79 %)	<0.0001
Number of courses of antibiotics dispensed			
First year			
0 (No antibiotic use)	2992 (42.03))	15,913 (74.52)	<0.0001
1-2 antibiotic courses	3035 (42.64)	4697 (22.00)	
≥3 antibiotic courses	1091 (15.33)	744 (3.48)	
Second year			
0 (No antibiotic use)	4024 (56.53)	16,013 (74.99)	<0.0001
1-2 antibiotic courses	2456 (34.50)	4639 (21.72)	
≥3 antibiotic courses	638 (8.96)	702 (3.29)	
B/N ratio			
Broad spectrum	4740	7378	
Narrow spectrum	1232	2184	
B/N ratio	3.8	3.4	

*Comparison excluded 22 children due to missing matches

The frequency of antibiotic use among participants with and without asthma also had considerable variation in the follow up years. Out of 4126 asthma patients who took antibiotics in the first year 42.64 % and 15.33 % of them had 1-2 and ≥3 courses respectively, prescribed in the year. Participants without asthma in contrast to this had a relatively lower proportion of users receiving multiple antibiotic courses. When one fifth (22%) of total non-asthmatic participants received 1-2 courses, 3 or more courses were taken by 744 subjects. Similar findings but variable in proportion were also observed in the second year. Majority of the asthmatic patients were issued 1-2 courses of antibiotic prescriptions and this proportion was still higher and significant in comparison with participants without asthma (p: <0.0001). The proportion of users taking broad spectrum to narrow spectrum antibiotics in the 2-year period evinced marked difference between asthma (B/N: 3.4) and participants without asthma (B/N: 3.8) indicating extensive imbalance that may lead to the risk of antibiotic resistance.

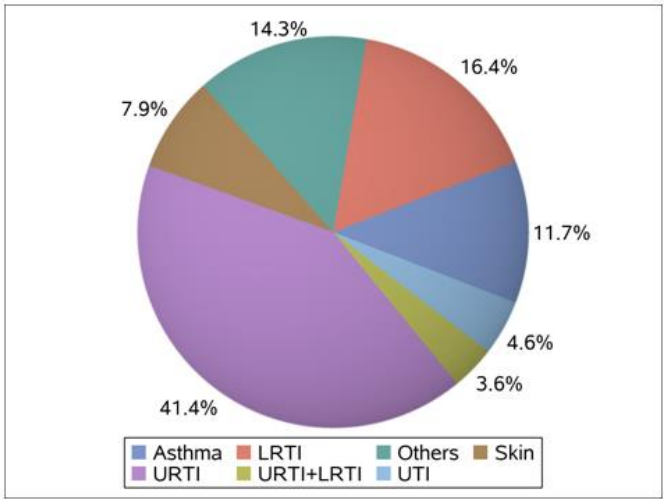
3.8.4 Indications for antibiotic prescriptions among asthma patients and non-asthmatic control

Out of a total of 14,570 prescriptions issued to 5025 patients with asthma, linkage of indication corresponding to each prescription on the same day could be established for 14,117 (96.9%) of them. Of these, more than two-fifth of these prescriptions were issued for upper respiratory tract infections (URTI), followed by lower respiratory tract infections (LRTI) and infections on other sites including eye and gastroenteric systems. Bronchitis (13%) and pneumonia (2.9%) were the most common indications of LRTIs. While asthma was the reason for 11.7 % of the prescriptions, urinary tract infections (UTI) and infections of the skin also accounted for slightly more than one-tenth (12.5%) of the total antibiotic prescriptions. In matched 8370 children and adolescents without asthma who were issued 17,636 prescriptions in total, 87.6% of them could be matched to their corresponding indications. Similar to patients with asthma, URTI was still the common reason for antibiotic prescribing (7772, 50.30%) prescriptions) for these non-asthmatic subjects among which tonsillitis and otitis were more frequent. Among patients who received prescriptions for LRTIs, bronchitis accounted for the majority (79.57%) of LRTI prescriptions, ensued by pneumonia (15.68%), influenza, and tracheitis. Skin

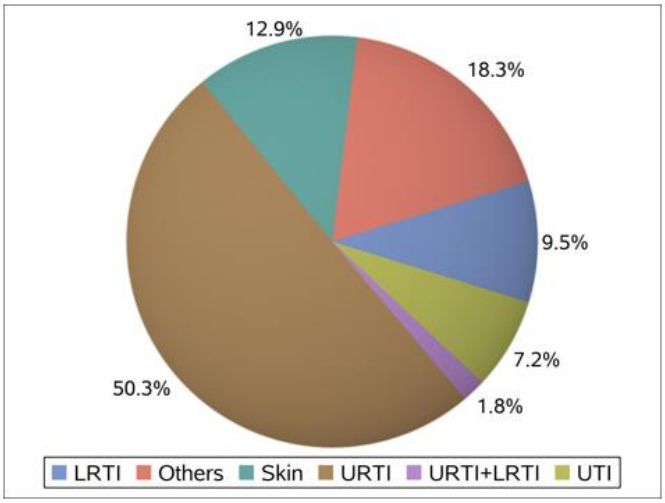
infections and UTIs were other indications that initiated antibiotic prescriptions which together constituted 20% of the total prescriptions.

Figure 6: Indications for antibiotic prescriptions among asthma patients and non-asthmatic matched controls

(a) Patients with asthma



(b) Non-asthmatic matched controls



3.9 Vaccination in asthma patients

Table 20: Vaccination among asthma patients

Type of vaccine	**Number of patients, n (%)**	
	First year	**Second year**
Influenza vaccine	1363 (19.09)	1162 (16.27)
Pneumococcal vaccine	16 (0.22)	6 (0.08)

Vaccinations among asthma patients particularly flu and pneumococcal vaccines upon evaluation indicated that slightly less than one-fifth of the patients (19.09 %) in first year had taken flu vaccine whereas only a negligible fraction of 0.22 % received a pneumococcal vaccine. In second year, these proportions were lowered to 16.27% and 0.08 % for flu and pneumococcal vaccines respectively.

3.10 Asthma exacerbations during follow up period

The primary clinical outcome measured as exacerbations of asthma, defined by ED visits or hospitalization for primary diagnosis of asthma or receipt of oral corticosteroids among the new persistent asthma patients within the follow-up period demonstrated that a total of 984 patients experiencing exacerbations during the first year. Out of the total occasions of exacerbations, a majority involved the requirement of OCS, followed by emergency department visits in hospitalizations. In contrast to this, only 490 patients experienced exacerbations in the second year with 20% of them experiencing two or more events.

Table 21: Asthma exacerbation for 2 years follow up

Asthma exacerbation	**Number of patients, n (%)**	
	First year	**Second year**
Emergency department visits	109 (1.52 %)	48 (0.67 %)
Hospitalization	39 (0.55 %)	23 (0.32 %)
Delivery of oral corticosteroids	891 (12.47 %)	436 (6.11 %)
Total exacerbation	984 (13.78 %)	490 (6.86 %)
Number of exacerbations		
No exacerbation	6156 (86.21 %)	6650 (93.13 %)
1	787 (11.02 %)	388 (5.43 %)
≥2	197 (2.75 %)	102 (1.42 %)

3.11 Asthma-related outcomes according to the risk factors in 2 years

Model 1: First year predictors to the risk of asthma exacerbation in the first year

Assessment of the risk of asthma exacerbation in the first-year follow-up period from the index date revealed that a total of 984 patients among the total 7140 new persistent asthma patients had exacerbations. In comparison to children, no difference was noted among adolescents, however, a significant reduction of 23 % in the event was apparent among females as compared

to male patients [OR (unadjusted): 0.77 (0.68-0.88)]. Concerning the socioeconomic status and region of residence, patients from high affluent households and living in urban areas respectively had no association observed in comparison to controls. Nevertheless, the severity of asthma as expected was highly correlated to the event, with patients under moderate and high severity having higher odds as compared to mild asthma patients. Even though the receipt of flu vaccination was expected to decrease the risk of the event, it was not found statistically significant [OR: 1.06 (0.89-1.26)]. Comorbidities such as pneumonia [OR: 1.34 (0.97-1.82) and bronchitis [OR: 1.27 (1.07-1.51)] at baseline also had influence on risk of exacerbation.

Patients receiving non- compliant prescriptions were not found significant to be having a risk of being experiencing exacerbation [aOR: 0.84 (0.65-1.10)]. The ratio of the controller to total asthma medication had a notable influence on the incidence of exacerbation with 2.36 odds greater risk noted among low ratio group (<50%) as compared to the null ratio. Even though patients with high ratio or adequate controller treatment also experienced exacerbations, it was considerably lower than the low ratio group. This effect was still noticed even after adjustment of confounders: high ratio [aOR: 2.02 (1.67-2.43)], the low ratio [aOR: 2.10 (1.73-2.52)] as compared to the reference. An increase in annual receipt of 3 or more SABA canisters had more than 30% higher likelihood of asthma exacerbation in first year [OR: 1.32 (1.14-1.52)] as compared to patients with appropriate SABA use. It was still significant even after adjusting for confounders [aOR: 1.25 (1.07-1.46)].

Table 22: Factors influencing risk of asthma exacerbation in first year

Parameters		Asthma exacerbation	
		Crude OR (95% CI)	P value
Age	Children	Reference	
	Adolescents	0.92 (0.80-1.06)	0.2805
Sex	Male	Reference	
	Female	0.77 (0.68-0.88)	0.0002 *
SEFI	Low	Reference	

	High	0.94 (0.82-1.09)	0.4582
Asthma severity	Mild	Reference	
	Moderate	12.94 (7.05-23.74)	<0.0001 *
	Severe	156.16 (85.63-284.77)	<0.0001 *
Region of residence	Rural	Reference	
	Urban	0.90 (0.78-1.04)	0.1619
Flu vaccination status	No	Reference	
	Yes	1.06 (0.89-1.26)	0.4778
Baseline comorbidities	Atopy	1.11 (0.89-1.38)	0.3252
	Rhinosinusitis	1.23 (0.87-1.74)	0.2291
	Pneumonia	1.34 (0.97-1.82)	0.0685
	Anxiety	0.33 (0.14-0.75)	0.0086 *
	Depression	0.99 (0.63-1.56)	0.9654
	Bronchitis	1.27 (1.07-1.51)	0.0056 *
	GERD	0.81 (0.24-2.72)	0.7401
ICS/R03 ratio	0 (No ICS)	Reference	
	Low (<50%)	2.36 (1.97-2.83)	<0.0001 *
	High (≥50%)	1.98 (1.65-2.36)	<0.0001 *
ICS dose	Low	Reference	
	Medium	1.18 (0.93-1.51)	0.1669
	High	1.22 (0.92-1.60)	0.1564
Non-compliant prescriptions	No	Reference	
	Yes	0.72 (0.55-0.93)	0.0114 *
Number of SABA packs	Low (0-2)	Reference	
	High (≥3)	1.32 (1.14-1.52)	0.0001 *
Number of antibiotic courses	0	Reference	
	1-2	1.71 (1.46-1.99)	<0.0001 *
	≥3	2.41 (1.99-2.92)	<0.0001 *

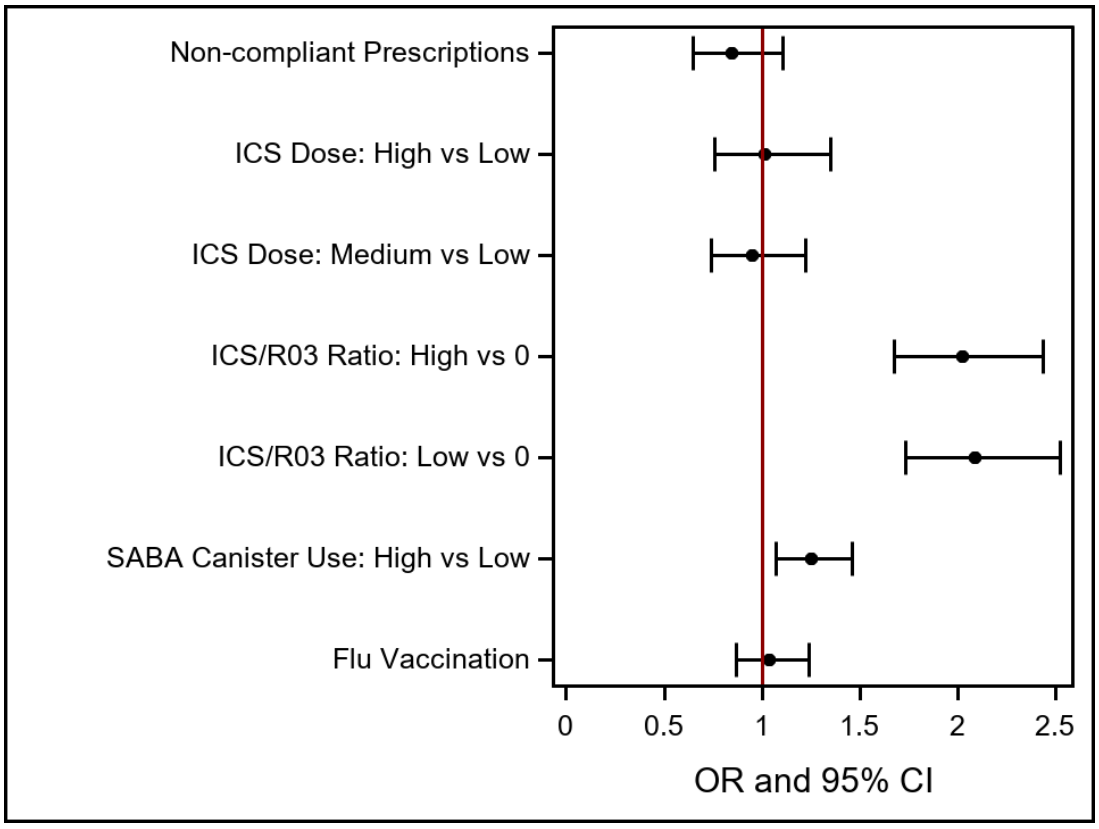
*Significant observations with P-value <0.05

Table 23: Model 1- Predictors to the risk of asthma exacerbation in the first year after adjusting confounders

	Crude OR (95% CI)	Adjusted OR (95% CI)	P value
Non-compliant prescriptions			
Exposed	0.72 (0.55-0.93) *	0.84 (0.65-1.10)	0.2203
ICS Dose			
Medium	1.18 (0.93-1.51)	0.95 (0.74-1.23)	0.6967
High	1.22 (0.92-1.60)	1.01 (0.76-1.35)	0.9379
ICS/R03 ratio			
Low	2.36 (1.97-2.83) *	2.10 (1.73-2.52) *	<0.0001*
High	1.98 (1.65-2.36) *	2.02 (1.67-2.43) *	<0.0001*
Number of SABA packs			
High	1.32 (1.14-1.52) *	1.25 (1.07-1.46) *	0.0049 *
Flu vaccination			
Exposed	1.06 (0.89-1.26)	1.03 (0.87-1.24)	0.6748

Adjusted for confounders: age, sex, region of residence, socioeconomic status, antibiotic courses, baseline comorbidities: Atopy, GERD, anxiety, depression, bronchitis, pneumonia, rhinosinusitis, *Significant observations with P-value <0.05

Figure 7: Association between first year non-complaint prescriptions, ICS dose, ICS/R03 ratio, and flu vaccination to the risk of asthma exacerbation in first year



Adjusted for confounders: age, sex, region of residence, socioeconomic status, antibiotic courses, baseline comorbidities: Atopy, GERD, anxiety, depression, bronchitis, pneumonia, rhinosinusitis

Model 2: Second year predictors to the risk of asthma exacerbation in second year

Evaluation of the risk of asthma exacerbation in the second-year follow-up period from the index date exhibited consistent findings in comparison to the first year. Among the total 7140 patients in the second year, an exacerbation was experienced by 490 children and adolescents. In contrast to the first year, adolescents in the second year were 30% more likely to have an exacerbation. [unadjusted OR: 1.30 (1.08-1.56)]; however there was no variability in risk across both sexes. Region of residence and flu vaccination also exhibited no major differences in predisposing patients to any associated risk. On the contrary, changes in asthma severity were still associated with the event with higher odds among moderate [OR: 1.32 (1.02-1.68)] and severe [OR: 2.54 (1.96-3.30)] asthma patients. Patients experiencing comorbidities such as depression and bronchitis were more likely to experience the exacerbation, however other comorbidities such as atopy, rhinosinusitis, pneumonia, GERD, and anxiety were not significant.

Table 24: Exposures of interest and probable confounders on the anti-asthma drug prescribing and exacerbation in the second year

Parameters		Asthma exacerbation	
		Crude OR (95% CI)	P value
Age	Children	Reference	
	Adolescents	1.30 (1.08-1.56)	0.0051 *
Sex	Male	Reference	
	Female	1.13 (0.93-1.35)	0.1964
SEFI	Low	Reference	
	High	1.06 (0.87-1.29)	0.5201
Asthma severity	Mild	Reference	
	Moderate	1.32 (1.02-1.68)	0.0301*
	Severe	2.54 (1.96-3.30)	<0.0001*
Region of residence	Rural	Reference	

	Urban	0.91 (0.75-1.10)	0.3306
Flu vaccination status	No	Reference	
	Yes	1.01 (0.77-1.33)	0.9151
Baseline comorbidities	Atopy	0.95 (0.69-1.30)	0.7550
	Rhinosinusitis	1.22 (0.76-1.94)	0.4021
	Pneumonia	1.07 (0.68-1.69)	0.7560
	Anxiety	0.72 (0.31-1.65)	0.4440
	Depression	1.62 (0.97-2.70)	0.0631
	Bronchitis	1.33 (1.05-1.67)	0.0150*
	GERD	1.13 (0.26-4.80)	0.8669
ICS/R03 ratio	0 (No ICS)	Reference	
	Low (<50%)	3.92 (3.07-4.99)	<0.0001*
	High (≥50%)	2.48 (2.01-3.07)	<0.0001*
ICS dose	Low	Reference	
	Medium	1.85 (1.25-2.74)	0.0021*
	High	1.26 (0.77-2.06)	0.3563
Non-compliant prescriptions	No	Reference	
	Yes	1.55 (1.29-1.87)	<0.0001*
Number of SABA packs	Low (0-2)	Reference	
	High (≥3)	2.72 (2.18-3.41)	<0.0001*
Number of antibiotic courses	0	Reference	
	1-2	3.29 (2.66-4.07)	<0.0001*
	≥3	5.15 (3.91-6.77)	<0.0001*

*Significant observations with P-value <0.05

Patients receiving non-compliant prescriptions had a greater likelihood of having exacerbation in the second year. However, this change was not evident after adjusting confounding variables. As similar from the first year, receipt of a higher number of SABA canisters (≥3) [aOR: 1.57 (1.19-2.06)] and lower controller to total asthma drug ratio (<50%) [aOR: 2.50 (1.84-3.39)] had noticeable likelihood of asthma exacerbation also in the second year even

after adjustment. The latter had a more prominent association of having an exacerbation than from the first year even with additional adjustment of severity. However, adjusted risk of experiencing exacerbation was not obvious among patients treated with medium doses of ICS [aOR: 1.18 (0.78-1.80)] even though the unadjusted value was significant.

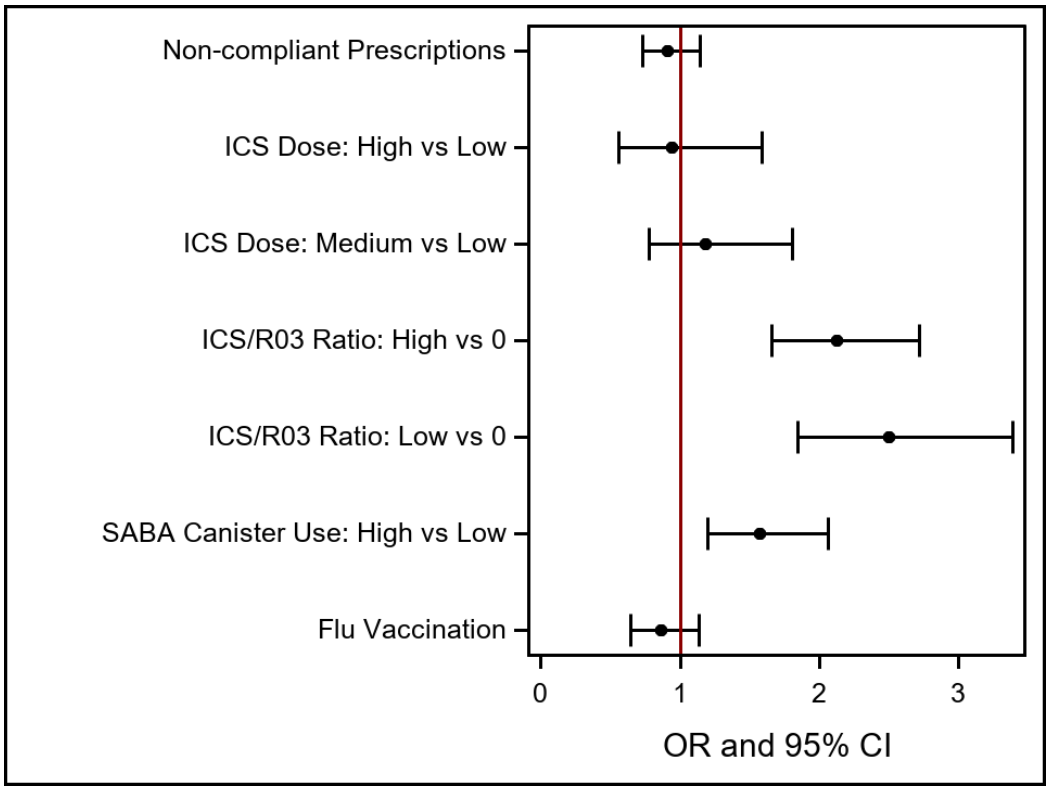
Table 25: Model 2- Predictors to risk of asthma exacerbation in second year after adjustment

	Crude OR (95% CI)	Adjusted OR (95% CI)	P value
Non-compliant prescriptions			
Exposed	1.55 (1.29-1.87) *	0.91 (0.73-1.14)	0.4179
ICS Dose			
Medium	1.85 (1.25-2.74) *	1.18 (0.78-1.80)	0.4338
High	1.26 (0.77-2.06)	0.94 (0.56-1.58)	0.8141
ICS/R03 ratio			
Low	3.92 (3.07-4.99) *	2.50 (1.84-3.39) *	<0.0001 *
High	2.48 (2.01-3.07) *	2.12 (1.66-2.71) *	<0.0001 *
Number of SABA packs			
High	2.72 (2.18-3.41) *	1.57 (1.19-2.06) *	0.0012 *
Flu vaccination			
Exposed	1.01 (0.77-1.33)	0.86 (0.65-1.14)	0.2898

Adjusted for confounders: age, sex, region of residence, socioeconomic status, asthma severity (assessed by dispensed R03 class), antibiotic courses, baseline comorbidities: Atopy, GERD, anxiety, depression, bronchitis, pneumonia, rhinosinusitis

*Significant observations with P-value <0.05

Figure 8: Association between second year non-complaint prescriptions, ICS dose, ICS/R03 ratio and flu vaccination to the risk of asthma exacerbation in second year



Adjusted for confounders: age, sex, region of residence, socioeconomic status, asthma severity (assessed by dispensed drug class), antibiotic courses, baseline comorbidities: Atopy, GERD, anxiety, depression, bronchitis, pneumonia, rhinosinusitis

Model 3: First year predictors to the risk of asthma exacerbation in the second year

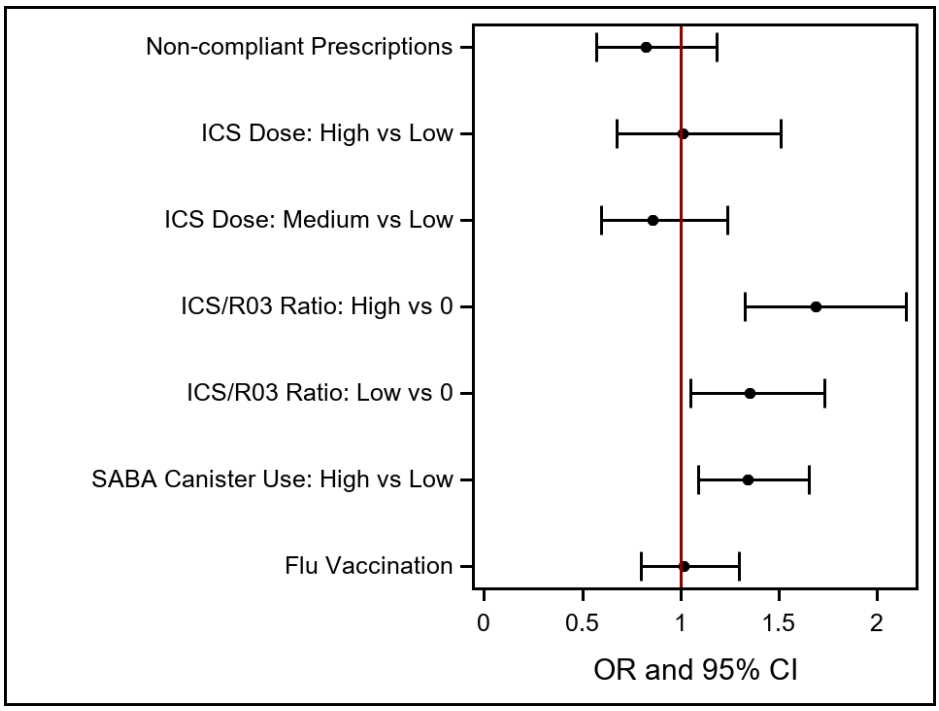
Exposure of the predictors in the first year to the risk of asthma exacerbation in the second year indicated several findings as similar to previous models. Receipt of ≥3 SABA canisters in first year of treatment was still associated with persistent risk of asthma exacerbation [aOR: 1.35 (1.09-1.66)] even in the second year. However, with regard to the controller to total asthma drug ratio, higher events of exacerbation was surprisingly noted with high ratio group in both unadjusted and adjusted results, unlike previous findings.

Table 26: Model 3- First year predictors to risk of asthma exacerbation in the second year

	Crude OR (95% CI)	Adjusted OR (95% CI)	P value
Non-compliant prescriptions			
Exposed	0.75 (0.52-1.06)	0.82 (0.57-1.18)	0.2978
ICS Dose			
Medium	0.94 (0.66-1.35)	0.86 (0.59-1.24)	0.4113
High	1.03 (0.70-1.53)	1.01 (0.67-1.51)	0.9618
ICS/R03 ratio			
Low	1.45 (1.14-1.84) *	1.35 (1.05-1.74)	0.0178
High	1.51 (1.20-1.90) *	1.69 (1.32-2.15)	<0.0001*
Number of SABA packs			
High	1.35 (1.11-1.64) *	1.35 (1.09-1.66)	0.0051 *
Flu vaccination			
Exposed	0.99 (0.78-1.27)	1.02 (0.80-1.30)	0.8793

Adjusted for confounders: age, sex, region of residence, socioeconomic status, antibiotic courses, baseline comorbidities: Atopy, GERD, anxiety, depression, bronchitis, pneumonia, rhinosinusitis; *Significant observations with P value <0.05

Figure 9: Association between first year non-complaint prescriptions, ICS dose, ICS/R03 ratio and flu vaccination to the risk of asthma exacerbation in second year



Adjusted for confounders: age, sex, region of residence, socioeconomic status, antibiotic courses, baseline comorbidities: Atopy, GERD, anxiety, depression, bronchitis, pneumonia, rhinosinusitis

Chapter 4. DISCUSSION

This retrospective longitudinal cohort study aimed at investigating the anti-asthmatic drug prescribing in children and adolescents in the province of Manitoba found that more than one-tenth of the total study population were prescribed at least one anti-asthmatic drug during the study period. Although there has been variability in this proportion among literature, the values generally range from 7.5 % to 26% [147-149]. Consistent with previous assumptions and reports from a Canadian poll [150], the number of children and adolescents receiving anti-asthmatic drugs was higher among patients living in urban areas and from high socioeconomic status. As noticed by *Kozyrskyj et al* [151] in a Manitoban study, the conversion to income-based drug policy did not significantly alter the receipt of prescriptions among patients from high affluent households. This might be associated with rural health disparity or changes in asthma prevalence[152] [153].

Changes in crude prevalence of anti-asthmatic medication users with confirmed asthma measured in our study demonstrated fluctuations over the study period. Even though an increase in prevalence was noticed in 2014 (58.50/1000 PY) and 2016 (57.59/1000 PY), the overall change was insignificant. With regard to incidence, a downward trend was observed with a 15% decrease every year. Prevalence rate over the years stratified by sex and age groups showed an upward trend among females, adolescents and a downward trend among males, children. As compared to females, males had a higher prevalence consistent with findings from Statistics Canada [154]. In contrast to prevalence, a consistent decline in incident rate was noticed across all strata as similar to the trend noted in a study in Alberta [155].

Assessment of anti-asthmatic drug prescribing only concerned children who were newly diagnosed with asthma or didn't receive a prescription in the two years before their entry into the study. This was previously investigated by *Bianchi et al* in a retrospective study in Italy reporting conspicuous inappropriateness in drug use among new users [131]. The classification of users based on the frequency of anti-asthmatic drugs (occasional, moderate, and frequent) in their first year seems to be a reliable measure in assessing severity. More than half of the

users were occasional (52.49%) who were issued anti-asthma medications only once in their index year and a majority of them used either SABA (86.60%) or ICS (33.13 %). In addition to this, sporadic delivery of their prescriptions also in the second follow-up year with a mean 0.420 dispensing suggested them to be patients with mild intermittent asthma or exercise-induced asthma [156]. Comparably, a study conducted by *Henderson et al* using the GP data of Australia underlined a similar higher proportion of children (73 to 83%) to be having infrequent asthma or episodic asthma [157].

In the absence of clinical spirometric data, further assessment of the severity undertaken based on the number of dispensed drug classes [1,2, ≥3 (including OCS)] [84, 136] identified more than half (58 %) of the children and adolescents with asthma having moderate severity. Estimation of the ratio between the number of prescriptions issued by a pediatrician/immunologist to general physician indicated a lower occurrence of pediatric prescriptions (ratio: 0.73). This low ratio indicating the issuance of majority of prescriptions/refills from a non-specialist might be one among the reasons for the inappropriate use of asthma drugs and a challenge to the validity of asthma diagnosis.

Anti-asthmatic drug prescribing in the first two years of the treatment had considerable variations noted with respect to the count and frequency of prescriptions. Among the first-year users, only 54.47 % took medications in the second year. Even though there is no definite advised proportion for this, we expected at least 60% or more patients to be taking medications in second year since our analysis only included children with first intention of treatment who needs to be treated appropriately. Comparable results observed in a French study by *Naiim et al* however had a lower proportion than our cohort and reported drug use only in 27% of the first-year users. Considering the limitation that *Naiim et al's* study was not supported by physician-diagnosed asthma unlike our study, they attributed this trend to be caused by the pervasive use of anti-asthmatic medications for diagnosis other than asthma or potential under treatment [158]. Another possible explanation for this trend is reduced physician visits due to poor patient adherence commonly noted among adolescents [159, 160]. Forgetfulness about medications, lack of parental monitoring, and desire for independence among adolescents are

few reasons for this [161]. In addition, complexity of treatment regimen, apprehension regarding cost, side effects and dependence of medications particularly steroids, lack of training on inhalation techniques, failure in recognising symptoms, and insufficient knowledge about the need for preventive long-term therapy are other reasons for noncompliance particular to asthma medications [162, 163]. Given that reduced medication intake was unequivocally apparent among both children and adolescents, lower physician visits due to non-compliance would most likely be the reasons for it. Among the first-year users, SABA and ICS as expected were the most frequently used reliever and controller medication for asthma management in a vast majority (92.33% and 65.95%) of the children and adolescents respectively. In comparison to 62% and 44% reported by *Bianchi et al* [131] among new asthmatic patients, this represented a better and effective use of these medications. However, there were less than one-tenth of the first-year users who did not receive any SABA. It was also apparent in the second year in 9.41 % of the total 7140 asthma medication users. Among patients receiving controller therapy, three-quarters of them were managed with ICS alone without association with LABA or any other controller options which was more than twice higher as compared to *Bianchi et al* [131]. In contrast to their findings among Italian children, the percentage of patients treated without an inhaled corticosteroid was much higher in our study at a proportion of 31.04% as compared to 8% reported by them. Immunization with flu vaccine was observed only in 19.09% of the patients in the first year and 16.27% of total patients in the second year. This was similar to the provincial vaccination rate of 21.8 % in a general population [164]. Ambiguities and apprehensions experienced by the physicians and patients regarding safety, effectiveness and necessity of vaccination might be the reason for this underexposure. Appropriate measures on vaccine promotion, education through counselling or information aids, and vaccine administration tracking at units/departmental/ entire hospital levels can be adopted to mitigate this. Moreover, implementation of hospital standing orders to facilitate patient eligibility check for vaccination during routine physician visits or predominantly in flu season by team members even without their physicians' supervision can be advocated and incorporated into hospital protocols. These measures can minimise vaccine related stigma, misconceptions and thereby improve flu vaccination rates.

4.1 Impact of non-compliant prescriptions

Issuance of prescriptions regarded as not in compliance to the expert recommendations (GINA) with changes over time in our study, identified 9.18% of the first year and 33.10 % (after excluding recommendation for spacer device) of the second-year patients as having managed not in concordance with the expert recommendations. A Dutch study by *de Vries et al* [89] attempted to consider this exposure by comparing it against the Dutch guidelines. However, it was only limited to a cross-sectional evaluation. Performance of longitudinal examination with an additional two years of follow-up for newly treated patients in our study helped in estimating this issue particularly in patients with the first intention of treatment. Unlike greater incidence of LABA monotherapy ranging from 9% to 17.7%[89] [87] noted among parallel studies, only a negligible fraction of our patients were treated with LABA without an association. In addition to absence of SABA as noted previously, absence of dispensing of any type of inhalational device was also apparent in first year. As opposed to findings from *de Vries et al*, dispensing of DPI in children under 8 years (35.6%) was negligible among our patients in both first and second years. Nonetheless, a noticeable proportion of 28.9% and 22.7% users in first and second year, consistent with 35.4% reported by *de Vries et al* was observed receiving treatment with an MDI without the association with an inhalation chamber. A possible explanation to this might be the chance of spacer purchase as ‘over the counter’ which is not captured by our database and therefore this parameter was not further considered. Other reason would be usage of same spacer purchased in the first year for a longer duration even after expiry. Underuse of ICS marked by lack of ICS or ICS use for a duration less than 3 months was another observation in second year. It might be associated with prescriptions from generalist providers than a specialist, due to ineffective provider-patient communication or implications of prescribing upon patient request/convenience. Overall, after applying the recommendations except for the use of spacer devices, only 656 and 2364 users in the first and second year respectively were detected being treated not according to the recommendations and was not significantly associated with the likelihood of having asthma exacerbations [first year: aOR-0.84 (0.65-1.10); second year: aOR-0.91 (0.73-1.14)].

These results underline the deviation in the recommendations advised by the guidelines to the actual physician or patient-centered treatment most notably in the second year. Possible other prescriber related reasons for not following the recommendations apart from aforementioned factors includes lack of the prescriber's knowledge, accessibility issues to the guidelines /updates to guideline recommendations. However, these expert recommendations are readily available online and have been published in many national and international literature. Moreover, a buffer time allowed for the dissemination of updates/changes in recommendation in this study would also have addressed this issue. Even though a complete adherence to the guidelines is not expected, considering these findings in the future may help physicians on the importance to stay up to date.

4.2 Overuse of SABA and risk of asthma exacerbation

The prevalence of overuse of SABA during asthma management and its deleterious impact on hospitalization and healthcare outcomes have been previously examined and validated in existing literature [165-167]. Dispensing data from our study demonstrated that close to one-third of the users in the first year and one-fifth in the second year had been prescribed with ≥3 SABA canisters/year which is considered as overuse. It has further been associated with the likelihood of experiencing exacerbations of asthma in both first [aOR: 1.25 (1.07-1.46)] and second year [aOR: 1.57 (1.19-2.06)] as compared to children and adolescents receiving appropriate SABA treatment. Lack of provider-patient communication, poor adherence to controller therapy or changes in severity might be some potential reasons contributing to this overuse. In contrast to several previous studies [168, 169] that reported SABA overuse associative to increase in hospitalization, we used a composite outcome of hospitalization or ED visits or delivery of oral corticosteroids as measure for exacerbations in primary and secondary care. In response to this accumulating evidence, the SABA crisis has been addressed by recent updates in GINA [60] and the CTS [120] guidelines which now recommends considering 'pro re nata' ICS/LABA as a reliever instead of SABA.

4.3 High dose of ICS

Patients treated with daily ICS doses considered to be 'high' based on the fluticasone equivalent dose accounted for slightly more than one-tenth of the anti-asthmatic medication users in both first (11.51 %) and second year (12.80%). It was twice higher as compared to 4% reported by a study by *Elkout et al* [77] that described the daily doses based on the beclomethasone dipropionate equivalents measured using the prescriber dosing instructions. Despite this, interestingly the majority of the patients in our study were receiving low doses indicating the effective inception of maintenance treatment. Assessment of the consequence of high dose ICS prescriptions on the clinical outcome found no significant differences between the rate of exacerbation in both first and second year. Even though there was a positive association observed with medium-dose ICS in the second year with a crude odds ratio of 1.85 (1.25-2.74), it was insignificant after adjusting for the confounders.

4.4 Influence of inhaled corticosteroid to total asthma drug ratio on asthma exacerbation

Estimation of the controller to total asthma drug ratio was used in our study as a tool to investigate the instances of undertreatment with ICS and found 30.17% of the first-year anti-asthmatic medication users as having ratio <50% and 35.78 % with ratio ≥50%. Unlike sporadic receipt of medications noted earlier due to poor patient compliance, this pattern is suggestive to be resulting from insufficient prescribing. These findings were comparable to the proportion (<50%: 36%; ≥50%-45%) reported by *Laforest* et al [84] using French data. Patients with a high ratio had a lower risk of exacerbation in both the first and second years as compared to null and high ratios. Comparably, evidence from similar studies reported a lower risk of asthma-related adverse clinical outcomes among patients treated with a high ICS/R03 ratio [140, 170, 171]. As per the findings from *Laforest* et al, the high ratio group had lower risk [Relative risk: 0.89 (0.80–0.98)] [84] of receiving an oral corticosteroid prescription even after adjustment of confounders and baseline severity.

4.5 Impact of antibiotic prescriptions in patients with asthma

Higher use of antibiotics in new persistent asthma patients as compared to participants without asthma was noticed in both the first and second years of the follow-up period. Penicillin was

the most frequently prescribed antibiotic drug class occurring in 51.32 % of the total patients in the first year and 39.20 % in the second year followed by macrolides. A similar trend in the issuance of antibiotics was observed in a parallel study by *Fong* et al [172]which also reported high use of penicillin and macrolides. In consistence with our findings, acute URTIs and LRTIs including bronchitis were identified as the major indications for antibiotic prescriptions in a study by *Baan et al* [99]. Despite the evidence that respiratory tract infections predominantly URTIs [173] are notoriously triggered by viral infections for which the use of antibiotics is ineffective, it is still widely prescribed [93, 174]. Examination of the use of antibiotics between asthma patients and non-asthmatic matched controls by *Baan et al* also presented consistent findings to our study with a higher antibiotic prescription rate among asthma patients. It implies that even though antibiotics are not recommended to be used in asthma exacerbation considering its underlying viral induced nature, it has been widely used among asthma patients against the guideline recommendations. B/N ratio used in our study to further examine the balance between the use of broad-spectrum and narrow-spectrum antibiotics suggested a disproportionate use or higher use of the former over the later. A higher ratio of 3.8 was noticed among asthma patients in comparison to 3.4 among the participants without asthma ($p<0.0001$). Even though this was slightly lower than the B/N ratio reported by *Baan* et al (asthma: 4.7, non-asthma: 3.2), it is evident that this can potentiate the development of antimicrobial resistance and therefore needs to be controlled. The presence of respiratory infectious syndromes with symptom expression on the lower respiratory tract and cooccurring in asthma patients can be one potential reason that confounds the distinct identification between bacterial and viral infections. Additionally, a beneficial anti-inflammatory effect in particular with macrolide antibiotics among asthma patients has been reported by some studies. This can be another reason behind the extensive of macrolides as the second-largest preferred class of antibiotic used in asthma [175-177].

Literature evidence suggests that evaluation of the C- reactive protein (CRP) levels [99]and procalcitonin-guided antibiotic decisions (for LRTIs) [178] can be effective in minimizing unnecessary antibiotic prescriptions without prolonging the infection. Principles advised by the American Academy of Pediatrics (AAP) [179] for guiding judicious antibiotic prescribing

in URTIs can also be considered. Adoption of such interventions if needed and adhering to the treatment recommendations among asthma patients are therefore vital in minimizing the antibiotic over-prescription and thereby resistance.

4.6 Strengths and limitations

Common limitations pertaining to longitudinal epidemiological research are applicable to our study. As seen with other administrative database studies, the case definition used for identifying asthma cases is subjected to imperfections as it is based on the dispensing data of anti-asthmatic prescriptions and diagnostic codes from physician claims and hospital visits. A similar case definition for 5-year longitudinal database studies that has been validated by MCHP with reference to previous literature and expert opinions denoted 84.3 % sensitivity and 88.6% specificity for detecting asthma patients [180]. However, since a majority of our prescriptions were made by a general practitioner as compared to pediatricians/immunologists, the validity of the diagnosis can be questionable. To account for this, we restricted our study population to age group between 5 and 17 years since diagnosis of asthma under 5 years can be subjected to misinterpretations. Additionally, we also used a strict cohort definition which is a combination of at least one anti-asthmatic prescription and a confirmed diagnosis to minimize mistakes in diagnosis. Conversely, there is a chance that this stricter definition may be subject to underreporting of asthma. Apart from that, as we wanted to measure the medication prescribing in new persistent asthma patients, only those patients after excluding the occasional users were kept in the final analysis. Further to this, several other probable errors concerning the diagnosis such as coding errors are possible even if the data entry staffs are well trained to minimize these errors. Moreover, issues associated with databases and inadequacy of information can also be confounders. For instance, lack of information regarding physician samples, services delivered in hospital pharmacies, nursing stations, and outpatient visits can be sources of missing information in DPIN. Besides this, visits made to salaried health care providers in primary health settings are not captured in the physician claims database. Even though a majority of the physician services are rendered on a fee-for-service scheme, there might be chances that the patients have consulted salaried physicians. A

report by *Katz et al* [181] denoted that a proportion of up to one-third of visits made to a salaried primary health care provider was not captured in this database. The inappropriateness measured in the study was extrapolated from the pattern of dispensing or prescription fills and not on the actual intake even if it is possible to approach this based on renewals. Thus lack of information on consumption of medication can be a confounder. Non-compliance or medication non-adherence with chronic therapy is common, especially in adolescents, and can be a reason for misinterpretations.

Several other limitations can be attributed to parameters concerning exposures and outcomes. Firstly, as indications are not captured in prescription database, they were identified by linking date of prescription to claims diagnosis on the same date. Even though this has been found to be accurate, a very minority of prescriptions could be linked misdiagnosed since the claims database can only code one diagnosis. Therefore improper coding among patients with multiple indications can affect this. Concerning the outcome, oral corticosteroids were used as a parameter for measuring the risk of exacerbation. However, in several cases, oral corticosteroids can be prescribed preemptively prior to asthma exacerbations.

Major strengths of our study include larger sample size and the use of drug prescription as the gold standard for marking asthma patients. Since all children, especially children presenting with current asthma symptoms considered for the study receive an asthma medication at least once at some point in the study, this definition would have captured them. Secondly, since we included children from all strata regardless of their socioeconomic status, we were able to exclude underestimations due to lower-income children. More importantly, to our knowledge, no study in Canada has done a longitudinal evaluation of prescription non-compliance with expert recommendations. In this regard, our study was the state of art to draw conclusions associated with the inappropriateness in anti-asthmatic drug prescribing.

Chapter 5: CONCLUSION

Our study was the first of its kind to our knowledge, in longitudinally evaluating anti-asthmatic drug prescribing trends, prescription non-compliance to expert recommendations, and measuring prescribing compliance impact on the clinical consequences in Canadian children with asthma.

The trends in prevalence and incidence of anti-asthmatic medication prescribing among asthma patients varied across the years. Even though no significant changes in the crude prevalence were noticeable, an inverse trend among prevalence stratified by sex and age groups was apparent with an annual upward trend among females, adolescents, and a downward trend among males, and children. On the contrary, with regard to incidence, a downward trend over the years was observed in all strata.

Concerning anti-asthmatic drug prescribing, we found that majority of the children and adolescents with persistent asthma who are newly treated with anti-asthmatic medications used their medication only sporadically in their second year. Among the total prescription issued within two years, the majority of them were by a general practitioner as compared to a pediatrician/immunologist. Short-acting bronchodilators and inhaled corticosteroids that are considered the mainstay of the reliever and controller therapy were the most frequently prescribed medications. Out of the total patients who received a controller medication, inhaled corticosteroids were used alone in most of the occasions at low and medium doses (daily doses calculated as fluticasone equivalents). In comparison to adolescents, a greater number of children were also exposed to high dose of inhaled corticosteroids. Nevertheless, it was not associated with any likelihood of having a risk of asthma exacerbation.

Whenever asthma was not adequately controlled by one controller, the addition of a secondary controller was preferred, and it was most predominantly long-acting bronchodilators ensued by leukotriene receptor antagonists or other controller options. The requirement of oral corticosteroids for treating asthma was more common in the first year with only half of the

first-year patients taking it in the second year. Even though medication-based severity assessed at the baseline of the second year reported a greater proportion of patients with moderate asthma (2 medication classes), these reductions in OCS might be an indication of the decrease in severity across the second year.

We assessed the prescriber compliance to expert recommendations (GINA guidelines) among the children and adolescents based on several parameters. In the first year, the absence of SABA inhalers, the absence of an inhalational device, and dispensing of devices without inhalation chambers were apparent. But in the second year, the absence of ICS, using ICS for a short term among moderate, severe patients, and using MDIs without a spacer device were more frequent. However, these occasions of non-compliance had no effect among patients with asthma exacerbation. Similarly, a number of patients in both the first and second years used more SABA inhalers (≥3), and this use had more likelihood of precipitating asthma exacerbations. Among patients using ICS, a lesser risk of exacerbation was observable with the use of ≥50% ICS out of total asthma medications, in both first and second years. Substantial use of antibiotics, predominantly broad-spectrum antibiotics was prominent among asthma patients as compared to children and adolescents without asthma. In addition to the fact that they are prescribed against the guidelines, they also predispose patients to antimicrobial resistance especially at a younger age, and therefore should not be recommended.

Our findings indicating drop in anti-asthmatic drug prescriptions in the second year among newly treated patients, and the relationship of overuse of SABA, underuse of ICS on the likelihood of having exacerbation warrants the necessity of both effective treatment and patient education to improve adherence. Occasions with non-compliant prescriptions particularly absence of SABA dispensing and ICS underuse in addition to unnecessary antibiotic prescriptions during first intention of treatment, should also be considered and controlled to tailor effective asthma management.

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APPENDIX

Appendix Table 1: ATC codes for anti-asthmatic drug classes

DRUG CLASSES	**ATC CODES**
Alpha- and beta-adrenoreceptor agonists	R03AA01 (Epinephrine)
Nonselective B adrenergic receptor agonist	R03AB02 (Isoprenaline)
Selective B adrenergic receptor agonist	R03AB03 (Orciprenaline)
ICS	R03BA01 (Beclometasone Dipropionate) R03BA02 (Budesonide) R03BA03 (Flunisolide) R03BA05 (Fluticasone Propionate) R03BA / R03BA06 (Triamcinolone Acetonide) R03BA07 (Mometasone Furoate) R03BA08 (Ciclesonide) R03BA09 (Fluticasone furoate)
LABA	R03AC12 (Salmeterol) R03AC13 (Formoterol) R03AC16 (Procaterol) R03AC18 (Indacaterol) R03AC19 (Olodaterol)
Association of LABA+ICS	R03AK06 (Salmeterol + Fluticasone) R03CK / R03AK07 (Budesonide + Formoterol) R03AK08 (Beclometasone + Formoterol) R03AK09 (Formoterol Fumarate Dihydrate/Mometasone Furoate) R03AK10 (Vilanterol Trifenatate + Fluticasone Furoate) R03AK11 (Formoterol and Fluticasone)
LTRA	R03DC01 (Zafirlukast) R03DC03 (Montelukast)
Xanthines	R03DA01 (Diprophylline) R03DA02 (Oxtriphylline) R03DA04 (Theophylline) R03DA05 (Aminophylline) R03DA08 (Bamifylline)

	R03DA54 (Alcohol Anhydrous/Oxtriphylline) R03DA52 (Alcohol Anhydrous/Oxtriphylline)
Cromones	R03BC01 (Sodium Cromoglycate) R03BC03 (Nedocromil Sodium)
Anti-IgE	R03DX05 (Omalizumab) R03DX09 (Mepolizumab) R03DX10 (Benralizumab)
SABA	R03AC02 (Salbutamol) R03AC03 (Terbutaline Sulfate) R03AC04/ R03CC04 (Fenoterol Hydrobromide) R03AC08 (Pirbuterol Acetate)
Anticholinergics	R03BB01 (Ipratropium Bromide) R03BB02 (Oxitropium Bromide) R03BB04 (Tiotropium Bromide) R03BB05 (Aclidinium bromide) R03BB06 (Glycopyrronium Bromide) R03BB/ R03BB07 (Umeclidinium Bromide) R03BB54 (Tiotropium Bromide, Combinations)
Association of anticholinergics + SABA	R03AL01 (Fenoterol and Ipratropium Bromide) R03AL02 (Salbutamol and ipratropium bromide) R03AK04 (Salbutamol and Sodium Cromoglicate)
Association of anticholinergics + LABA	R03AL03 (Vilanterol and Umeclidinium Bromide) R03AL04 (Indacaterol and Glycopyrronium Bromide R03AL05 (formoterol and aclidinium bromide) R03AL/ R03AL06 (olodaterol and tiotropium bromide) R03AL07 (formoterol and glycopyrronium bromide)
Association of anticholinergics + LABA+ ICS	R03AL08 (Vilanterol, umeclidinium bromide and fluticasone furoate)

SYSTEMIC BA	R03CB03 (Orciprenaline Sulfate) R03CC02 (Salbutamol) R03CC03 (Terbutaline Sulfate) R03CC12 (Bambuterol)
OTHERS	R03DX03 (Fenspiride) R03DX07 (Roflumilast) R03DX08 (Reslizumab) R03DB04 (theophylline and adrenergics combination)

Appendix Table 2: ATC codes for antibiotic drug classes

SPECTRUM	**ANTIBIOTIC CLASS**	**DRUGS**	**DRUG ATC CODES**
BROAD	Macrolides, oral dosage forms	Azithromycin Clarithromycin Erythromycin Spiramycin Telithromycin	J01FA10 J01FA09 J01FA01 J01FA02 J01FA15
BROAD	Fluoroquinolones	Ciprofloxacin	J01MA02
		Gatifloxacin	J01MA16
		Gemifloxacin	J01MA15
		Levofloxacin	J01MA12
		Moxifloxacin	J01MA14
		Nalidixic Acid	J01MB02
		Norfloxacin	J01MA06
		Ofloxacin	J01MA01
BROAD	Second gen cephalosporin	Cefaclor	J01DA08 J01DC04
NARROW	First-gen cephalosporins	Cefadroxil	J01DA09 J01DB05
BROAD	Carbapenems	Meropenem	J01DH02
BROAD	Carbapenems	Ertapenem Sodium	J01DH03
NARROW	First-gen cephalosporins	Cefazolin Sodium	J01DA04 J01DB04
BROAD	Third gen cephalosporin	Cefotaxime	J01DD01 J01DA10
BROAD	Second gen cephalosporin	Cefotetan Disodium	J01DC05

			J01DA14
BROAD	Second gen cephalosporin	Cefoxitin Sodium	J01DA05 J01DC01
BROAD	Second gen cephalosporin	Cefprozil	J01DA41 J01DC10
BROAD	Third gen cephalosporin	Ceftazidime	J01DA11 J01DD02
BROAD	Third gen cephalosporin	Ceftriaxone	J01DD04 J01DA13
BROAD	Second gen cephalosporin	Cefuroxime Axetil	J01DA06 J01DC02
NARROW	First-gen cephalosporins	Cephalexin	J01DA01 J01DB01
BROAD	Carbapenems	imipenem + Cilastatin Sodium	J01DH51
BROAD	Third gen cephalosporin	Cefixime	J01DD08 J01DA23
NARROW	Narrow spectrum penicillins	Benzathine phenoxymethylpenicillin Benzylpenicillin Phenoxymethylpenicillin Benzathine benzylpenicillin Cloxacillin Flucloxacillin	J01CE10 J01CE01 J01CE02 J01CE08 J01CF02 J01CF05
BROAD	Broad spectrum penicillins	Ampicillin Pivampicillin Amoxicillin Amoxicillin + B-lactamase inhibitor Pivmecillinam HCL Piperacillin Piperacillin/Tazobactam	J01CA01 J01CA02 J01CA04 J01CR02 J01CA08 J01CA12 J01CR05
BROAD	Trimethoprin and sulphonamides oral dosage forms	Sulfadiazine /Trimethoprim	J01EE02
		Sulfamethoxazole /Trimethoprim	J01EE01
		Sulfisoxazole	J01EB05
		Trimethoprim	J01EA01
BROAD	Tetracyclines, oral dosage forms	Doxycycline Lymecycline Metacycline Tetracycline Minocycline	J01AA02 J01AA04 J01AA05 J01AA07 J01AA08
	Others		
NARROW	*Lincosamides*	Clindamycin	J01FF01
NARROW	*Lincosamides*	Lincomycin	J01FF02
BROAD	*Aminoglycoside*	Streptomycin	J01GA01

BROAD	*Aminoglycoside*	Tobramycin	J01GB01
BROAD	*Aminoglycoside*	Gentamicin Sulfate	J01GB03
BROAD	*Aminoglycoside*	Amikacin	J01GB06
BROAD	Macrolide/sulfonamide	Erythromycin/Sulfisoxazole	J01RA02
BROAD	*Glycopeptide*	Vancomycin	J01XA01
NARROW	*Polymixin*	Colistin	J01XB01
NARROW	*Others*	Fusidic acid	J01XC01
NARROW	*Nitroimidazoles*	Metronidazole	J01XD01
BROAD	*Nitrofuran*	Nitrofurantoin	J01XE01
BROAD	*Others*	Fosfomycin	J01XX01
BROAD	*Others*	Spectinomycin	J01XX04
BROAD	*Others*	Methenamine	J01XX05
BROAD	*Oxazolidinones*	Linezolid	J01XX08

Appendix Table 3: PIN numbers for inhalation chambers

PIN & PRODUCT	900222 Inspirachamber Mouthpiece
903175 Space Chamber	900224 Inspirachamber – Small
900100 Aerochamber	900226 Inspirachamber – Medium
900200 Aerochamber with Mask Adult	907243 Optichamber
900210 Aerochamber with Mask Child	973408 Optichamber Mask Large
900333 Anti-Static Compact Space Chamber Plus - Mouthpiece	973394 Optichamber Mask S/M
900335 Anti-Static Compact Space Chamber Plus - Small	
900337 Anti-Static Compact Space Chamber Plus - Medium	
900339 Anti-Static Compact Space Chamber Plus – Large	
960918 Optihaler	

Appendix Table 4: ATC codes for glucocorticoids

GLUCOCORTICOIDS	**ATC CODES**
Prednisone	H02AB07
Prednisolone	A07EA01, H02AB06
Methylprednisolone	H02AB04
Dexamethasone	H02AB02

Appendix Table 5: ATC and Tariff codes for vaccines

VACCINE	ATC CODES	TARIFF CODES
Anti- influenza	J07AG01, J07AG51, J07AG52, J07AG53, J07BB01, J07BB02, J07BB03,	8791, 8775, 8901, 8908, 8968, 8969
Anti-pneumococcal	J07AL01, J07AL02 J07AL52	8896, 8961, 8962, 8681

Appendix Table 6: ICD codes of indications identified for antibiotic use (Disease categories adapted from *Baan et al* [99])

Disease group	ICD 9	ICD 10	Specific disease	Description
SKIN	706.0	L70.2	ACNE	Acne varioliformis
OTHERS	540*	K35*	GASTROENTERITIS	Acute appendicitis
LRTI	466.19	J21.8	BRONCHITIS	Acute bronchiolitis due to other infectious organisms
LRTI	466.0	J20.9	BRONCHITIS	Acute bronchitis
LRTI	466	J20, J21	BRONCHITIS	Acute bronchitis and bronchiolitis
UTI	595.0	N30.00	CYSTITIS	Acute cystitis
LRTI	464.3*	J05.1*	TRACHEITIS	Acute epiglottitis
LRTI	464*	J04*	TRACHEITIS	Acute laryngitis and tracheitis
URTI	465.0	J06.0	URTI	Acute laryngopharyngitis
SKIN	683	L04.9	SKIN	Acute lymphadenitis
URTI	460	J00	URTI	Acute nasopharyngitis [common cold]
URTI	462	J02.9	TONSILLITIS	Acute pharyngitis
URTI	461*	J01*	SINUSITIS	Acute sinusitis
URTI	382.00	H66.009	OTITIS	Acute suppurative otitis media without spontaneous rupture of eardrum
URTI	463	J03.90	TONSILLITIS	Acute tonsillitis
URTI	465	J06	URTI	Acute URTI

URTI	465.8	J06.9	URTI	Acute URTI, other multiple sites
URTI	465.9	J06.9	URTI	Acute URTI, unspecified site
URTI	477*	J30*	URTI	Allergic rhinitis
OTHERS	300*	F41*	OTHERS	Anxiety, dissociative and somatoform disorders
ASTHMA	493*	J45*	ASTHMA	Asthma
SKIN	691*	L20*	SKIN	Atopic dermatitis
SKIN	216*	D23*	SKIN	Benign neoplasm of skin
LRTI	494	J47	BRONCHIECTASIS	Bronchiectasis
LRTI	494.0	J47.9	BRONCHIECTASIS	Bronchiectasis without acute exacerbation
LRTI	490*	J40*	BRONCHITIS	Bronchitis
SKIN	694	L13.9	SKIN	Bullous dermatoses
SKIN	680.2	L02.22*, L02.23*	SKIN	Carbuncle and furuncle of trunk
SKIN	680.9	L02.92, L02.93	SKIN	Carbuncle and furuncle of unspecified site
SKIN	680.3	L02.429, L02.439	SKIN	Carbuncle and furuncle of upper arm and forearm
SKIN	681	L03.0	SKIN	Cellulitis and abscess of finger and toe
OTHERS	995, 995.3	T7840XA	OTHERS	Certain adverse effects not elsewhere classified; allergy unspecified not elsewhere classified
URTI	474.01	J35.02	TONSILLITIS	Chronic adenoiditis
LRTI	491	J41	BRONCHITIS	Chronic bronchitis
LRTI	491.9	J42	BRONCHITIS	chronic bronchitis, unspecified
URTI	474	J35	TONSILLITIS	Chronic disease of tonsils and adenoids
URTI	472.2	J31.1	URTI	Chronic nasopharyngitis
URTI	472.1	J31.2	URTI	Chronic pharyngitis
URTI	472	J31	URTI	Chronic pharyngitis and nasopharyngitis
UTI	590.00	N11.0	UTI	Chronic pyelonephritis
URTI	472.0	J31.0	URTI	Chronic rhinitis
URTI	473*	J32*	SINUSITIS	Chronic sinusitis
URTI	474.00	J35.01	TONSILLITIS	Chronic tonsillitis
SKIN	692,692.9	L24.0, L25.9	SKIN	Contact dermatitis and other eczema
LRTI	464.4	J05.0	TRACHEITIS	Croup

UTI	595	N30	CYSTITIS	Cystitis
UTI	595.9	N30.90, N30.91	CYSTITIS	Cystitis, unspecified
OTHERS	311	F32.9	OTHERS	Depressive disorder, not elsewhere classified
OTHERS	530*	K22*	GASTROENTERITIS	Diseases of esophagus
OTHERS	704	L65*	OTHERS	Diseases of hair and hair follicles
SKIN	703, 703.0	L60, L60.0	SKIN	Diseases of nail
OTHERS	522*	K04*	OTHERS	Diseases of pulp and periapical tissues
SKIN	706	L73.9	SKIN	Diseases of sebaceous glands
OTHERS	372*	H10-H13*	EYE INFECTION	Disorders of conjunctiva
URTI	380	H60-H62	OTITIS	Disorders of external ear
OTHERS	367*	H52*	OTHERS	Disorders of refraction and accommodation
SKIN	695.9	J53.9	SKIN	Erythematous conditions, unspecified
OTHERS	578	K92	GASTROENTERITIS	Gastrointestinal hemorrhage
OTHERS	V70	Z00.0	OTHERS	General medical examination
OTHERS	V70.0	Z00.00	OTHERS	General medical examination at a health care facility
OTHERS	780, 780.60	R68.8	OTHERS	General symptoms; Fever, unspecified
OTHERS	959.01	S098XXA S0990XA	OTHERS	Head injury, unspecified
OTHERS	314*	F90*	OTHERS	Hyperkinetic syndrome of childhood
URTI	474.11	J35.1	TONSILLITIS	Hypertrophy of tonsils
URTI	474.10	J35.3	TONSILLITIS	Hypertrophy of tonsils and adenoids
OTHERS	009*	A09	GASTROENTERITIS	Ill-defined intestinal infections
SKIN	684	L01.00, L01.03	SKIN	Impetigo
SKIN	694.3	L40.1	SKIN	Impetigo herpetiformis
OTHERS	373*	H01*	EYE INFECTION	Inflammation of eyelids
LRTI	487*	J11*	INFLUENZA	Influenza
OTHERS	008*	A04*, A08*	GASTROENTERITIS	Intestinal infections due to other organisms
SKIN	078.0	B08.1	SKIN	Molluscum contagiosum

URTI	381*	H65*	OTITIS	Nonsuppurative otitis media
OTHERS	521.05	K03.89	OTHERS	Odontoclasia
SKIN	879.4	S31109A	SKIN	Open wound of abdominal wall lateral without complication
SKIN	881.01	S51009A	SKIN	Open wound of elbow without complication
SKIN	873.40	S0993XA	SKIN	Open wound of face unspecified site uncomplicated
SKIN	883.2	S61109A, S61209A, S66529A	SKIN	Open wound of fingers with tendon involvement
SKIN	883.0	S61209A	SKIN	Open wound of fingers without complication
SKIN	892.0	S91309A	SKIN	Open wound of foot except toe(s) alone without complication
SKIN	881.20	S56929A, S51809A	SKIN	Open wound of forearm with tendon involvement
SKIN	881.00	S51809A	SKIN	Open wound of forearm without complication
SKIN	873.42	S0180XA	SKIN	Open wound of forehead uncomplicated
SKIN	882.1	S61429A	SKIN	Open wound of hand except fingers alone complicated
SKIN	882.0	S61409A	SKIN	Open wound of hand except fingers alone without complication
SKIN	891.0	S81009A, S81809A	SKIN	Open wound of knee, leg [except thigh], and ankle
SKIN	873.43	S01501A	SKIN	Open wound of lip uncomplicated
SKIN	893.0	S91109A	SKIN	Open wound of toe(s) without complication
SKIN	879.8	S31000A	SKIN	Open wound(s) (multiple) of unspecified site(s) without complication
URTI	388.7	H92.09	OTITIS	Otalgia
SKIN	706.1	L70.0, L70.1, L70.8	ACNE	Other acne
URTI	478.9	J39.8, J39.9	URTI	Other and unspecified diseases of upper respiratory tract

SKIN	959.5	S6980XA S6990XA	SKIN	Other and unspecified injury to finger
OTHERS	558, 558.9	K52, K52.89, K52.9	GASTROENTERITIS	Other and unspecified non-infectious gastroenteritis and colitis
SKIN	682*	K12.2, L031-3*, L038*	SKIN	Other cellulitis and abscess
URTI	478.19	J340, J341, J34.89	URTI	Other diseases of nasal cavity and sinuses
URTI+LRTI	519	J95-J99	URTI+LRTI	Other diseases of respiratory system
URTI	478	J30-J39	URTI	Other diseases of upper respiratory tract
URTI	388	H90-H95	OTITIS	Other disorders of ear
URTI	385	H74	EAR INFECTION	Other disorders of middle ear and mastoid
SKIN	709	L80-L99	SKIN	Other disorders of skin and subcutaneous tissue
UTI	599	N36*	UTI	Other disorders of urethra and urinary tract
SKIN	686*	L08*	SKIN	Other local infections of skin and subcutaneous tissue
URTI	380.2	H60.4 -9	OTITIS	Other otitis externa
SKIN	703.8	L601-4, L608	SKIN	Other specified diseases of nail
URTI	478.22	J390	TONSILLITIS	Parapharyngeal abscess
URTI	475	J36	TONSILLITIS	Peritonsillar abscess
OTHERS	078.12	B07.0	OTHERS	Plantar wart
LRTI	480 - 486*	J12*	PNEUMONIA	Pneumonia
SKIN	696	L40, L41, L42, L44.8	SKIN	Psoriasis and similar disorders
UTI	590.80	N12	PYELONEPHRITIS	Pyelonephritis unspecified
OTHERS	555	K50	GASTROENTERITIS	Regional enteritis
OTHERS	555.9	K50.90	GASTROENTERITIS	Regional enteritis of unspecified site
SKIN	706.2	L72.3	SKIN	Sebaceous cyst
LRTI	491.0	J41.0	BRONCHITIS	Simple chronic bronchitis
OTHERS	V72*	Z01*	OTHERS	Special investigation

URTI	034*	J02.0, J03.00, A389	TONSILLITIS	Streptococcal sore throat and scarlet fever
OTHERS	041.00	B95.5	OTHERS	Streptococcus infection in conditions classified elsewhere and of unspecified site
URTI	382	H66	OTITIS	Suppurative and unspecified otitis media
OTHERS	787	R10-R19	OTHERS	Symptoms involving digestive system
URTI+LRTI	786	R20, R21, R22	URTI+LRTI	Symptoms involving respiratory system
UTI	788	R30-R39	CYSTITIS	Symptoms involving urinary system
URTI	474.9	J35.9	TONSILLITIS	Unspecified chronic disease of tonsils and adenoids
OTHERS	521.00	K02.9	OTHERS	Unspecified dental caries
UTI	599.9	N36.9, N39.9	UTI	Unspecified disorder of urethra and urinary tract
SKIN	959.09	S0993XA S199XXA	SKIN	Unspecified injury of face, initial encounter
OTHERS	919.4	T07	OTHERS	Unspecified multiple injuries
URTI	382.9	H66.90	OTITIS	Unspecified otitis media
OTHERS	789.00	R10.9	OTHERS	Unspecified site abdominal pain
URTI	382.4	H66.40	OTITIS	Unspecified suppurative otitis media
URTI	478.8	J393	URTI	Upper respiratory tract hypersensitivity reaction site unspecified
UTI	599.0	N39.0	UTI	Urinary tract infection site not specified
OTHERS	079.99	B97.89	OTHERS	Viral infection, unspecified
OTHERS	078.10	B07.9	OTHERS	Viral wart, unspecified
LRTI	033*	A37*	TRACHEITIS	Whooping cough

*Wild cards were used