

**EFFECTS OF MANITOBA PHARMACARE FORMULARY
POLICY ON UTILIZATION OF PRESCRIPTION
MEDICATIONS**

December 2009

Manitoba Centre for Health Policy

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Members of MCHP consult extensively with government officials, health care administrators, and clinicians to develop a research agenda that is topical and relevant. This strength, along with its rigorous academic standards, enables MCHP to contribute to the health policy process. MCHP undertakes several major research projects, such as this one, every year under contract to Manitoba Health and Healthy Living (MHHL). In addition, our researchers secure external funding by competing for research grants. We are widely published and internationally recognized. Further, our researchers collaborate with a number of highly respected scientists from Canada, the United States, Europe and Australia.

We thank the University of Manitoba, Faculty of Medicine, and Health Research Ethics Board for their review of this project. MCHP complies with all legislative acts and regulations governing the protection and use of sensitive information. We implement strict policies and procedures to protect the privacy and security of anonymized data used to produce this report and we keep the provincial Health Information Privacy Committee informed of all work undertaken for MHHL.

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TABLE OF CONTENTS

Executive Summary	xii
Introductory and Methods Chapter	1
Specific Research Questions.....	2
Methods.....	3
Focus of the report.....	3
Data sources.....	3
Definitions of prescription medication users	3
Modeling.....	5
How this report is organized	5
Data limitations.....	5
Chapter 1: Narcotics	7
1.1 Methods	7
1.2 Results	7
Prevalence	7
Incidence	13
1.3 Discussion	16
Chapter 2: COX 2 and NSAIDs	19
2.1 Methods	19
2.2 Results.....	20
Prevalence.....	20
Incidence	26
2.3 Discussion	29
Chapter 3: Bisphosphonates.....	31
3.1 Methods	31
3.2 Results.....	32
Prevalence.....	32
Incidence	36
3.3 Discussion	38
Chapter 4: Antipsychotics	41
4.1 Methods	41
4.2 Results.....	41
Prevalence.....	41
Incidence	47
4.3 Discussion	50

Chapter 5: Antihypertensives	53
5.1 Methods	53
5.2 Results	53
Prevalence	53
Incidence	56
5.3 Discussion	57
Chapter 6: Statins	59
6.1 Methods	59
6.2 Results	59
Prevalence	59
Incidence	63
6.3 Discussion	65
Chapter 7: Medications for Diabetes Mellitus	67
7.1 Methods	67
7.2 Results	68
Prevalence	68
Incidence	73
7.3 Discussion	74
Chapter 8: Proton Pump Inhibitors	75
8.1 Methods	75
8.2 Results	75
Prevalence	75
Incidence	78
8.3 Discussion	80
Chapter 9: Medications for Asthma and Chronic Lung Disease	83
9.1 Methods	83
9.2 Results	84
Prevalence	84
Incidence	94
9.3 Discussion	98
Chapter 10: Stimulants	101
10.1 Methods	101
10.2 Results	101
Prevalence	101
Incidence	105
10.3 Discussion	108

Chapter 11: Antibiotics	111
11.1 Methods	111
11.2 Results	112
Prevalence	112
11.3 Discussion	119
Chapter 12: Analysis Strengths and Challenges	121
12.1 Conclusions and Recommendations	121
12.1.1 Key Findings and Recommendations	122
12.1.2 Data Recommendations.....	125
12.1.3 Recommendations for Future Research	125
Reference List.....	127
Glossary.....	140
Appendix One: Modeling Approach	145
Appendix Two: Appendix Figures	151
Appendix Three: ICD Codes for Medical Conditions.....	171

LIST OF FIGURES

Figure 1.1	Narcotics Quarterly Prevalence (crude user rates)	8
Figure 1.2	Narcotics Quarterly Prevalence (crude prescription rates)	8
Figure 1.3	Narcotics Quarterly Prevalence (crude user rates without Tylenol #3®)	9
Figure 1.4	Tylenol #3® Quarterly Prevalence by Age	11
Figure 1.5	Oxycontin® Quarterly Prevalence by Age	12
Figure 1.6	Narcotics Quarterly Incidence	13
Figure 1.7	Narcotics (Including Chronic Tylenol #3®) Quarterly Incidence	14
Figure 1.8	Tylenol #3® Quarterly Incidence by Age	15
Figure 1.9	Oxycontin® Quarterly Incidence by Age	16
Figure 2.1	Older NSAIDs and COX 2 Inhibitors Quarterly Prevalence (crude user rates)	20
Figure 2.2	Older NSAIDs and COX 2 Inhibitors Quarterly Prevalence (crude prescription rates)	21
Figure 2.3	Older NSAIDs and COX 2 Inhibitors Quarterly Prevalence (crude rates by medication group)	22
Figure 2.4	COX 2 Inhibitors Quarterly Prevalence by Age	24
Figure 2.5	Older NSAIDs Quarterly Prevalence by Age	25
Figure 2.6	Older NSAIDs and COX 2 Inhibitors Quarterly Incidence (by medication group)	26
Figure 2.7	Older NSAIDs and COX 2 Inhibitors Quarterly Incidence (by specific medication)	28
Figure 2.8	COX 2 Inhibitors Quarterly Incidence by Age	28
Figure 2.9	Older NSAIDs Quarterly Incidence by Age	29
Figure 3.1	Medications for Osteoporosis, Quarterly Prevalence (crude user rates)	32
Figure 3.2	Medications for Osteoporosis, Quarterly Prevalence (crude prescription rates)	33
Figure 3.3	Alendronate and Risedronate Dosing, Quarterly Prevalence	33
Figure 3.4	Alendronate Quarterly Prevalence	34
Figure 3.5	Bisphosphonates Quarterly Prevalence by Age	35
Figure 3.6	Hormone Replacement Therapy, Quarterly Prevalence by Age	35
Figure 3.7	Medications for Osteoporosis, Quarterly Incidence	36
Figure 3.8	Bisphosphonates Quarterly Incidence by Age	37
Figure 3.9	Hormone Replacement Therapy Quarterly Incidence by Age	38
Figure 4.1	Antipsychotics Quarterly Prevalence (crude user rates)	42
Figure 4.2	Antipsychotics Quarterly Prevalence (crude prescription rates)	42
Figure 4.3	Antipsychotics aged 65+ Quarterly Prevalence	43
Figure 4.4	Antipsychotics (Atypicals) Quarterly Prevalence by Age Group	45
Figure 4.5	Antipsychotics (Atypicals) Quarterly Prevalence Excluding Residents of Personal Care Homes by Age Group	46
Figure 4.6	Antipsychotics Quarterly Incidence	47
Figure 4.7	Antipsychotics Quarterly Incidence aged 65+	48
Figure 4.8	Antipsychotics (Atypicals) Quarterly Incidence by Age	49
Figure 4.9	Antipsychotics (Atypicals) Quarterly Incidence by Age, Excluding Personal Care Home Residents	50

Figure 5.1	Antihypertensives Quarterly Prevalence (crude user rates)	54
Figure 5.2	Antihypertensives Quarterly Prevalence (crude prescription rates)	54
Figure 5.3	Antihypertensives Quarterly Incidence	56
Figure 5.4	Antihypertensives Quarterly Incidence with Uncomplicated Hypertension	57
Figure 6.1	Statins Quarterly Prevalence (crude user rates).....	60
Figure 6.2	Statins Quarterly Prevalence (crude prescription rates)	60
Figure 6.3	Statins Quarterly Prevalence by Age	62
Figure 6.4	Statins Quarterly Incidence	63
Figure 6.5	Statins Quarterly Incidence by Age.....	64
Figure 6.6	Statins Quarterly Incidence by Cardiovascular Risk.....	65
Figure 7.1	Medications for Diabetes Mellitus Quarterly Prevalence (crude user rates)	68
Figure 7.2	Medications for Diabetes Mellitus Quarterly Prevalence (crude prescription rates)	69
Figure 7.3	Medications for Diabetes Mellitus Quarterly Prevalence by Therapy Type	71
Figure 7.4	Metformin Quarterly Prevalence by Age.....	72
Figure 7.5	Glitazones Quarterly Prevalence by Age.....	72
Figure 7.6	Medications for Diabetes Mellitus Quarterly Incidence	73
Figure 8.1	Proton Pump Inhibitors Quarterly Prevalence (crude user rates).....	76
Figure 8.2	Proton Pump Inhibitors Quarterly Prevalence (crude prescription rates)	76
Figure 8.3	Proton Pump Inhibitors Quarterly Prevalence (by generic and brand name Omeprazole)	77
Figure 8.4	Proton Pump Inhibitors Quarterly Prevalence by Age.....	78
Figure 8.5	Proton Pump Inhibitors Quarterly Incidence	79
Figure 8.6	Proton Pump Inhibitors Quarterly Incidence by Age.....	79
Figure 8.7	Proton Pump Inhibitors Quarterly Incidence by Duration of Use	80
Figure 9.1	Medications for Asthma and Chronic Lung Disease Quarterly Prevalence, Adults (crude user rates)	84
Figure 9.2	Medications for Asthma and Chronic Lung Disease Quarterly Prevalence, Adults (crude prescription rates).....	85
Figure 9.3	Medications for Asthma and Chronic Lung Disease Quarterly Prevalence, Children (crude user rates)	86
Figure 9.4	Medications for Asthma and Chronic Lung Disease Quarterly Prevalence, Children (crude prescription rates).....	86
Figure 9.5	Medications for Asthma and Chronic Lung Disease Quarterly Prevalence, Adults with Chronic Lung Disease (crude user rates).....	87
Figure 9.6	Medications for Asthma and Chronic Lung Disease Quarterly Prevalence, Adults with Chronic Lung Disease (crude prescription rates)	89
Figure 9.7	Steroid Quarterly Prevalence by Age, Adults.....	89
Figure 9.8	LABA/Steroid Combinations Quarterly Prevalence by Age, Adults.....	90
Figure 9.9	SABA Quarterly Prevalence by Age, Adults	90
Figure 9.10	Medications for Asthma and Chronic Lung Disease Quarterly Prevalence, Children with Asthma (crude user rates)	92
Figure 9.11	Medications for Asthma and Chronic Lung Disease Quarterly Prevalence, Children with Asthma (crude prescription rates)	92

Figure 9.12	Medications for Asthma and Chronic Lung Disease Quarterly Incidence, Adults	94
Figure 9.13	Medications for Asthma and Chronic Lung Disease Quarterly Incidence, Adults with Asthma and Chronic Lung Disease.....	95
Figure 9.14	Medications for Asthma and Chronic Lung Disease Quarterly Incidence, Children.....	96
Figure 9.15	Medications for Asthma and Chronic Lung Disease Quarterly Incidence, Children with Asthma.....	97
Figure 10.1	Stimulants Quarterly Prevalence (crude user rates)	102
Figure 10.2	Stimulants Quarterly Prevalence (crude prescription rates)	102
Figure 10.3	Stimulants Quarterly Prevalence (crude prescription user rates, children aged 5-18).....	103
Figure 10.4	Stimulants Quarterly Prevalence by Age	105
Figure 10.5	Stimulants Quarterly Incidence (crude user rates).....	106
Figure 10.6	Stimulants Quarterly Incidence (crude user rates, children aged 5-18).....	106
Figure 10.7	All Stimulants Quarterly Incidence by Age.....	107
Figure 11.1	Antibiotics Quarterly Prevalence (crude user rates).....	112
Figure 11.2	Antibiotics Quarterly Prevalence (crude prescription rates).....	113
Figure 11.3	Antibiotics Quarterly Prevalence (macrolides only)	115
Figure 11.4	Antibiotics Quarterly Prevalence, Children (crude user rates)	116
Figure 11.5	Antibiotics Quarterly Prevalence, Children (crude prescription rates).....	117
Figure 11.6	Antibiotics Quarterly Prevalence, Children (macrolides only).....	119

LIST OF TABLES

Table 1.1	Prevalent Use (Users/1,000 Adults) of Tylenol #3® (and Generics), 1995-2005	10
Table 1.2	Incident Use (New Users/1,000 Adults) of Chronic Tylenol #3® (and Generics) Only, 1996-2005.....	15
Table 2.1	Prevalent Use (Users/1,000 Adults) of NSAIDs, 1995-2005.....	23
Table 2.2	Incident Use (New Users/1,000 Adults) of NSAIDs, 1996-2005.....	27
Table 3.1	Prevalent Use (Users/1,000 Adults) of Bisphosphonates, 1995-2005	32
Table 3.2	Incident Use (New Users/1,000 Adults) of Bisphosphonates, 1996-2005	37
Table 4.1	Prevalent Use (Users/1,000 Adults aged 65+) of Antipsychotics, 1995-2005 ...	44
Table 4.2	Incident Use (New Users/1,000 Adults aged 65+) of Atypical Antipsychotics, 1996-2005	49
Table 5.1	Prevalent Use (Users/1,000 Adults) of Antihypertensives, 1995-2005.....	55
Table 6.1	Prevalent Use (Users/1,000 Adults) of Statins, 1995-2005.....	61
Table 7.1	Therapy Types for Medical Treatment of Diabetes Mellitus	67
Table 7.2	Prevalent Use (Users/1,000 Adults) of Medications for Diabetes Mellitus, 1995-2005	70
Table 8.1	Prevalent Use (Users per 1,000 Adults) of Proton Pump Inhibitors, 1995-2005	77
Table 9.1	Prevalent Use (Users/1,000 Adults with Asthma and Chronic Lung Disease) of Treatment Medications, 1995-2005	88
Table 9.2	Prevalent Use (Users/1,000 Children with Asthma) of Treatment Medications, 1995-2005	93
Table 9.3	Incident Use (New Users/1,000 Adults with Asthma or Chronic Lung Disease) of Inhaled Corticosteroids, 1995-2005.....	96
Table 9.4	Incident Use (New Users/1,000 Children with Asthma) of Inhaled Corticosteroids, 1996-2005.....	97
Table 10.1	Prevalent Use (Users/1,000 Children aged 5-18) of Stimulants, 1995-2005	104
Table 10.2	Incident Use (New Users/1,000 Children aged 5-18) of Stimulants, 1996-2005	107
Table 11.1	Prevalent Use (Users/1,000 Adults) of Antibiotics, 1995-2005	114
Table 11.2	Prevalent Use (Users/1,000 Children) of Antibiotics, 1995-2005	118

LIST OF APPENDIX FIGURES AND TABLES

Note: The first number in Appendix Figure Numbers refers to the related subject's chapter number.

Appendix Table 1.1	Medication List for Drug Categories.....	146–150
Appendix Figure A.1.1	Oxycodone Quarterly Prevalence by Age	151
Appendix Figure A.1.2	Hydromorphone, Meperidine & Morphine Quarterly Prevalence by Age	151
Appendix Figure A.1.3	Oxycodone Quarterly Incidence by Age	152
Appendix Figure A.1.4	Hydromorphone, Meperidine & Morphine Quarterly Incidence by Age	152
Appendix Figure A.3.1	Alendronate Quarterly Incidence.....	153
Appendix Figure A.3.2	Alendronate and Risedronate Dosing, Quarterly Incidence	153
Appendix Figure A.5.1	ACE Inhibitors Quarterly Prevalence by Age	154
Appendix Figure A.5.2	Angiotensin Receptor Blockers Quarterly Prevalence by Age	154
Appendix Figure A.5.3	Thiazides Quarterly Prevalence by Age	155
Appendix Figure A.5.4	Beta Blockers Quarterly Prevalence by Age	155
Appendix Figure A.5.5	Calcium Channel Blockers Quarterly Prevalence by Age	156
Appendix Figure A.7.1	Insulins Quarterly Prevalence by Age.....	156
Appendix Figure A.7.2	Sulfonylureas Quarterly Prevalence by Age	157
Appendix Figure A.7.3	Meglitinides Quarterly Prevalence by Age.....	157
Appendix Figure A.7.4	Acarbose Quarterly Prevalence by Age	158
Appendix Figure A.7.5	Insulins Quarterly Incidence by Age.....	158
Appendix Figure A.7.6	Metformin Quarterly Incidence by Age.....	159
Appendix Figure A.7.7	Sulfonylureas Quarterly Incidence by Age	159
Appendix Figure A.7.8	Glitazones Quarterly Incidence by Age.....	160
Appendix Figure A.7.9	Acarbose Quarterly Incidence by Age	160
Appendix Figure A.7.10	Meglitinides Quarterly Incidence by Age.....	161
Appendix Figure A.9.1	SABA Quarterly Prevalence by Age, Children.....	161
Appendix Figure A.9.2	Steroids Quarterly Prevalence by Age, Children.....	162
Appendix Figure A.9.3	LABA Quarterly Prevalence by Age, Children	162
Appendix Figure A.9.4	LABA/Steroid Combinations Quarterly Prevalence by Age, Children.....	163
Appendix Figure A.9.5	Montelukast & Zafirlukast Quarterly Prevalence by Age, Children.....	163
Appendix Figure A.9.6	SABA Quarterly Incidence by Age, Adults.....	164
Appendix Figure A.9.7	Steroids Quarterly Incidence by Age, Adults.....	164
Appendix Figure A.9.8	SABA Quarterly Incidence by Age, Children.....	165
Appendix Figure A.9.9	Steroids Quarterly Incidence by Age, Children.....	165
Appendix Figure A.11.1	Azithromycin Quarterly Prevalence by Age.....	166
Appendix Figure A.11.2	Clarithromycin Quarterly Prevalence by Age	166
Appendix Figure A.11.3	Erythromycin Quarterly Prevalence by Age	167
Appendix Figure A.11.4	Penicillins Quarterly Prevalence by Age	167
Appendix Figure A.11.5	Fluoroquinolones Quarterly Prevalence by Age	168

Appendix Figure A.11.6	Azithromycin Quarterly Prevalence by Age, Children.....	168
Appendix Figure A.11.7	Clarithromycin Quarterly Prevalence by Age, Children	169
Appendix Figure A.11.8	Erythromycin Quarterly Prevalence by Age, Children	169
Appendix Figure A.11.9	Penicillins Quarterly Prevalence by Age, Children	170

EXECUTIVE SUMMARY

Introduction

Prescription drug coverage policies vary widely across Canada and drug benefit managers are frequently searching for good quality evidence on real-world medication cost-effectiveness and safety, in order to make informed decisions on formulary listing policies. Manitoba Health and Healthy Living offers a province-wide, income-based drug insurance program, according to a published list of prescription benefits in its Pharmacare Formulary that are reimbursed as open listing (Part 1), according to established criteria (Part 2) or with prior approval (Part 3). This MCHP deliverable evaluated the impact of Manitoba's Pharmacare Formulary policies and other societal factors on the utilization of prescription medications in Manitoba. The main research questions were:

- How did the timing of the formulary addition of the narcotic analgesic, Oxycontin[®], impact the utilization of Tylenol #3[®] (and generics)?
- Did the timing of the change in Pharmacare formulary listing for COX 2 inhibitors from Part 1 to Part 2 (formulary listing according to established criteria) formulary status reduce their utilization?
- Has utilization of bisphosphonates been impacted by the timing of publication of the Women's Health Initiative trial in 2002 which demonstrated harm associated with hormone replacement therapy (HRT)?
- Has utilization of atypical antipsychotics been impacted by the timing of Health Canada warnings about risks associated with the use of these agents in elderly patients?
- Has utilization of first line antihypertensive medications for uncomplicated hypertension changed over time?
- Has utilization of statins in patients with high cardiovascular risk changed over time?
- Has utilization of older and newer medications for diabetes changed over time?
- Has short-term utilization of proton pump inhibitors changed over time?
- How did the timing of the formulary addition of long-acting beta-agonist (LABA) corticosteroid combination inhalers (Advair[®], Symbicort[®]) impact the utilization of inhaled corticosteroids in adults and children with chronic lung disease and asthma?
- How did the timing of the launch of a long-acting methylphenidate, Concerta[®], impact the overall utilization of stimulants in children?
- Has utilization of older and newer antibiotics changed over time?

Focus of the Report

Findings in this report are presented under subheadings for the above 11 research questions. Each research question originated from questions put forward by Manitoba Pharmacare, as topics relevant to the administration of their program. Not all questions were amenable to testing the impact of a Pharmacare policy on prescription medication utilization due to the unavailability of prescription data for a sufficient time period before and after the introduction of a policy of interest. As such, results in the Executive Summary are presented under the following headings: 1) impact of change in Pharmacare formulary status from Part 1 (open listing) to Part 2 (utilization for established criteria) (COX 2 inhibitors), 2) impact of Pharmacare formulary addition or launch of a newly marketed medication (Oxycontin®, Advair®, Symbicort®, and Concerta®), 3) impact of the timing of Health Canada warnings or clinical trial publications (bisphosphonates, atypical antipsychotics) on prescription drug utilization, and 4) utilization trends of commonly prescribed medications (antihypertensives, statins, medications to treat diabetes, proton pump inhibitors, antibiotics).

Study Methods

Overall study methods

This report captures all Manitoba residents who had coverage by Manitoba Health and Healthy Living and filled prescriptions in Manitoba from 1995 through the end of 2005. The following databases were accessed: population registry, prescription medication records, physician reimbursement claims, hospital files, personal care home files, social assistance, vital statistics, and Statistics Canada census files.

Measures of use and determinants of use

Prevalent users and incident (new) users who had not used a medication for one year for each medication or medication group were determined for each quarter from 1995–2005. Both prevalent and incident utilization is expressed as users per 1,000 residents per quarter. The influence of sociodemographic characteristics, including age, rural or urban region of residence, and prescription cost sharing on medication utilization over time, was evaluated with generalized estimating equation (GEE) modeling to determine if individuals in one group were more likely to receive a prescription than those in another group.

Testing for the effects of policies or events

Generalized estimating equation (GEE) modeling was used to compare the rate of increase (or decrease) in medication utilization as compared to the previous quarter's rate before and after the time period of an event of interest.

Findings

Impact of change in Pharmacare formulary status from Part 1 to Part 2

- *COX 2 inhibitors*. Less than two years after being listed as an unrestricted benefit in Part 1 of the Pharmacare formulary, 4% of all adult Manitobans had been prescribed a COX 2 inhibitor. During Part 1 listing, the rate of new use climbed at 20% per quarter for celecoxib (Celebrex®) and 84% for rofecoxib (Vioxx®). Following a change in their formulary listing to Part 2 (reimbursement for prescribing according to established criteria) in 2000, a reduction in use of COX 2 inhibitors was observed. New use of both agents fell until the end of 2004, at which time rofecoxib was withdrawn from the market and COX 2 formulary listing was further modified to Part 3 (prior approval required for reimbursement). The decline in use after the transition in listing from Part 1 to Part 2 was slightly greater for celecoxib than for rofecoxib. These changes were independent of sociodemographic and regional differences, strongly suggesting that the change to Part 2 formulary restricted reimbursement curtailed their prescribing.

Impact of Pharmacare formulary addition or launch of a newly marketed medication

- *Oxycontin®*. The utilization of Oxycontin® increased rapidly in adults upon addition to the Manitoba formulary. However, chronic use of Tylenol #3® and its generics did not decrease after the formulary addition of Oxycontin®, which indicates that Oxycontin® was not being prescribed as a replacement for Tylenol#3®. In fact, the timing of the formulary addition of Oxycontin® was associated with a slight increase in new chronic use of Tylenol #3®. In 2005, 2% of Manitoba residents had received three or more prescriptions for Tylenol #3® or its generics; the use of Oxycontin® was 0.2%.
- *LABA corticosteroid inhalers (Advair®, Symbicort®)*. In 2005, 19% of adults with asthma and chronic lung disease had received a LABA corticosteroid inhaler, such as Advair®. Five percent of children with asthma had received this type of combination inhaler. New use of single–entity inhaled corticosteroids in adults with asthma or chronic lung disease had declined since 1996; and following the formulary addition of Advair®, utilization declined at a faster rate. In asthmatic children however, new use of inhaled steroid medications had risen prior to Advair® and continued to do so afterwards. These findings suggest that LABA corticosteroid products were being prescribed in place of single–entity inhaled corticosteroids for adults but not children. LABA corticosteroid combination inhalers are currently recommended as add–on therapies for children and adults whose asthma is not optimally controlled with single–entity inhaled corticosteroids. In adults, they are also recommended as combination therapy with anticholinergics in moderate to severe chronic obstructive lung disease, which may explain the switching to these products for adults but not children.

- *Long-acting methylphenidate (Concerta®)*. Close to 2% of schoolchildren had received a prescription for a stimulant in 2005, almost triple the rate from 10 years previous. In that year, less than 0.5% of children had received the newly marketed stimulant Concerta®, which was not listed on the Pharmacare formulary. In the seven-year period before the introduction of Concerta® in 2003, new use of stimulants had been rising at a rate of 1% per quarter. Afterwards, independent of changes to sociodemographics, new use of all stimulants leveled off. Overall use of stimulants did not increase following the introduction of Concerta® and stabilization in new use may be the outcome of societal concern over the inappropriate prescribing of stimulants.

Impact of Health Canada warnings and clinical trial publications

- *Bisphosphonates*. In 2005, almost 2% of Manitoba adults had received a bisphosphonate; among those 85 years and older, it was 9%. Prior to the publication of the Women's Health Initiative (WHI) trial results about hormone replacement therapy in 2002, new use of bisphosphonates had risen 4% every quarter since 1996. In the period after the publication of the WHI trial, hormone replacement therapy dropped dramatically and new use of bisphosphonates leveled off. The lack of subsequent increases to the rate of new prescribing for bisphosphonates after the publication of the WHI trial suggests that they did not replace hormone replacement therapy in Manitoba.
- *Atypical antipsychotics*. Prior to the first Health Canada (2002) warning about the possible association of risperidone with an increased risk of strokes in patients with dementia, atypical antipsychotics were being prescribed at an increasing rate in the elderly, such that by end of 2002, 2% of elderly Manitobans had received these medications. Following the first Health Canada warning, new use of atypical antipsychotics in the elderly leveled off. This change was independent of age and other sociodemographic factors and indicates an impact of the warnings. Despite this suggested impact, almost 3% of elderly Manitobans were prescribed atypical antipsychotics in 2005, indicating the need for further study of their use.

Utilization trends of commonly prescribed medications

- *Medications to treat Diabetes Mellitus*. The most dramatic increase in the use of medications to treat diabetes was for the first-line therapy metformin, such that metformin was the most commonly prescribed medication for diabetes by 2005 in adults, followed by sulfonylureas and insulins. However, independent of sociodemographic characteristics, new use of glitazones (whose reimbursement required prior approval under their Part 3 listing) increased the most (11% per quarter). In 2005, their use was comparable to that for insulin. In addition, there was evidence of more aggressive treatment of diabetes over the study period. The new prescription of triple therapy (three medications for diabetes) rose at a higher rate than that for dual and monotherapy.
- *Antihypertensives*. The use of all commonly prescribed antihypertensive medications in adults increased over the study time. Angiotensin-converting enzyme (ACE) inhibitors were used the most often, followed by beta blockers, calcium channel blockers, and thiazide diuretics.

At a rate of 9%, increases in prevalent use were the highest for the angiotensin receptor blockers (ARBs). For adult Manitobans with uncomplicated hypertension, the recommended first-line agents, thiazide diuretics, were the most commonly prescribed, followed by ACE inhibitors. The use of ACE inhibitors for uncomplicated hypertension declined after 2002, coinciding with an increase in thiazide and ARB use. These changes can potentially be attributed to the publication of the ALLHAT trial and require further study to determine if they were sustained.

- *Statins.* Large increases in prevalent and new use of statins were observed over the 10-year study period. In 2005, 8% of adult Manitobans had received a statin prescription, more so for atorvastatin than any other statin. Just over half of new statin users had evidence of a high cardiovascular risk medical condition. Independent of sociodemographic factors, statin use for high cardiovascular risk rose at a quarterly rate of 3%, marginally greater than new use in persons with low cardiovascular risk.
- *Proton pump inhibitors (PPI).* Prevalent use of all PPIs increased from less than 1% of Manitoba adults in 1995 to 6% of adults in 2005. Omeprazole was used the most commonly prescribed PPI. The majority of new PPI users had received these medications for less than three months of treatment. However, independent of sociodemographic characteristics, new use of PPIs that resulted in three months or more of treatment had increased at a significantly greater rate than short-term use.
- *Antibiotics.* Overall, a reduction in the use of antibiotics was observed for adults and children from 1995 to 2005. In adults and children, penicillins were prescribed the most often, followed by the macrolide antibiotics. The macrolides and cephalosporins were used increasingly more often over the study period. In adults, increases were also observed for the fluoroquinolones. The rise in use of the Part 2 restricted macrolides over the same time that use of erythromycin declined indicates a substitution effect. As a result of the potential for newer antibiotics to increase antibiotic resistance in Manitoba, further study is needed to determine the appropriateness of this substitution.

Analysis Strengths and Challenges

This report provides a complete picture of prescribing across several categories of medications for all adult Manitobans over a 10-year period. It assessed a range of societal influences on medication use, such as that of provincial drug program policies, federal agency warnings about safety, and published evidence for medication effectiveness. Further, as costs are a consideration in the decision to fill a prescription and Manitoba has an income-based Pharmacare deductible, medication utilization in Manitoba varies according to prescription cost sharing. Many Manitobans receiving medications at no charge are covered by federal drug plans, such as the First Nations and Inuit Health Branch plan. While these formularies may not have the same formulary criteria as Manitoba Pharmacare, we grouped prescription medication users by type of drug plan and household income to account for the effect of medication cost on utilization.

The limitations of the analyses in this report are due to the limitations of using prescription and health care administrative databases. Prescription use was derived from records of dispensed prescriptions. Not everyone who seeks medical attention and receives a prescription for a medication fills the prescription. This may incompletely capture the intent of physician prescribing in Manitoba. It may also underestimate the number of medications actually used because physician–provided samples of medications are not captured in the prescription medication records in the Population Health Research Data Repository in Manitoba. Alternately, individuals may fill prescriptions, but not actually take the medication, thus potentially overestimating the number of users of medications in Manitoba. Further, medical histories to describe underlying conditions were derived from diagnosis data on physician claims and hospitalization data. These medical histories may underestimate the prevalence of a given condition in the population because they require contact with the health care system and were dependent on physician reimbursement records, which may not completely record all underlying comorbidities. Of note, there is no presumption of appropriateness of utilization in this report, only observations that may lead to further study of appropriateness.

Finally, this report lags behind changes in Pharmacare policy that have been implemented since its completion.

Study Conclusions and Recommendations

With the exception of oral antibiotics, prevalent and incident utilization of medications in the population of Manitoba rose from 1995 to 2005. Many societal factors contribute to population trends in medication utilization. We documented the impact of Pharmacare formulary policies, such as changes to formulary listing category (COX 2 inhibitors), and formulary addition of newly–marketed medications (Oxycontin®, LABA/corticosteroid inhalers, Concerta®) and generic medications (bisphosphonates, proton pump inhibitors, stimulants). As observed in other jurisdictions, we found evidence for the influence of large randomized controlled trials (hormone replacement therapy, antihypertensives, statins) or newly–emerging literature and Health Canada warnings of harm (antipsychotics in elderly) on medication use. Other factors such as age, level of prescription cost sharing, and region of residence also affected the utilization of medications. It is very likely that several unmeasured factors also had an influential role on use of medications. These include, but are not limited to: physician access, prescriber characteristics, prescriber–patient interactions, pharmaceutical marketing, physician sampling of newly marketed medications, and patient perception of benefits and safety of medications. The impact of these factors on prescribing at a population level deserves further investigation. This report is one of several in the continued series on pharmaceutical use in Manitoba and lays the foundation for others that will assess the appropriateness and health outcomes of medication use in Manitobans.

INTRODUCTORY AND METHODS CHAPTER

A common mission of provincial drug insurance programs is to identify “cost-effective drugs to ensure proper prescribing, availability, and utilization to needy populations” (Jacobs & Bachynsky, 2000). To achieve this, various formulary listing policies have been implemented by provincial drug programs for newly-marketed and existing **prescription**¹ drugs. Manitoba Health and Healthy Living offers a province-wide drug insurance program to all adult Manitobans according to a published list of drug benefits in its Pharmacare Formulary and under conditions of an income-based deductible. Prescription medications are given Part 1, Part 2, or Part 3 status on the Pharmacare Formulary. The first designation provides open listing, while the second two designations limit access according to established criteria. Part 2 listings, which are usually second-line therapeutic agents or agents to be used only in specific clinical situations, require an indication on the prescription by physicians or pharmacists that the prescription drug meets Exception Drug Status (EDS) for patient-specific criteria. Part 3 status is reserved for products that require physicians to contact Pharmacare to obtain prior approval for use. Pharmacare program managers monitor the utilization of prescriptions and, if required, make changes to their formulary status from any combination of Part 1 to Part 2 to Part 3. For example, the anti-inflammatory medication, celecoxib (Celebrex[®]), was added to Part 1 in December 1999, and then moved to Part 2 in August 2000 and to Part 3 in November 2004.

Various frameworks for prescription drug benefit coverage have been proposed to ensure reliable and affordable access to needed medications (Teagarden, Daniels, & Sabin, 2003). Despite this goal, prescription drug coverage varies widely across Canada, as identified by the Romanow Commission and others (Romano, Baillargeon, Wu, Robaey, & Tremblay, 2002; Anis, Guh, & Wang, 2001). This variability has led to recommendations for a national formulary. In the interim, drug benefit managers are frequently searching for good quality evidence, which extends to real-world effectiveness, cost-effectiveness, and safety in order to make evidence informed decisions on formulary listings. Evidence on the outcome of drug program policies which limit formulary listing by number of prescriptions or type of drug is increasingly becoming available worldwide, although evaluations of special authorization policies are not plentiful (Schneeweiss et al., 2006). For example, the implementation of a prior authorization formulary listing policy for celecoxib (Celebrex[®]), in Oregon, USA in 1999, resulted in a reduced number of dispensed prescriptions for this drug (Hartung, Touchette, Ketchum, Haxby, & Goldberg, 2004). However, many of these examples are health care system and population specific. There has been little systematic evaluation of the Pharmacare Formulary listing policy in Manitoba (Kozyrskyj, Racher, Alessi-Severini, Kvern, & Collins, 2004a).

¹Throughout this report, terms in bold typeface are defined in the Glossary at the end of this report.

The goal of this research was to evaluate the impact of the Part 1, 2 and 3 status listings and changes to these listings in the Pharmacare Formulary on prescription medication utilization over the time period 1995–2005. This MCHP deliverable will evaluate the impact of Manitoba's Pharmacare Formulary policy on the utilization of prescription medications in Manitoba. The general research questions were:

- Do formulary decisions, formulary listing category (Part 1, 2, 3), have any effects on the utilization of medications in the entire Manitoba population?
- What is the impact of specific **sociodemographic** characteristics on utilization of medications in the entire Manitoba population?

Incident and prevalent medication utilization were explored by age groups and prescription cost sharing as well as region of residence. Medication classes of interest include: narcotic analgesics, non-steroidal anti-inflammatories (NSAIDs), osteoporosis medications, antipsychotics, antihypertensives, statins, diabetes medications, proton pump inhibitors, inhaled medications for asthma and chronic lung disease, stimulants for children, and antibiotics.

Specific Research Questions

- How did the timing of the formulary addition of the narcotic analgesic, Oxycontin®, impact the utilization of Tylenol #3® (and generics)? How has the utilization of narcotics changed over time?
- Did the timing of the change in Pharmacare formulary listing for COX 2 inhibitors from Part 1 to Part 2 (formulary listing according to pre-determined criteria) formulary status reduce their utilization? How has the utilization of COX 2 inhibitors and NSAIDs changed over time?
- Has utilization of bisphosphonates been impacted by the timing of the publication of the Women's Health Initiative trial in 2002, which demonstrated harm associated with hormone replacement therapy? How has the utilization of medications for osteoporosis changed over time? Did the introduction of weekly dosing and **generic** bisphosphonates impact utilization of these medications?
- Has utilization of atypical antipsychotics been impacted by the timing of the Health Canada warnings about risks associated with the use of these agents in elderly patients? How has the use of antipsychotics changed over time? How does utilization of antipsychotics differ for residents of Personal Care homes and for other Manitobans?
- Has utilization of first line antihypertensive medications for uncomplicated **hypertension** changed over time? How has the use of antihypertensives changed over time?
- Has utilization of statins in patients with high cardiovascular risk changed over time? How has the utilization of statins changed over time?
- Has utilization of newer and older medications for diabetes changed over time? How has the overall utilization of medications for diabetes changed over time?

- Has short term utilization of proton pump inhibitors changed over time? How has the overall utilization of proton pump inhibitors changed over time? Has utilization been impacted by the introduction of generic omeprazole?
- How did timing of the formulary addition of long-acting beta-agonist (LABA) corticosteroid combination inhalers (Advair®, Symbicort®) impact the utilization of inhaled corticosteroids in adults and children with chronic lung disease and asthma? How has the utilization of medications for asthma and chronic lung disease changed over time? Are there different patterns of utilization of these medications for adults and children?
- How did the timing of the launch of the long-acting methylphenidate, Concerta®, impact the overall utilization of stimulants in children? How has the utilization of stimulants in children changed over time? Has utilization been impacted by the introduction of generic products?
- Has utilization of older and newer antibiotics changed over time? How has the utilization of antibiotics, in particular azithromycin changed over time?

Methods

Focus of the report

This report focuses on all adult Manitobans with provincial health cards from Manitoba Health and Healthy Living who filled prescriptions in Manitoba from 1995 through the end of 2005. Individuals had to be in the Manitoba Health and Healthy Living registry for at least 275 days in the year to be included in the study population.

Data sources

Data for this report were derived from anonymized (no names, no addresses) health care administrative data contained in the **Population Health Research Data Repository**, housed at the Manitoba Centre for Health Policy. We used the following databases: population registry, prescription medication records, physician reimbursement claims, hospital files, personal care home files, social assistance, vital statistics, and Statistics Canada census files. Records from these files were linked through the use of a scrambled health identification number. Data from the calendar years 1995 through the end of 2005 were used. For this analysis, the first quarter (Q1) of each year was January – March, the second quarter (Q2) April – June, the third quarter (Q3) was July – September and the fourth quarter (Q4) was October – December.

Definitions of prescription medication users

For each medication group a descriptive analysis was performed as follows:

Prevalent users for each medication or medication group were determined and described by sociodemographic characteristics. Prevalent users were Manitobans registered for 275 days of 365 days in a calendar year, who had filled at least one prescription for the medication or medication group of interest in a particular quarter. In order to calculate **prevalence** for each quarter, the total count of prevalent users was divided by the population of Manitobans registered for 275 days of

365 days in a calendar year (calculated per quarter by geometric interpolation of annual population counts), and then described by sociodemographic characteristics. Prevalence is presented by two methods: 1) users per resident population, 2) prescriptions per resident population.

Incident users for each medication or medication group were determined and described by sociodemographic characteristics. Incident users were Manitobans registered for 275 days of 365 days in a calendar year, who had not filled a prescription for the medication or medication class of interest for at least one year, and then filled a first prescription for the medication or medication group of interest in a particular quarter. In order to calculate **incidence** for each quarter, total count of incident users was divided by the population of Manitobans registered for 275 days of 365 days in a calendar year (calculated per quarter by geometric interpolation of annual population counts), and then described by sociodemographic characteristics. Incident rates are presented as users per resident population.

Prevalent and incident utilization parameters (users per population, prescriptions per population) are presented for each quarter of every calendar year. Users per population and prescriptions per population are presented per 1,000 population. All years are calendar years.

The **Anatomical Therapeutic Chemical (ATC) classification** was used to define medication categories for prescription cost and utilization comparisons.

Sociodemographic characteristics were defined as follows:

- Age group (<18, 19–44, 45–64, 65–84, 85 up). For analyses where children were evaluated separately (medications for **asthma** and chronic lung disease, stimulants, and antibiotics), the age groups were as follows: from birth to four years, five to eight, nine to 12, and 13–18.
- Regional analysis. **Rural/urban** location as determined by the postal code registered with Manitoba Health and Healthy Living: 14 areas = 12 Winnipeg **Community Areas** + 1 Brandon + 1 Rural. Regional analyses compared rural to urban locations or Point Douglas to Fort Garry.
- Prescription cost sharing: As Manitoba has an income based deductible for Pharmacare, prescription medication users were divided into three groups based on out of pocket expenses for prescription medications and median neighborhood **income quintile**.
 - No cost prescription: individuals with all medication expenses covered. This category includes those on income assistance in calendar year or those who had drug coverage through a federal plan such as First Nations and Inuit Health Branch.
 - Low income: individuals in the lowest median neighborhood income quintile who have no cost prescriptions
 - High income: includes individuals residing in the neighborhoods with all but the lowest median neighborhood income quintile.

Modeling

Extended Segmented time series modeling approach (see Appendix 1 for more details) was used in this project. The segments are the times before and after a particular event (change in prescription drug policy coverage or Health Canada warnings).

Variables included in the models were age, gender, prescription cost sharing, region of residence, and time. Age, gender, prescription cost sharing, and region were entered in the models as categorical variables, whereas time was entered as a continuous variable. We used Poisson or negative binomial distributions in the modeling because of the stratification of the data by the above variables and the rareness of some of the outcomes. Also, these distributions are best suited for modeling of count outcomes and rates.

Given that people of the same age, gender, prescription cost sharing group, and region exhibit similar patterns of utilization over time, we then used **generalized estimating equation (GEE)** to account for cluster correlation over time.

All models were implemented in SAS version 9.2 software using PROC GENMOD.

How this report is organized

The findings of this report are divided into eleven sections, each representing a medication group or category for analysis.

Data limitations

All data included in this report are derived from contacts with the healthcare system. Because not everybody seeks medical attention and not everybody who seeks medical attention and receives a prescription for a medication actually fills the prescription, this may underestimate the number of prescriptions written for medications in Manitoba. As costs are a consideration in the decision to fill a prescription, this phenomenon may occur across a socioeconomic gradient. Alternately, individuals may fill prescriptions, but not actually take the medication, thus potentially overestimating the number of users of medications in Manitoba. For several analyses, we evaluated medical diagnoses through administrative data. These medical diagnoses may underestimate the prevalence of a given condition in the population, again, because these definitions require individuals to seek contact with the health care system.

CHAPTER 1: NARCOTICS

Oxycontin® is a sustained release formulation of the narcotic analgesic oxycodone and was marketed in Canada at the end of 1996 (Risचितelli & Karbowicz, 2002). This sustained release opioid was added to the Manitoba formulary in the second quarter of 1999. We assessed how the formulary addition of Oxycontin® impacted the utilization of Tylenol #3® (and generics), hereafter referred to as Tylenol #3®. Furthermore, we evaluated the utilization of all narcotic analgesics as listed in Part 1 (open listing) of the Pharmacare formulary from 1995 to 2005.

1.1 Methods

Prevalent and incident users were identified for the population of Manitoba for the following medication groups: Tylenol #3®, Oxycontin®, oxycodone (other oxycodone products, single entity and combination), morphine, hydromorphone and meperidine (all dosage forms). For a list of the medications included in the categories, please refer to Appendix Table 1. Incident users were those users of a narcotic who had not used any prior narcotics in the one year prior to this first narcotic prescription.

In order to ascertain whether Oxycontin® was used as a substitute therapy for Tylenol #3® in the management of chronic pain, we compared the prevalent and incident utilization of chronic Tylenol #3® before and after the formulary addition of Oxycontin®. Several studies, including a study conducted by the First Nations and Inuit Health Branch, have reported that the majority of persons prescribed controlled analgesics receive one or two prescriptions over a one year period (Eggen, 1996; Anderson & McEwan, 2000). Therefore, our definition of chronic utilization was one of exclusion. Those Tylenol #3® users who filled one or two prescriptions for Tylenol #3®, in a calendar year were considered to be users of Tylenol #3® for non-chronic pain. All other Tylenol #3® users were considered to be chronic users.

The addition of Oxycontin® to the Manitoba formulary occurred in the second quarter of 1999. The incident and prevalent utilization of overall and chronic Tylenol #3® was compared before and after this event using GEE modeling.

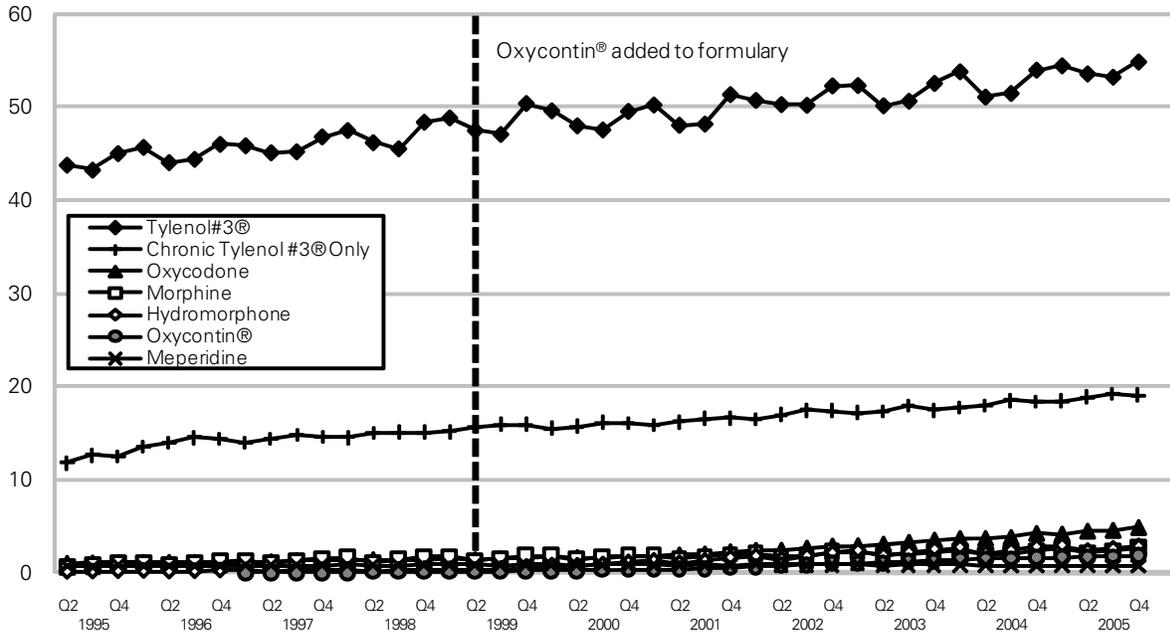
1.2 Results

Prevalence

Overall, we observed a general increase in prevalent utilization of each medication over time, with much greater utilization of Tylenol #3® than other narcotics for the total population. In the adult population of Manitoba, prevalent users of Tylenol #3® increased from 43.8 to 48.9 per 1,000 just before Oxycontin® coverage, to 54.8 per 1,000 by the end of the study period. Prevalent use of chronic Tylenol #3®, which was limited to use of Tylenol #3® only, increased from 11.8 to 15.1 user per 1,000 just before Oxycontin® coverage to 19.0 users per 1,000 residents by the end of the study period.

Figure 1.1: Narcotics Quarterly Prevalence

Crude user rates per 1,000 adults, Q2 1995–Q4 2005

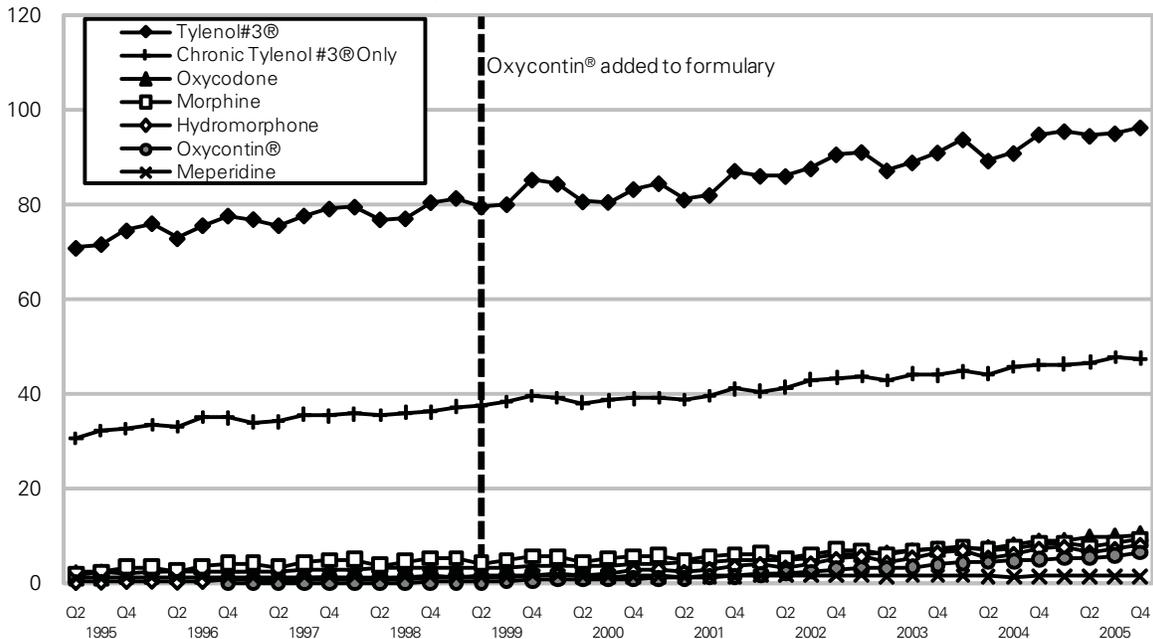


'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled
 Narcotics includes Tylenol #3® and generics, oxycodone, hydromorphone, meperidine, morphine, and Oxycontin®.

Source: Manitoba Centre for Health Policy, 2009

Figure 1.2: Narcotics Quarterly Prevalence

Crude prescription rates per 1,000 adults, Q2 1995–Q4 2005

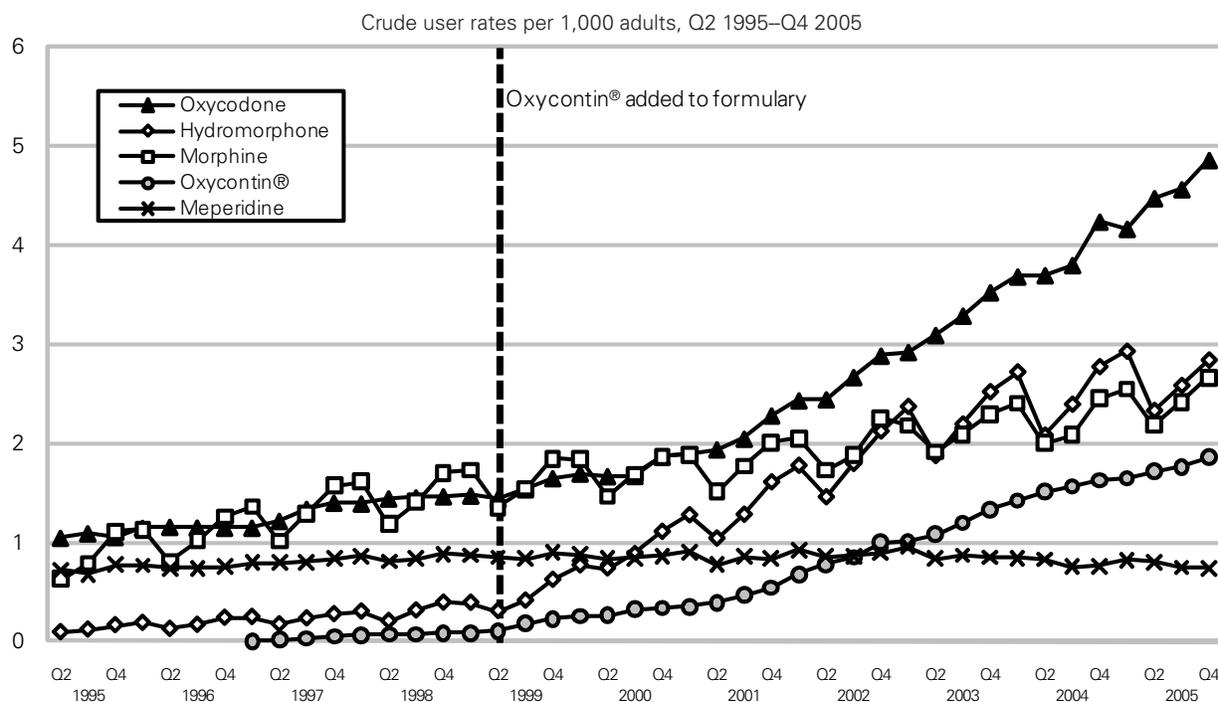


'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled
 Narcotics includes Tylenol #3® and generics, oxycodone, hydromorphone, meperidine, morphine, and Oxycontin®.

Source: Manitoba Centre for Health Policy, 2009

While considerably lower than Tylenol #3[®] utilization, when other narcotics were evaluated more closely, Oxycontin[®] and oxycodone had the greatest change in numbers of users per population with time. Users of oxycodone increased from 1.0 to 4.9 per 1,000 over the study period, while users of Oxycontin[®] increased from 0.02 per 1,000 in the second quarter of 1997 (prior to formulary addition) to 1.9 per 1,000 at the end of the study period.

Figure 1.3: Narcotics Quarterly Prevalence



'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled
 Narcotics includes Tylenol #3[®] and generics, oxycodone, hydromorphone, meperidine, morphine, and Oxycontin[®].

Source: Manitoba Centre for Health Policy, 2009

Prior to the addition of Oxycontin[®] onto the Pharmacare formulary, prevalent use of both Tylenol #3[®] and chronic Tylenol #3[®] (who only used Tylenol #3[®]) were increasing, although at a very small rate of 1% over the previous quarterly rate ($p < 0.05$) (Table 1.1). Following addition onto the Pharmacare formulary, quarterly rates of prevalent Oxycontin[®] use increased by 12% over successive rates for each quarter ($p < 0.05$). Independent of sociodemographic characteristics, prevalent use of Tylenol #3[®] and chronic Tylenol #3[®] (who only used Tylenol #3[®]) continued to increase after the launch of Oxycontin[®] ($p < 0.05$).

Table 1.1: Prevalent Use (Users/1,000 Adults) of Tylenol #3® (and Generics), 1995-2005

Medication	Baseline users/1,000§	Change in rate* + 1% **	Oxycontin® Part1 users/1,000 adults, 1999Q1	Change in rate* + 0.4% **	End 2005 users/1,000 adults	Age effect* Age 19-44 vs 85+ -18% †	Prescription cost sharing* No cost vs high income 3-fold higher†	Region effect* Point Douglas vs Ft Garry 1.82 2-fold higher†
Tylenol #3® (and generics)	43.80	1.01 + 1% **	48.86	1.00 + 0.4% **	54.84	0.82 -18% †	3.31 3-fold higher†	1.82 2-fold higher†
Tylenol #3® (and generics) only non-acute	11.81	1.01 + 1% **	15.16	1.00 + 0.5% **	19.07	0.42 -58% †	6.33 6-fold higher†	2.75 3-fold higher†
Oxycontin®			0.08	1.12 +12% **	1.86	0.42 -58% †	1.81 +81% †	0.94 -6%

* Results are presented as relative rates (adjusted for age, prescription cost sharing, region and time) and then, for ease of interpretation, as percentages

** Indicates a slope significantly different from zero (p<.05)

† Indicates a statistically significant effect (p<.05)

§ Baseline rates are users per 1,000 adults at the second quarter of 1995 or when prescriptions were first filled for a drug

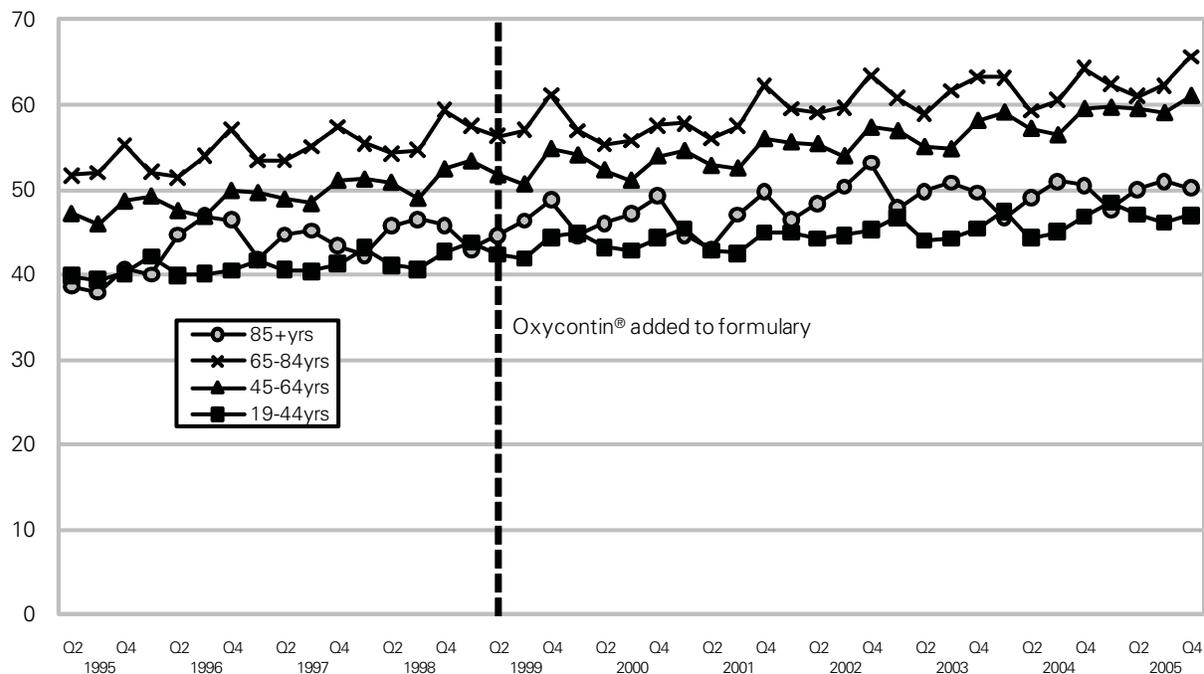
|| Regional analysis for the Oxycontin® model compares rural areas to urban areas

Source: Manitoba Centre for Health Policy, 2009

When evaluated by age, Tylenol #3[®] had a different utilization pattern when compared to the other medications. The greatest utilization of Tylenol #3[®] was in those aged 65–84 (51.7 to 65.7 per 1,000 over the study period), followed by 45–64 (increased from 47.2 to 61.1 per 1,000), then 85 up (38.6 to 50.2 per 1,000) and 19–44 (39.9 to 47.0 per 1,000). Independent of other characteristics, young adults (age 19–44) were 18% less likely to use Tylenol #3[®] than those age 85 and up, but for chronic Tylenol #3[®] this lower use widened to a 58% difference (Table 1.1).

Figure 1.4: Tylenol #3[®] Quarterly Prevalence by Age

Crude user rates per 1,000 adults, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)

'Q4' indicates prevalence for the 4th quarter (October to December)

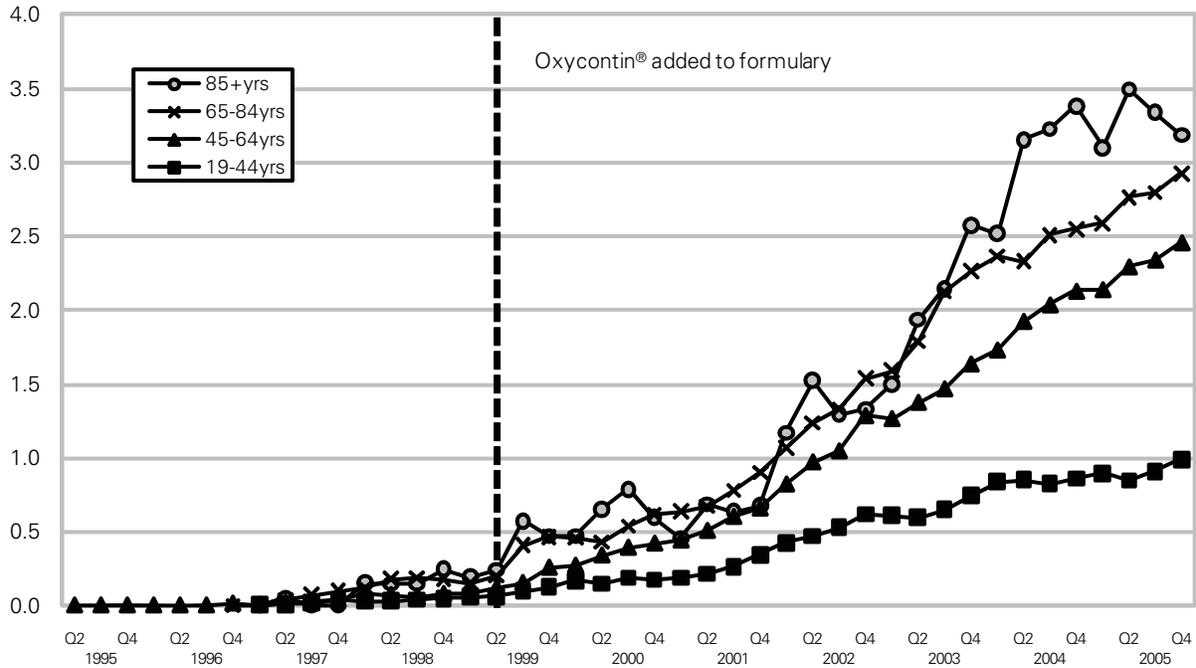
'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

All the other narcotics had increasing prevalence with increasing age, as demonstrated by prevalent Oxycontin® users.

Figure 1.5: Oxycontin® Quarterly Prevalence by Age

Crude user rates per 1,000 adults, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Similar to chronic Tylenol #3®, young adults were 58% less likely to use Oxycontin® than their older counterparts. The prevalent utilization of other narcotics by age groups appears in Appendix 2, Figures A.1.1 and A.1.2.

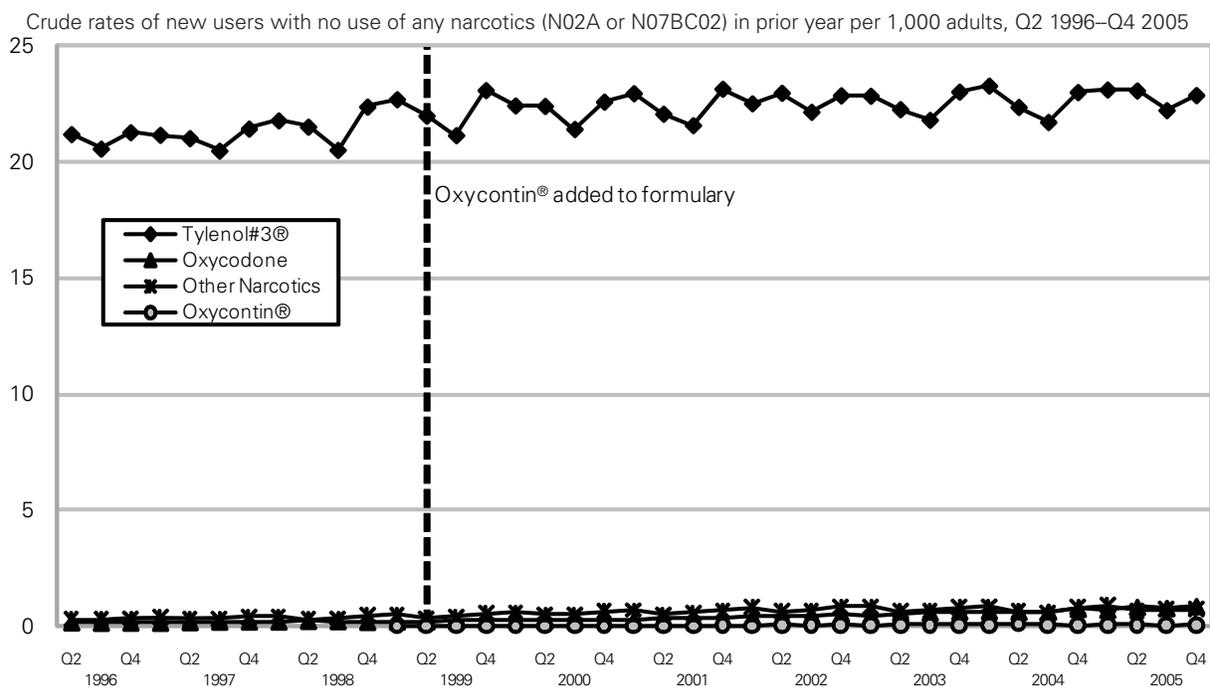
Independent of other characteristics, the utilization of chronic Tylenol #3® by persons receiving no-cost prescriptions was six-fold higher than the highest income Pharmacare recipients (Table 1.1). For Oxycontin®, this same difference was only 81% greater.

In urban areas, prevalent use of Tylenol #3® was significantly greater in Point Douglas than Fort Garry (Table 1.1).

Incidence

Similar to prevalent use, the greatest incident utilization of any narcotic evaluated was for Tylenol #3[®] overall. Incident Tylenol #3[®] users increased from 21.2 to 22.9 users per 1,000 residents per quarter over the study period.

Figure 1.6: Narcotics Quarterly Incidence



'Q2' indicates incidence for the 2nd quarter (April to June)

'Q4' indicates incidence for the 4th quarter (October to December)

'Q1' and 'Q3' data points are displayed, but not labeled

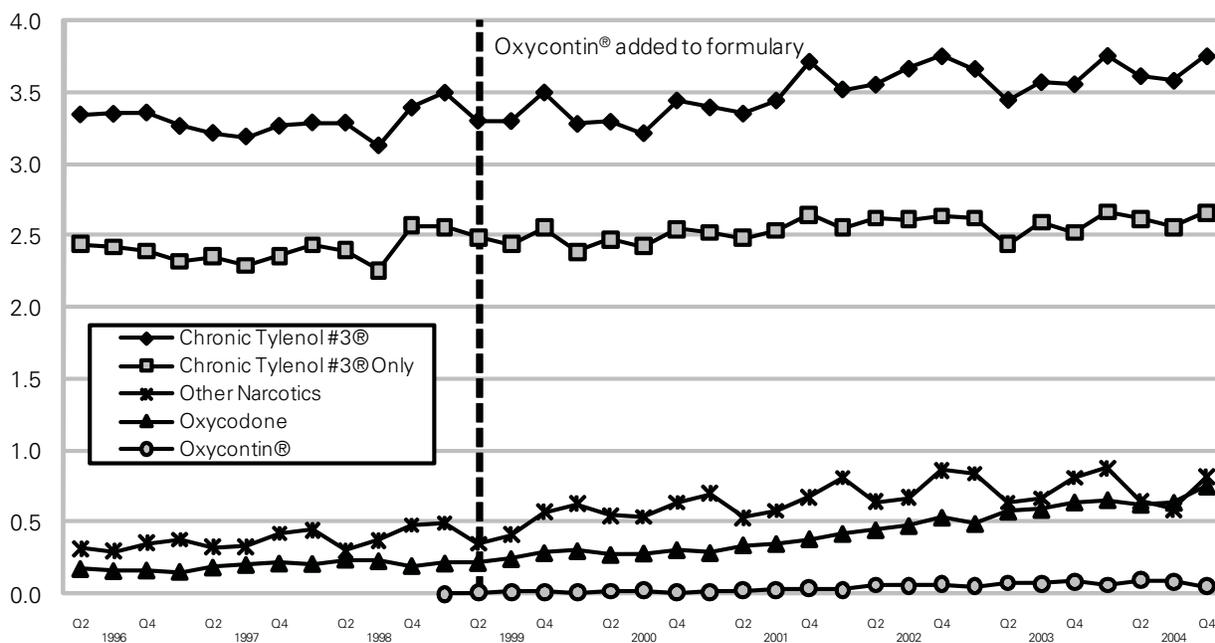
Other narcotics include hydromorphone, meperidine, and morphine.

Source: Manitoba Centre for Health Policy, 2009

Incident chronic Tylenol #3[®] users (who only used Tylenol #3[®]) increased from 2.44 to 2.56 in the first quarter of 1999 just before Oxycontin[®] was added to formulary to 2.68 per 1,000 by the end of 2004. By contrast, we observed the incident utilization of other medications to be lower than Tylenol #3[®], but increasing over time. For example, incident Oxycontin[®] use increased from <0.01 to 0.07 users per 1,000 residents per quarter, while incident oxycodone increased from 0.2 to 0.9 users per 1,000 residents per quarter, while incidence use of other narcotics (morphine, hydromorphone, meperidine) increased from 0.3 to 0.8 users per 1,000 residents per quarter.

Figure 1.7: Narcotics (Including Chronic Tylenol #3[®]) Quarterly Incidence

Crude rates of new users with no use of any narcotics (N02A or N07BC02) in prior year per 1,000 adults, Q2 1996–Q4 2004



'Q2' indicates incidence for the 2nd quarter (April to June)

'Q4' indicates incidence for the 4th quarter (October to December)

'Q1' and 'Q3' data points are displayed, but not labeled

Other narcotics include hydromorphone, meperidine and morphine

Source: Manitoba Centre for Health Policy, 2009

When adjusted for age, medication cost to patient, and region, incident chronic Tylenol #3[®] use (who only used Tylenol #3[®]) was 2.34 users per 1,000 residents per quarter in 1999, right before the availability of Oxycontin[®] as a Pharmacare benefit and 2.52 per 1,000 residents in 2005, six years after the addition of Oxycontin[®] (Table 1.2). Prior to the launch of Oxycontin[®], the rate for new users of chronic Tylenol #3[®] (who only used Tylenol #3) was constant (not significantly different from zero). Independent of sociodemographic characteristics, incident use of chronic Tylenol #3[®] (who only used Tylenol #3) increased over time after the launch of Oxycontin[®] ($p < 0.05$). Additionally, the slope of the increasing rate for new users of chronic Tylenol #3[®] (who only used Tylenol #3) was steeper after Oxycontin[®] than before ($p < 0.05$).

Table 1.2: Incident Use (New Users/1,000 Adults) of Chronic Tylenol #3® (and Generics) Only, 1996-2005

	Before Oxycontin® on Formulary (1996Q2-1999Q1)		Oxycontin® on Formulary (1999Q2-2005Q1)
	First Quarter 1996Q2	Last Quarter 1999Q1	Last Quarter 2005Q1
Crude rate	2.44	2.56	2.68
Adjusted rate *		2.34	2.52
Adjusted rate of change* per quarter		0.998	1.006 **†

* Adjusted for age, prescription cost sharing, region and time

Rate of change results are presented as relative rates

** Indicates a slope significantly different from zero ($p < .05$)

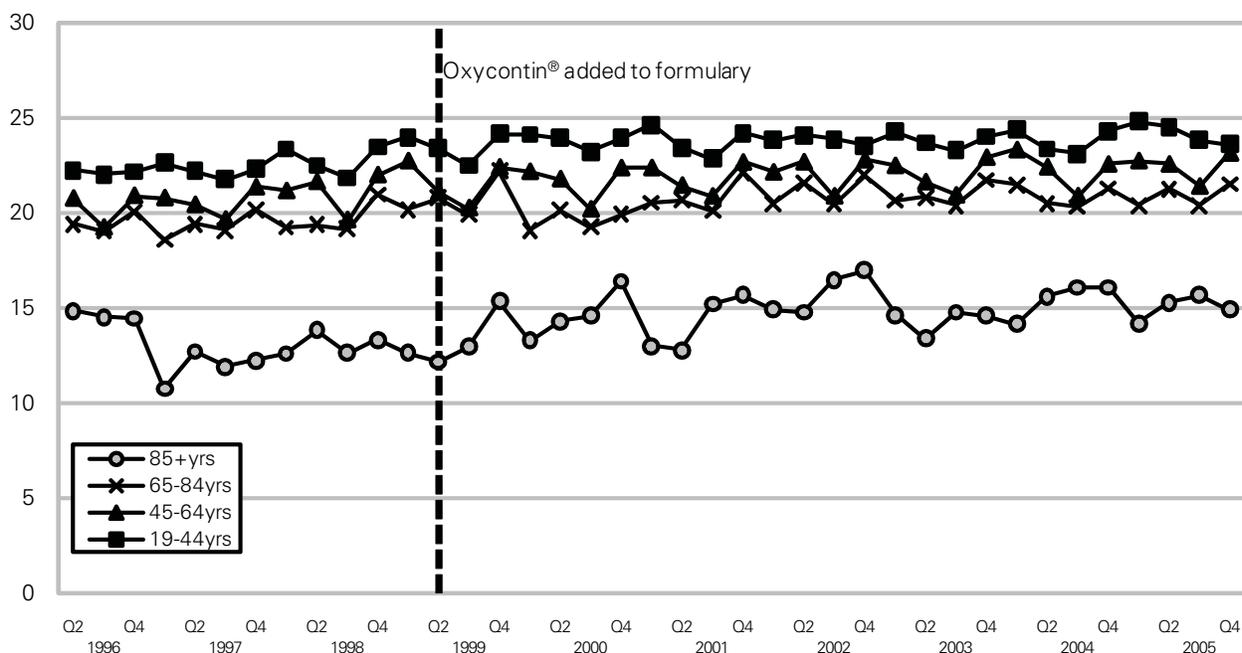
† Indicates a significant change in the slope after the intervention ($p < .05$)

Source: Manitoba Centre for Health Policy, 2009

New use of Tylenol #3® was relatively constant over time in each age group and lowest for those aged 85 and older (14.8 to 14.9 users per 1,000 residents per quarter).

Figure 1.8: Tylenol #3® Quarterly Incidence by Age

Crude rates of new users with no use of any narcotics (N02A or N07BC02) in prior year per 1,000 adults, Q2 1996–Q4 2005



'Q2' indicates incidence for the 2nd quarter (April to June)

'Q4' indicates incidence for the 4th quarter (October to December)

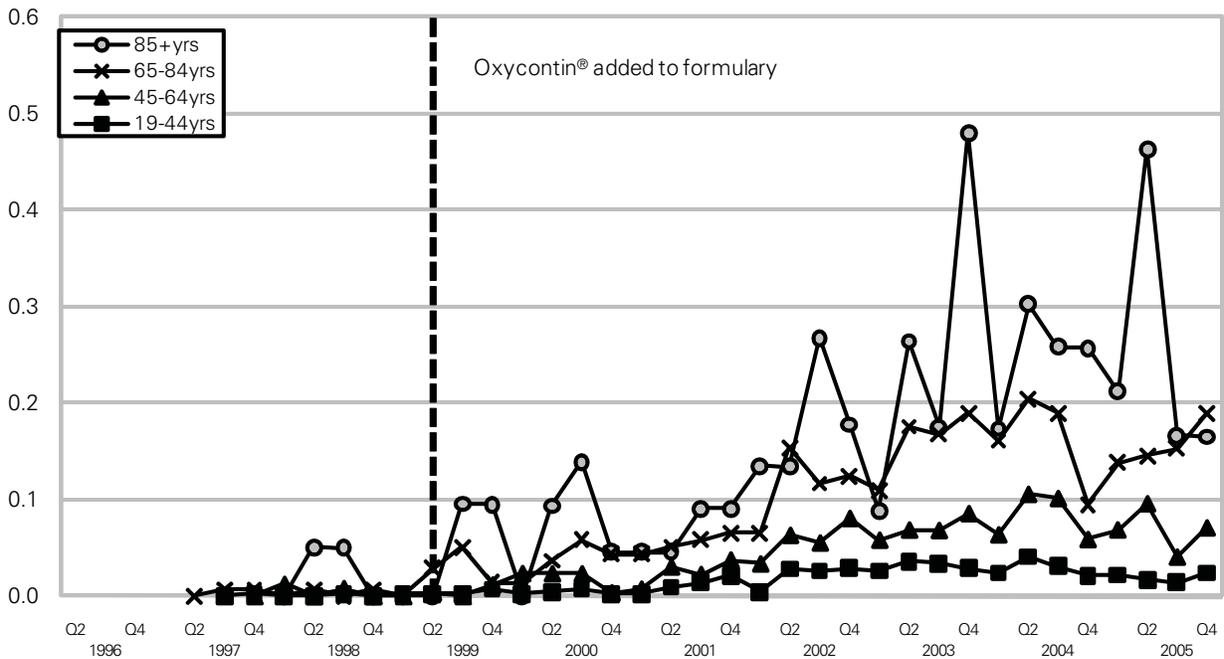
'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

All the other narcotics demonstrated increasing incidence with increasing age, as with incident Oxycontin® users.

Figure 1.9: Oxycontin® Quarterly Incidence by Age

Crude rates of new users with no use of any narcotics (N02A or N07BC02) in prior year per 1,000 adults, Q2 1996–Q4 2005



'Q2' indicates incidence for the 2nd quarter (April to June)
 'Q4' indicates incidence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

The incident utilization of other narcotics by age groups appears in Appendix 2, Figures A.1.3 and A.1.4.

1.3 Discussion

We generally observed an increase in prevalent and incident utilization of all narcotic analgesics over 10 years, consistent with other studies (Caudill-Slosberg, Schwartz, & Woloshin, 2004; Joranson, Ryan, Gilson, & Dahl, 2000; Olsen, Daumit, & Ford, 2006; Braden et al., 2008). Also consistent with the literature, we observed an increase in the utilization of more potent opioid analgesics, such as oxycodone, Oxycontin®, hydromorphone, and morphine over time (Caudill-Slosberg et al., 2004; Franklin et al., 2005; Braden et al., 2008). Factors that may contribute to the increase in utilization of opioids with time include: a greater willingness to prescribe opioids for pain or a greater recognition for the need to aggressively manage pain before complex pain syndromes result (Caudill-Slosberg et al., 2004; Gardner-Nix, 2003; Zech, Grond, Lynch, Hertel, & Lehmann, 1995; Braden et al., 2008). Variability in prescribing of opioids has also been ascribed to aggressive pharmaceutical marketing, heightened awareness of the under-treatment of pain, reports of abuse of certain opioids, pain management guidelines, new analgesics, physician training, and issues of documentation (Olsen et al., 2006). Many factors contribute to physician prescribing of long acting

opioid analgesics (Nwokeji, Rascati, Brown, & Eisenberg, 2007; Dickinson, Altman, Nielsen, & Williams, 2000). Like others, Pletcher, Kertesz, Kohn, & Gonzales (2008), we also observed an influence of prescription cost sharing on utilization of prescription narcotics, with greater utilization amongst those with no cost prescriptions.

An important policy influence on the prescribing of opioid analgesics is that of legislation and documentation. All the medications studied, except for Tylenol #3[®], are part of the Multiple Prescribing Practices Program (M3P) in Manitoba (formerly known as the Multiple Prescription Program and the Triplicate Prescription Program). The program was developed jointly by the Manitoba Pharmaceutical Association, the Manitoba College of Physicians and Surgeons, the Manitoba Dental Association, the Manitoba Veterinary Association, the Manitoba Medical Association, the Manitoba Health Services Commission, and the Drug Control Unit of the Health Protection Branch. This prospective at-source risk management system seeks to minimize drug diversion for controlled and Narcotic medications and facilitate communication among health care professions, regulatory authorities, and governments regarding drug utilization issues and information (Manitoba Pharmaceutical Association, 2006). It is known that programs such as the M3P program reduce prescription claims for opioids (Curtis et al., 2006).

Clearly Tylenol #3[®] demonstrated a unique utilization pattern as compared to the other medications studied; incident and prevalent use were far greater, reflecting both the relative ease of prescribing (not part of M3P) and the efficacy and safety of this analgesic for a wide variety of conditions. The fewer number of prescriptions per population for chronic Tylenol #3[®] likely indicates that many Tylenol #3[®] users were using it for acute pain. These estimates are in fact, conservative because the prescription database sources in this report did not capture many low potency analgesics available over the counter, including acetaminophen and aspirin each (with 8 mg codeine).

We observed a rapid increase in the utilization of oxycodone and Oxycontin[®] upon the availability of these medications. Such an increase in utilization of Oxycontin[®] has been widely, but not universally reported (Franklin et al., 2005). With respect to the question of interest, the assessment of the impact of the introduction of Oxycontin[®] on the utilization of Tylenol #3[®], our data demonstrated that the formulary addition of Oxycontin[®] was not associated with a decrease in the rate of new chronic users of Tylenol #3[®]. Independent of other factors, the timing of the formulary addition of Oxycontin[®] was associated with a slight increase in the rate of new chronic users of Tylenol #3[®]. These results suggest that the introduction of Oxycontin[®] or other factors, such as pharmaceutical marketing or increased awareness of the need to effectively manage pain, were associated with the observed trends in prescribing of narcotic analgesics.

CHAPTER 2: COX 2 AND NSAIDS

Non-steroidal anti-inflammatories (NSAIDs) are a large class of medications used to treat pain and inflammation for a variety of medical conditions. The overall class of NSAIDS consists of two types of medications, those which are selective to cyclo-oxygenase type 2 (hereafter, COX 2 inhibitors), an example is celecoxib (Celebrex[®]), and older agents (hereafter, older NSAIDs), which inhibit the enzyme cyclo-oxygenase non-selectively. Selectivity for COX 2 inhibition reduces gastrointestinal toxicity of NSAIDs (Kaplan-Machlis & Klostermeyer, 1999).

The rapid adoption of COX 2 inhibitors when marketed in 1999 in Manitoba has been well described (Kozyrskyj, Raymond, & Racher, 2007). However, in April 2002, safety concerns about the cardiac safety of these medications began to emerge, and Health Canada issued a warning about the increased risk of cardiovascular adverse effects, including **myocardial infarctions**, that emerged during clinical trials (Health Canada, 2002a). A second warning was issued at the end of 2002 (Health Canada, 2002b; Health Canada, 2002d). Finally, at the end of 2004, amidst controversy about cardiovascular side effects, rofecoxib was withdrawn from the market, and further warnings were issued about other COX 2 inhibitors (Health Canada, 2004a; Health Canada, 2002b; Health Canada, 2002c).

Soon after their market availability, the COX 2 inhibitors were added to Part 1 of the Manitoba Pharmacare formulary as an open listing. Following an unprecedented growth in utilization, the COX 2 inhibitors were transitioned from Part 1 to Part 2 (utilization for established criteria) in the third quarter of 2000. Finally, the formulary listing of the remaining available COX 2 inhibitors were moved to Part 3 (prior approval required) at the end of 2004.

We assessed the effectiveness of Part 2 formulary listing for COX 2 inhibitors in reducing their utilization. In addition, we evaluated utilization of the COX 2 inhibitors and the prescribed older NSAIDs in the population of Manitoba from 1995 to 2005. It is important to note that some strengths of some of the older NSAIDs, such as ibuprofen and aspirin are available over the counter without a prescription, so not all older NSAIDs were included in this analysis.

2.1 Methods

Prevalent and incident users were identified for the population of Manitoba for the following medication groups: celecoxib, rofecoxib, valdecoxib (COX 2 inhibitors), naproxen, diclofenac, ibuprofen, meloxicam (older NSAIDs). Although there are many other medications included in the older NSAIDs category, the specific agents chosen are commonly prescribed NSAIDs. For a list of the medications included in the categories, please refer to Appendix Table 1.

Incident users were those users of a COX 2 or older NSAID who had not used any NSAID (any older NSAID—defined as any member of ATC category M01A) or COX 2 inhibitor in the one year prior to their first NSAID or COX 2 inhibitor prescription. The incident and prevalent utilization of COX 2 inhibitors was compared before and after Part 2 formulary listing using GEE modeling.

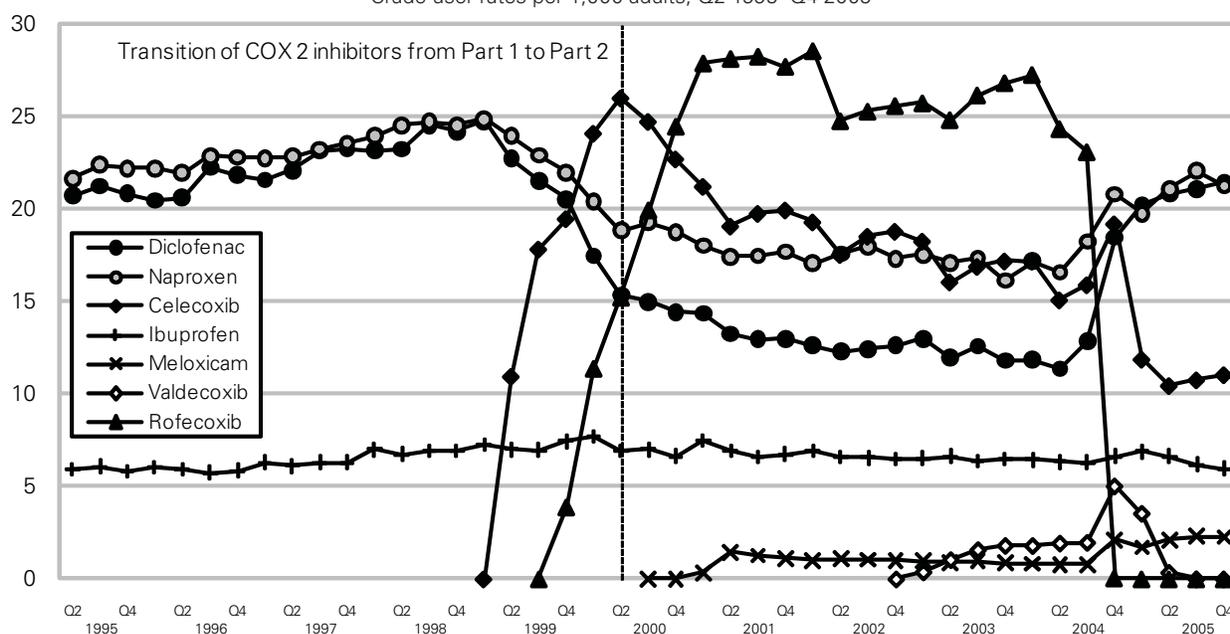
2.2 Results

Prevalence

There was a dramatic increase in prevalent utilization of COX 2 inhibitors when brought to market at the end of 1999. This was mirrored by decrease in the older NSAIDs. The initial rapid uptake was followed by a dramatic decrease in COX 2 inhibitor utilization at the end of 2004 and a subsequent increase in the utilization of older NSAIDs. The most commonly used COX 2 inhibitor was rofecoxib, followed by celecoxib; the utilization of rofecoxib plummeted to zero after market withdrawal. The most commonly utilized older NSAID in Manitoba was naproxen.

Figure 2.1: Older NSAIDs and COX 2 Inhibitors Quarterly Prevalence

Crude user rates per 1,000 adults, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)

'Q4' indicates prevalence for the 4th quarter (October to December)

'Q1' and 'Q3' data points are displayed, but not labeled

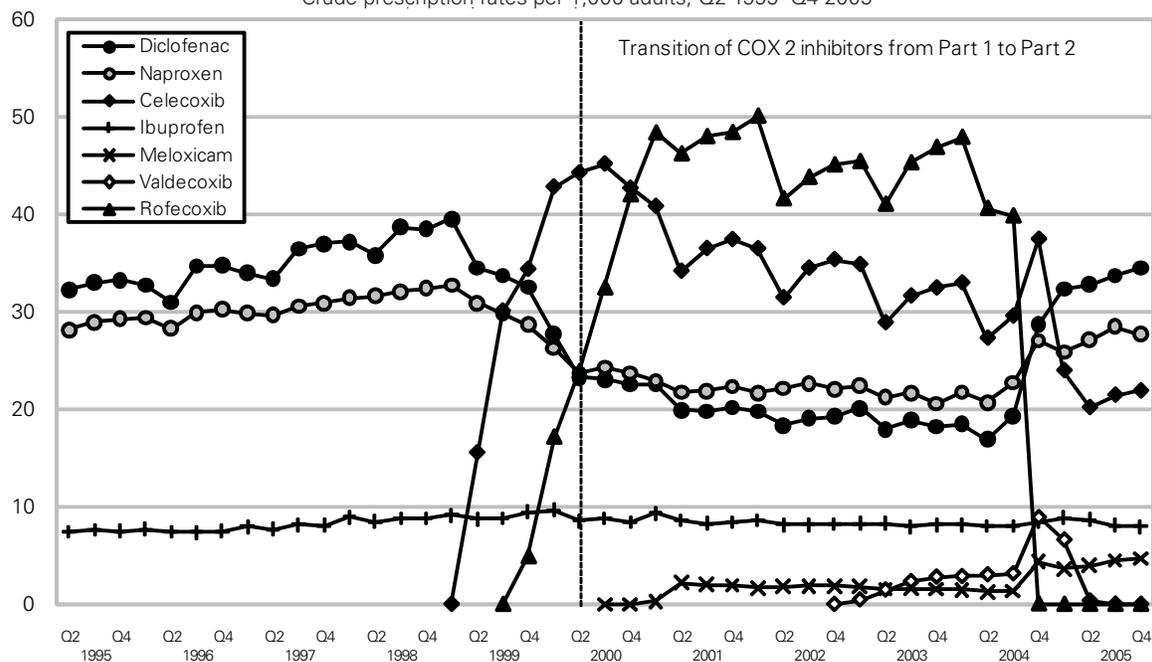
NSAIDs include meloxicam, naproxen, diclofenac, and ibuprofen

COX2 inhibitors include celecoxib, rofecoxib, and valdecoxib

Source: Manitoba Centre for Health Policy, 2009

Figure 2.2: Older NSAIDs and COX 2 Inhibitors Quarterly Prevalence

Crude prescription rates per 1,000 adults, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled
 NSAIDs include meloxicam, naproxen, diclofenac, and ibuprofen
 COX2 inhibitors include celecoxib, rofecoxib, and valdecoxib

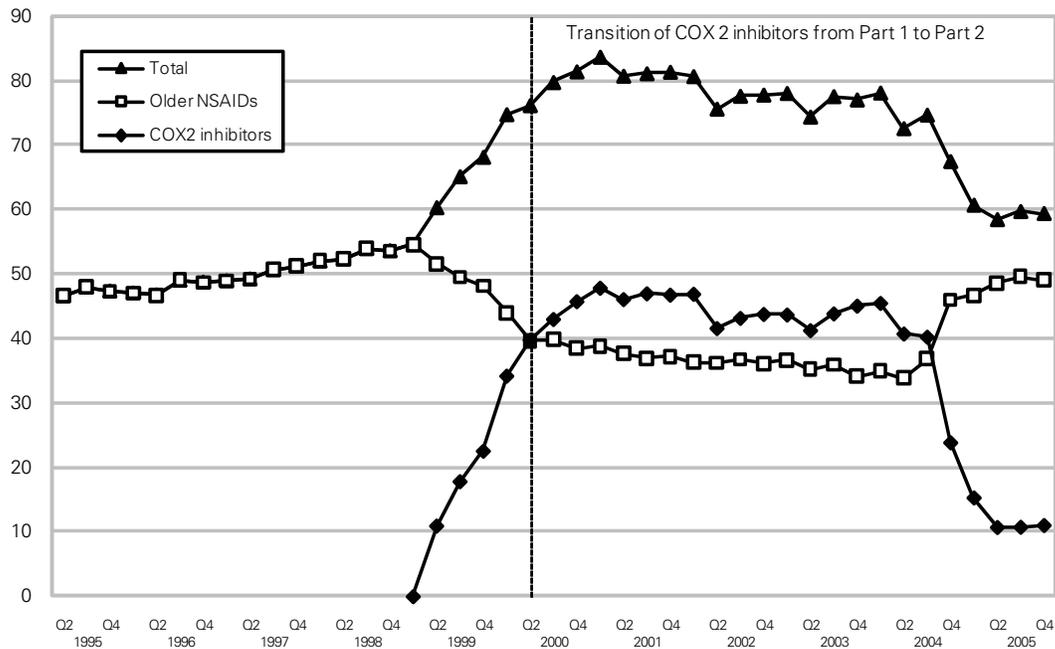
Source: Manitoba Centre for Health Policy, 2009

Prevalent use of any NSAID (older NSAIDs or COX 2 inhibitors) increased from 46.6 users per 1,000 residents at the beginning of the study to 76.2 users per 1,000 residents at the second quarter of 2000, just before COX 2 inhibitors were added to Part 1. Prevalent use of any NSAID (older NSAIDs or COX 2 inhibitors) peaked at 83.7 users per 1,000 residents at the beginning of 2001, and then fell to 59.4 users per 1,000 residents by the end of the study period. Prevalent use of COX 2 inhibitors increased from 10.9 per 1,000 in the second quarter of 1999 when celecoxib was marketed to 39.8 in the second quarter of 2000 just before COX 2 inhibitors were moved to Part 2. Their use decreased to 40.2 users per 1,000 residents in the third quarter of 2004, just before COX 2 inhibitors were moved to Part 3, and to 23.4 users per 1,000 residents by the end of 2004 just as the COX 2 inhibitors were moved to Part 3 and rofecoxib was withdrawn.

Following market introduction of the COX 2 inhibitors, prevalent use of diclofenac and naproxen declined at a rate of 11% and 8% per quarter ($p < 0.05$) (Table 2.1). Independent of sociodemographic characteristics, prevalent use of both diclofenac and naproxen continued to decline after COX 2 inhibitors were moved to Part 2 ($p < 0.05$). After COX 2 inhibitors were changed to Part 2, their prevalent utilization declined ($p < 0.05$).

Figure 2.3: Older NSAIDs and COX 2 Inhibitors Quarterly Prevalence

Crude user rates per 1,000 adults, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled
 NSAIDs include meloxicam, naproxen, diclofenac, and ibuprofen
 COX2 inhibitors include celecoxib, rofecoxib, and valdecoxib

Source: Manitoba Centre for Health Policy, 2009

Table 2.1: Prevalent Use (Users/1,000 Adults) of NSAIDs, 1995-2005

Medication	Celecoxib Part 1		Celecoxib End Part 1		Change in rate *	Celecoxib End Part 2		Age effect *		Prescription cost sharing *		Region effect *
	Baseline rate/1,000 \$	Change in rate *	2000Q2 rate/1,000	2004Q3 rate/1,000		Age 19-44 vs 85+	No cost vs high income	Point Douglas vs Ft Garry				
Celecoxib	10.95	1.26 + 26% **	26.00	15.90	0.98 - 2% **	0.10 - 90% ‡	2.42 2 1/2-fold higher ‡	1.17 + 17% ‡				
Rofecoxib	3.89	1.85 + 85% **	15.23	23.10	1.00 + 0.09%	0.19 - 81% ‡	1.65 + 65% ‡	0.92 - 8%				
All COX2	10.95	1.40 + 40% **	39.77	40.23	0.99 - 1% **	0.20 - 80% ‡	1.92 2 fold higher ‡	1.10 + 10%				
Naproxen	21.64	0.92 - 8% **	18.82	18.24	0.99 - 1% **	2.63 2 1/2 fold higher ‡	2.31 2 fold higher ‡	1.36 + 36% ‡				
Diclofenac	20.72	0.89 - 11% **	15.35	12.85	0.98 - 2% **	0.38 - 52% ‡	2.83 3 fold higher ‡	1.86 + 86% ‡				

* Results are presented as relative rates (adjusted for age, prescription cost sharing, region and time) and then, for ease of interpretation, as percentages

** Indicates a slope significantly different from zero (p<.05)

‡ indicates a statistically significant effect (p<.05)

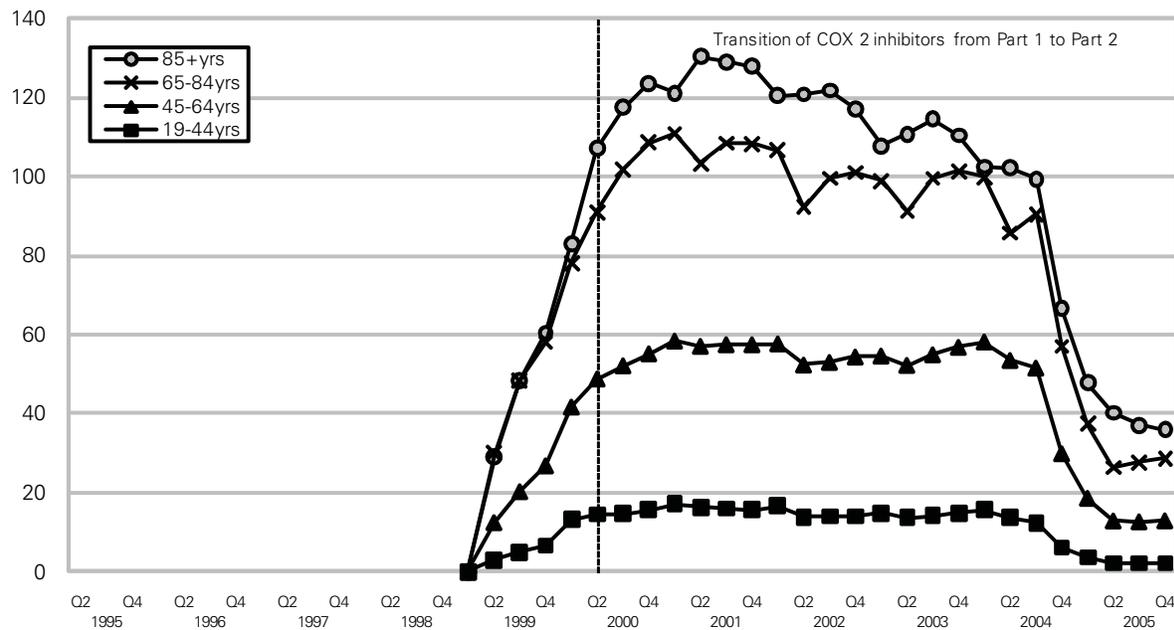
§ Baseline rates are users per 1,000 adults at the second quarter of 1995 or when prescriptions were first filled for a drug

Source: Manitoba Centre for Health Policy, 2009

When evaluated by age, the greatest utilization of the COX 2 inhibitors was in those aged 85 and older and the lowest utilization in those aged 19–44.

Figure 2.4: COX 2 Inhibitors Quarterly Prevalence by Age

Crude user rates per 1,000 adults, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)

'Q4' indicates prevalence for the 4th quarter (October to December)

'Q1' and 'Q3' data points are displayed, but not labeled

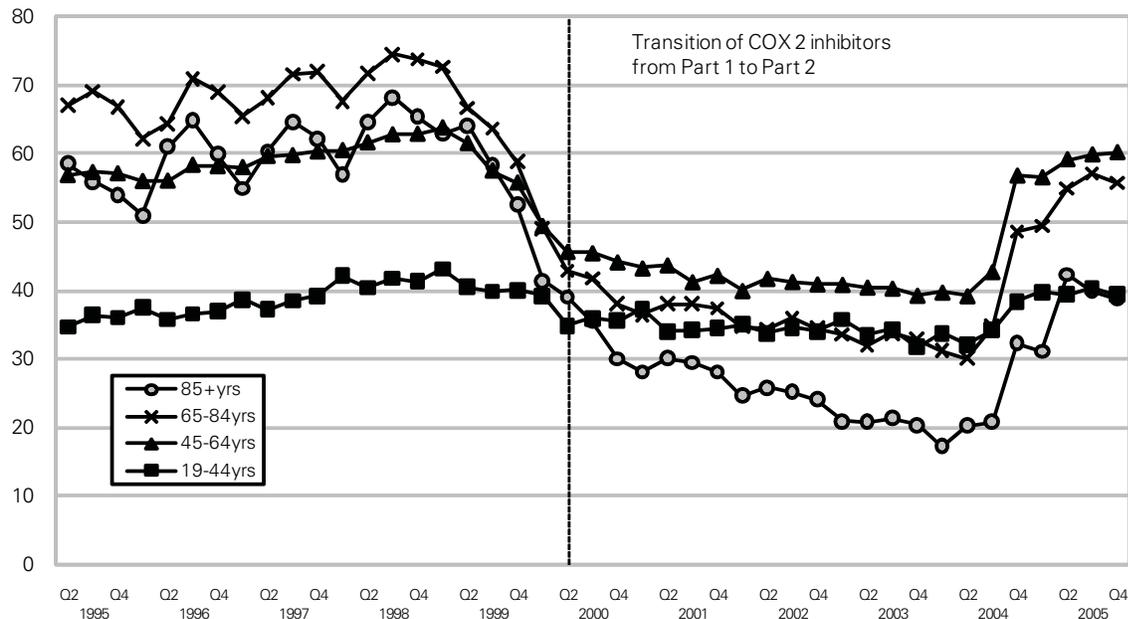
COX2 inhibitors include celecoxib, rofecoxib, and valdecoxib

Source: Manitoba Centre for Health Policy, 2009

This pattern was not observed in the older NSAIDs, where greatest utilization was amongst those aged 65–84 and then 85 and older before market availability of COX 2 inhibitors, after which those aged 45–64 were most commonly prescribed older NSAIDs.

Figure 2.5: Older NSAIDs Quarterly Prevalence by Age

Crude user rates per 1,000 adults, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)

'Q4' indicates prevalence for the 4th quarter (October to December)

'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

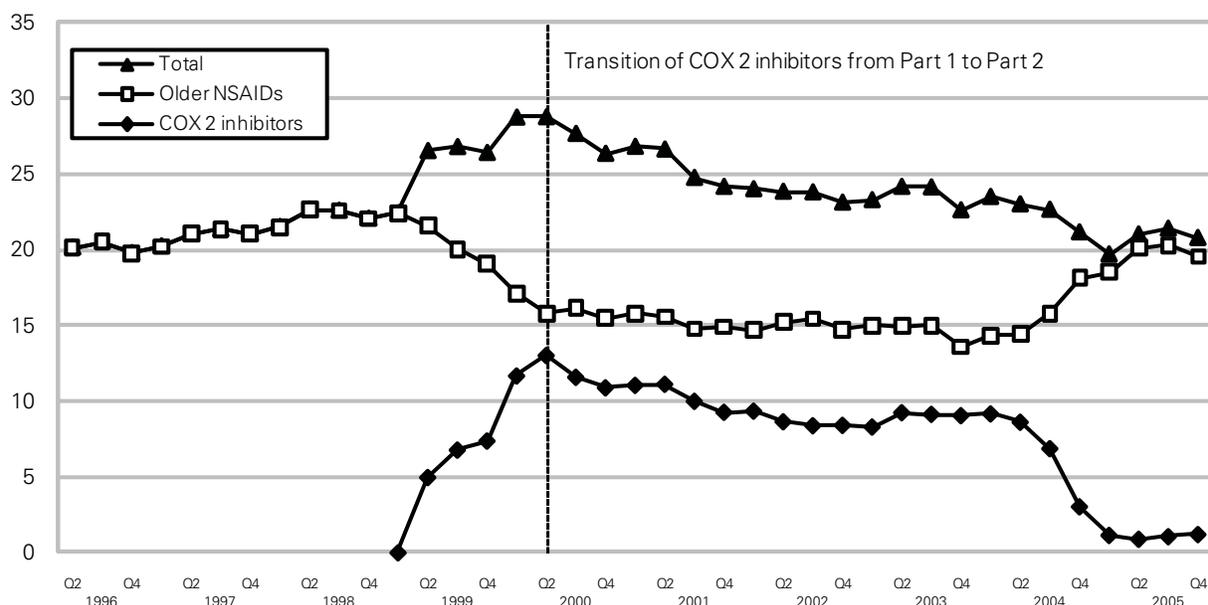
On average, older NSAIDs were used to the greatest extent by persons receiving prescriptions at no-cost, even after controlling for age, region, and prescribing trend over time (Table 2.1). However, for COX 2 inhibitors, the pattern changed over the study period. Initially, the greatest utilization was amongst Pharmacare recipients with intermediate and highest incomes; but after mid-2002, we observed the greatest utilization (users per population) among those with no-cost prescriptions. When evaluated by region of residence, user rates of celecoxib, naproxen, and diclofenac were significantly greater in Point Douglas than Fort Garry (Table 2.1).

Incidence

During the time of Part 1 Pharmacare formulary listing and following their introduction onto the market, incident use of the COX 2 inhibitors rose at a rate of 34% per quarter over the previous quarter's rate ($p < 0.05$) (Table 2.2). New users of COX 2 inhibitors increased from 5.0 users per 1,000 residents in the first quarter of the study period to 13.0 users per 1,000 residents in the second quarter of 2000, just before COX 2 inhibitors were moved to Part 2. Independent of sociodemographic characteristics, the rate of new use of COX 2 inhibitors declined after being moved to Part 2 at 2% per quarter as compared to the previous quarter's rate ($p < 0.05$). The incident rate of COX 2 inhibitors was 6.9 new users per 1,000 residents just before the COX 2 inhibitors were moved to Part 3 at the end of 2004.

Figure 2.6: Older NSAIDs and COX 2 Inhibitors Quarterly Incidence

Crude rates of new users with no use of any NSAIDs or COX 2 inhibitors (M01A) in prior year per 1,000 adults, Q2 1996 – Q4 2005



'Q2' indicates incidence for the 2nd quarter (April to June)
 'Q4' indicates incidence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled
 NSAIDs include meloxicam, naproxen, diclofenac, and ibuprofen
 COX 2 inhibitors include celecoxib, rofecoxib, and valdecoxib

Source: Manitoba Centre for Health Policy, 2009

Table 2.2: Incident Use (New Users/1,000 Adults) of NSAIDs, 1996-2005

	Before COX2 Part II (1996Q2-2000Q2)		After COX2 Part II (2000Q3-2004Q3)
	First Quarter 1996Q2	Last Quarter 2000Q2	Last Quarter 2004Q3
COX2 crude rate	4.96	13.00	6.87
COX2 adjusted rate *		15.12	7.86
COX2 adjusted rate of change* per quarter		1.34**	0.98 **†
Celecoxib crude rate	4.96	7.62	1.98
Celecoxib adjusted rate *		9.97	2.44
Celecoxib adjusted rate of change* per quarter		1.20**	0.96 **†
Rofecoxib crude rate	1.46	5.39	4.49
Rofecoxib adjusted rate *		5.25	5.05
Rofecoxib adjusted rate of change* per quarter		1.84**	0.98 **†

* Adjusted for age, prescription cost sharing, region and time

Rate of change results are presented as relative rates

** Indicates a slope significantly different from zero ($p < .05$)

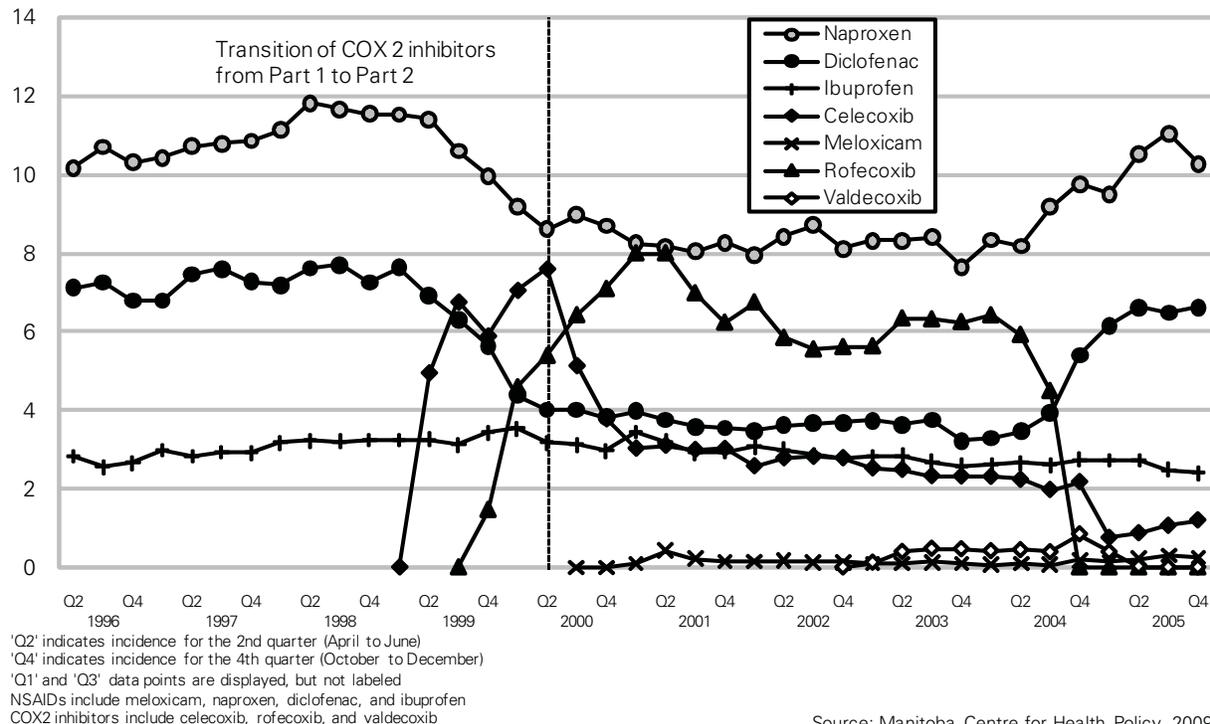
† Indicates a significant change in the slope after the intervention ($p < .05$)

Source: Manitoba Centre for Health Policy, 2009

The rate of increase was 20% per quarter over the previous quarter's rate for celecoxib and 84% per quarter over the previous quarter's rate for rofecoxib prior to the transition of these agents to Part 2 ($p < 0.05$ for each) (Table 2.2). Independent of sociodemographic characteristics, the rate of new use for both celecoxib and rofecoxib declined after being moved to Part 2. Most of the new users of COX 2 were prescribed rofecoxib until its removal from the market. Incident use of celecoxib declined further to 1.2 users per 1,000 residents per quarter by the end of the study period. Overall, the incident utilization (users per population) of older NSAIDs remained greater than incident utilization of COX 2 inhibitors throughout the study period. Incident use of naproxen was the greatest amongst all NSAID (older NSAIDs and COX 2 inhibitors) medications at all time points. This was followed by diclofenac (until 1999), then celecoxib, then rofecoxib, then diclofenac again at the end of 2004.

Figure 2.7: Older NSAIDs and COX 2 Inhibitors Quarterly Incidence

Crude rates of new users with no use of any NSAIDs or COX 2 inhibitors (M01A) in prior year per 1,000 adults, Q2 1996 – Q4 2005

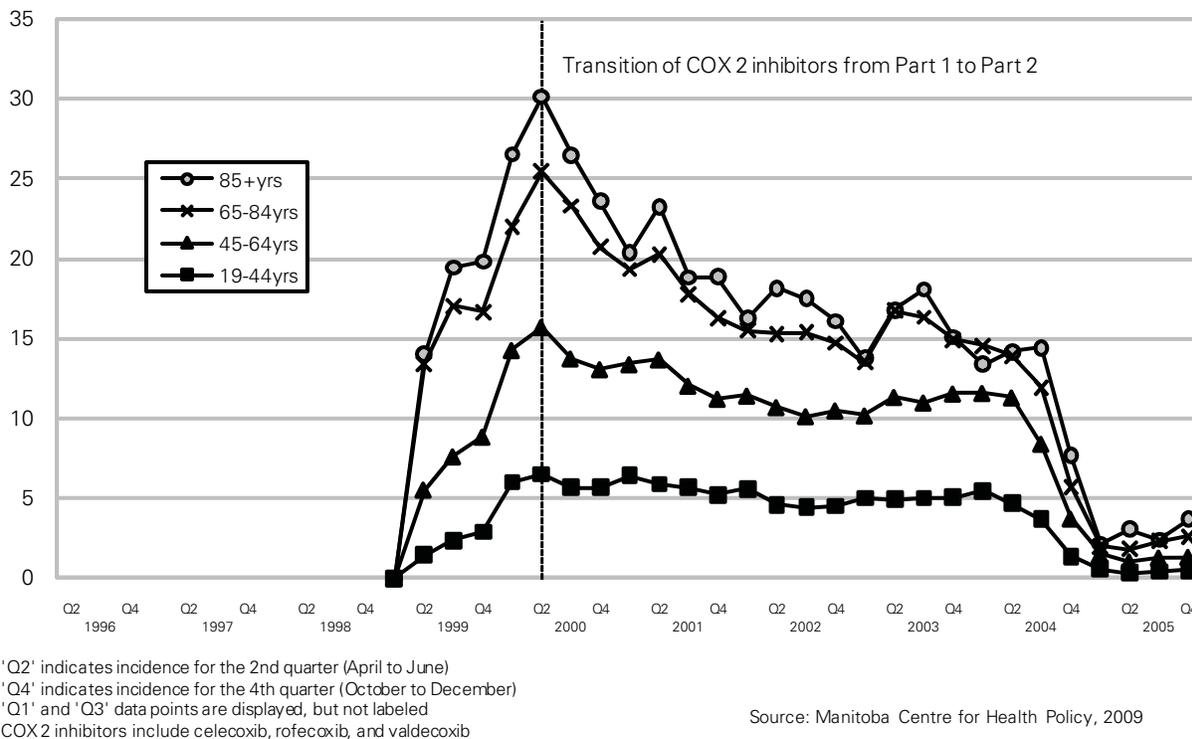


Source: Manitoba Centre for Health Policy, 2009

The greatest number of new users of COX 2 inhibitors per population was in persons age 85 and older.

Figure 2.8: COX 2 Inhibitors Quarterly Incidence by Age

Crude rates of new users with no use of any NSAIDs or COX2 inhibitors (M01A) in prior year per 1,000 adults, Q2 1996 – Q4 2005

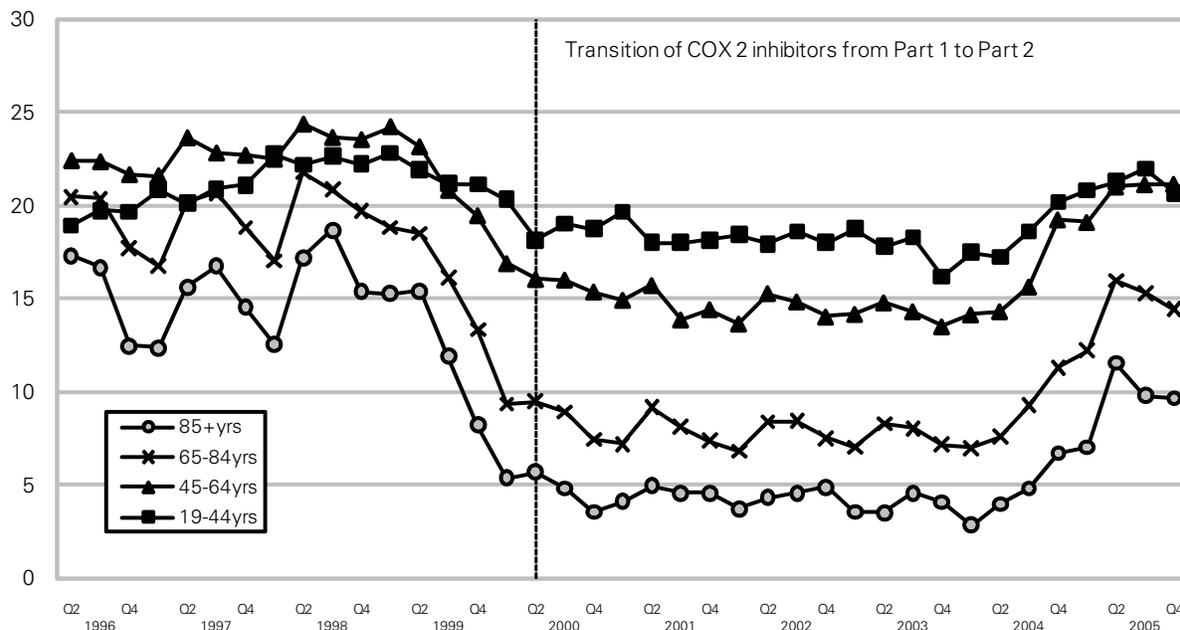


Source: Manitoba Centre for Health Policy, 2009

For older NSAIDs, the greatest new utilization was amongst those aged 45–64 years until the last quarter of 1999; thereafter, residents aged 19–44 years represented the highest incidence for new users of older NSAIDs.

Figure 2.9: Older NSAIDs Quarterly Incidence by Age

Crude rates of new users with no use of any NSAIDs or COX 2 inhibitors (M01A) in prior year per 1,000 adults, Q2 1996 – Q4 2005



'Q2' indicates incidence for the 2nd quarter (April to June)
'Q4' indicates incidence for the 4th quarter (October to December)
'Q1' and 'Q3' data points are displayed, but not labeled
NSAIDs include meloxicam, naproxen, diclofenac, and ibuprofen

Source: Manitoba Centre for Health Policy, 2009

2.3 Discussion

Population use of COX 2 inhibitors increased dramatically following their market launch, then declined subsequently due to a variety of events. Utilization of diclofenac and naproxen, the two most commonly prescribed older NSAIDs, returned to pre COX 2 inhibitor levels after the withdrawal of rofecoxib, warnings about celecoxib and valdecoxib, and changing to Part 3 (prior approval) listing. Other studies have observed a similar rise and subsequent decline in COX 2 inhibitors, with a converse decline (Schussel & Schulz, 2006) and then rise in older NSAIDs (Barozzi & Tett, 2007; Pearson et al., 2007). Like others, we observed an influence of age on utilization of COX 2 inhibitors (Steinman, McQuaid, & Covinsky, 2006).

While the patterns of COX 2 inhibitor use can be attributed to numerous events, we were particularly interested in evaluating the effectiveness of changing the formulary listing to Part 2 (utilization for established criteria). We found that the transition from Part 1 to Part 2 listing in the Pharmacare formulary was associated with a decline in the rate of new use of COX 2 inhibitors. Some of the decline in new use of celecoxib may have been the outcome of market availability and marketing of rofecoxib; however, rofecoxib utilization was also reduced, as was the utilization of both agents combined.

Several studies have demonstrated that restricted formulary listing and change in formulary listing policies, have influenced the prescribing of COX 2 inhibitors (Roughead, Zhang, Ross-Degnan, & Soumerai, 2006; Hartung et al., 2004; Fischer, Schneeweiss, Avorn, & Solomon, 2004). The influence of formulary listing policy on utilization of COX 2 inhibitors has been evaluated in other Canadian provinces (Mamdani et al., 2006). In a comparative analysis of prescribing of these agents among seniors in Ontario (open formulary listing of COX 2 inhibitors) and British Columbia (restricted formulary listing of COX 2 inhibitors), COX 2 inhibitor utilization was greater in Ontario. A subsequent increase in hospitalizations for gastro-intestinal bleeding was observed amongst Ontario seniors, pointing to unintended consequences of utilizing these medications in patients at high risk for adverse effects from non-steroidal anti-inflammatory medications (Mamdani et al., 2006).

CHAPTER 3: BIPHOSPHONATES

Bisphosphonates are a class of medications used to treat and prevent osteoporosis. **Hormone replacement therapy (HRT)** consists of estrogen and progesterones generally taken by postmenopausal women in order to reduce menopausal symptoms, to prevent and treat osteoporosis, and until recently, to minimize cardiovascular risk. After the publication of the Women's Health Initiative (WHI) trial in 2002, which revealed that HRT in postmenopausal women did not mitigate cardiovascular risk but instead increased the risk of undesirable outcomes such as thromboembolic complications and breast cancer (Rossouw et al., 2002), there was an abrupt and sustained decrease in prescriptions for hormone replacement (Huot et al., 2008; Farley, Blalock, & Cline, 2008; Udell, Fischer, Brookhart, Solomon, & Choudhry, 2006; Usher, Teeling, Bennett, & Feely, 2006; Kim et al., 2005; Lee, Wutoh, Xue, Hillman, & Zuckerman, 2006; Austin, Mamdani, Tu, & Zwarenstein, 2004). Calcitonin and raloxifene are second line agents for the treatment of osteoporosis.

During the majority of the study period, bisphosphonates were listed under Part 2 (use for established criteria) of the Pharmacare formulary while calcitonin and raloxifene were listed under Part 3 (prior approval). Bisphosphonates were transitioned from Part 2 to Part 3 in July of 2005. The addition of generic alendronate as being interchangeable with brand name alendronate on the Manitoba Pharmacare formulary occurred in the third quarter of 2003. The weekly dosage form of alendronate became available at the beginning of 2002, and the weekly dosage form of risedronate became available at the beginning of 2003. All bisphosphonates were transitioned to Part 3 of the Pharmacare formulary in late 2005.

We assessed the impact of publication of the WHI trial and subsequent decline in HRT on the utilization of bisphosphonates as both medications are used for the treatment and prevention of osteoporosis. We also evaluated the utilization of bisphosphonates in the population of Manitoba over time, in particular the effect on prescribing daily or weekly doses of bisphosphonates and the formulary addition of the generic bisphosphonates.

3.1 Methods

Prevalent and incident users were identified for the population of Manitoba for the following medication groups: bisphosphonates (etidronate, alendronate, risedronate), raloxifene, calcitonin and HRT (systemic estrogen and progesterone therapy for the treatment of menopausal symptoms). Although this list of bisphosphonates is not exhaustive, these bisphosphonates are the most commonly prescribed oral agents for the treatment of osteoporosis. Additionally, alendronate prescriptions were further categorized by brand and generic, and alendronate and risedronate prescriptions were categorized by daily or weekly dosage forms. For a list of the medications included in the categories, please refer to Appendix Table 1.

Incident users were those users of the medication of interest who had not used any bisphosphonates, calcitonin, raloxifene or HRT in the one year prior to this first prescription of interest. The incident and prevalent utilization of bisphosphonates was compared before and after the publication of the WHI trial using GEE modeling.

3.2 Results

Prevalence

A general increase in prevalent utilization of bisphosphonates was observed over the study period. Prior to the time of publication of the WHI trial results, the rate of prevalent use of bisphosphonates was increasing by 8% per quarter over the previous quarter's rate ($p < 0.05$) (Table 3.1). Total utilization of bisphosphonates in the population increased from 0.3 to 17.1 users per 1,000 residents in 2005. Independent of sociodemographic characteristics, prevalent use of bisphosphonates continued to increase after the timing of the WHI study ($p < 0.05$).

Table 3.1: Prevalent Use (Users/1,000 Adults) of Bisphosphonates, 1995-2005

	Baseline users/1,000 §	Change in rate*	Before WHI Trial users/1000 2002Q2	Change in rate*	End 2005 users/1,000	Age effect* Age 45-64 vs 85+	Prescription cost sharing* No cost vs high income	Region effect* Point Douglas vs Fort Garry
Bisphosphonates, all	0.25	1.08 + 8% **	9.93	1.03 + 3% **	17.10	0.17 - 83% ‡	1.70 + 70% ‡	0.61 - 39% ‡

* Results are presented as relative rates (adjusted for age, prescription cost sharing, region and time) and then, for ease of interpretation, as percentages

** Indicates a slope significantly different from zero ($p < .05$)

‡ Indicates a statistically significant effect ($p < .05$)

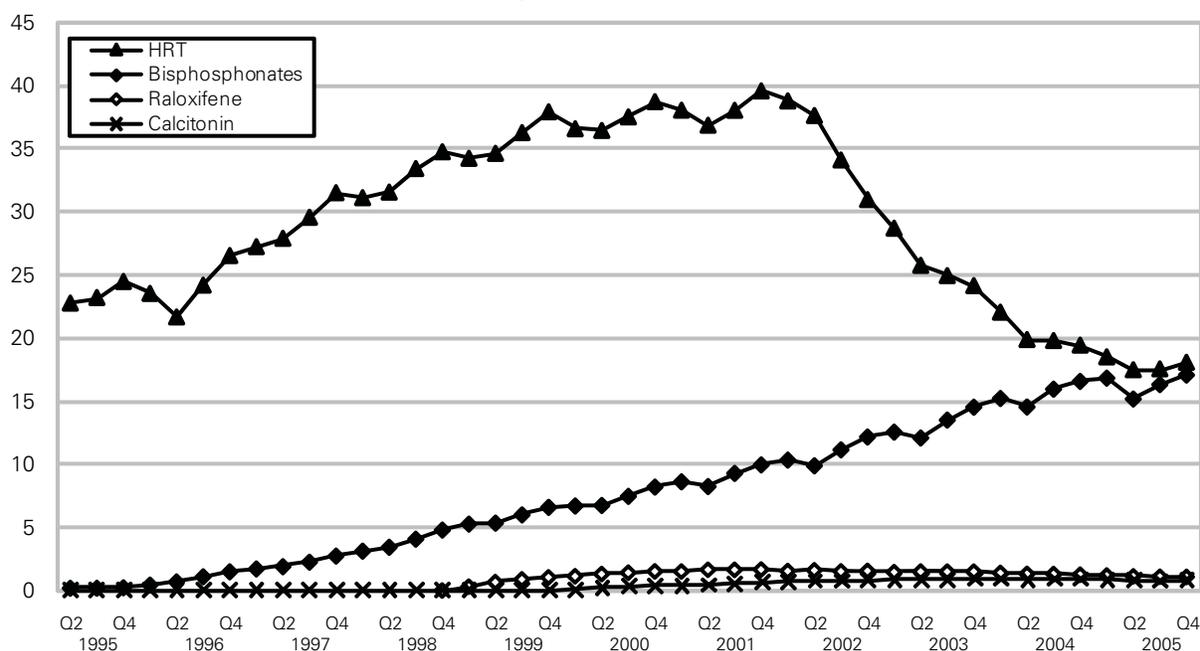
§ Baseline rates are users per 1,000 adults at the second quarter of 1995 or when prescriptions were first filled for a drug

Source: Manitoba Centre for Health Policy, 2009

The prevalence of HRT increased until the beginning of 2002 (22.7 to 39.6 users per 1,000 residents) and then rapidly declined to 18.0 users per 1,000 residents by the end of the study period. Utilization of raloxifene and calcitonin remained low throughout the study period.

Figure 3.1: Medications for Osteoporosis, Quarterly Prevalence

Crude user rates per 1,000 adults, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)

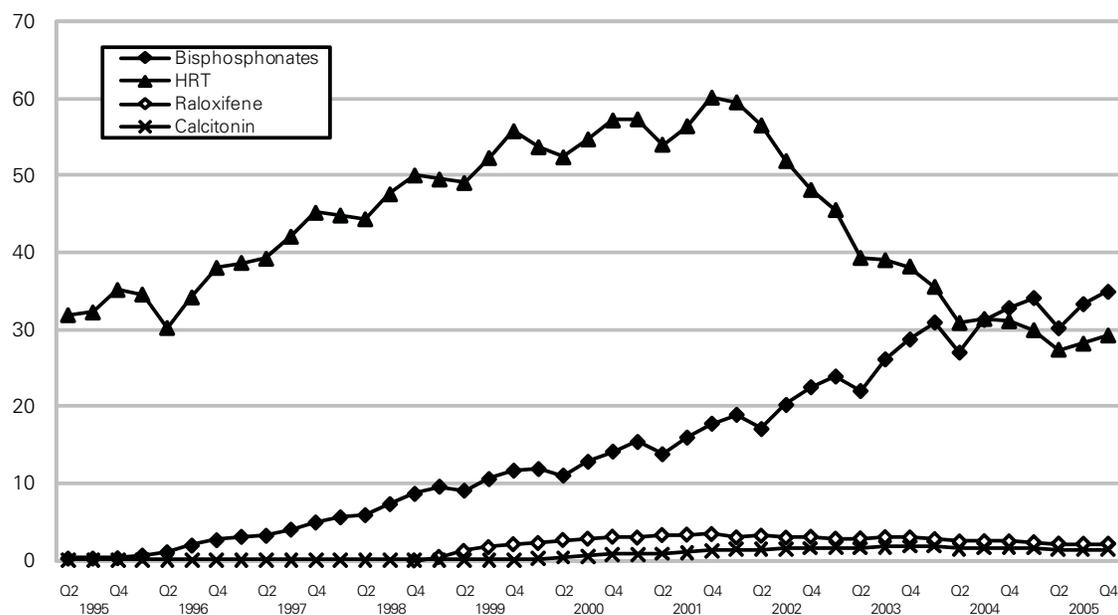
'Q4' indicates prevalence for the 4th quarter (October to December)

'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Figure 3.2: Medications for Osteoporosis, Quarterly Prevalence

Crude prescription rates per 1,000 adults, Q2 1995–Q4 2005



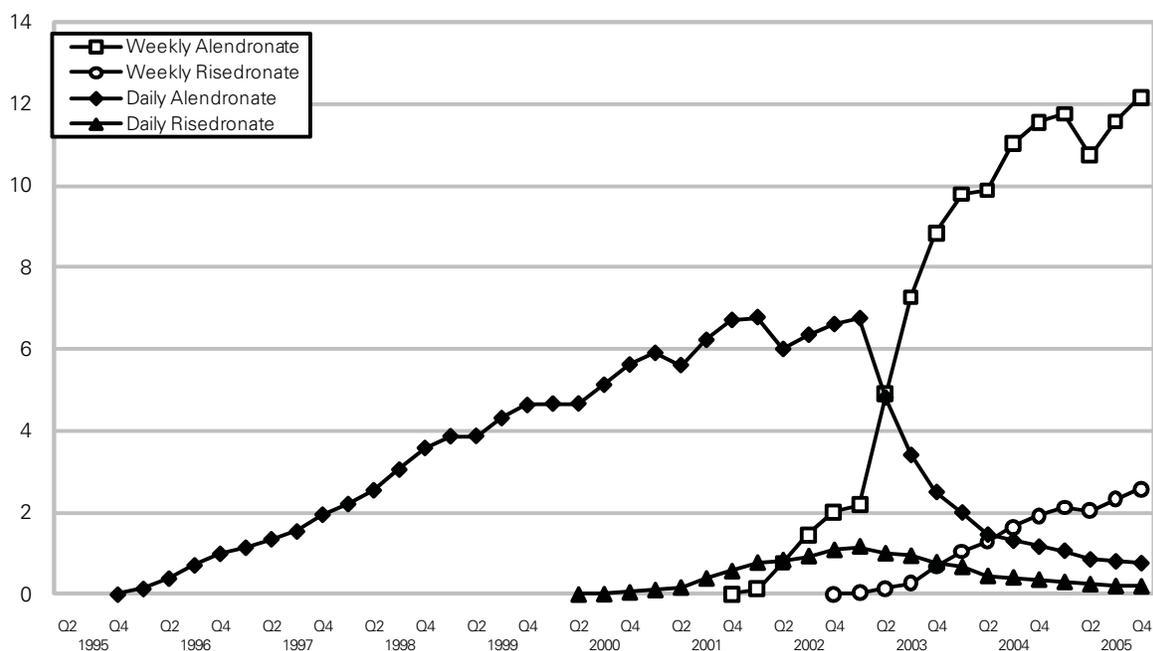
'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Weekly dosing for alendronate and risedronate had rapid uptake upon availability of these dosage forms. By the third quarter of 2003, weekly dosing had nearly replaced daily dosing for alendronate. For risedronate, weekly dosing began to replace daily dosing in at the beginning of 2004.

Figure 3.3: Alendronate and Risedronate Dosing, Quarterly Prevalence

Crude weekly and daily dosing rates per 1,000 adults, Q2 1995–Q4 2005



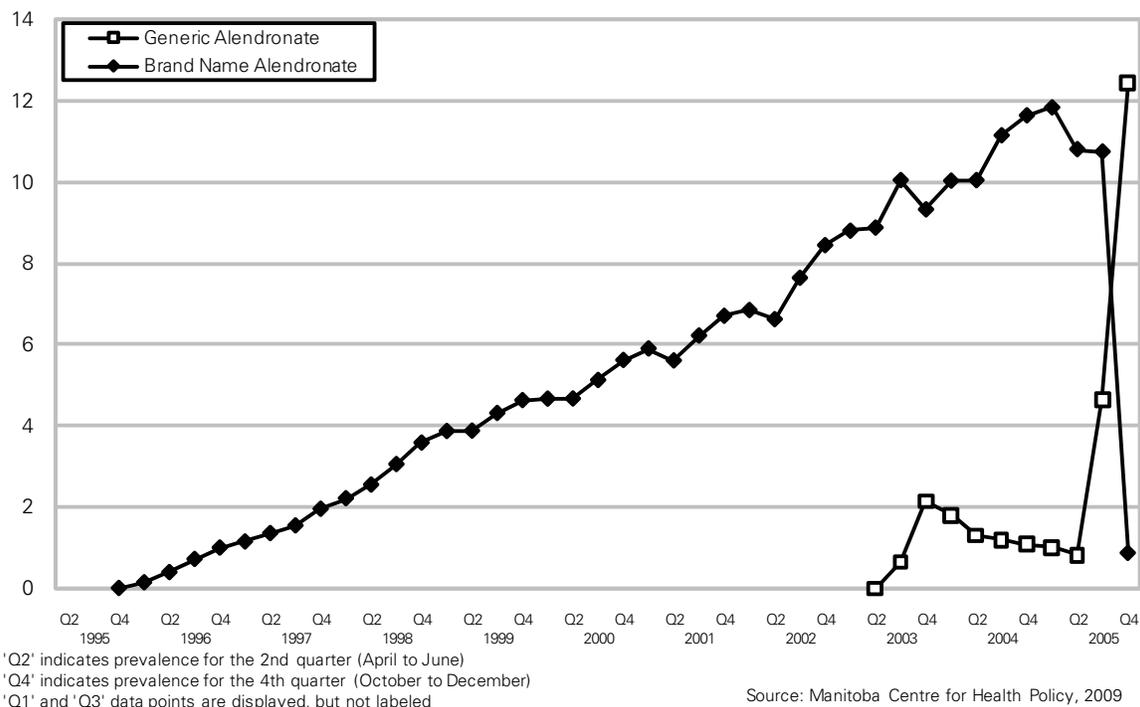
'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Generic alendronate had rapid uptake after market launch; utilization of generic alendronate replaced brand alendronate by the end of 2005. Although generic alendronate was available in 2003, it was only available in the daily dosing formulation until 2005. When weekly generic alendronate became available in 2005, its utilization increased dramatically.

Figure 3.4: Alendronate Quarterly Prevalence

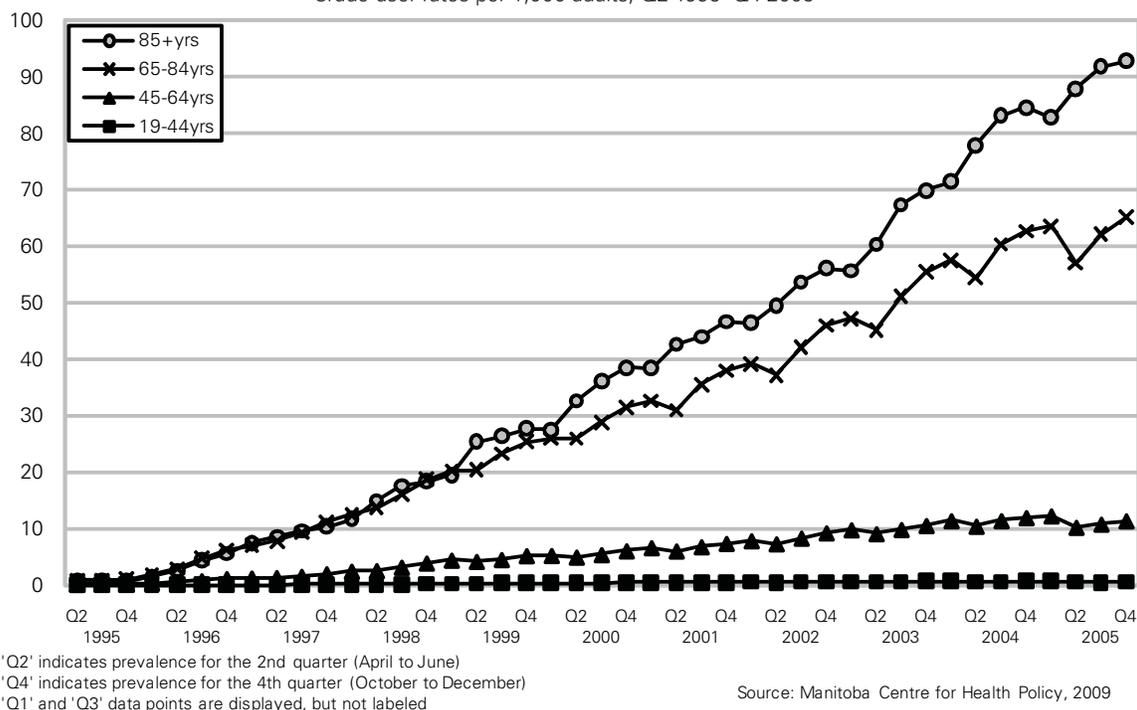
Crude brand name and generic alendronate rates per 1,000 adults, Q2 1995–Q4 2005



Bisphosphonates were prescribed most often in persons aged 85 and older (use increased from 0.8 to 92.9 users per 1,000 residents over the study period), followed by age 65–84 (0.6 to 65.2 users per 1,000 residents), then age 45–64 (0.1 to 11.5 users per 1,000 residents), and age 19–44 (0 to 0.6 users per 1,000 residents).

Figure 3.5: Bisphosphonates Quarterly Prevalence by Age

Crude user rates per 1,000 adults, Q2 1995–Q4 2005



For HRT, utilization was greatest in those aged 45–64 and 65–84.

Figure 3.6: Hormone Replacement Therapy, Quarterly Prevalence by Age

Crude user rates per 1,000 adults, Q2 1995–Q4 2005



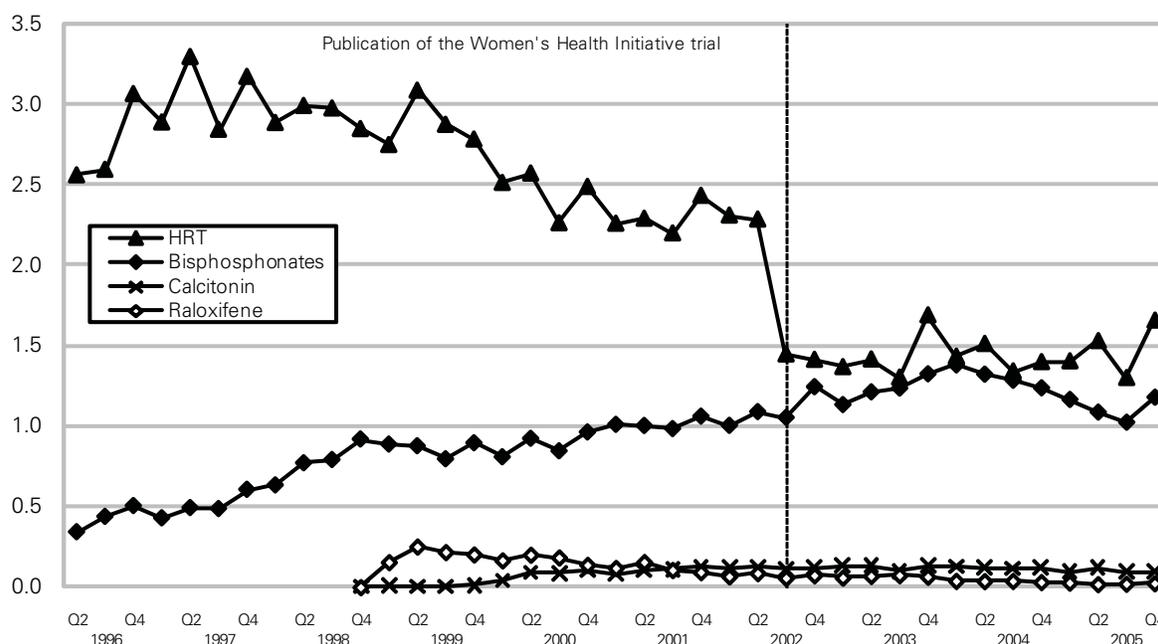
When bisphosphonate utilization was evaluated by prescription cost sharing, prevalence was greatest (users per population) among persons receiving no-cost prescriptions. Regional comparisons revealed a significantly lower prevalent use of bisphosphonates in Point Douglas than Fort Garry (Table 3.3).

Incidence

New prescribing of all bisphosphonates increased over time, from 0.3 to 1.2 users per 1,000 residents per quarter over the study period. Just prior to the publication of the WHI Trial results about HRT in 2002, incident use of bisphosphonates had risen to 1.09 per 1,000 persons. Adjustment for sociodemographic characteristics did not alter the rate of incident use.

Figure 3.7: Medications for Osteoporosis, Quarterly Incidence

Crude rates of new users with no use of HRT, bisphosphonates, raloxifene or calcitonin in prior year per 1,000 adults, Q2 1996–Q4 2005



'Q2' indicates incidence for the 2nd quarter (April to June)

'Q4' indicates incidence for the 4th quarter (October to December)

'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

The adjusted incident rate of bisphosphonates at the end of 2005 was 1.14 users per 1,000 residents per quarter (Table 3.3). Prior to the time of publication of the WHI trial results the rate of new use of bisphosphonates was increasing at 4% per quarter over the previous quarter's rate ($p < 0.05$). No further increases in the rate of new prescribing of bisphosphonates were observed following publication of the WHI trial. Thereafter, independent of sociodemographic characteristics, incident use of bisphosphonates became constant (not statistically significantly different from zero). Incident utilization of HRT decreased over the study period, with a steep decline in 2002.

Table 3.2: Incident Use (New Users/1,000 Adults) of Bisphosphonates, 1996-2005

	Before WHI trial (1996Q2-2002Q2)		After WHI trial (2002Q3-2005Q4)
	First Quarter 1996Q2	Last Quarter 2002Q2	Last Quarter 2005Q4
Crude rate	0.34	1.09	1.18
Adjusted rate*		1.09	1.14
Adjusted rate of change* per quarter		1.04**	1.00†

* Adjusted for age, prescription cost sharing, region and time

Rate of change results are presented as relative rates

** Indicates a slope significantly different from zero ($p < .05$)

† Indicates a significant change in the slope after the intervention ($p < .05$)

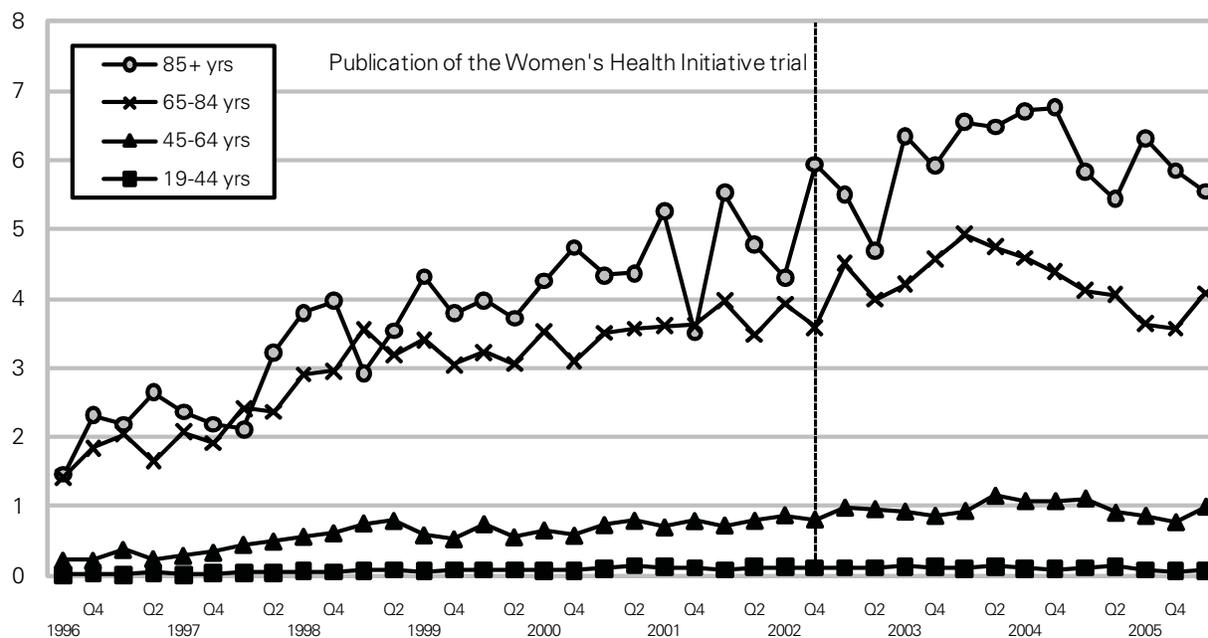
Source: Manitoba Centre for Health Policy, 2009

Similar patterns to prevalent use of bisphosphonates were observed when incident utilization was evaluated by brand and generic name and when daily dosing was compared to weekly dosing (see Appendix 2, Figures A.3.1 and A.3.2).

The greatest number of new users of bisphosphonates per population was in the group aged 85 years and older.

Figure 3.8: Bisphosphonates Quarterly Incidence by Age

Crude rates of new users with no use of HRT, bisphosphonates, raloxifene or calcitonin in prior year per 1,000 adults, Q2 1996–Q4 2005



'Q2' indicates incidence for the 2nd quarter (April to June)

'Q4' indicates incidence for the 4th quarter (October to December)

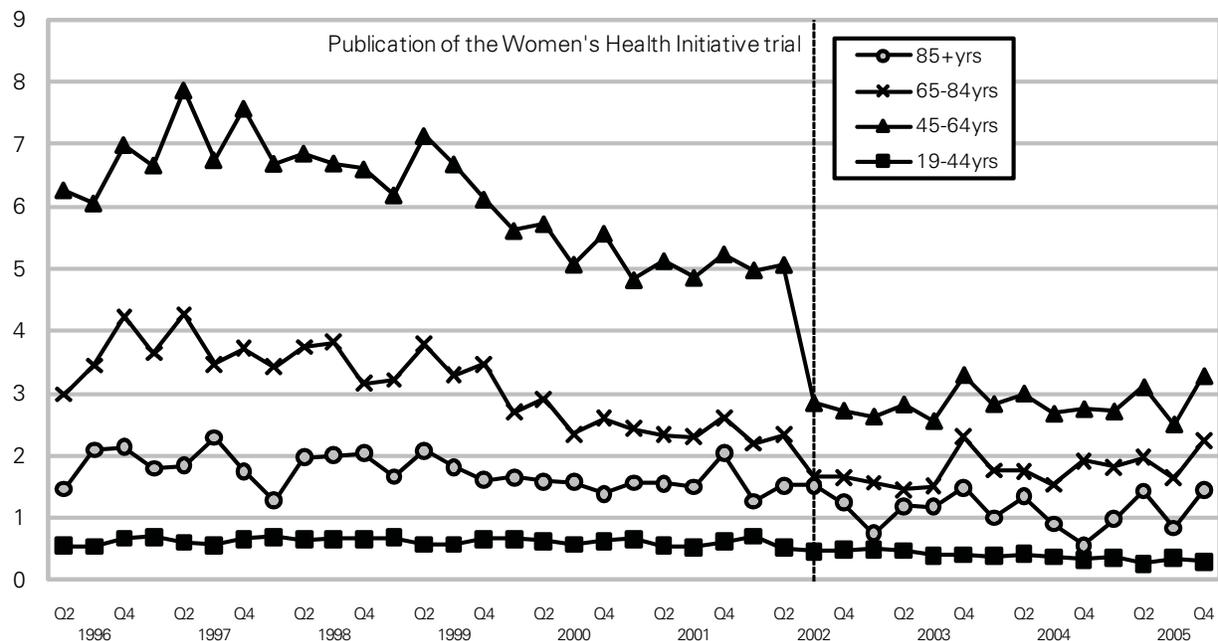
'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

For HRT, the highest incident utilization was in those aged 45–64, followed by those aged 65–84.

Figure 3.9: Hormone Replacement Therapy Quarterly Incident Incidence by Age

Crude rates of new users with no use of HRT, bisphosphonates, raloxifene or calcitonin in prior year per 1,000 adults, Q2 1996–Q4 2005



'Q2' indicates incidence for the 2nd quarter (April to June)
'Q4' indicates incidence for the 4th quarter (October to December)
'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

3.3 Discussion

As with many other published studies, we observed a general decrease in HRT and an increase in bisphosphonates over time (Stafford, Drieling, & Hersh, 2004; Huot et al., 2008; Farley et al., 2008; Udell et al., 2006; Usher et al., 2006; Kim et al., 2005; Lee et al., 2006; Austin et al., 2004; Watson, Wise, & Green, 2007). The decline in prevalent and incident utilization of HRT after publication of the WHI trial was expected. Further, we did not observe a subsequent increase in the rate of new prescribing for bisphosphonates after the timing of the publication of the WHI trial, which suggests that bisphosphonates did not replace HRT in Manitoba.

The WHI trial has had a differential impact worldwide. Although a rise in bisphosphonates and raloxifene utilization was seen in France after the publication of the trial, it occurred to a lesser extent than the decline in HRT prescriptions (Huot et al., 2008). In a survey study of prescribing in the US, the WHI trial led to increased utilization of newer medications for osteoporosis (Farley et al., 2008). One US study of **Medicaid** residents suggested that the prevalence of bisphosphonate prescriptions increased significantly in the post-WHI period with a decline in estrogen prescriptions (to the end of 2002) (Lee et al., 2006). Another US study of Medicaid beneficiaries reported no change to bisphosphonates' nearly linear rate of increase (to the end of 2004) (Udell et al., 2006). Many factors could contribute to an absence of an increase in bisphosphonate utilization after the

study period, including the possibility that many women were not using HRT for osteoporosis and that women may have been less inclined to start a new therapy after such negative media attention towards HRT (Canales, Breslau, Nelson, & Ballard-Barbash, 2008). Our study was limited by the fact that Manitoba's prescription drug databases do not capture information about over the counter calcium or vitamin D. Both medications are commonly consumed for the prevention and treatment of osteoporosis (Dawson-Hughes, Harris, Dallal, Lancaster, & Zhou, 2002). It is conceivable that the WHI trial results may have encouraged their use rather than bisphosphonates.

We found evidence for the replacement of daily dosing of bisphosphonates with weekly dosing and for the replacement of brand name bisphosphonates with generic products. The former has also been described in the United Kingdom (Watson et al., 2007). Increased use of weekly dosing of bisphosphonates is likely attributed to greater patient convenience and may lead to improved patient compliance (Ettinger, Gallagher, & MacCosbe, 2006). As reported by others, utilization of calcitonin and raloxifene remained low throughout the study period (Farley et al., 2008; Udell et al., 2006; Huot et al., 2008). Potential reasons for lower utilization may include adverse effects, the fact that calcitonin is not considered first line therapy for osteoporosis, and that raloxifene has less randomized controlled trial evidence for reducing fractures than bisphosphonates (Brown et al., 2006; Brown & Josse, 2002). Additionally, because they are listed under Part 3 of the Pharmacare formulary (prior approval), the utilization of calcitonin and raloxifene is limited in Manitoba. The transitioning of all bisphosphonates to Part 3 of the Pharmacare formulary in 2005 will provide an opportunity for further study of the influence policy change has on utilization. One area for further study were our observed differences in utilization of bisphosphonates by medication cost to patient (Farley, Cline, & Gupta, 2006; Farley et al., 2008). A second area of further study is about factors influencing underutilization of bisphosphonates in populations who could benefit from them, such as individuals who have already experienced an osteoporotic fracture (Metge, Kozyrskyj, Dahl, Yogendran, & Roos, 2003).

CHAPTER 4: ANTIPSYCHOTICS

Antipsychotics are a broad class of medication used to treat multiple psychiatric conditions. The class consists of newer agents, termed 'atypical' antipsychotics (olanzapine, risperidone, quetiapine and clozapine), and the older agents, including commonly used agents such as chlorpromazine and haloperidol. During the study period, all antipsychotics on the Pharmacare formulary were covered under Part 1 (open listing). In the fourth quarter of 2002, Health Canada issued a warning about the possible association between the utilization of risperidone and cerebrovascular accidents in patients with **dementia** (Health Canada, 2002c). In early 2004, Health Canada issued a similar warning about olanzapine, which advised physicians to reassess the risk and benefits of prescribing these medications to elderly patient with dementia (Health Canada, 2004c).

We evaluated the utilization of antipsychotics, more specifically the atypical agents, in the Manitoba population over time. These evaluations were also conducted in specific populations according to age and place of residence. We also assessed the impact of the first Health Canada warning on the utilization of atypical antipsychotics in the elderly (Health Canada, 2002c; Health Canada, 2004c).

4.1 Methods

Unless stated otherwise, individuals residing in personal care homes in Manitoba are included in the numerator and denominator for this analysis. For several graphs, we excluded individuals residing in personal care homes in order to compare antipsychotic utilization amongst individuals residing in personal care homes to those residing in the community.

Prevalent and incident use of antipsychotics for the population of Manitoba was determined for the following medications: olanzapine, risperidone, quetiapine, and clozapine (atypical antipsychotics). Older antipsychotics were all members of the ATC class N05A (excluding lithium carbonate). For a list of the medications included in the categories, please refer to Appendix Table 1.

Incident users were those users of an antipsychotic who had not received an antipsychotic (atypical or older agent) in the one year prior to their first antipsychotic prescription. The incident and prevalent utilization of antipsychotics was compared before and after the Health Canada warnings using GEE modeling.

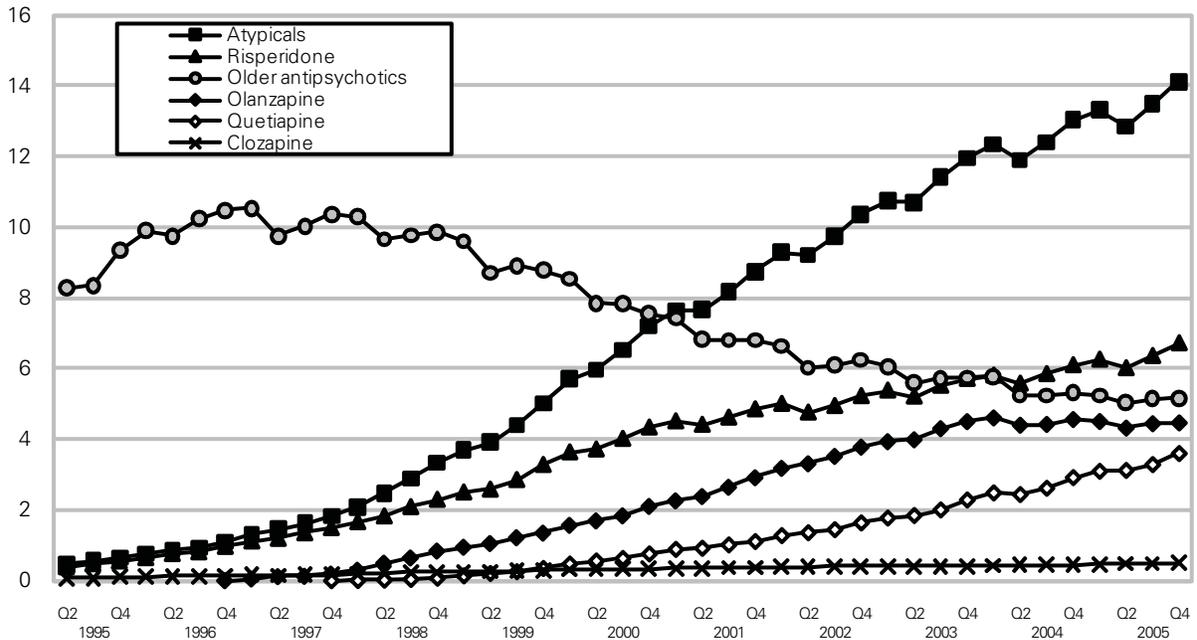
4.2 Results

Prevalence

Prevalent utilization of olanzapine, risperidone and quetiapine increased from 1995 to 2005. The atypical antipsychotic, risperidone, was prescribed the most often. Utilization of atypical antipsychotics in the adult population of Manitoba increased from 0.5 to 14.1 users per 1,000 residents over the study period. The utilization of risperidone and olanzapine increased from 0.4 to 6.7 users per 1,000 residents and 0.1 to 4.5 users per 1,000 residents, respectively. Utilization of quetiapine increased from 0.01 to 3.6 users per 1,000 residents, while the utilization of older antipsychotics declined from 8.3 to 5.2 per 1,000.

Figure 4.1: Antipsychotics Quarterly Prevalence

Crude user rates per 1,000 adults, Q2 1995–Q4 2005

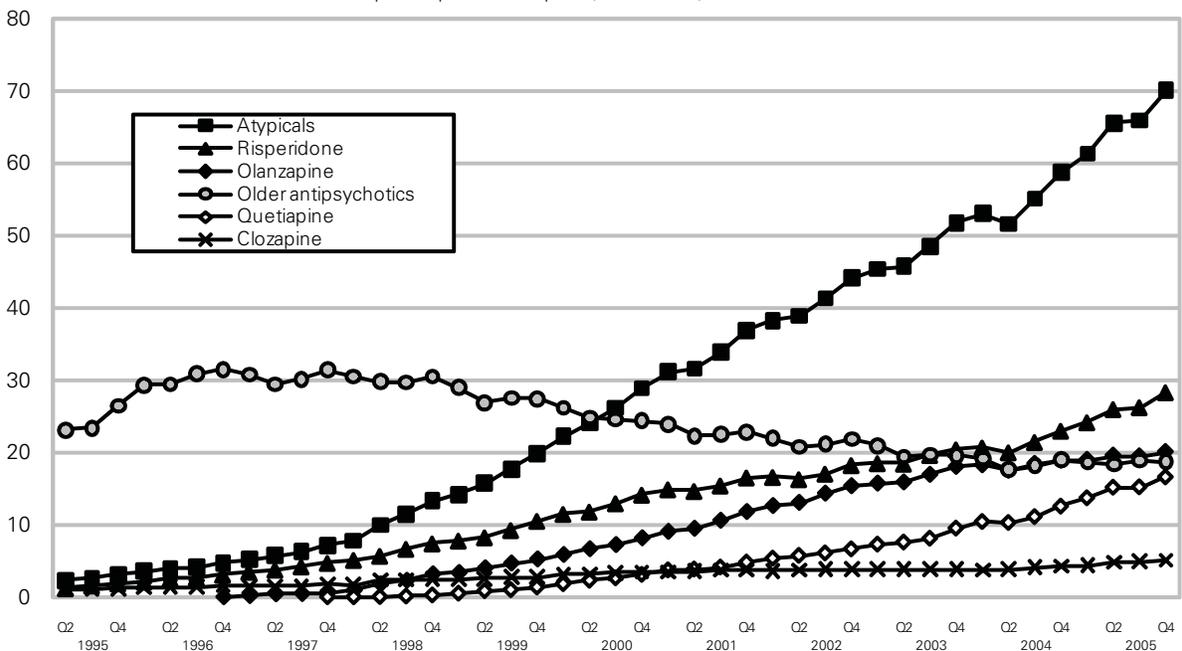


'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Figure 4.2: Antipsychotics Quarterly Prevalence

Crude prescription rates per 1,000 adults, Q2 1995–Q4 2005



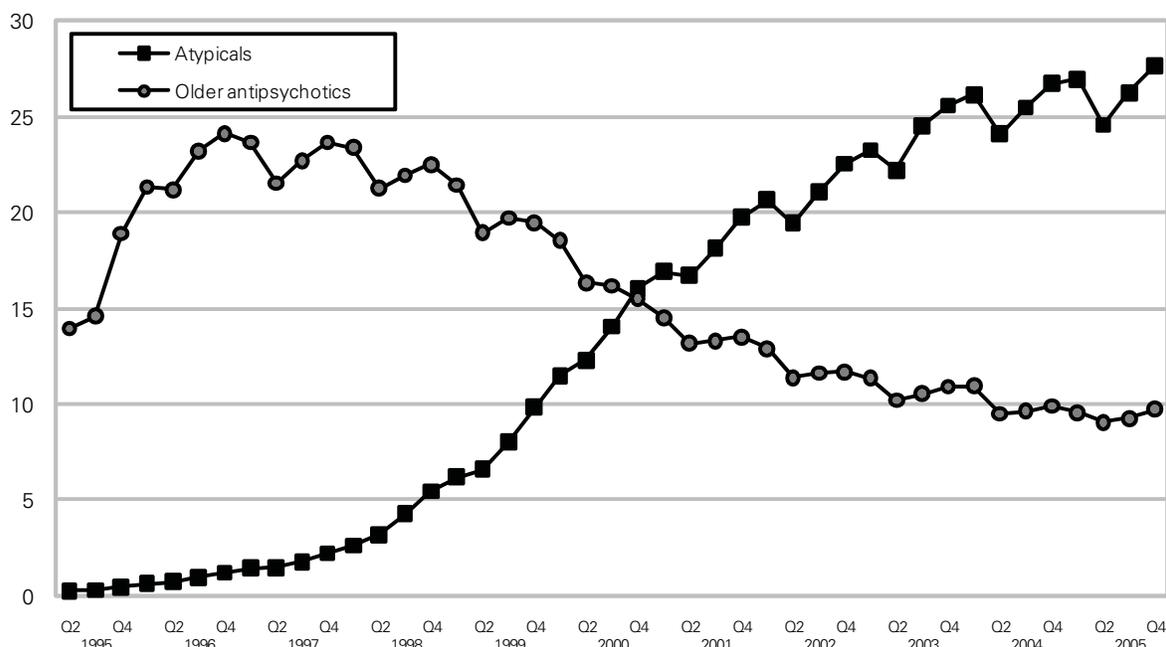
'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

When individuals aged 65 and older were analyzed separately, prevalent utilization of atypical antipsychotics increased from 0.25 to 27.7 users per 1,000 residents, while prevalent utilization of older antipsychotics in this population declined from a maximum of 24.1 users per 1,000 residents in late 1996 to 9.7 users per 1,000 residents by the end of the study period. Prior to the first Health Canada warning about risperidone, prevalent use was increasing for all atypical antipsychotics in the elderly. Quetiapine exhibited the greatest rate of quarterly increase in prevalent use prior to the warnings, 25% over the previous quarter's rate ($p < 0.05$). After the first Health Canada warning, prevalent utilization of all atypicals, olanzapine, and quetiapine continued to increase ($p < 0.05$), while prevalent utilization of risperidone became constant (did not differ significantly from zero) and prevalent utilization of older antipsychotics declined ($p < 0.05$) (Table 4.1).

Figure 4.3: Antipsychotics aged 65+ Quarterly Prevalence

Crude user rates per 1,000 adults, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)

'Q4' indicates prevalence for the 4th quarter (October to December)

'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Table 4.1: Prevalent Use (Users/1,000 Adults aged 65+) of Antipsychotics, 1995-2005

Medication	Baseline rate/1,000§	Change in Rate*	Before 1st HC Warning rate/1,000 2002Q3	Change in Rate*	After Warning rate/1,000 2005Q4	Age effect* 65-84 vs 85+	Prescription cost		Region effect* Rural vs Urban
							No cost vs high income	sharing*	
All atypicals	0.25	1.16 + 16% **	21.06	1.05 + 5% **	27.67	0.47 - 53% †	1.10 + 10%	0.64 - 36%	
Risperidone	0.25	1.14 + 14% **	12.78	1.01 + 1%	15.62	0.41 - 58% †	0.75 - 25%	1.06 + 6%	
Olanzapine	0.02	1.21 + 21% **	6.62	1.10 + 10% **	7.65	0.64 - 36% †	1.27 + 27%	0.28 - 72% †	
Quetiapine	0.01	1.25 + 25% **	2.36	1.10 + 10% **	5.70	0.76 - 24%	0.89 - 11%	0.41 - 59% †	
Older antipsychotics ††	13.94	0.98 - 2% **	11.63	0.97 - 3% **	9.73	0.64 - 36% †	1.81 + 81%	1.84 †† + 84%	

* Results are presented as relative rates (adjusted for age, prescription cost sharing, region and time)

and then, for ease of interpretation, as percentages

** Indicates a slope significantly different from zero (p<.05)

† Indicates a statistically significant effect (p<.05)

§ Baseline rates are users per 1,000 elderly adults at the second quarter of 1995

or when prescriptions were first filled for a drug

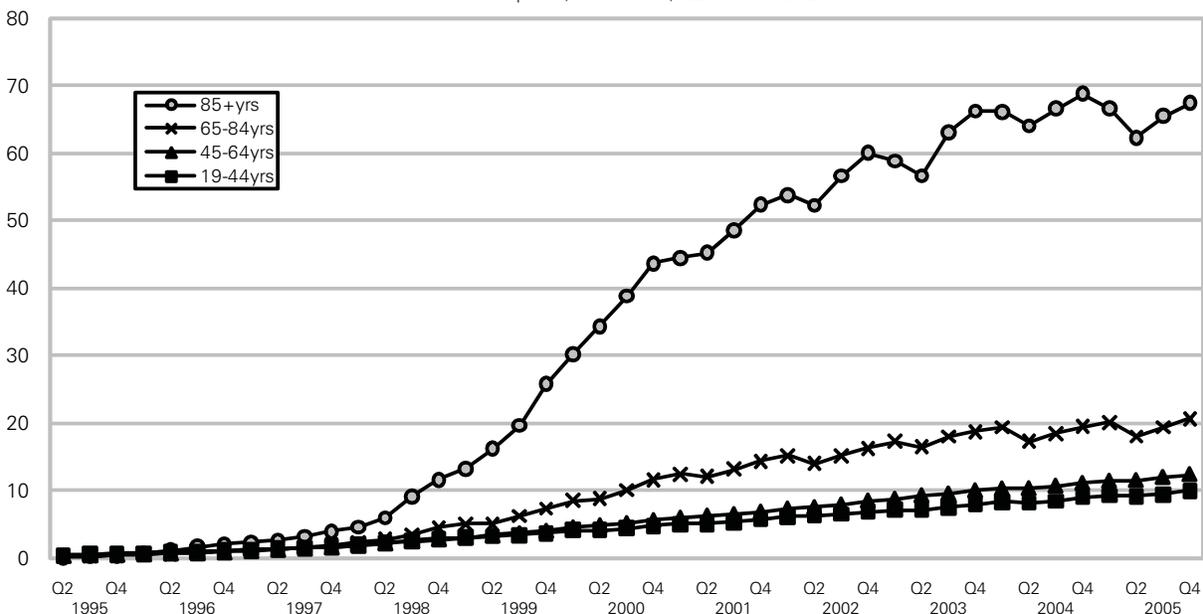
†† model includes sex as a covariate. Regional analysis for this model compares Point Douglas to Fort Garry

Source: Manitoba Centre for Health Policy, 2009

When evaluated by age, atypical antipsychotics were used most often in persons aged 85 and older (from 0.2 to 67.5 users per 1,000 residents over the study period), followed by age 65–84 (0.3 to 20.7 users per 1,000 residents), then age 45–64 (0.5 to 12.4 users per 1,000 residents), and age 19–44 (0.5 to 10.0 users per 1,000 residents).

Figure 4.4: Antipsychotics (Atypicals) Quarterly Prevalence by Age Group

Crude user rates per 1,000 adults, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)

'Q4' indicates prevalence for the 4th quarter (October to December)

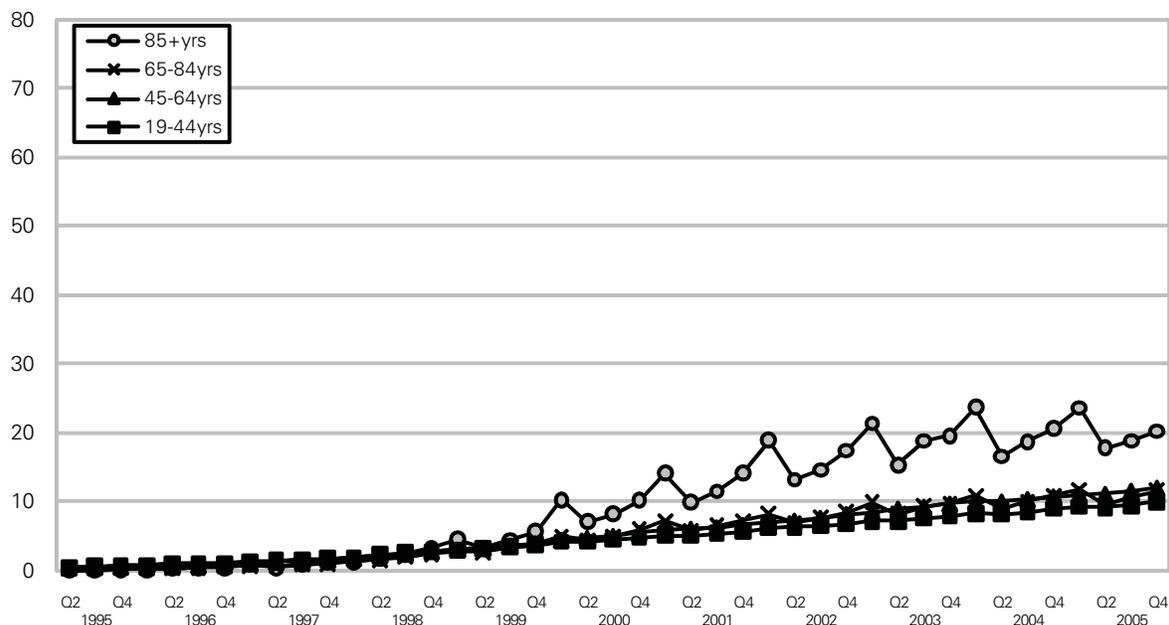
'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

The majority of atypical antipsychotic users resided in personal care homes; however, when residents of personal care homes were excluded from the analysis, persons aged 85 and older continued to show relatively high user rates of atypical antipsychotics compared to other age groups (0.008 to 20.2 prevalent users per 1,000 residents).

Figure 4.5: Antipsychotics (Atypicals) Quarterly Prevalence Excluding Residents of Personal Care Homes by Age Group

Crude user rates per 1,000 adults, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

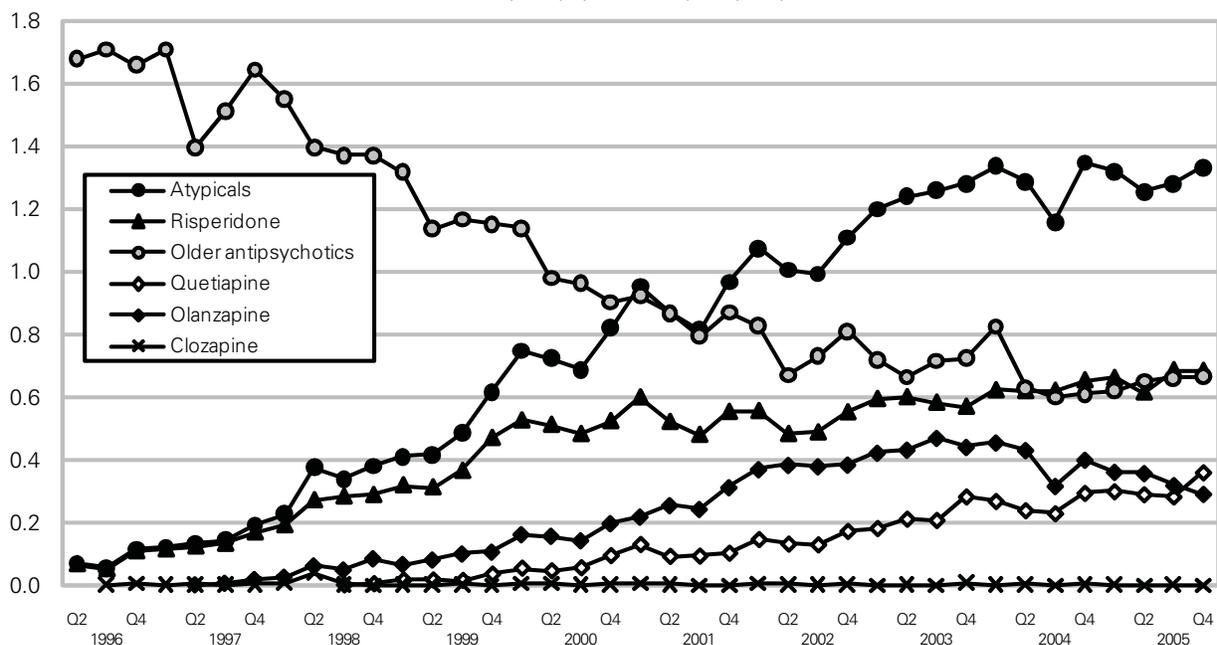
In the elderly (65 years and older), we did not observe significant differences in prevalent atypical antipsychotic utilization by prescription cost sharing. Atypical antipsychotic utilization was lower in rural than urban areas, which was significant only for olanzapine and quetiapine following adjustment for other factors (Table 4.1).

Incidence

Similar to prevalent use, risperidone showed the highest incident utilization compared to other atypical antipsychotics. New prescribing of atypical antipsychotics increased from 0.07 to 1.3 users per 1,000 residents per quarter, while that for older agents decreased from 1.7 to 0.7 users per 1,000 residents per quarter over the same period. The highest incident utilization rates of atypical antipsychotics were for risperidone (0.07 to 0.7 users per 1,000 residents per quarter), followed by olanzapine (0.01 to 0.3 users per 1,000 residents per quarter) and quetiapine (0.01 to 0.4 users per 1,000 residents per quarter).

Figure 4.6: Antipsychotics Quarterly Incidence

Crude rates of new users with no use of any antipsychotics in prior year per 1,000 adults, Q2 1996–Q4 2005



'Q2' indicates incidence for the 2nd quarter (April to June)

'Q4' indicates incidence for the 4th quarter (October to December)

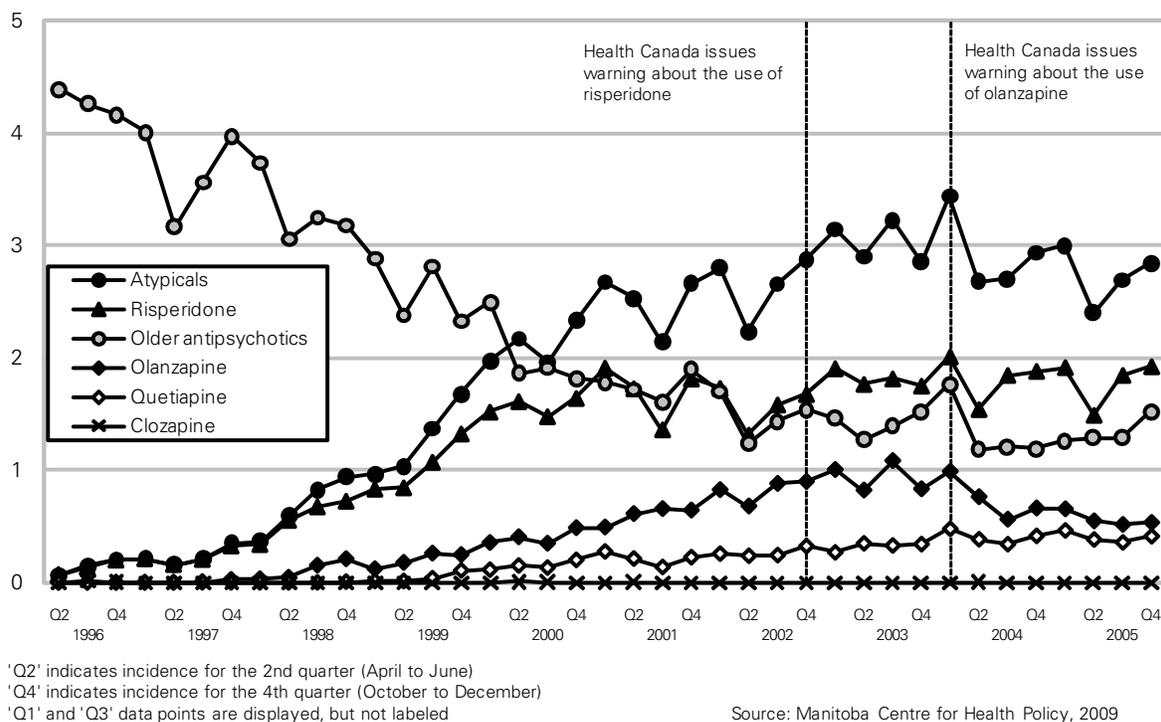
'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

For those age 65 and older, quarterly incident utilization of atypical antipsychotics overall increased from 0.07 to 2.8 users per 1,000 residents per quarter over the study period.

Figure 4.7: Antipsychotics Quarterly Incidence aged 65+

Crude rates of new users with no use of any antipsychotics in prior year per 1,000 adults aged 65+ years, Q2 1996–Q4 2005



Just prior to the first Health Canada warning about risperidone in 2002, incident use of atypical antipsychotics in the elderly had risen to 2.66 per 1,000 persons. When further adjusted for sociodemographic characteristics, this incidence was 2.52 per 1,000 (Table 4.2). It increased to 2.68 per 1,000 in the last quarter of 2005. Prior to the first Health Canada warning about risperidone the rate of new users of all atypical antipsychotics in the elderly was increasing, at 13% over the previous quarter's rate ($p < 0.05$). Thereafter, independent of sociodemographic characteristics, incident use of atypical antipsychotics in the elderly became constant (was not statistically different from zero). However, the slope of the rate of increase of new users of atypical antipsychotics was less steep after the warning than before ($p < 0.05$).

Table 4.2: Incident Use (New Users/1,000 Adults aged 65+) of Atypical Antipsychotics, 1996-2005

	Before 1st Health Canada Warning (1996Q2-2002Q3)		After 1st Warning (2002Q4-2005Q4)
	First Quarter 1996Q2	Last Quarter 2002Q3	Last Quarter 2005Q4
Crude rate	0.07	2.66	2.84
Adjusted rate*		2.52	2.68
Adjusted rate of change* per quarter		1.13**	1.03†

* Adjusted for age, prescription cost sharing, region and time

Rate of change results are presented as relative rates

** Indicates a slope significantly different from zero ($p < .05$)

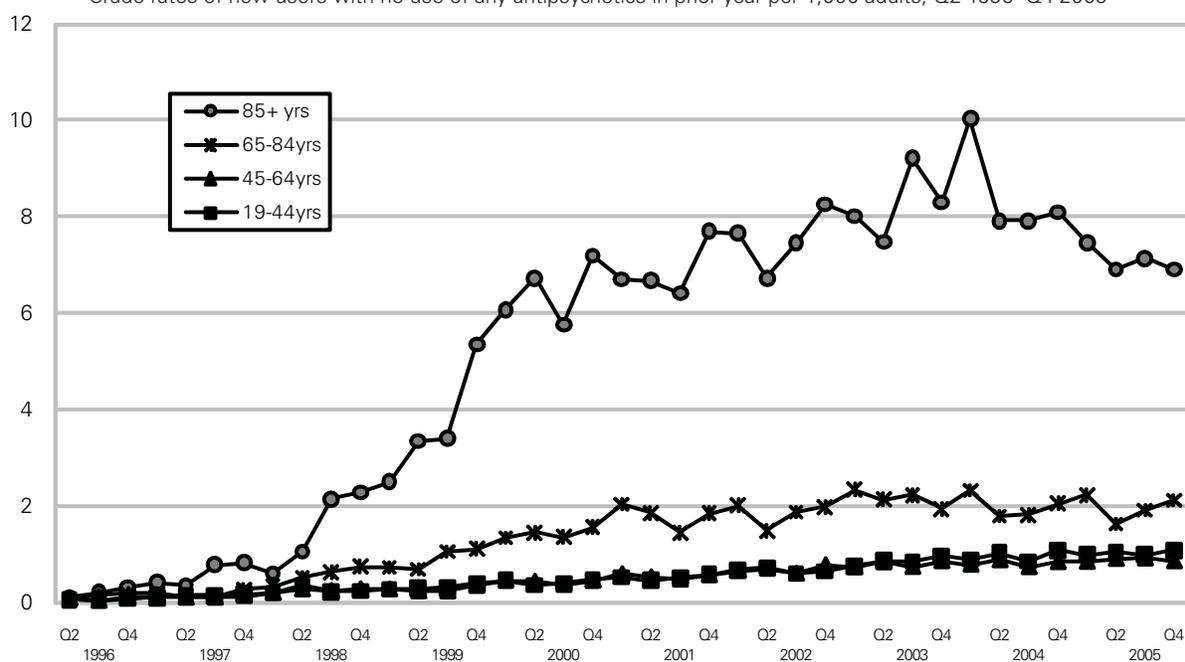
† Indicates a significant change in the slope after the intervention ($p < .05$)

Source: Manitoba Centre for Health Policy, 2009

Total incident atypical antipsychotic use in the entire population of Manitoba increased by age, with the greatest number of new users per population in the over 85 age group.

Figure 4.8: Antipsychotics (Atypicals) Quarterly Incidence by Age

Crude rates of new users with no use of any antipsychotics in prior year per 1,000 adults, Q2 1996–Q4 2005



'Q2' indicates incidence for the 2nd quarter (April to June)

'Q4' indicates incidence for the 4th quarter (October to December)

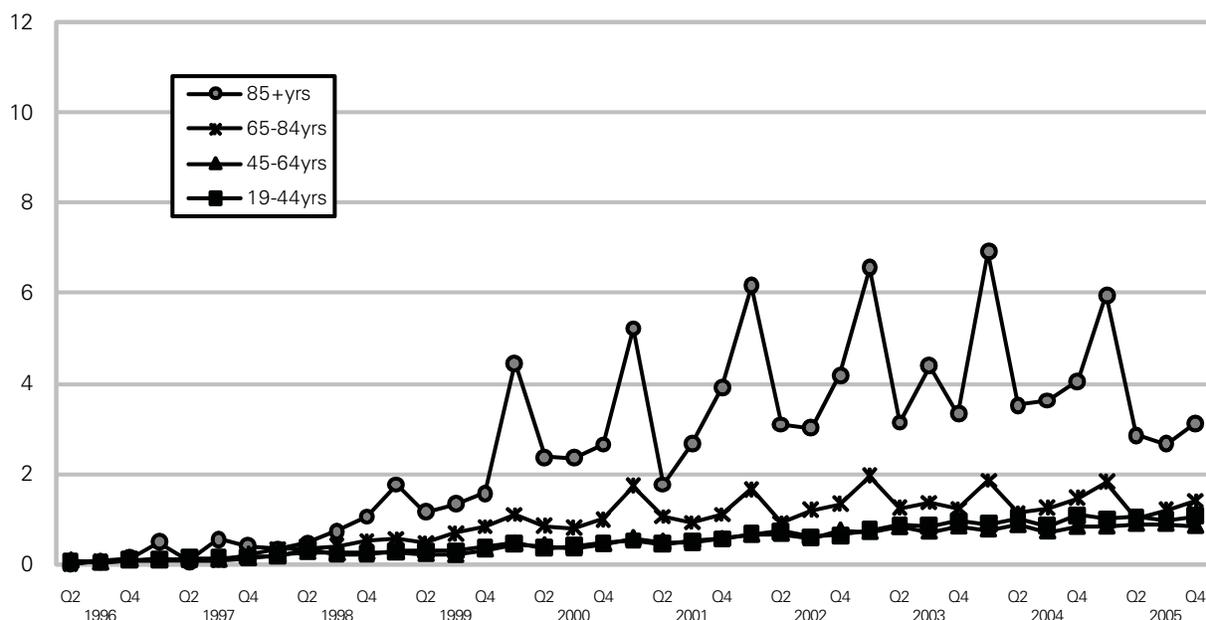
'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Similar to prevalent use of atypical antipsychotics, incident use was highest among the oldest age group, even when personal care home residents were excluded from the analysis.

Figure 4.9: Antipsychotics (Atypicals) Quarterly Incidence by Age Excluding Personal Care Home Residents

Crude rates of new users with no use of any antipsychotics in prior year per 1,000 adults, Q2 1996–Q4 2005



'Q2' indicates incidence for the 2nd quarter (April to June)
 'Q4' indicates incidence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

4.3 Discussion

There was a dramatic increase in prevalent and incident utilization of atypical antipsychotics (particularly risperidone and olanzapine) in Manitoba over the 10-year study period, with a concurrent decline in utilization of older antipsychotics. Numerous studies have described these patterns in utilization of antipsychotic medications (Mamdani, Rapoport, Shulman, Herrmann, & Rochon, 2005; Alessi-Severini et al., 2008; Aparasu, Bhatara, & Gupta, 2005; Caceres, Penas-Lledo, de la, & Llerena, 2008; Jano, Chen, Johnson, & Aparasu, 2007; Aparasu & Bhatara, 2006; Wang et al., 2005) and the subsequent increase in expenditures associated with their use (Banthin & Miller, 2006; Alessi-Severini et al., 2008; Jano et al., 2007; Aparasu & Bhatara, 2006; Rapoport et al., 2005; Mamdani et al., 2005; Mirandola et al., 2006; Morgan et al., 2008). Further, this study has replicated the observation of increased utilization of antipsychotic medications in the elderly (Alessi-Severini et al., 2008; Domino & Swartz, 2008; Percudani, Barbui, Fortino, & Petrovich, 2005; Dewa et al., 2002; Trifiro et al., 2005; Daumit et al., 2003).

After the publication of the Health Canada warnings, we observed that new prescribing of atypical antipsychotics among elderly individuals was constant; however, the rate of increase for new users of atypical antipsychotics was less steep after the warnings than before ($p < 0.05$). The impact of these

warnings has also been observed in elderly patients with dementia in Ontario (Valiyeva, Herrmann, Rochon, Gill, & Anderson, 2008). It has since been determined that antipsychotics are associated with adverse effects such as sudden cardiac death in elderly patients (Wang et al., 2005), leading to a recommendation that patients using these medications must be closely monitored (Gill et al., 2007; Schneider, Dagerman, & Insel, 2005). Further to the Health Canada warnings in 2002 and 2004, another warning has been issued, advising against the use of atypical antipsychotic medications to treat behavioural disorders in elderly persons due to an increased risk of mortality (Health Canada, 2002c; Health Canada, 2004b; Health Canada, 2004c). The ongoing utilization of these antipsychotics in elderly individuals, particularly those residing in personal care homes, is a subject of further study.

CHAPTER 5: ANTIHYPERTENSIVES

Antihypertensives are a large and diverse group of medications, commonly prescribed to reduce blood pressure, but also to manage many other cardiac and medical conditions. All antihypertensives on the Manitoba Pharmacare formulary are listed as open Part 1 benefits.

We evaluated the utilization of antihypertensives in the population of Manitoba over time. In addition, we determined the rate of new prescribing for antihypertensive medications in uncomplicated hypertension and how the utilization of antihypertensives for uncomplicated hypertension has changed.

5.1 Methods

Prevalent and incident users of antihypertensive medications in the Manitoba population were identified for the following classes of medications: angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers, beta blockers, thiazide diuretics, and alpha blockers. For a list of the medications included in the categories, please refer to Appendix Table 1.

Incident users were users of any antihypertensive medication who had not received antihypertensive medications in the one year prior to their first antihypertensive prescription. The incident and prevalent utilization of antihypertensives, adjusted for age, region, and prescription cost-sharing, was conducted over time using GEE modeling.

Manitobans with uncomplicated hypertension were defined as individuals with at least one physician visit (excluding tests) or hospitalization for essential hypertension (ICD9 code 401) in a two-year time period. In addition, persons with uncomplicated hypertension could not have hospital or physician billing records for the following medical conditions: diabetes, peripheral vascular disease, cerebrovascular disease, **ischemic heart disease**, atherosclerosis, arrhythmias or cardiomyopathy, hyperlipidemia, congestive heart failure, or **renal failure** in the three years before date of the incident antihypertensive prescription (Metge et al., 2003). More details about ICD codes used to create these diagnosis claims can be found in Appendix 3.

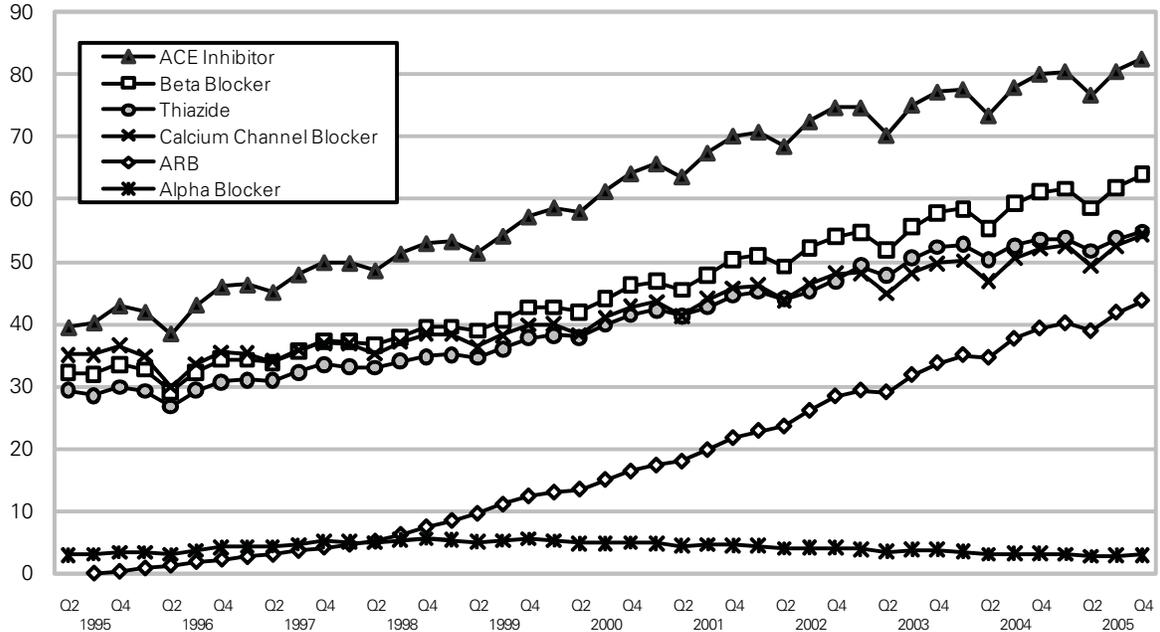
5.2 Results

Prevalence

Overall, prevalent utilization of antihypertensive medications rose over time. Utilization was greatest for ACE inhibitors, followed by beta blockers, calcium channel blockers, and thiazide diuretics. The only class of antihypertensives that did not show an increase in utilization over the 10 year period was alpha blockers. Total prevalent ACE inhibitor utilization in the population increased from 39.4 users per 1,000 residents to 82.6 users per 1,000 residents. Total ARB utilization increased the most over the study period at 9% per quarter, from 0.3 to 43.7 per 1,000 (Table 5.1).

Figure 5.1: Antihypertensives Quarterly Prevalence

Crude user rates per 1,000 adults, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)

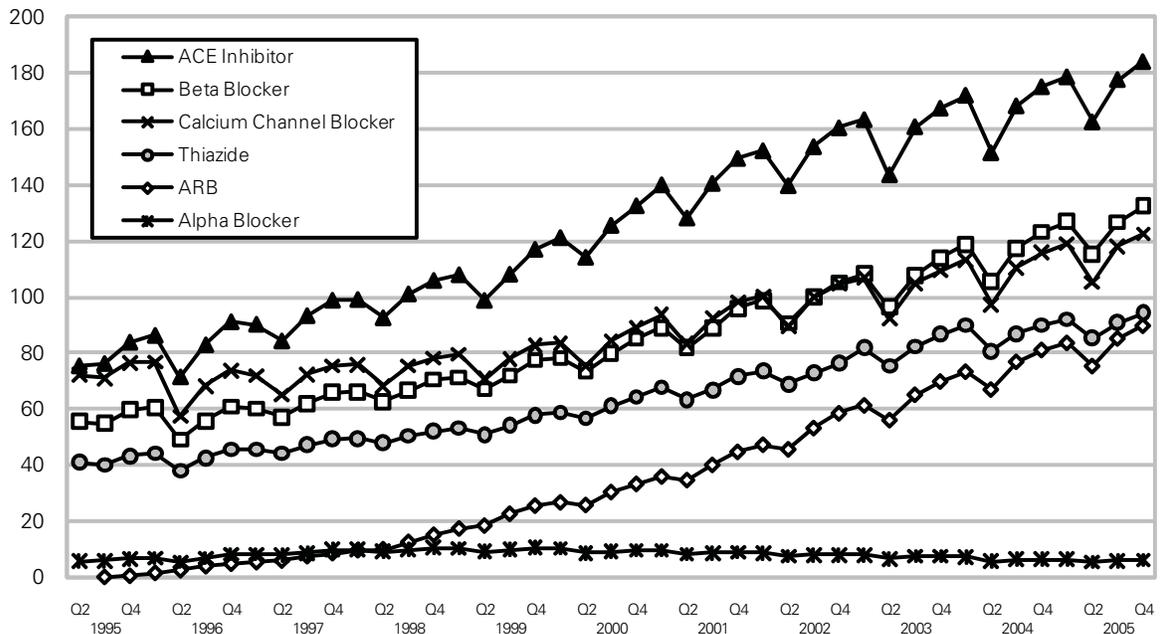
'Q4' indicates prevalence for the 4th quarter (October to December)

'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Figure 5.2: Antihypertensives Quarterly Prevalence

Crude prescription rates per 1,000 adults, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)

'Q4' indicates prevalence for the 4th quarter (October to December)

'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Table 5.1: Prevalent Use (Users/1,000 Adults) of Antihypertensives, 1995-2005

Medication	Baseline users/1,000 §	End 2005 users/1,000	Change in rate*	Age effect* Age 45-64 vs 85+	Prescription cost sharing* No cost vs high income	Region effect* Rural vs Urban
Thiazides	29.43	54.81	1.02 + 2% **	0.48 - 52% †	0.94 - 6%	1.18 + 18%
Beta blockers	32.18	64.00	1.02 + 2% **	0.57 - 43% †	1.07 + 7%	0.94 - 6%
ACE Inhibitors	39.44	82.58	1.02 + 2% **	0.32 - 68% †	1.49 + 49% †	1.20 + 20%
Angiotensin II receptor blockers	0.29	43.69	1.09 + 9% **	0.82 - 18%	0.66 - 34% †	0.97 - 3%
Calcium channel blockers	35.12	54.29	1.01 + 1% **	0.36 - 64% †	1.26 + 26%	0.98 - 2%
Alpha blockers	2.98	2.93	0.99 - 1% **	0.33 - 67% †	1.05 + 5%	1.04 + 4%

* Results are presented as relative rates (adjusted for age, prescription cost sharing, region and time) and then, for ease of interpretation, as percentages

** Indicates a slope significantly different from zero (p<.05)

† Indicates a statistically significant effect (p<.05)

§ Baseline rates are users per 1,000 adults at the second quarter of 1995 or when prescriptions were first filled for a drug

Source: Manitoba Centre for Health Policy, 2009

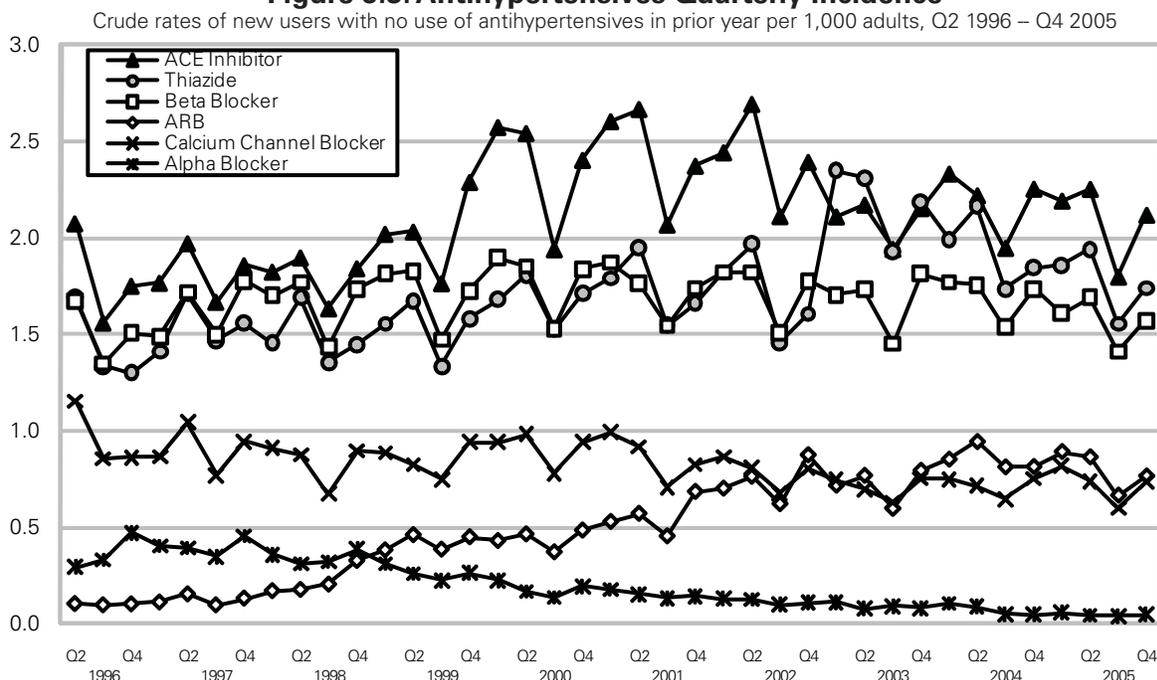
Antihypertensive medications were used the most often by persons older than 65 years. For most medication categories, utilization was greatest in the oldest age group, except for the ARBs, when adjusted for other sociodemographic variables (Table 5.1). Prevalence for antihypertensive medications by age group is available in Appendix 2, Figures A.5.1 to A.5.5.

When evaluated by prescription cost sharing, only ARB utilization was significantly lower in the no-cost prescription group. Finally, there were no statistically significant differences in antihypertensive utilization between rural and urban areas (Table 5.1).

Incidence

Similar to prevalent use, new prescribing was greatest for ACE inhibitors, followed by thiazides and beta blockers. Incident utilization of ACE inhibitors increased from 2.1 to 2.7 users per 1,000 residents per quarter until the second quarter of 2002, at which time it began to decrease to 2.1 users per 1,000 residents per quarter in 2005. New use of thiazide diuretics was approximately 1.5 users per 1,000 residents per quarter until the end of 2002. It peaked at 2.4 users in the beginning of 2003, then declined to 1.7 users per 1,000 residents per quarter by 2005. The age patterns for new prescribing of antihypertensives were similar to those observed for prevalent utilization.

Figure 5.3: Antihypertensives Quarterly Incidence



'Q2' indicates incidence for the 2nd quarter (April to June)

'Q4' indicates incidence for the 4th quarter (October to December)

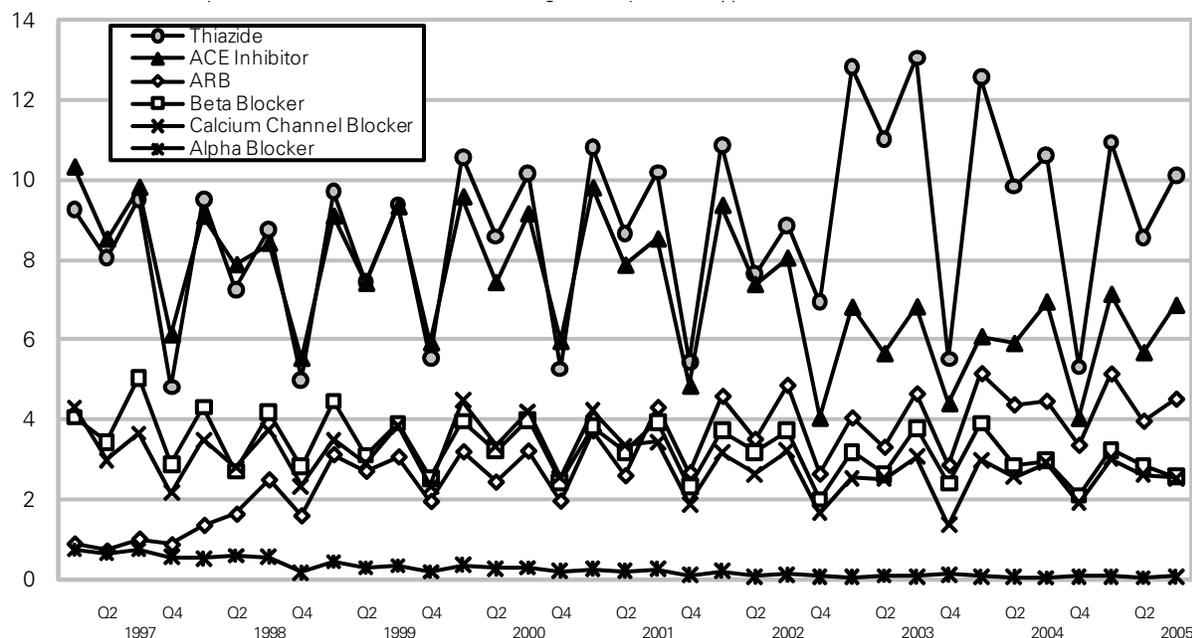
'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

For Manitobans with uncomplicated hypertension, therapy was initiated most often with thiazide diuretics over the study period (from 9.3 to 10.1 users per 1,000 residents per quarter), followed by ACE inhibitors. The new prescription of ACE inhibitors fell from 10.3 to 6.9 users per 1,000 residents per quarter over the study period, particularly after late 2002.

Figure 5.4: Antihypertensives Quarterly Incidence with Uncomplicated Hypertension

Crude rates of new users with no use of antihypertensives in prior year
per 1,000 adults classified as having uncomplicated hypertension, Q2 1997–Q4 2005



'Q2' indicates incidence for the 2nd quarter (April to June)
'Q4' indicates incidence for the 4th quarter (October to December)
'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

5.3 Discussion

We observed a large increase in the prevalent and incident use of antihypertensive medications by Manitobans over the study period. Similar increases in the utilization of antihypertensives have been described in several studies (Xie, Petitti, & Chen, 2005; Weiss, Buckley, & Clifford, 2006; Banthin & Miller, 2006; Nelson & Knapp, 2000; Campbell et al., 2003; Hemmelgarn et al., 2008; Morgan et al., 2008), as have the patterns of predominant treatment with ACE inhibitors and the increasing use of both ACE inhibitors and ARBs (Blak et al., 2008; Hemmelgarn et al., 2008). Other Canadian studies have also observed increased utilization antihypertensives in older age groups (Neutel & Campbell, 2007; Morgan et al., 2008).

For uncomplicated hypertension, we observed incident utilization to be similar to the pattern observed in the entire population. The patterns of new prescribing of specific antihypertensives for uncomplicated hypertension are also similar to other studies (Weiss, Buckley, & Clifford, 2002; Campbell et al., 2003). In keeping with the most recent Canadian hypertension guidelines, we observed that the most frequently prescribed antihypertensives for individuals with uncomplicated hypertension were the thiazide diuretics (Khan et al., 2008). Our findings also show the possible impact of the ALLHAT trial, as evidenced by the temporal increase in incident use of thiazides after the publication of the trial results in December 2002. The impact of the ALLHAT trial on thiazide prescribing has been reported by others (Austin et al., 2004; Xie et al., 2005; Player, Gill, Fagan, & Mainous, III, 2006; Weiss et al., 2006).

CHAPTER 6: STATINS

Statins are a class of commonly prescribed medications indicated to reduce serum cholesterol and to lower the risk of cardiovascular events such as myocardial infarctions (Genest, Frohlich, Fodor, & McPherson, 2003). All statin medications in Manitoba are listed as Part 1 (open listing) on the Manitoba Pharmacare formulary.

We evaluated the utilization of statins in the population of Manitoba over time. Additionally, we determined how cardiovascular history influenced the receipt of statin medications and whether utilization of statins for the management of individuals with high cardiovascular risk had changed over the study period.

6.1 Methods

Prevalent and incident users were identified for the population of Manitoba for the following medications: atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, simvastatin, and rosuvastatin. For a list of the medications included in this category, please refer to Appendix Table 1.

Incident users were those users of any statin who had not used any prior statin in the one year prior to this first statin prescription. The incident and prevalent utilization of statins, adjusted for age, region, and prescription cost-sharing, was determined over time using GEE modeling.

High cardiovascular risk was defined by the presence of a hospital or physician billing record for any one of the following medical conditions: diabetes, peripheral vascular disease, cerebrovascular disease, ischemic heart disease, atherosclerosis, congestive heart failure, or renal failure in the three years before date of the incident statin prescription. In the absence of these conditions (defined in Appendix 3), individuals were classified as having low cardiovascular risk.

6.2 Results

Prevalence

Overall, prevalent utilization of statins rose over the study period; with each successive quarter, there was an increase of 6% in prevalent use over the previous quarter's rate (Table 6.1). Atorvastatin was the most commonly prescribed statin and its use increased the most over the 10-year period. Utilization of atorvastatin was followed by simvastatin. Total statin utilization in the population increased from 13.7 to 81.8 users per 1,000 residents over the study period, while utilization of atorvastatin increased from 0.5 when launched to 47.2 users per 1,000 residents by the end of the study. Prevalent utilization of other statins declined.

Figure 6.1: Statins Quarterly Prevalence

Crude user rates per 1,000 adults, Q2 1995–Q4 2005

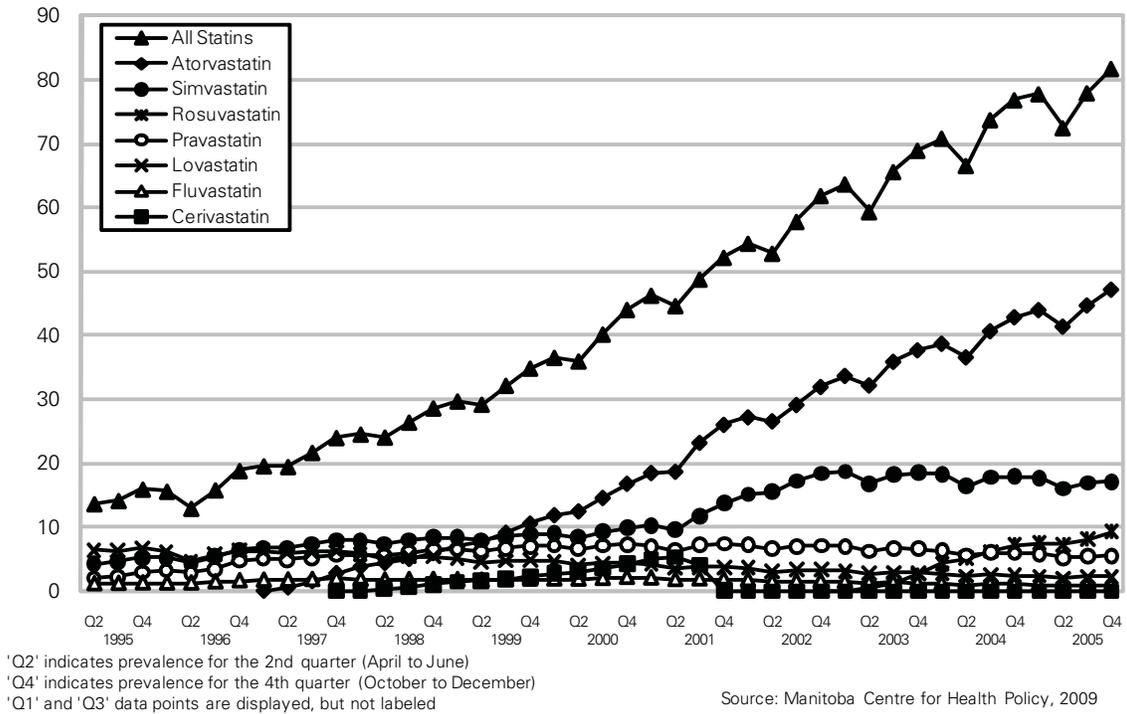


Figure 6.2: Statins Quarterly Prevalence

Crude prescription rates per 1,000 adults, Q2 1995–Q4 2005

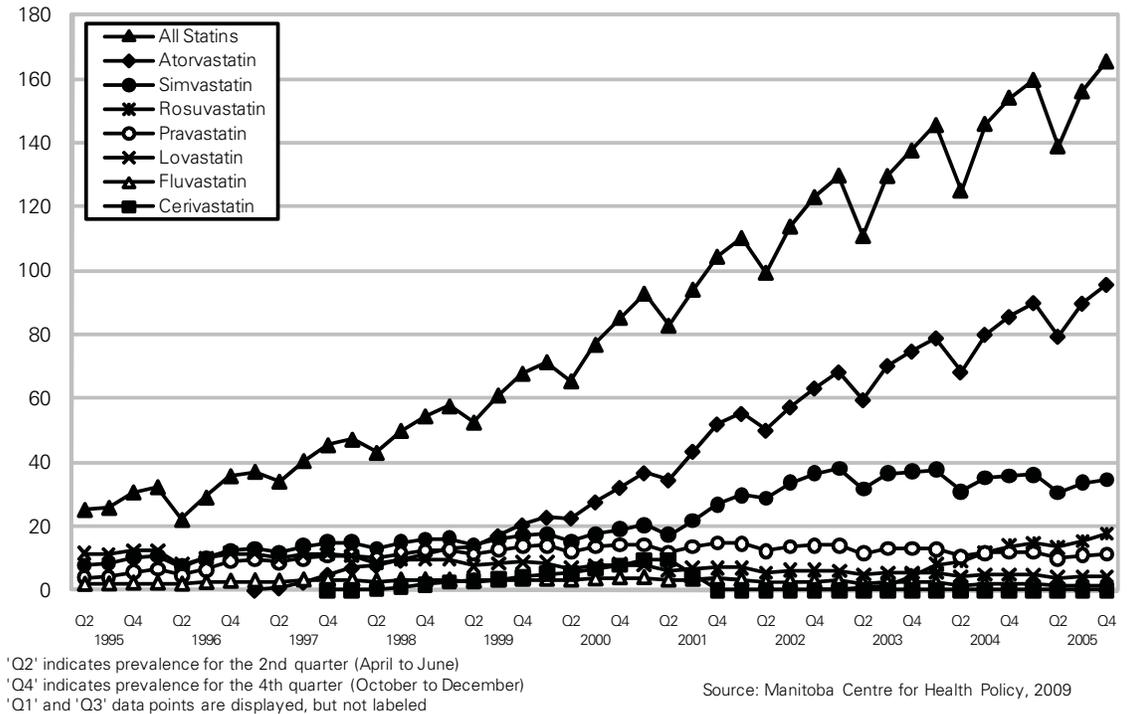


Table 6.1: Prevalent Use (Users/1,000 Adults) of Statins, 1995-2005

	Baseline users/1,000\$	End 2005 users/1,000	Change in rate*	Age effect* Age 65-84 vs 85+	Prescription cost sharing* No cost vs high income	Region effect* Rural vs Urban
Statins, all	13.65	81.78	1.06 + 6% **	2.61 2 1/2 fold increase †	1.02 + 2%	1.07 + 7%

* Results are presented as relative rates (adjusted for age, prescription cost sharing, region and time) and then, for ease of interpretation, as percentages

** Indicates a slope significantly different from zero (p<.05)

† Indicates a statistically significant effect (p<.05)

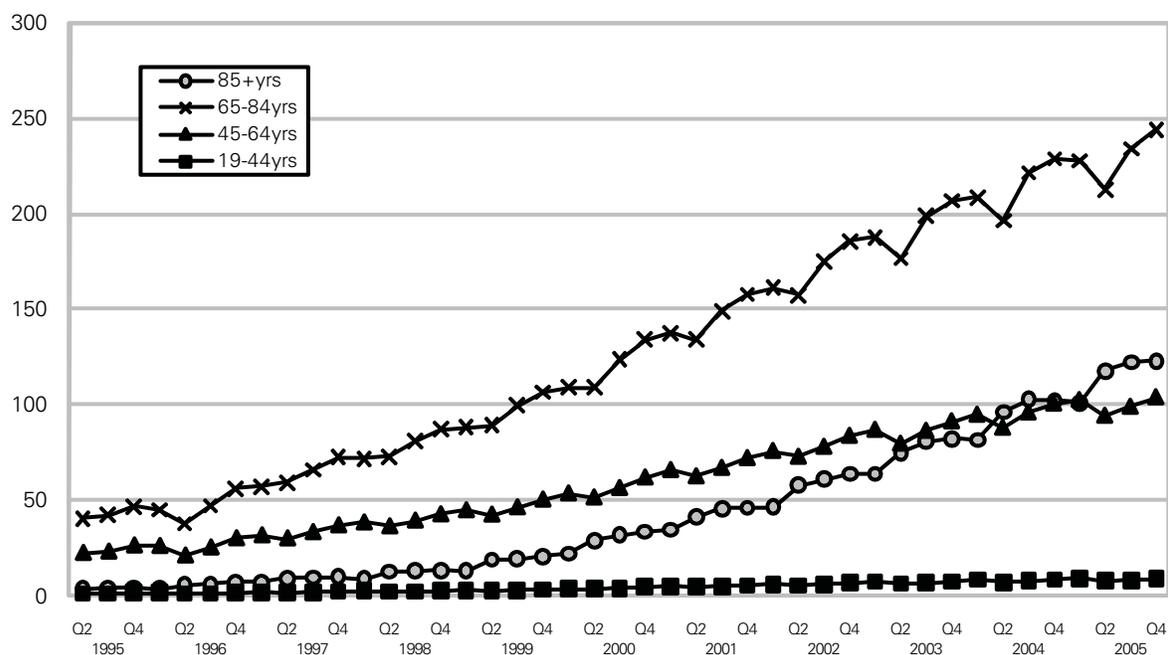
§ Baseline rates are users per 1,000 adults at the second quarter of 1995 or when prescriptions were first filled for a drug

Source: Manitoba Centre for Health Policy, 2009

When evaluated by age, statin utilization was highest in those aged 65–84 (40.7 to 244.0 users per 1,000 residents over the study period), then age 45–64 (22.4 to 104.1 users per 1,000 residents), followed by the 85 and older (3.9 to 123.1 users per 1,000 residents). This age pattern was independent of sociodemographic characteristics and prescribing trend over time (Table 6.1).

Figure 6.3: Statins Quarterly Prevalence by Age

Crude user rates per 1,000 adults, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)

'Q4' indicates prevalence for the 4th quarter (October to December)

'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

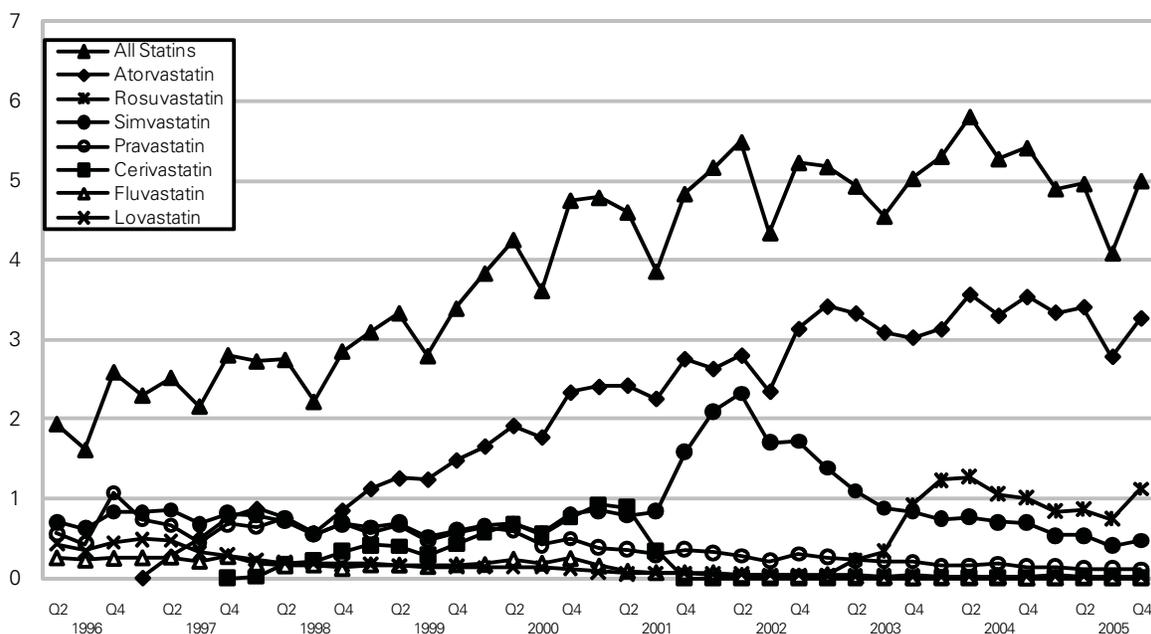
No statistically significant differences in statin utilization were found by prescription cost sharing, following adjustment for age, region, and time period (Table 6.1). Finally, when prevalent statin utilization was evaluated by region of residence, there was no statistically significant difference between rural and urban statin utilization independent of other factors (Table 6.1).

Incidence

Similar to prevalent use, new prescribing was greatest for atorvastatin. Overall, incident utilization of all statins increased from 1.9 to 5.0 users per 1,000 residents per quarter. The incident utilization of atorvastatin increased from 0.3 to 3.3 users per 1,000 residents per quarter by the end of the study period.

Figure 6.4: Statins Quarterly Incidence

Crude rates of new users with no use of statins in prior year per 1,000 adults, Q2 1996–Q4 2005



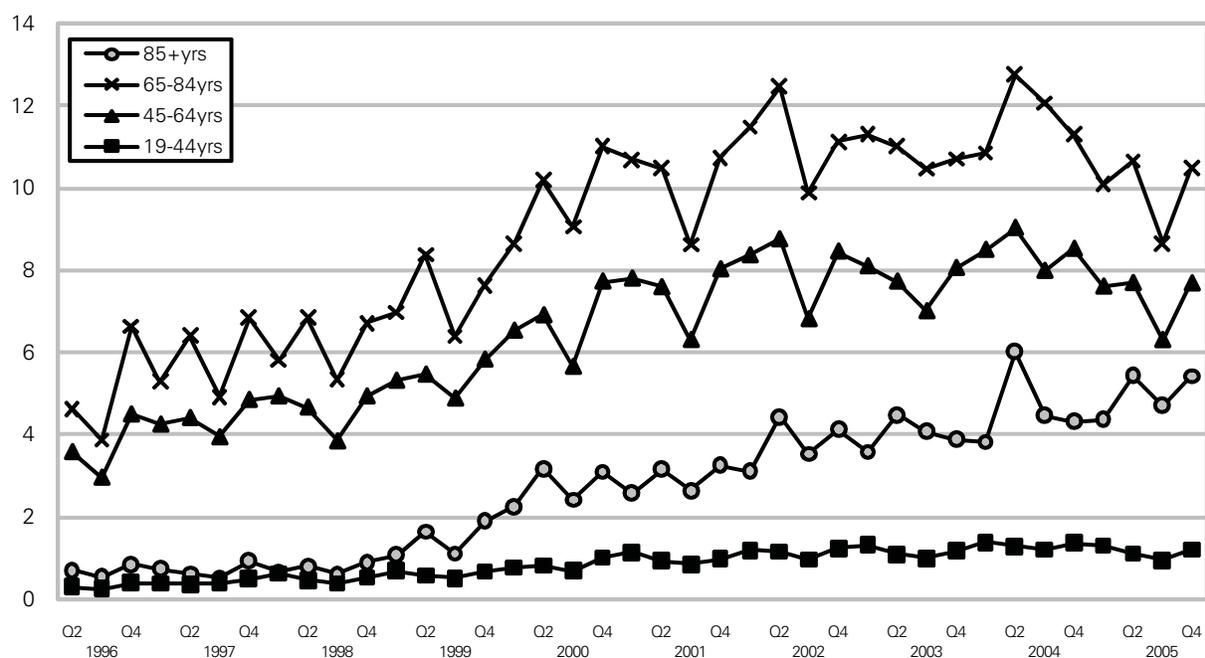
'Q2' indicates incidence for the 2nd quarter (April to June)
 'Q4' indicates incidence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Age patterns of incident statin use were similar to those observed with prevalent utilization.

Figure 6.5: Statins Quarterly Incidence by Age

Crude rates of new users with no use of statins in prior year per 1,000 adults, Q2 1996–Q4 2005



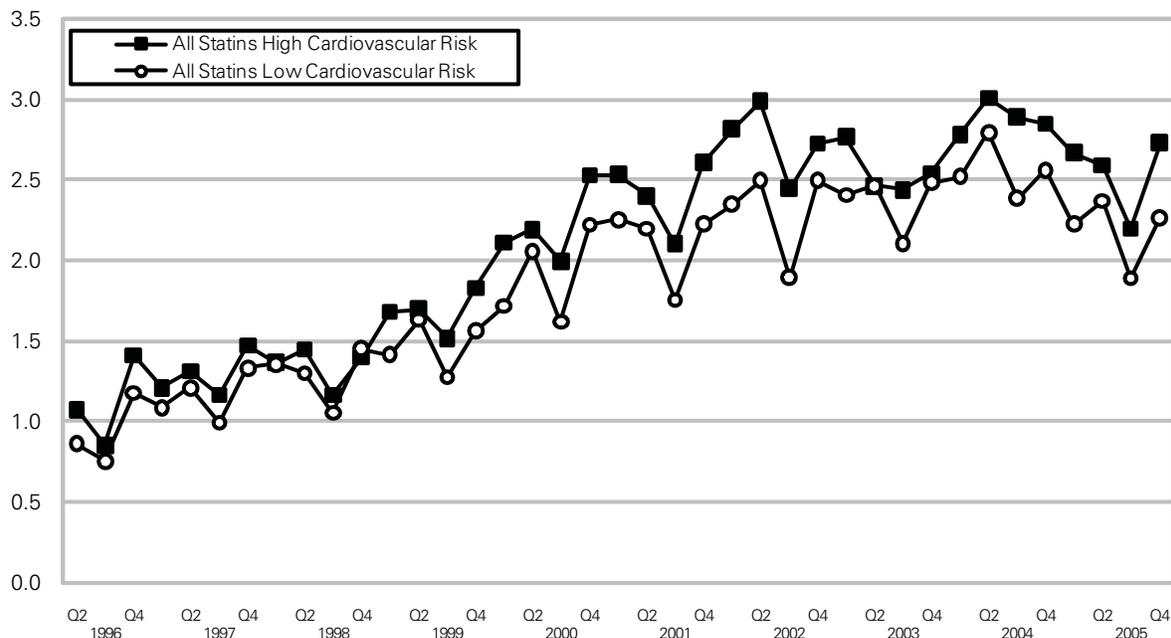
'Q2' indicates incidence for the 2nd quarter (April to June)
 'Q4' indicates incidence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

When statin utilization was evaluated according to cardiovascular history, 53% of persons receiving their first statin prescription were at high cardiovascular risk over the entire study period. Incident utilization for individuals with high cardiovascular risk increased from 1.0 to 2.7 users per 1,000 residents per quarter by the end of the study period. Statin utilization in low cardiovascular risk individuals increased from 0.9 to 2.3 users per 1,000 residents per quarter. Independent of sociodemographic characteristics, new prescribing for statins for high cardiovascular risk increased at a quarterly rate of 3.4% over the previous quarter's rate. This increase was marginally greater than the increase in incident use in persons with low cardiovascular risk (3.0% increase per quarter over the previous quarter's rate).

Figure 6.6: Statins Quarterly Incidence by Cardiovascular Risk

Crude rates of new users with no use of statins in prior year per 1,000 adults, Q2 1996–Q4 2005



'Q2' indicates incidence for the 2nd quarter (April to June)
 'Q4' indicates incidence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

6.3 Discussion

Overall, we observed a large increase in prevalent and incident statin utilization in Manitoba over the 10 year study period. By 2005, 8.1% of the total adult population, including 24% of those aged 65–84 and 12.3% of those aged 85 and older were prevalent statin users. Similar increases in utilization of statins have been reported in British Columbia, Ontario and Canada (Raymond, Morgan, Katz, & Kozyrskyj, 2007; Paterson et al., 2007; Levy et al., 2003; Jackevicius, Tu, Filate, Brien, & Tu, 2003; Morgan et al., 2008). We observed that although the incident utilization did not increase as dramatically, the prevalent utilization of statins did increase dramatically, suggesting that many statin users continued on therapy despite the advice that persistence with statins is less than optimal (Blackburn et al., 2005; Choudhry, Setoguchi, Levin, Winkelmayr, & Shrank, 2008).

Our observed increase in prescriptions for simvastatin and atorvastatin, but decline in the utilization of other statins is consistent with other Canadian studies (Mamdani & Tu, 2001; Levy et al., 2003; Cooke, Nissen, Sketris, & Tett, 2005). The timing of the decline in incident simvastatin utilization coincided with the introduction of generic simvastatin (and corresponding reduction in marketing), as well as the increase in market share of rosuvastatin (Schuster, 2003).

Greater utilization of statins in older age groups has been observed in other Canadian studies (Raymond et al., 2007; Levy et al., 2003; Savoie & Kazanjian, 2002; Metge et al., 2003; Morgan et al., 2008); however, an evaluation of statin utilization by socioeconomic status in other Canadian studies has produced conflicting results (Raymond et al., 2007; Ko, Mamdani, & Alter, 2004; Pilote

et al., 2004). The variable nature of Canadian drug formularies (as well as study design, measures of socioeconomic status, and prescription cost sharing) makes it difficult to determine whether a true socioeconomic gradient in statin utilization exists. We did not observe greater utilization of statins in those with no-cost prescriptions, although it would be anticipated that this variable would influence statin utilization based on an increased cardiac risk for those with lower socioeconomic status (Alter et al., 2006).

A slight majority (53%) of persons newly prescribed statin medications were at high cardiovascular risk (including those with ischemic heart disease, **diabetes mellitus**, peripheral vascular disease, cerebrovascular disease, or atherosclerosis), a finding very close to a similar study in British Columbia. In that study, 60% of statin users from 1999 to 2004 were at high cardiovascular risk (Raymond et al., 2007). Neither study of high cardiovascular risk were exhaustive because both used administrative data, and therefore, did not have access to important cardiac risk factors not recorded in health care administrative data, such as **body mass index**, smoking status, or family history. It is possible that a proportion of individuals with low cardiovascular risk (as defined by the absence of the medical conditions listed in Appendix 3) did in fact have high cardiovascular risk and were, therefore, appropriately taking a statin (Genest et al., 2003). Despite this possible misclassification, we identified a considerable proportion of statin utilization in the absence of high cardiovascular risk, which represents treatment that may not have been based on current best evidence for **morbidity** and mortality benefits from statins.

CHAPTER 7: MEDICATIONS FOR DIABETES MELLITUS

Medications for the management of diabetes include both injectable insulin and oral hypoglycemic agents, including metformin, sulfonylureas, and the newer agents—thiazonedindiones (hereafter called ‘glitazones’), meglitinides, and acarbose. In Manitoba, the newer oral agents (glitazones, meglitines, and acarbose) were placed on the Part 3 (prior approval) formulary listing when they were first approved for utilization in Manitoba; however, in general, these newer oral agents have since been transitioned to Part 1, whereas the majority of other agents for treatment of diabetes were consistently in the Part 1 (open listing) formulary listing.

We evaluated how the utilization of newer and older medications for diabetes changed over time. We also identified the proportion of patients who were using the various therapies—monotherapy, dual therapy, triple therapy, or insulin combinations—and how this pattern of utilization has changed over the study period.

7.1 Methods

Prevalent and incident users were identified for the population of Manitoba for the following medication groups: insulins, sulfonylureas, glitazones, metformin, meglitinides, and acarbose. For a list of the medications included in the categories, please refer to Appendix Table 1.

Incident users were those users of a medication for diabetes who had not used any medications for diabetes in the one year prior to this first prescription. Incident and prevalent utilization, adjusted for age, region, and prescription cost-sharing, was determined over time using GEE modeling. Prevalent users were determined to be using agents, such as monotherapy, dual therapy, triple therapy, or insulin/oral combination, to treat diabetes within a quarter (Table 7.1).

Table 7.1: Therapy Types for Medical Treatment of Diabetes Mellitus

Therapy Type	Description	
Monotherapy	Filled any one of the following within a quarter:	1 oral agent
		2+ oral agents within the same medication group
Dual Therapy	Filled any one of the following within a quarter:	2 oral agents
		1 combination product
		2+ oral agents within the same medication group, plus 1 other oral agent
Triple Therapy	Filled any one of the following within a quarter:	3 oral agents
		combination product, plus 1 other oral agent
		2+ oral agents within the same medication group, plus 2 other oral agents
Insulin Monotherapy	Filled any one of the following within a quarter:	1+ insulin products
Insulin and Oral Combination	Filled any one of the following within a quarter:	1+ insulin products, plus any combination of oral agents

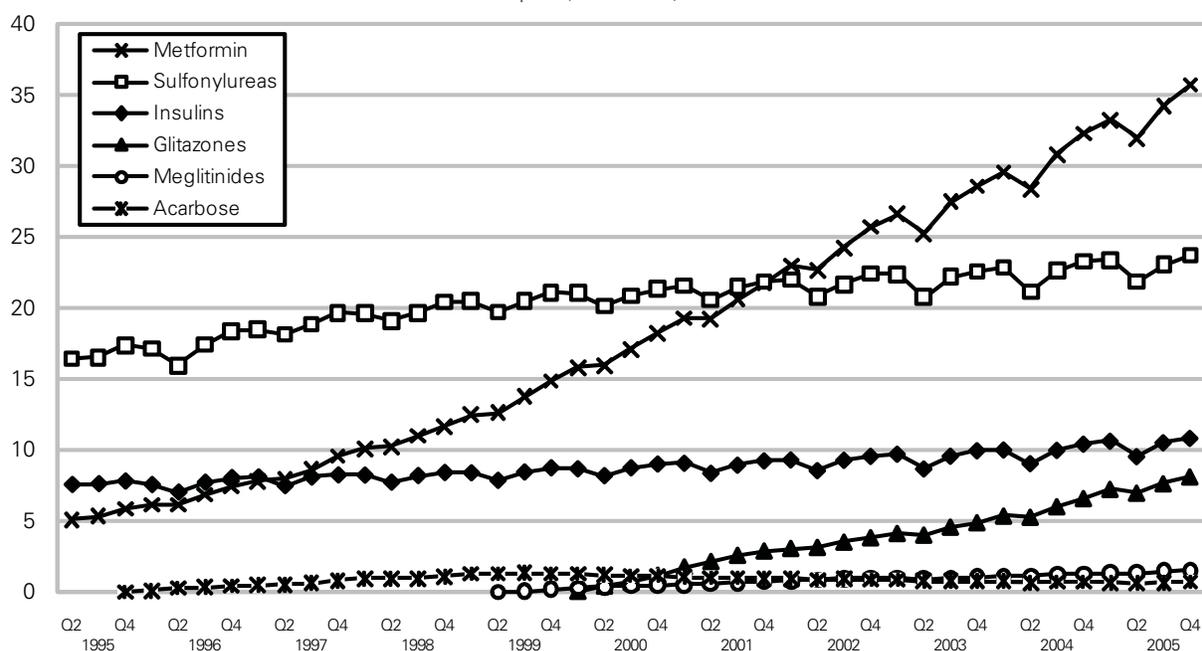
7.2 Results

Prevalence

The most utilized medication by the end of the study period was metformin. At the beginning of the study period, metformin utilization was low (5.1 users per 1,000 residents), however, with each successive quarter, there was an increase of 5% over the previous quarter's rate, such that metformin became the most commonly utilized medication for diabetes by the end of the study period (35.7 users per 1,000 residents). Metformin utilization was followed by sulfonylureas (increase from 16.5 to 23.7 users per 1,000 residents throughout the study period) and insulins (7.6 to 10.9 users per 1,000 residents). Despite initial Part 3 listing, the utilization of glitazones increased from 0.4 users per 1,000 residents in mid 2000, when marketed, to 8.1 users per 1,000 residents by the end of the study period. With the exception of meglitinides, all other antidiabetic medications increased at a rate of only 1% increase over the previous quarter's rate (Table 7.2). Utilization of other medications was very minimal.

Figure 7.1: Medications for Diabetes Mellitus Quarterly Prevalence

Crude user rates per 1,000 adults, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)

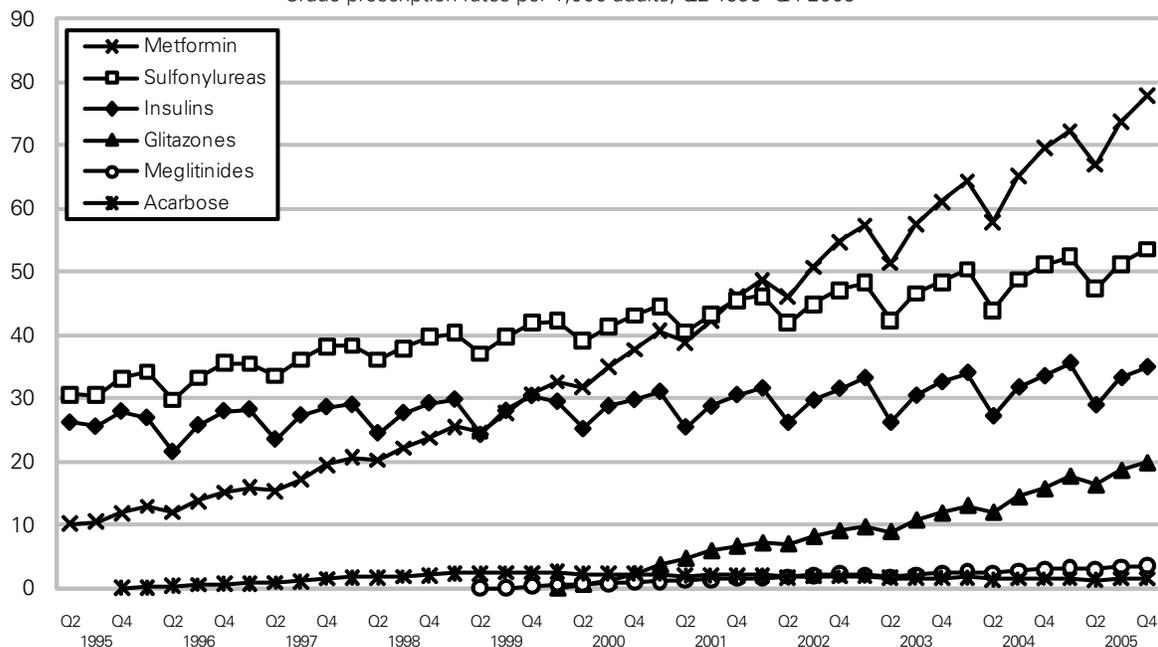
'Q4' indicates prevalence for the 4th quarter (October to December)

'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Figure 7.2: Medications for Diabetes Mellitus Quarterly Prevalence

Crude prescription rates per 1,000 adults, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Table 7.2: Prevalent Use (Users/1,000 Adults) of Medications for Diabetes Mellitus, 1995-2005

	Baseline users/1,000§	End 2005 users/1,000	Change in rate*	Age effect* Age 65-84 vs 85+	Prescription cost sharing*		Region effect* Rural vs urban
					No cost vs high income		
Insulins	7.56	10.85	1.01 +1% **	2.23 2 fold higher †	2.66 2 1/2 fold higher †	0.96 - 4% lower	
Sulfonylureas	16.45	23.70	1.01 + 1% **	1.58 + 58% higher	2.32 2 fold higher	0.74 - 26% lower	
Metformin	5.10	35.72	1.05 + 5% **	2.31 2 fold higher †	1.02 + 2% higher	1.27 + 27%	
Glitazones	0.37	8.12	1.11 + 11% **	4.24 4 fold higher †	3.05 3 fold higher †	1.23 + 23%	
Meglitinides	0.03	1.50	1.08 + 8% **	1.43 1 1/2 fold higher †	3.20 3 fold higher †	1.19 + 19% †	
Acarbose	0.09	0.67	1.01 + 1% **	2.00 2 fold higher †	3.47 3 1/2 fold higher †	1.03 + 3%	

* Results are presented as relative rates (adjusted for age, prescription cost sharing, region and time) and then, for ease of interpretation, as percentages

** Indicates a slope significantly different from zero (p<.05)

† Indicates a statistically significant effect (p<.05)

§ Baseline rates are users per 1,000 adults at the second quarter of 1995 or when prescriptions were first filled for a drug

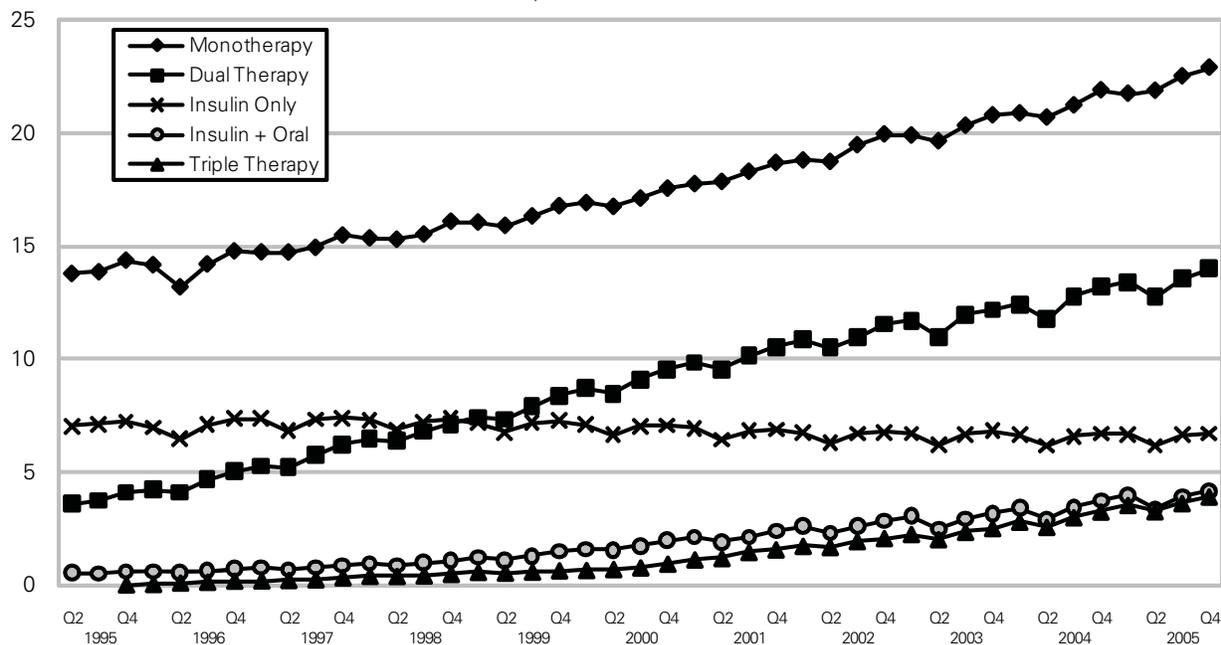
|| Regional analysis for the insulin model compares Point Douglas to Fort Garry

Source: Manitoba Centre for Health Policy, 2009

Overall, there was a steady increase in monotherapy (13.8 to 22.9 users per 1,000 residents) and dual therapy (3.6 to 14.0 users per 1,000 residents) through the entire study period, while the number of users taking insulin only remained consistent. Towards the end of 1999, utilization of combined therapy (insulin in addition to an oral agent), as well as utilization of triple oral therapy, had increased.

Figure 7.3: Medications for Diabetes Mellitus Quarterly Prevalence by Therapy Type

Crude user rates per 1,000 adults, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)

'Q4' indicates prevalence for the 4th quarter (October to December)

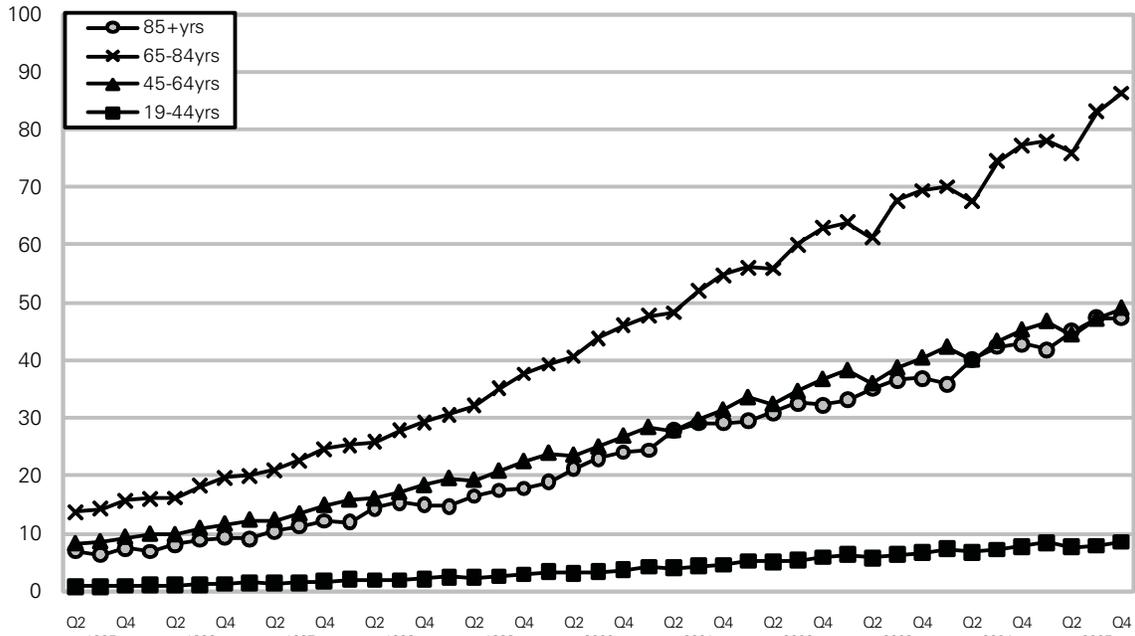
'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

When evaluated by age, there was a different pattern for each group of medications. For all medication categories and classes except sulphonylureas, greatest utilization was in the 65–84 age groups, which was significant when adjusted for other demographic characteristics (Table 7.2). Crude user rates by age for metformin and glitazones are illustrated below; user rates for insulins, sulphonylureas, meglitinides, and acarbose are available in Appendix 2, Figures A.7.1 to A.7.4.

Figure 7.4: Metformin Quarterly Prevalence by Age

Crude user rates per 1,000 adults, Q2 1995–Q4 2005

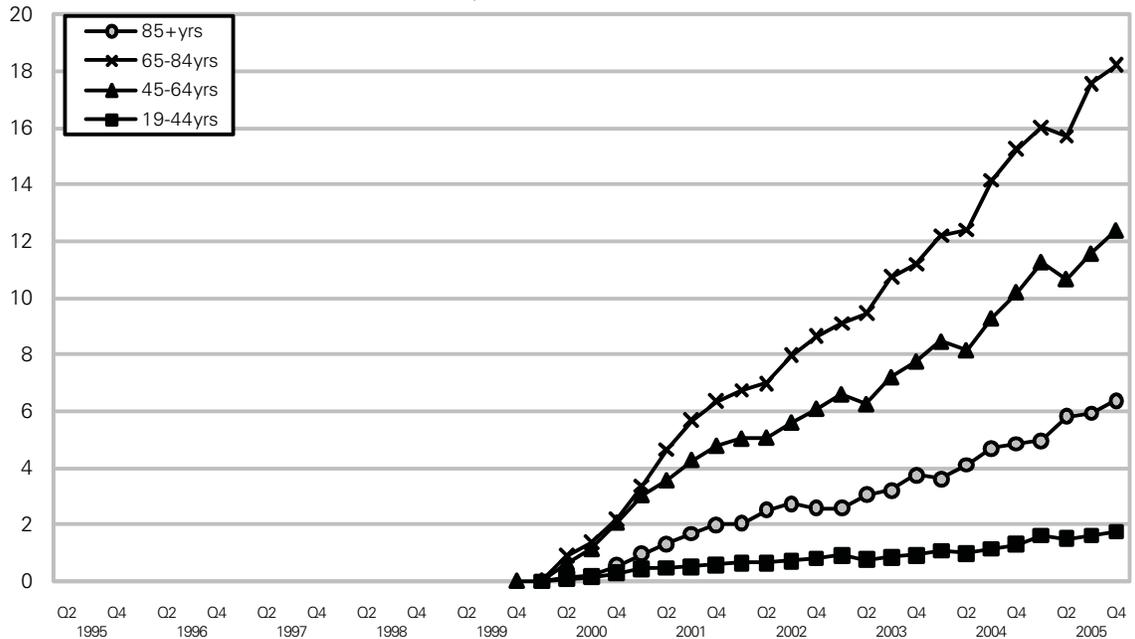


'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Figure 7.5: Glitazones Quarterly Prevalence by Age

Crude user rates per 1,000 adults, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

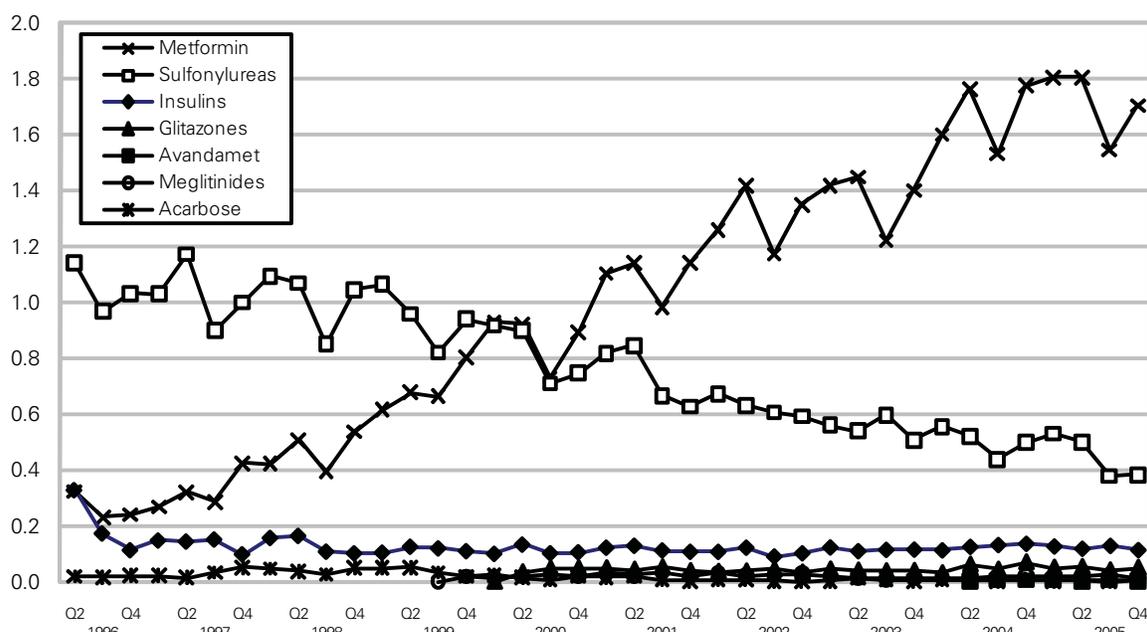
When evaluated by prescription cost sharing, we observed the greatest utilization among those with no-cost prescriptions, across all medication categories. With the exception of sulfonylureas and metformin, these differences were statistically significant when adjusted for age, region, and prescribing trend over time. Finally, when prevalent diabetes medication utilization was evaluated by region of residence, there were no statistically significant region effects when adjusted for other factors, except for meglitinides (Table 7.2).

Incidence

Similar to prevalent utilization, the greatest incident utilization of medications for diabetes was for metformin. Incident utilization of metformin increased from 0.3 to 1.7 users per 1,000 residents per quarter. This increase in first prescriptions for metformin was mirrored by a decrease in incident sulfonylureas with time (from 1.1 to 0.4 users per 1,000 residents per quarter).

Figure 7.6: Medications for Diabetes Mellitus Quarterly Incidence

Crude rates of new users with no use of diabetes medications in prior year per 1,000 adults, Q2 1996–Q4 2005



'Q2' indicates incidence for the 2nd quarter (April to June)
'Q4' indicates incidence for the 4th quarter (October to December)
'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

For the two most common incident medication classes, metformin and sulfonylureas, there was the greatest number of new users per population in those age 65–84, followed by 45–64, then 85 up, then 19–44. Incident rates by age for insulins, metformin, sulfonylureas, glitazones, acarbose, and meglitinides are available in Appendix 2, Figures A.7.5 to A.7.10.

Over the study period, there was evidence of more aggressive treatment of diabetes. The new prescription of triple therapy showed an increase of 8% over the previous quarter's rate. This was greater than the quarterly increase in rate that was observed with dual therapy (3%) and for monotherapy (1%), when adjusted for other factors.

7.3 Discussion

We observed an increase in prevalent and incident metformin utilization, with a subsequent decline in incident utilization of sulphonylureas in Manitoba over the study period. Despite limited formulary access to newer agents, we also observed an increase in utilization of these medications, most notably the glitazones, over the study period. Several other studies have described the increase in utilization of metformin and newer agents over time (Morgan et al., 2008; Boyc, Yurgin, & Lage, 2007; Patel, Srishanmuganathan, Car, & Majeed, 2007; Wysowski, Armstrong, & Governale, 2003; Doro et al., 2005; Skaer, Sclar, & Robison, 2006; Chiang, Chiu, Chen, Wu, & Yang, 2006; Lusignan et al., 2005; Walley, Hughes, & Kendall, 2005; Stalhammar, Berne, & Svardsudd, 2001; Cohen, Neslusan, Conklin, & Song, 2003). Other studies have observed increased utilization of medications for diabetes in middle to older age groups over time (Boyc et al., 2007; Wysowski et al., 2003; Doro et al., 2005; Skaer et al., 2006; Stalhammar et al., 2001; Cohen et al., 2003).

Part 3 formulary listing likely curtailed the uptake of the newer agents, as utilization was limited to those patients with a poor response, intolerance, or **contraindication** to conventional agents. It is known that type of coverage of medications for diabetes impacts utilization (Skaer et al., 2006; Cohen et al., 2003). However, despite the restricted listing, the glitazones had the highest rate of change of all medication categories evaluated. Likely, after increased cardiac risk for rosiglitazone was publicized in 2007, utilization of this class of medications will decrease (Health Canada, 2007).

The increased utilization of metformin is appropriate due to the fact that it is first line therapy for diabetes, and since the publication of the United Kingdom Prospective Diabetes Study (UKPDS) trial in 1998, the only medication for diabetes that has been shown to reduce diabetes related complications, diabetes related deaths, and all cause mortality (UK Prospective Diabetes Study Group, 1998). The increased utilization of insulin combinations and multiple medication combinations is consistent with guidelines, which recommend combination therapy to target tighter glucose control (Canadian Diabetes Association, 2003).

CHAPTER 8: PROTON PUMP INHIBITORS

Proton pump inhibitors are a class of medications used to treat multiple gastrointestinal acid related medical conditions, including gastroesophageal reflux disease, peptic ulcer disease, and non-ulcer dyspepsia (Canadian Agency for Drugs and Technologies in Health, 2007).

For the majority of the study period, all proton pump inhibitors (PPIs) were reimbursed under Part 2 (utilization for established criteria) of the Manitoba Pharmacare formulary; these agents were transitioned to Part 3 in 2006. The listing of generic omeprazole on the Manitoba formulary, as a product interchangeable with brand name omeprazole, occurred in the third quarter of 2004.

We evaluated the overall utilization of PPIs in the Manitoba population over time with a particular interest on how short or long-term utilization of PPIs has changed. Finally, we assessed how the formulary addition of generic omeprazole influenced prescribing of brand name omeprazole.

8.1 Methods

Prevalent and incident users were identified for the population of Manitoba for the following medication: rabeprazole, lansoprazole, esomeprazole, pantoprazole, and omeprazole (brand and generic). For a list of the medications included in this category, please refer to Appendix Table 1.

Incident users were those users of a PPI who had not used any PPI in the one year prior to this prescription. Short-term users were defined as incident PPI users in whom the days supply for the PPI prescription was less than 100 days or three months (Hurenkamp, Grundmeyer, Bindels, Tytgat, & Van Der Hulst, 2002). All other incident users were defined as long-term PPI users. The incident and prevalent utilization of PPIs, adjusted for age, region, and prescription cost-sharing, was determined over time using GEE modeling.

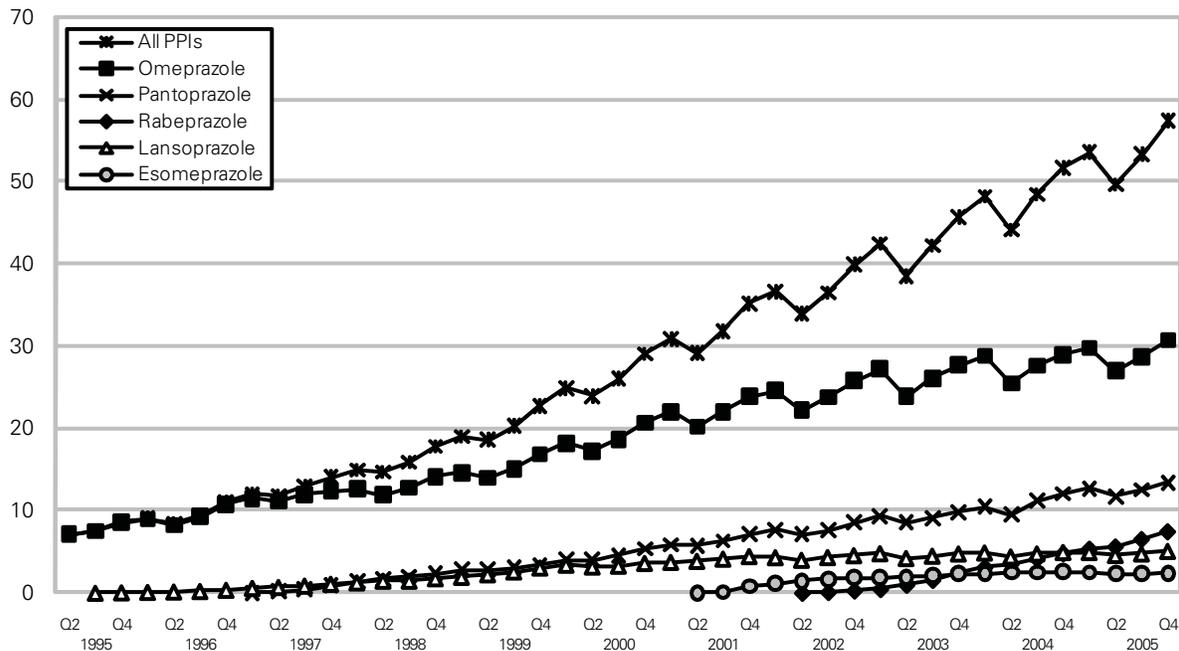
8.2 Results

Prevalence

There was a general increase in prevalent use of each PPI over time, with much greater utilization of omeprazole than other PPIs. Total PPI use in the population increased from 7.1 to 57.4 users per 1,000 residents over the study period (quarterly increase of 5% over the previous quarter's rate), while prevalent use of omeprazole increased from 7.1 to 30.8 users per 1,000 residents (Table 8.1).

Figure 8.1: Proton Pump Inhibitors Quarterly Prevalence

Crude user rates per 1,000 adults, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)

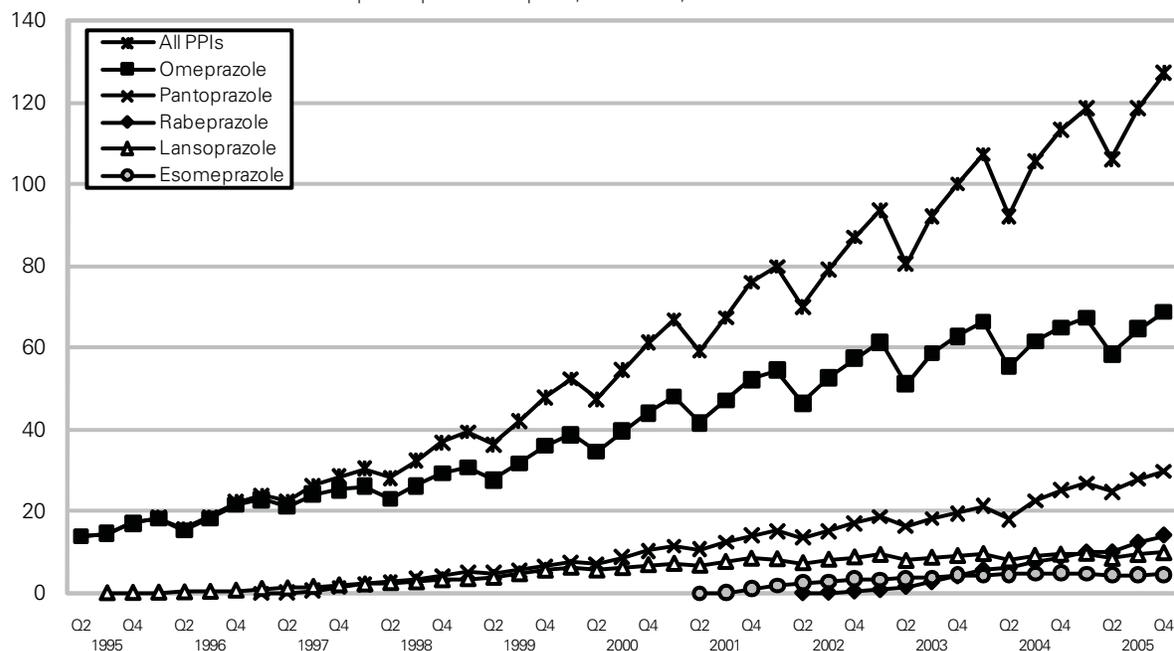
'Q4' indicates prevalence for the 4th quarter (October to December)

'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Figure 8.2: Proton Pump Inhibitors Quarterly Prevalence

Crude prescription rates per 1,000 adults, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)

'Q4' indicates prevalence for the 4th quarter (October to December)

'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Table 8.1: Prevalent Use (Users per 1,000 Adults) of Proton Pump Inhibitors, 1995-2005

	Baseline users/1,000§	End 2005 users/1,000	Change in rate*	Age effect* Age 45-64 vs 85+	Prescription cost sharing* No cost vs high income	Region effect* Rural vs urban
Proton pump inhibitors, all	7.12	57.41	1.05 + 5% **	0.44 - 54% ‡	1.53 1.5-fold higher ‡	0.92 - 8%

* Results are presented as relative rates (adjusted for age, prescription cost sharing, region and time) and then, for ease of interpretation, as percentages

** Indicates a slope significantly different from zero ($p < .05$)

‡ Indicates a statistically significant effect ($p < .05$)

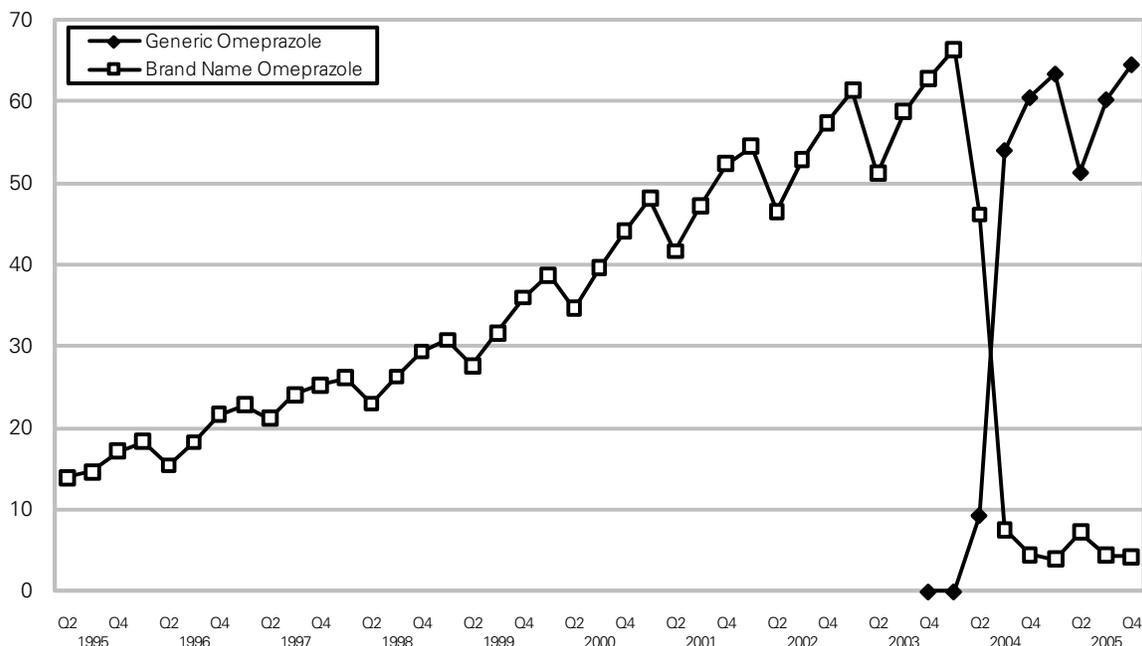
§ Baseline rates are users per 1,000 adults at the second quarter of 1995 or when prescriptions were first filled for a drug

Source: Manitoba Centre for Health Policy, 2009

Prescriptions for generic omeprazole began to be filled in early 2004; by the end of the study period, generic omeprazole accounted for 93.8% of all prevalent omeprazole (brand and generic) prescriptions. However, this accounted for only 50.8% of all prevalent PPI prescriptions.

Figure 8.3: Proton Pump Inhibitors Quarterly Prevalence

Crude brand name and generic prescriptions rates per 1,000 adults, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)

'Q4' indicates prevalence for the 4th quarter (October to December)

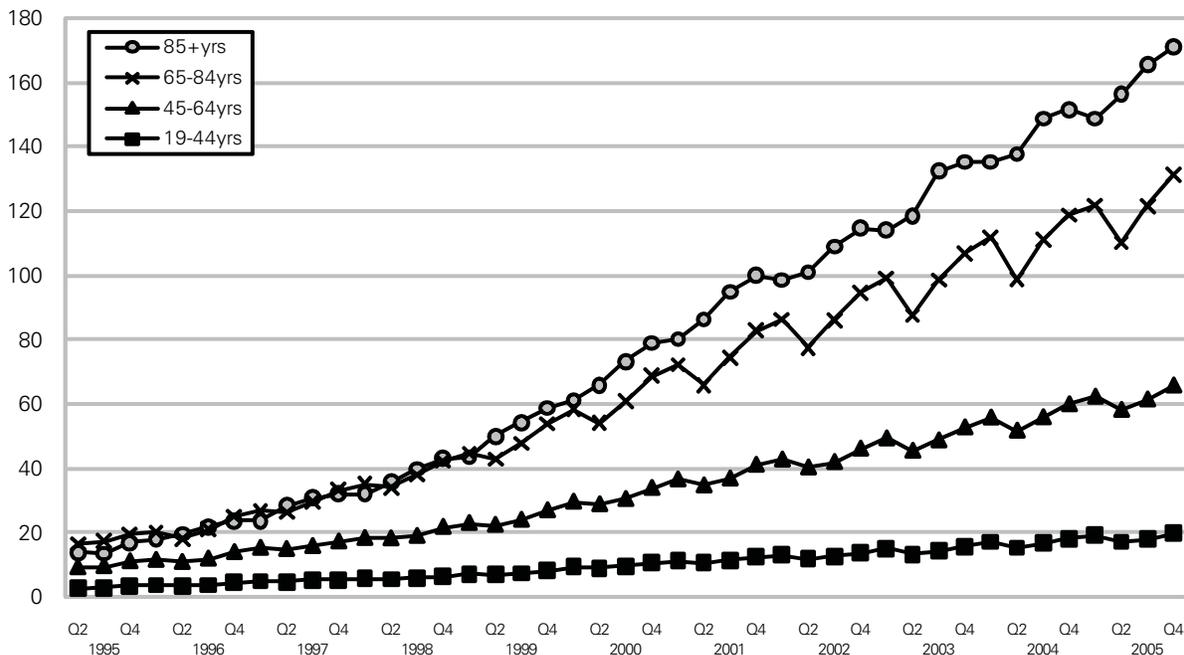
'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

When evaluated by age, PPI utilization was greatest in those aged 85 years and older (13.9 to 170.9 per 1,000 over the study period), followed by those aged 65–84 (16.6 to 131.2 per 1,000), then 45–64 (9.2 to 65.8 per 1,000), and 19–44 (2.9 to 19.9 per 1,000). This age effect was significant when adjusted for region, prescription cost sharing, and prescribing trends over time (Table 8.1).

Figure 8.4: Proton Pump Inhibitors Quarterly Prevalence by Age

Crude user rates per 1,000 adults, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)

'Q4' indicates prevalence for the 4th quarter (October to December)

'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

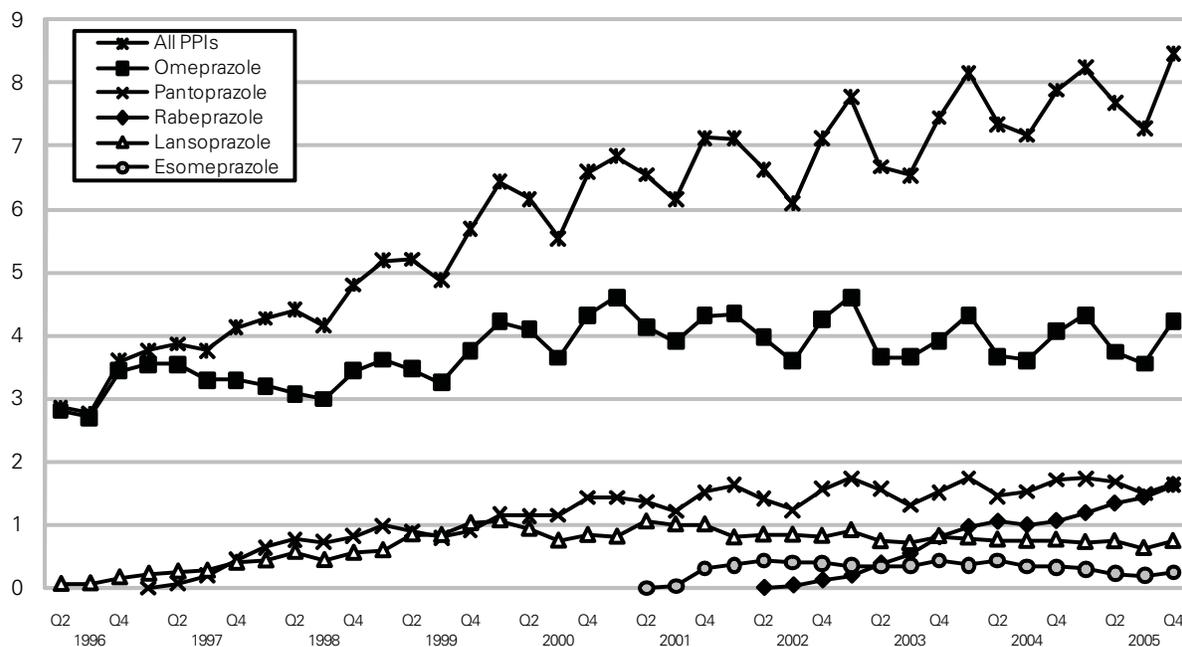
When PPI use was evaluated by prescription cost sharing, we observed 1.5 times greater utilization among those with no-cost prescriptions compared to persons with high income (Table 8.1). Finally, when prevalent PPI use was evaluated by region of residence, we did not observe significant differences between rural and urban utilization after adjusting for other factors.

Incidence

Similar to prevalent use, incident use was highest for omeprazole amongst all PPIs. Incident PPI use increased from 2.9 to 8.5 users per 1,000 residents per quarter, while incident omeprazole use rose from 2.8 to 4.2 users per 1,000 residents per quarter over the same period. Omeprazole utilization was followed by pantoprazole, lansoprazole, rabeprazole, and finally esomeprazole.

Figure 8.5: Proton Pump Inhibitors Quarterly Incidence

Crude rates of new users with no use of proton pump inhibitors in prior year per 1,000 adults, Q2 1996–Q4 2005



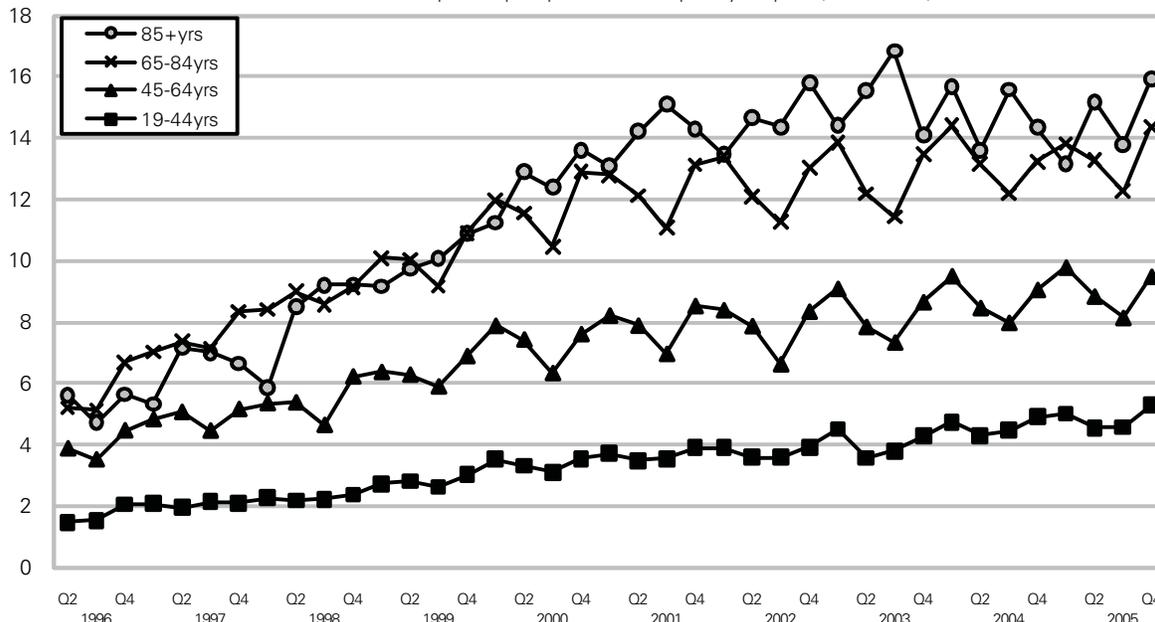
'Q2' indicates incidence for the 2nd quarter (April to June)
 'Q4' indicates incidence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

The greatest number of new PPI users per population was in the over 85 age group. By the end of the study period, generic omeprazole accounted for 94.6% of new prescriptions for omeprazole and 47.3% of new prescriptions for all PPIs.

Figure 8.6: Proton Pump Inhibitors Quarterly Incidence by Age

Crude rates of new users with no use of proton pump inhibitors in prior year per 1,000 adults, Q2 1996–Q4 2005



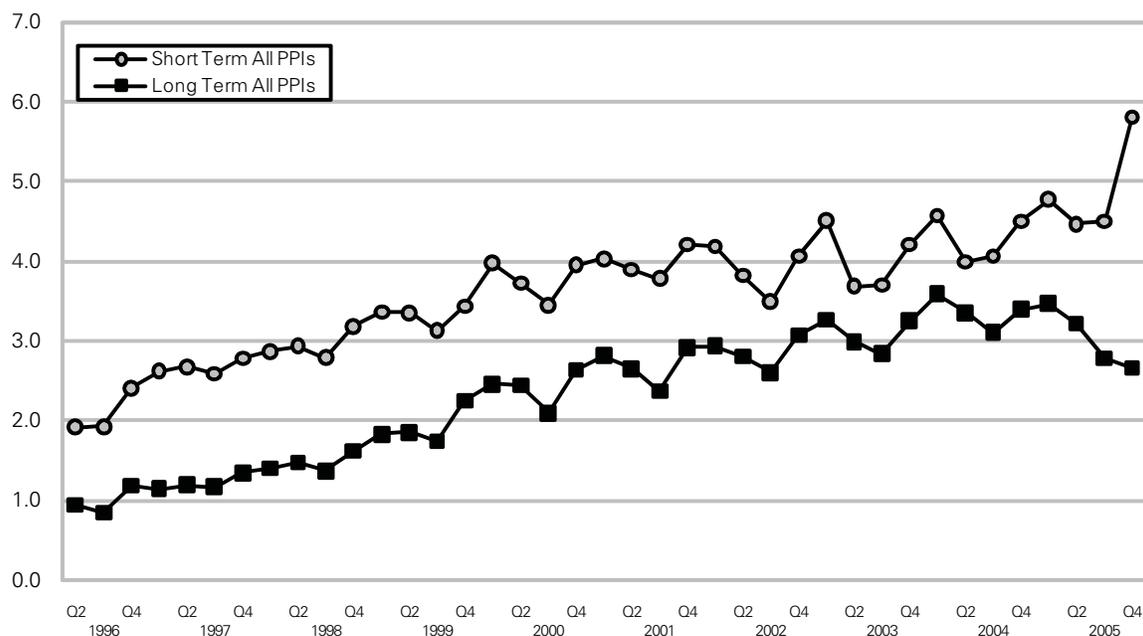
'Q2' indicates incidence for the 2nd quarter (April to June)
 'Q4' indicates incidence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

When PPI use was evaluated according to duration of therapy, the majority of new use was for short-term rather than long-term (longer than three months) therapy. The incidence of short-term PPI therapy increased from 1.9 to 5.8 users per 1,000 residents per quarter over the study period; while the incidence of long-term use increased from 0.9 to 2.7 users per 1,000 residents per quarter. However, independent of age, prescription cost sharing, and region, new use of a PPI for longer than three months increased at a significantly greater rate. With each successive quarter, incident use of long-term PPIs increased by 4% over the previous quarter's rate. This increase was 2% for incident short-term PPI users.

Figure 8.7: Proton Pump Inhibitors Quarterly Incidence by Duration of Use

Crude rates of users of proton pump inhibitors per 1,000 adults, Q2 1996–Q4 2005



'Q2' indicates incidence for the 2nd quarter (April to June)

'Q4' indicates incidence for the 4th quarter (October to December)

'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

8.3 Discussion

Overall, we observed a large increase in prevalent and incident use of PPIs in Manitoba over the study period. By 2005, 5.7% of the adult population, 13% of those aged 65–84 years, and 17.5% those aged 85 and older had received prescriptions for PPIs. PPIs were more likely to be prescribed for persons receiving prescriptions at no cost. Several other studies have reported similar increases in utilization of PPIs over time (Chen, Chou, & Hwang, 2003; Westbrook, Duggan, & McIntosh, 2001; Jones, 2001; Banthin & Miller, 2006; Dhipayom & Walker, 2006; Marshall et al., 2002; Lassen, Hallas, & Schaffalitzky De Muckadell, 2004). Others have also reported greater utilization of PPIs in older age groups (Morales Suarez-Varela, Perez-Benajas, Girbes, V, & Llopis-Gonzalez, 1998; Hall, Dodd, Durkin, & Sloan, 2002; Lassen et al., 2004) and among those with lower socioeconomic status (Dhipayom & Walker, 2006).

Our data clearly showed that generic omeprazole replaced brand name omeprazole upon availability in June 2004. This was the intended effect in view of the cost savings associated with generic omeprazole (\$1.47 per 20 mg tablet versus \$2.42 in 2006 Canadian dollars). However, generic omeprazole was not approved by Manitoba Pharmacare for the treatment of *Helicobacter pylori* in conjunction with appropriate antibiotic therapy. For this indication, brand name omeprazole was the appropriate medication, and this explains the incomplete replacement of brand with generic drug. Esomeprazole was not approved as a Pharmacare formulary benefit in 2003, and utilization of this medication remained low. The finding that generic omeprazole only accounted for approximately 50% of prevalent and incident prescriptions for PPIs is of note. No evidence exists to suggest that one agent is more effective than another, thus the least expensive agent should be used (Canadian Agency for Drugs and Technologies in Health, 2007). Some authors have proposed that the promotion of alternate brand name PPIs to physicians may have contributed to their utilization after generic omeprazole became available (Lu, Farley, & Hansen, 2006).

We found that the majority of new PPI users were using these medications in the short-term. Keeping in mind that definitions of long-term use vary amongst studies, prevalent utilization of long-term PPIs has ranged from 2% to 90% (Hurenkamp et al., 2002; Lassen et al., 2004). However, we found that long-term use of PPI prescriptions was increasing at a faster rate than short-term therapy. We await the results of the impact on PPI prescribing of the Canadian Optimal Medication Prescribing and Canadian Agency for Drugs and Technologies in Health report on evidence-based prescribing (Canadian Agency for Drugs and Technologies in Health, 2007). Additionally, changes in prescribing within this class of medications after March 2006, when PPIs were transitioned to Part 3 (prior approval), will be a further area of research.

CHAPTER 9: MEDICATIONS FOR ASTHMA AND CHRONIC LUNG DISEASE

Medications used to treat asthma and chronic lung disease are a diverse group of medications that includes short acting ‘rescue’ medications such as salbutamol, but also longer acting medications designed to prevent symptoms, such as inhaled corticosteroids and long acting beta agonists (LABA).

The addition of the first LABA/inhaled corticosteroid combinations inhaler, Advair® (fluticasone/salmeterol) to the Part 1 (open listing) of the Manitoba Pharmacare formulary occurred in the first quarter of 2000. This was followed by the addition of Symbicort® (budesonide/formoterol). With the exception of the oral agents, ketotifen, montelukast, and zafirlukast, which are listed under Part 2 (utilization for established criteria), all other medications for asthma and chronic lung disease in the Pharmacare formulary are Part 1.

We evaluated the utilization of medications used to treat asthma and chronic lung disease in the adult (18 years of age and older) and pediatric (less than 18 years old) population of Manitoba from 1995–2005. Utilization of these medications was evaluated both in the overall population and in persons with asthma or chronic lung disease. Additionally, we assessed how the formulary addition of LABA/inhaled corticosteroid combinations (Advair®, Symbicort®) impacted the utilization of inhaled corticosteroids in adults with asthma and chronic lung disease and children with asthma.

9.1 Methods

Prevalent and incident users were identified for the population of Manitoba for the following medication groups: inhaled corticosteroids (budesonide, fluticasone, ciclesonide, beclomethasone, triamcinaloone, flunisolide), short acting beta agonists (SABA) (salbutamol, fenoterol, terbutaline, isoproterenol), long acting beta agonists (LABA) (salmeterol, formoterol), and LABA/inhaled corticosteroid combinations (fluticasone and salmeterol (Advair®) and budesonide and formoterol (Symbicort®)), anticholinergics (ipratropium alone and in combination, tiotropium), leukotriene receptor antagonists (montelukast, zafirlukast) and other oral agents (aminophylline, theophylline, oxtriphylline, ketotifen, orciprenaline). For a list of the medications included in the categories, please refer to Appendix Table 1.

Incident users were those users of any medications used to treat asthma and chronic lung disease who had not used these medications (except SABA) in the one year prior to this medication for asthma and chronic lung disease prescription.

The incident and prevalent utilization of single–entity inhaled corticosteroids was compared before and after the formulary addition of LABA/inhaled corticosteroid combination products using GEE modeling.

Asthma or chronic lung disease was defined as at least one hospitalization (primary diagnosis) or two or more physician visits over one year for asthma (ICD-9-CM=493 or ICD-10-CA=J45: asthma) or two prescriptions for medications used to treat asthma in one year. These prescriptions included inhaled corticosteroids, SABAs, LABAs, LABA/inhaled corticosteroid combinations, montelukast or zafirlukast, or other oral agents, in addition to oral steroid and inhaled sodium cromoglycate (Kozyrskyj, Dahl, Ungar, Becker, & Law, 2006).

9.2 Results

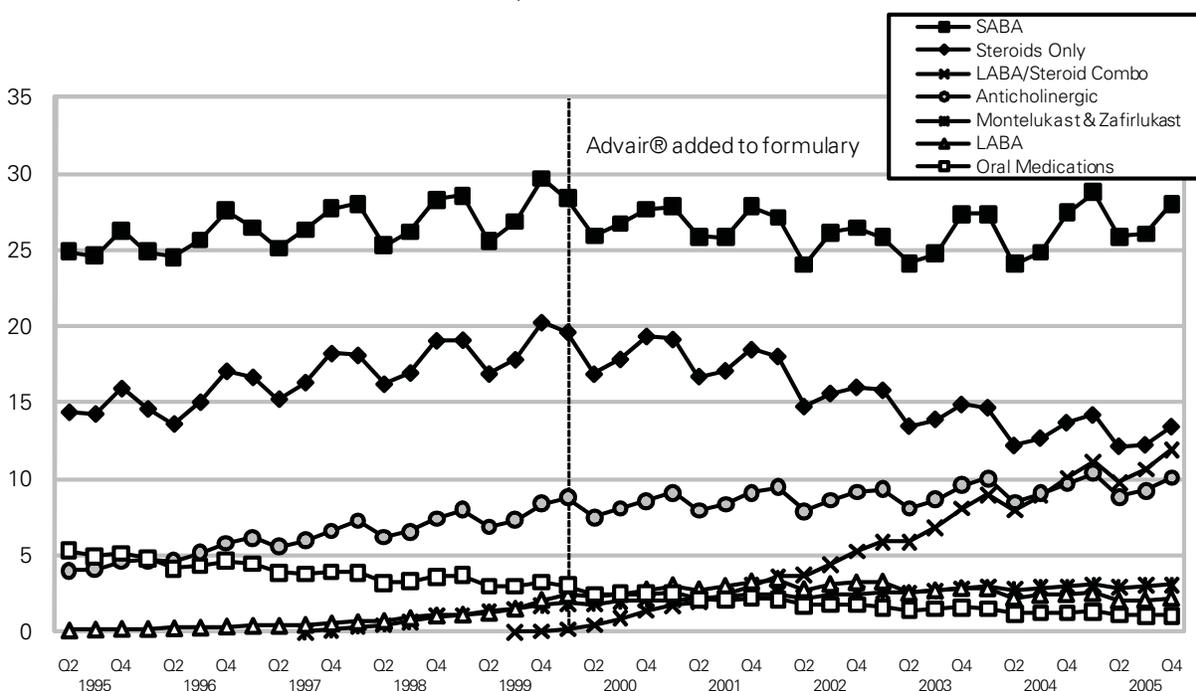
Prevalence

Adults

SABAs were the most commonly used medications in the overall adult population of Manitoba. Utilization of this group of medications showed little change over the study period (increased from 24.9 to 28.0 users per 1,000 residents). The LABA/inhaled corticosteroid combinations increased the most dramatically over the study duration from 0.03 to 11.9 users per 1,000 residents population. Use of inhaled corticosteroids increased from 14.4 to 20.3 users per 1,000 residents just before the formulary addition of LABA/inhaled corticosteroid combinations, and then declined to 13.4 users per 1,000 residents. Use of anticholinergics increased from 4.0 to 10.0 users per 1,000 residents.

Figure 9.1: Medications for Asthma and Chronic Lung Disease Quarterly Prevalence, Adults

Crude user rates per 1,000 adults, Q2 1995–Q4 2005

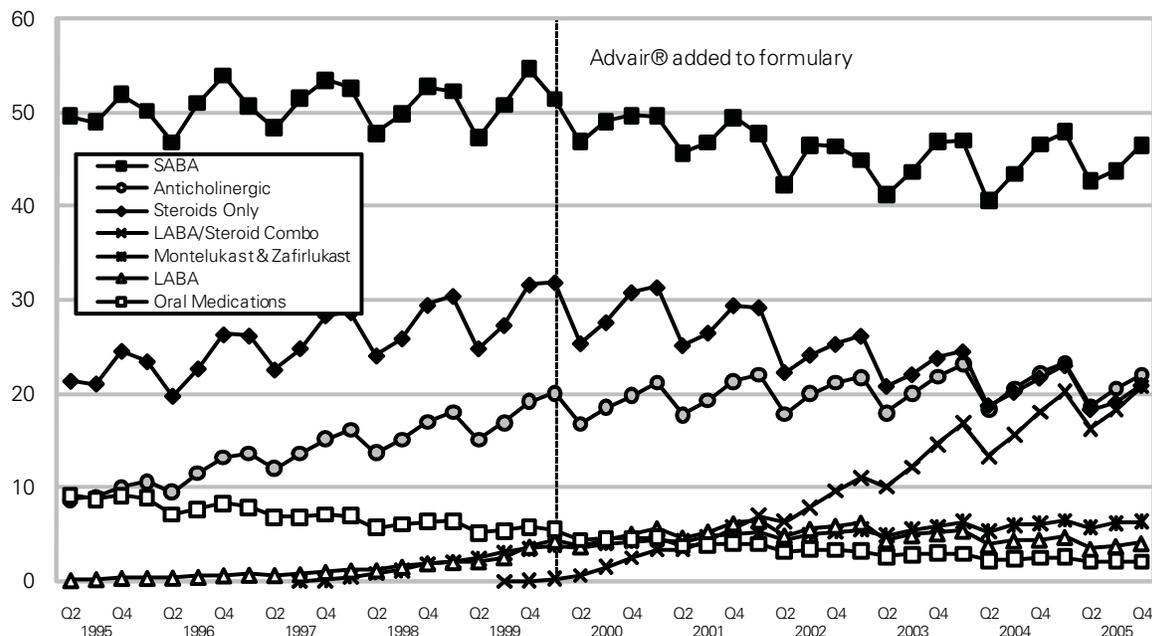


'Q2' indicates prevalence for the 2nd quarter (April to June)
'Q4' indicates prevalence for the 4th quarter (October to December)
'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Figure 9.2: Medications for Asthma and Chronic Lung Disease Quarterly Prevalence, Adults

Crude prescription rates per 1,000 adults, Q2 1995–Q4 2005



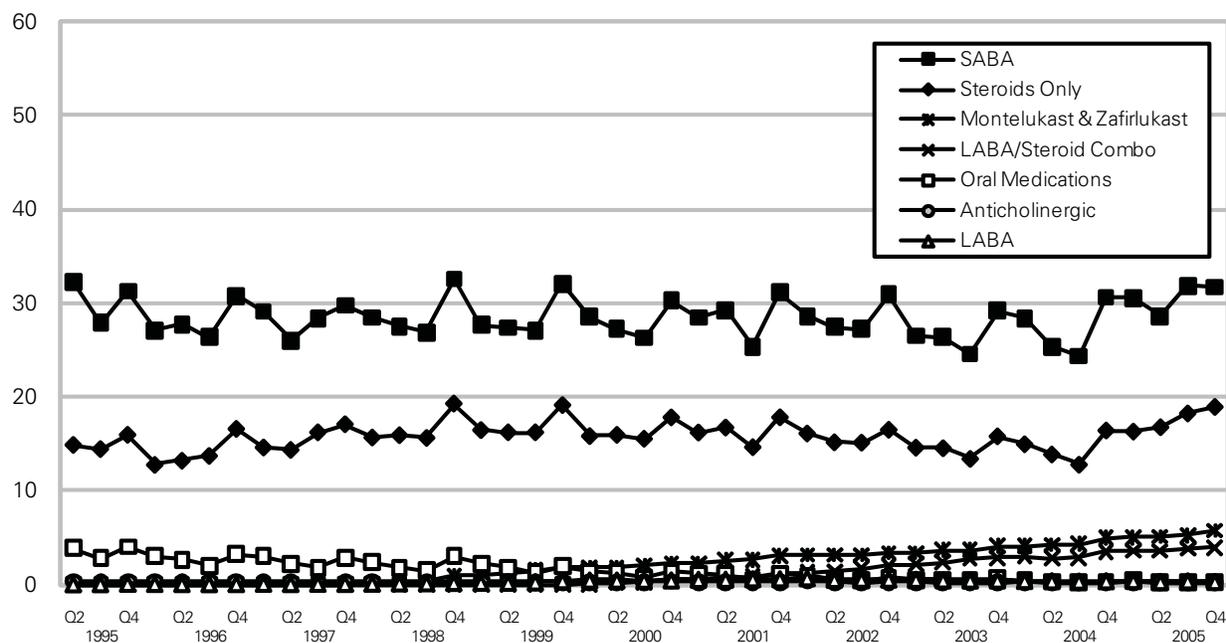
'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Children

Similar to adults, SABA were the most often prescribed asthma medication in all children, and their utilization changed very little over the study period (from 32.3 to 31.7 users per 1,000 residents). LABA/inhaled corticosteroid combinations increased from 0.01 to 3.9 users per 1,000 residents by the end of the study period. Use of inhaled corticosteroids increased from 14.9 to 19.1 users per 1,000 residents just before the formulary addition of LABA/inhaled corticosteroid combinations, and then declined to 18.9 users per 1,000 residents. However, the oral medications montelukast and zafirlukast increased most steeply during the study period; users per 1,000 residents increased from 0.01 to 5.7 over the study period.

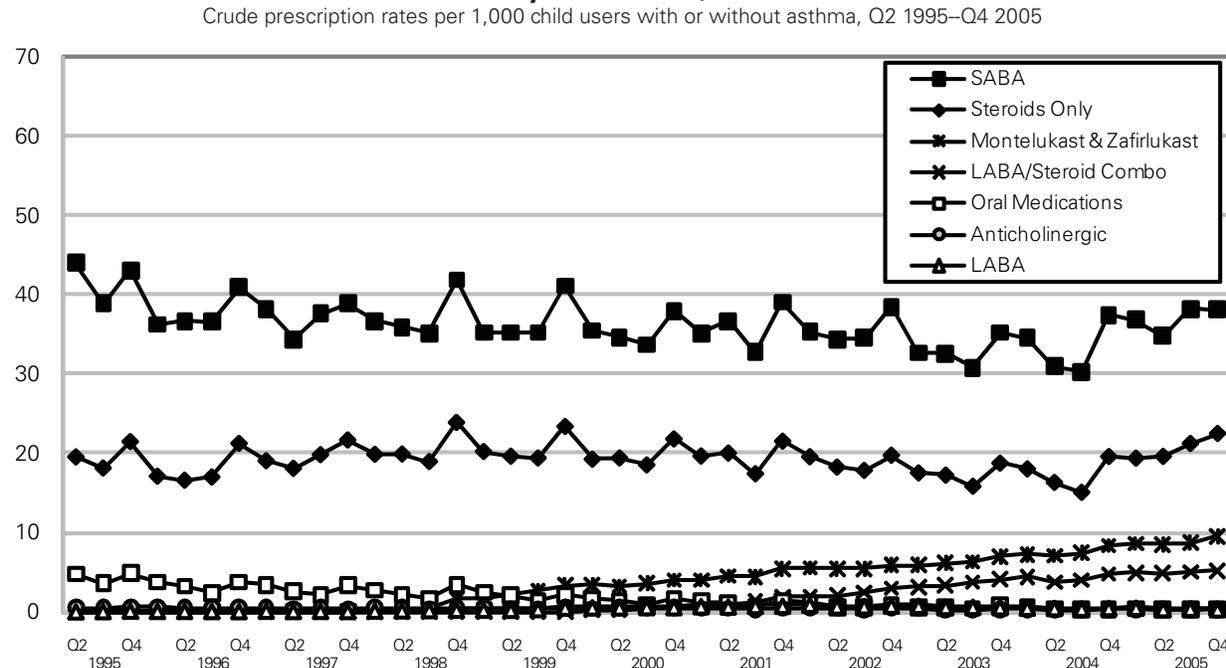
Figure 9.3: Medications for Asthma and Chronic Lung Disease Quarterly Prevalence, Children
Crude users per 1,000 children with or without asthma, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)
'Q4' indicates prevalence for the 4th quarter (October to December)
'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Figure 9.4: Medications for Asthma and Chronic Lung Disease Quarterly Prevalence, Children
Crude prescription rates per 1,000 child users with or without asthma, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)
'Q4' indicates prevalence for the 4th quarter (October to December)
'Q1' and 'Q3' data points are displayed, but not labeled

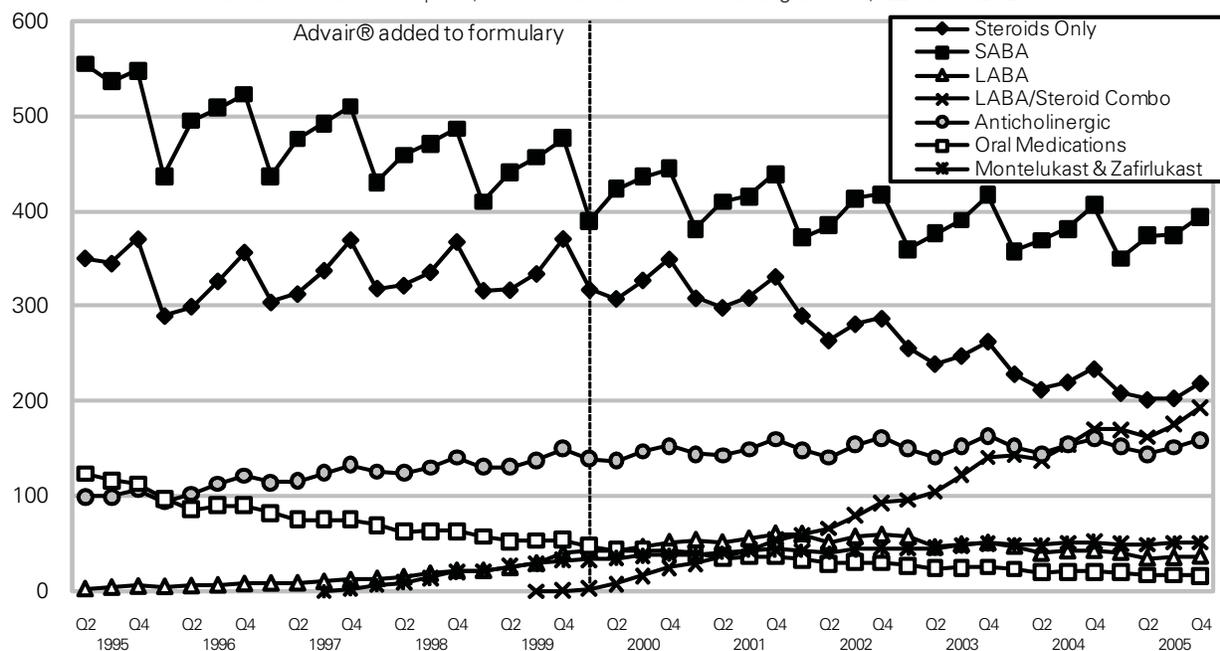
Source: Manitoba Centre for Health Policy, 2009

Adults with chronic lung disease

Use of LABA/inhaled corticosteroid combinations in adults with asthma and chronic lung disease rose dramatically over the study duration from 0.5 when added to the Pharmacare formulary to 193.0 users per 1,000 residents by the end of the study period, an increase of 12% per quarter over the successive quarter's rate ($p < 0.05$) (Table 9.1). While SABA was the most commonly used medication in the adult population with chronic lung disease, their use fell over the study period (554.7 to 394.2 users per 1,000 residents). Before the formulary addition of the LABA/inhaled corticosteroid combinations, use of SABA was declining by 1% per quarter over the previous quarter's rate ($p < 0.05$). Independent of sociodemographic characteristics, prevalent use of SABA in adults with asthma and chronic lung disease continued to decline after the formulary addition of the LABA/inhaled corticosteroid combinations ($p < 0.05$). Over the same time period, use of inhaled corticosteroids was 350.4 users per 1,000 at the beginning of the study and 370.6 per 1,000 just before the formulary addition of LABA/inhaled corticosteroid combinations. Independent of sociodemographic characteristics, prevalent use of inhaled corticosteroids in adults with asthma and chronic lung disease declined after the formulary addition of the LABA/inhaled corticosteroid combinations ($p < 0.05$) to 219.1 users per 1,000 residents. Before the formulary addition of the LABA/inhaled corticosteroid combinations, use of single-entire LABA products was increasing by 14% per quarter over the previous quarter's rate ($p < 0.05$). Independent of sociodemographic characteristics, prevalent use of LABA in adults with asthma and chronic lung disease declined after the formulary addition of the LABA/inhaled corticosteroid combinations ($p < 0.05$).

Figure 9.5: Medications for Asthma and Chronic Lung Disease
Quarterly Prevalence, Adults with Chronic Lung Disease

Crude asthma user rates per 1,000 adult users with chronic lung disease, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)

'Q4' indicates prevalence for the 4th quarter (October to December)

'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Table 9.1: Prevalent Use (Users/1,000 Adults with Asthma and Chronic Lung Disease) of Treatment Medications, 1995-2005

Medication	Baseline rate/1,000 [§]	Change in rate*	LABA/steroid combination added part 1 rate/1,000 1999Q4	Change in rate*	End 2005 users/1,000	Age effect* Age 20-44 vs 85+	Prescription cost sharing* No cost vs high income	Region effect* Point Douglas vs Fort Garry
SABA	554.66	0.99 - 1% **	476.98	0.99 - 0.5% **	394.20	1.19 + 19% †	1.29 1.3 times higher †	1.25 + 24% †
Inhaled steroids	350.35	1.00 no change	370.59	0.98 - 2% **	219.12	0.62 - 38% †	1.18 + 18% †	0.92 - 8%
LABA	2.61	1.14 + 14% **	39.51	0.99 - 1% **	36.69	0.22 - 78% †	1.49 1.5 fold higher †	0.90 - 10%
LABA/steroid combination			0.47	1.12 + 12% **	193.01	0.96 - 4%	0.90 - 10% †	0.86 - 14% †
Montelukast & Zafirlukast	2.36	1.26 + 26% **	32.30	1.02 + 2% **	50.69	1.71 2 fold higher †	1.07 + 7%	0.77 - 23% †

* Results are presented as relative rates (adjusted for age, prescription cost sharing, region and time) and then, for ease of interpretation, as percentages

** Indicates a slope significantly different from zero (p<.05)

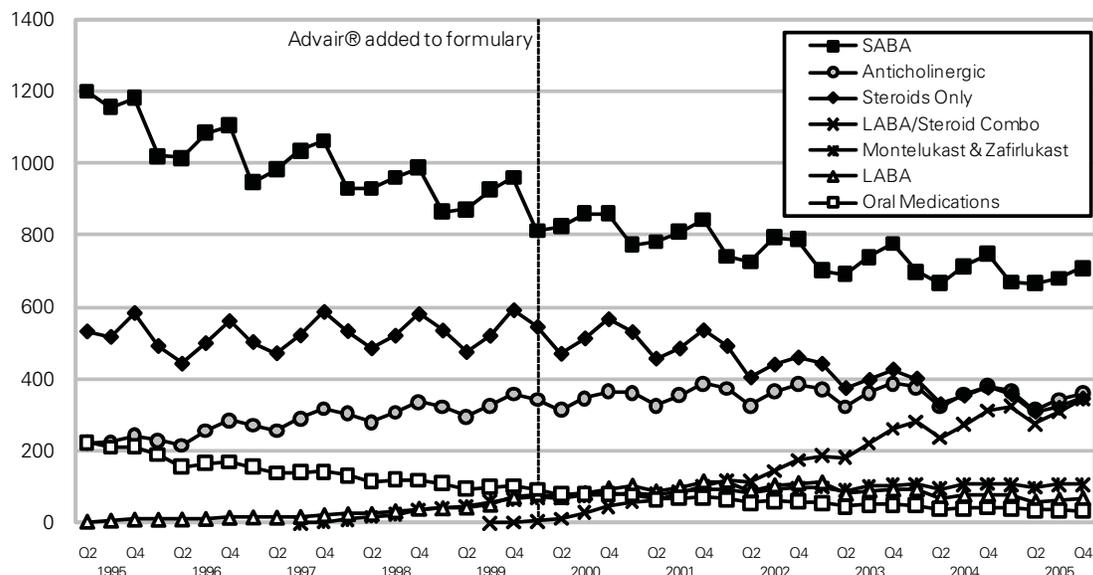
† Indicates a statistically significant effect (p<.05)

§ Baseline rates are users per 1,000 adults at the second quarter of 1995 or when prescriptions were first filled for a drug

Source: Manitoba Centre for Health Policy, 2009

Figure 9.6: Medications for Asthma and Chronic Lung Disease
Quarterly Prevalence, Adults with Chronic Lung Disease

Crude prescription rates per 1,000 adults with chronic lung disease, Q2 1995–Q4 2005



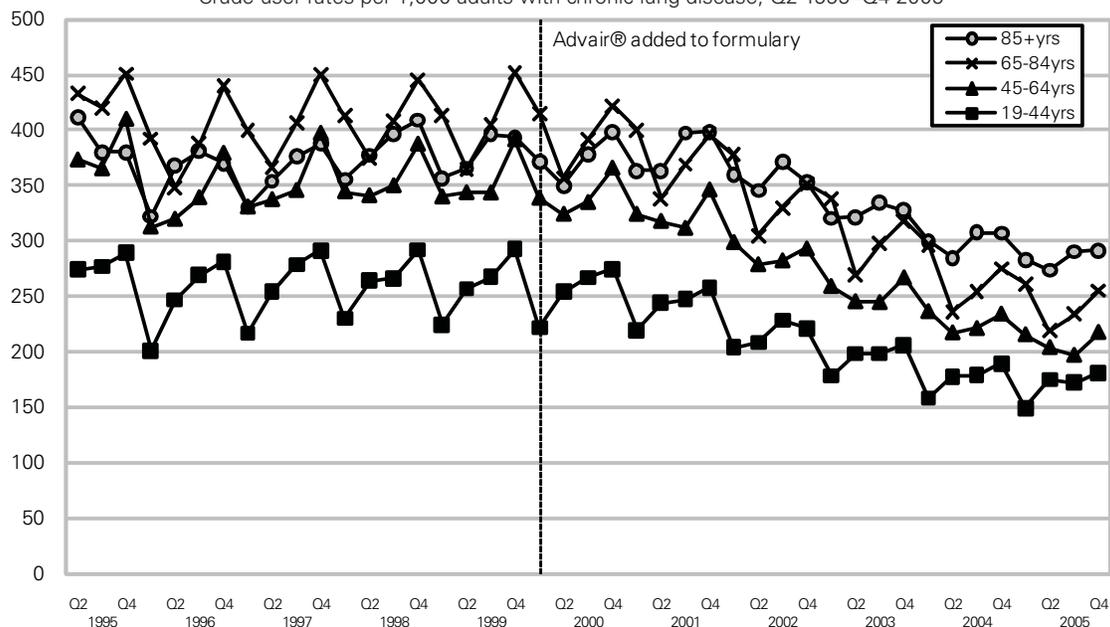
'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

When evaluated by age, young adults with asthma and chronic lung disease (aged 20–44 years) were almost 40% less likely to use inhaled corticosteroids than persons 85 years and older, when controlling for other sociodemographic characteristics (Table 9.1). They were also 80% less likely to use single-entirety LABA inhalers, but nearly twice as likely to receive montelukast/zafirlukast prescriptions.

Figure 9.7: Steroid Quarterly Prevalence by Age, Adults

Crude user rates per 1,000 adults with chronic lung disease, Q2 1995–Q4 2005

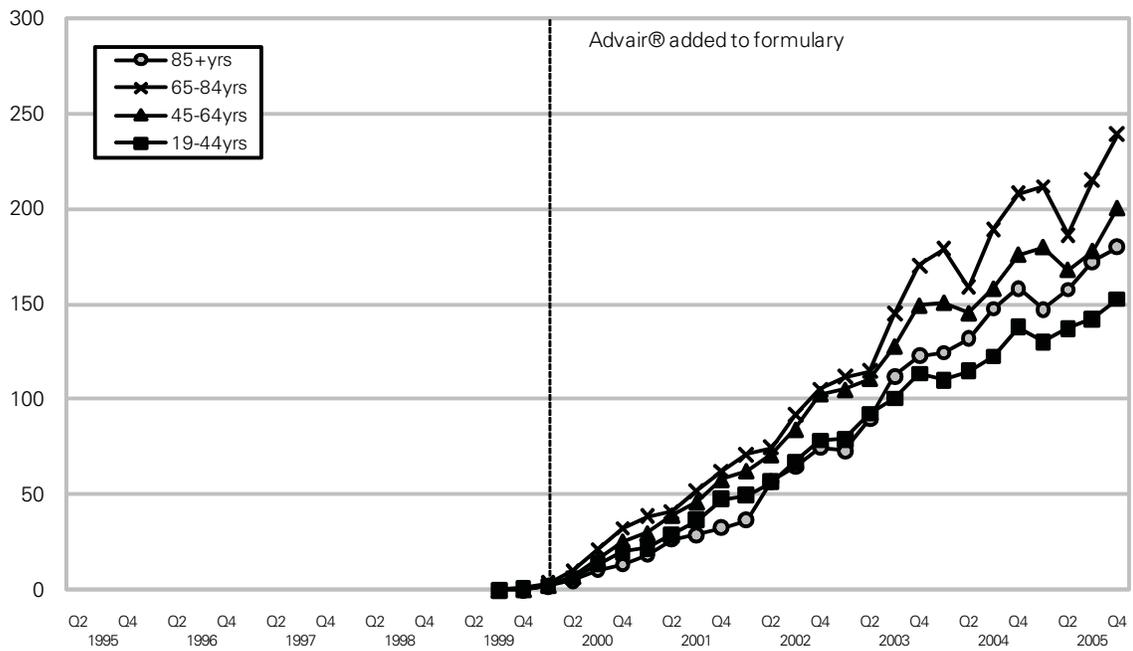


'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Figure 9.8: LABA/Steroid Combinations Quarterly Prevalence by Age, Adults

Crude user rates per 1,000 adults, with chronic lung disease Q2 1995–Q4 2005

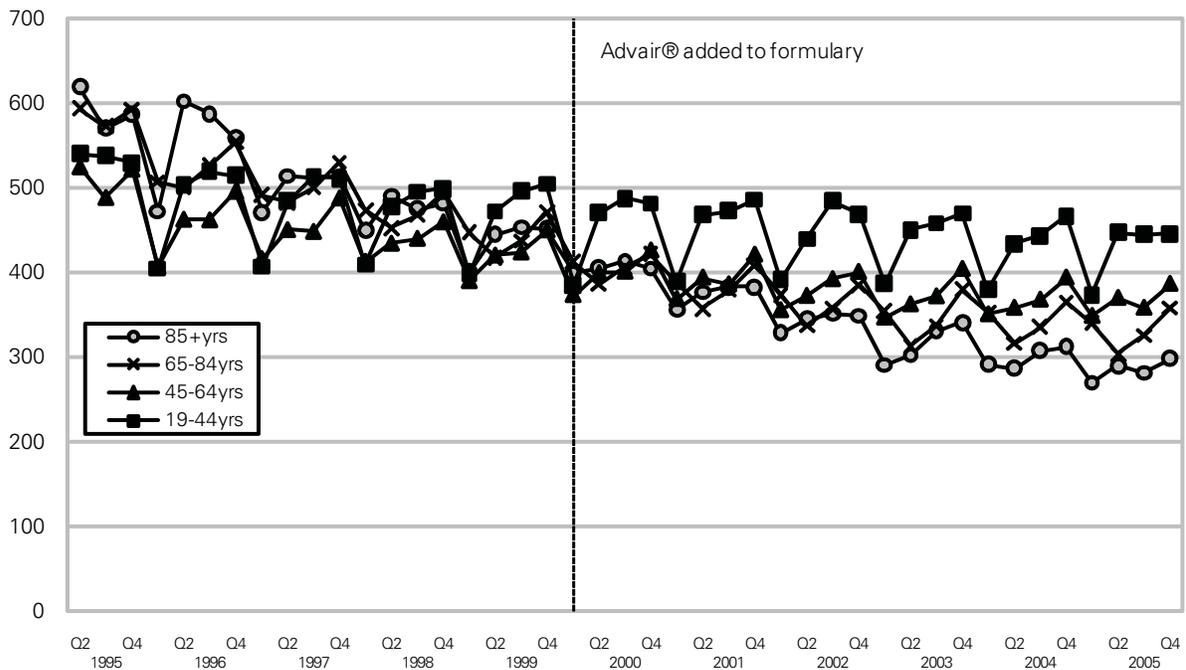


'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Figure 9.9: SABA Quarterly Prevalence by Age, Adults

Crude user rates per 1,000 adults with chronic lung disease, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

When evaluated by prescription cost sharing, adults receiving prescriptions at no cost were significantly more likely to receive medications for chronic lung disease, with the exception of LABA/inhaled corticosteroid combinations, montelukast, and zafirlukast prescriptions (Table 9.1).

Finally, prevalent use of LABA and prevalent use of inhaled steroids were similar between Point Douglas and Fort Garry areas; however, rates of LABA in combination with steroids and rates of montelukast and zafirlukast use were significantly lower in Point Douglas when compared to Fort Garry ($p < 0.05$). Conversely, rates for the use of SABA were significantly higher in Point Douglas when compared to Fort Garry (Table 9.1).

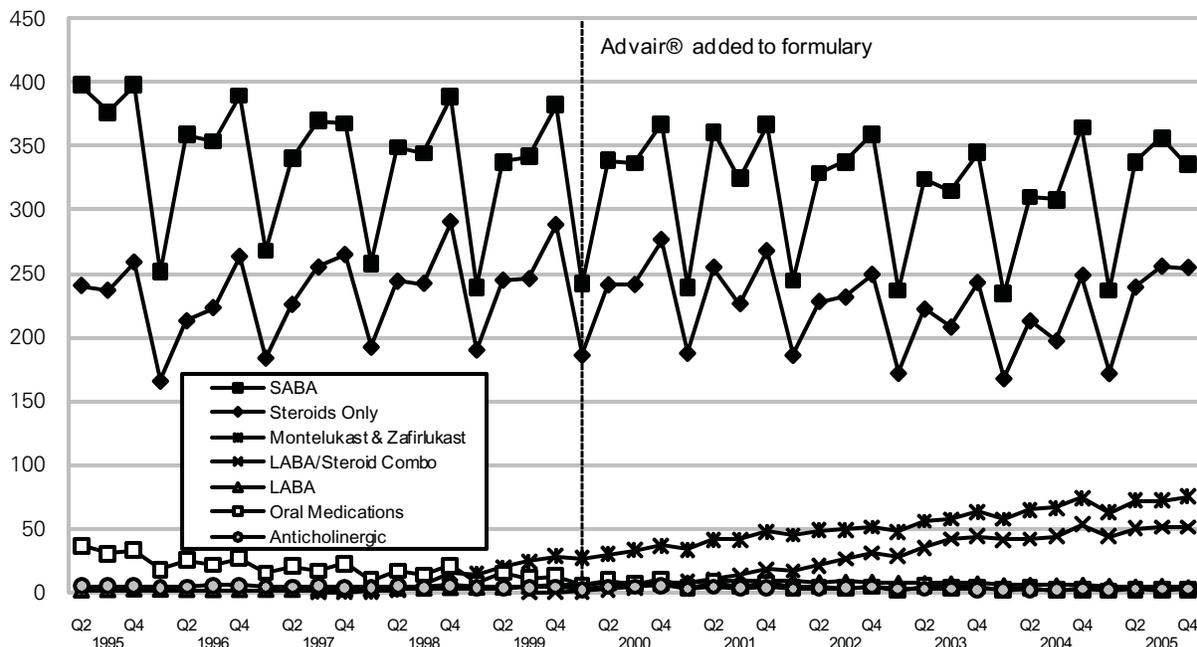
Children with asthma

The LABA/inhaled corticosteroid combinations increased at 14% per quarter over the previous quarter's rate after becoming a Pharmacare formulary benefit ($p < 0.05$) in children with asthma (Table 9.2). Medication use by the pediatric population with asthma was dominated by SABA; prevalent utilization of these medications was 398 per 1,000 in the first quarter and 335 per 1,000 in the last quarter of the study. Before the formulary addition of the LABA/inhaled corticosteroid combinations, use of SABA was declining by 0.4% per quarter over the previous quarter's rate ($p < 0.05$). Independent of sociodemographic characteristics, prevalent use of SABA in children with asthma and chronic lung disease became constant (not statistically significantly different from zero) after the formulary addition of the LABA/inhaled corticosteroid combinations. Before the formulary addition of the LABA/inhaled corticosteroid combinations, use of inhaled corticosteroids in this population was increasing by 0.8% per quarter over the previous quarter's rate ($p < 0.05$). Independent of sociodemographic characteristics, prevalent use of inhaled corticosteroids in children with asthma and chronic lung disease became statistically constant (not significantly different from zero) after the formulary addition of the LABA/inhaled corticosteroid combinations. Before the formulary addition of the LABA/inhaled corticosteroid combinations, use of single-entity LABA products in this population was increasing by 8% per quarter over the previous quarter's rate ($p < 0.05$). Independent of sociodemographic characteristics, prevalent use of single-entity LABA products in children with asthma and chronic lung disease declined after the formulary addition of the LABA/inhaled corticosteroid combinations ($p < 0.05$).

Finally, the oral medications montelukast and zafirlukast increased the most dramatically over the study duration, with an increase of 52% per quarter over the previous quarter's rate before the formulary addition of LABA/inhaled corticosteroid combinations ($p < 0.05$). Independent of sociodemographic characteristics, prevalent use of montelukast and zafirlukast in children with asthma and chronic lung disease continued to increase after the formulary addition of the LABA/inhaled corticosteroid combinations ($p < 0.05$).

Figure 9.10: Medications for Asthma and Chronic Lung Disease
Quarterly Prevalence, Children with Asthma

Crude users per 1,000 children with asthma, Q2 1995–Q4 2005

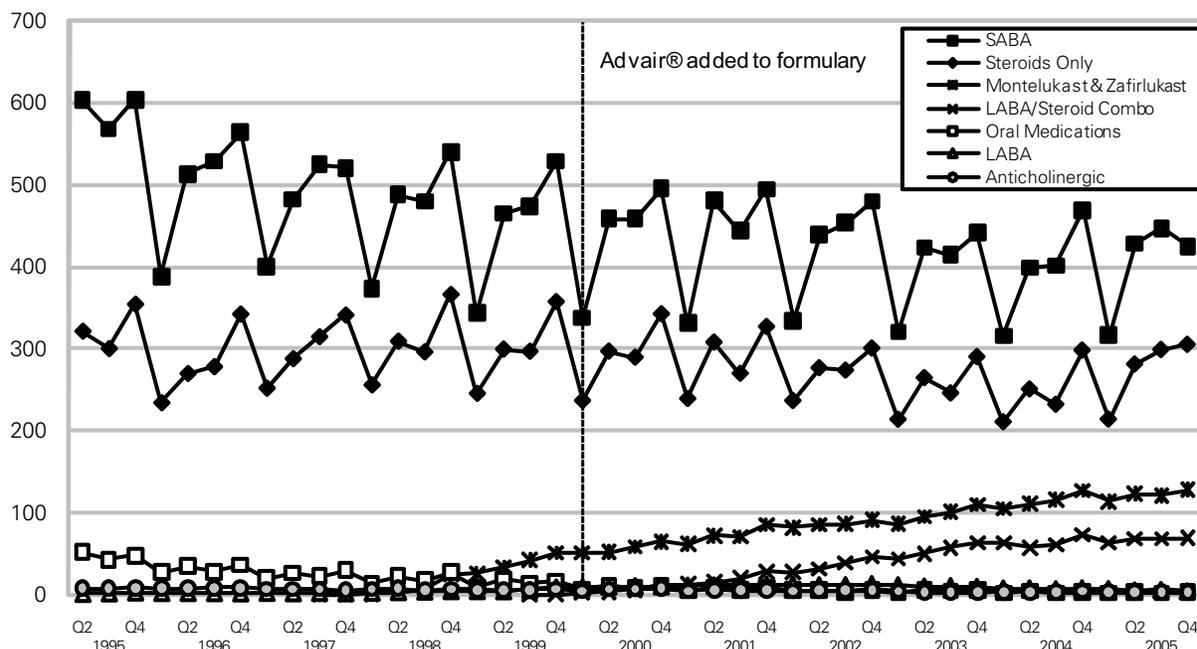


'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Figure 9.11: Medications for Asthma and Chronic Lung Disease
Quarterly Prevalence, Children with Asthma

Crude prescription rates per 1,000 children with asthma, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Table 9.2: Prevalent Use (Users/1,000 Children with Asthma) of Treatment Medications, 1995-2005

Medication	Baseline rate/1,000§	Change in rate* in rate*	LABA/steroid combination added part 1 rate/1,000 1999Q4	Change in rate* in rate*	End 2005 users/1,000	Age effect* Age 5-8 vs 13+	Prescription cost sharing* No cost vs high income	Region effect* Point Douglas vs Fort Garry
SABA	397.97	1 - 0.4% **	382.54	1.00 + 0.1%	335.74	0.77 - 23% †	1.28 1.3 times higher †	1.16 + 16% †
Inhaled steroids	240.54	1.01 + 0.8% **	287.74	1.00 no change	254.50	1.33 + 33% †	1.08 + 8% †	0.95 - 5%
LABA ‖	1.07	1.08 + 8% **	6.12	0.98 - 2% **	3.76	0.33 - 67% †	0.92 - 8%	
LABA/steroid combination	0.00		0.17	1.14 + 14%	51.41	0.29 - 71% †	0.73 - 27% †	1.16 + 16% †
Montelukast & Zafirlukast ‡	0.11	1.52 + 52% **	28.47	1.05 + 5% **	75.10	1.18 + 18%	0.53 - 47% †	

* Results are presented as relative rates (adjusted for age, prescription cost sharing, region and time) and then, for ease of interpretation, as percentages

** Indicates a slope significantly different from zero (p<.05)

† Indicates a statistically significant effect (p<.05)

§ Baseline rates are users per 1,000 children at the second quarter of 1995

|| or when prescriptions were first filled for a drug

‡ adjusted only for age

§ adjusted for age, sex, and prescription cost sharing

Source: Manitoba Centre for Health Policy, 2009

Prevalent use of LABA and LABA/inhaled corticosteroid combinations increased with increasing age. Inhaled corticosteroid use was highest in children aged five to eight and montelukast/zafirlukast use was highest in nine to 12 year olds (see Appendix 2, Figures A.9.1 to A.9.4).

Independent of other factors, inhaled corticosteroids and SABA were more likely to be used by children receiving prescriptions at no-cost than children in the higher income group (Table 9.2). On the other hand, prevalent use of LABA/inhaled corticosteroid combinations and montelukast and zafirlukast was substantially lower for children receiving prescriptions at no cost. User rates of SABA inhalers and LABA/inhaled corticosteroid combinations were significantly higher in Point Douglas than in Fort Garry (Table 9.2).

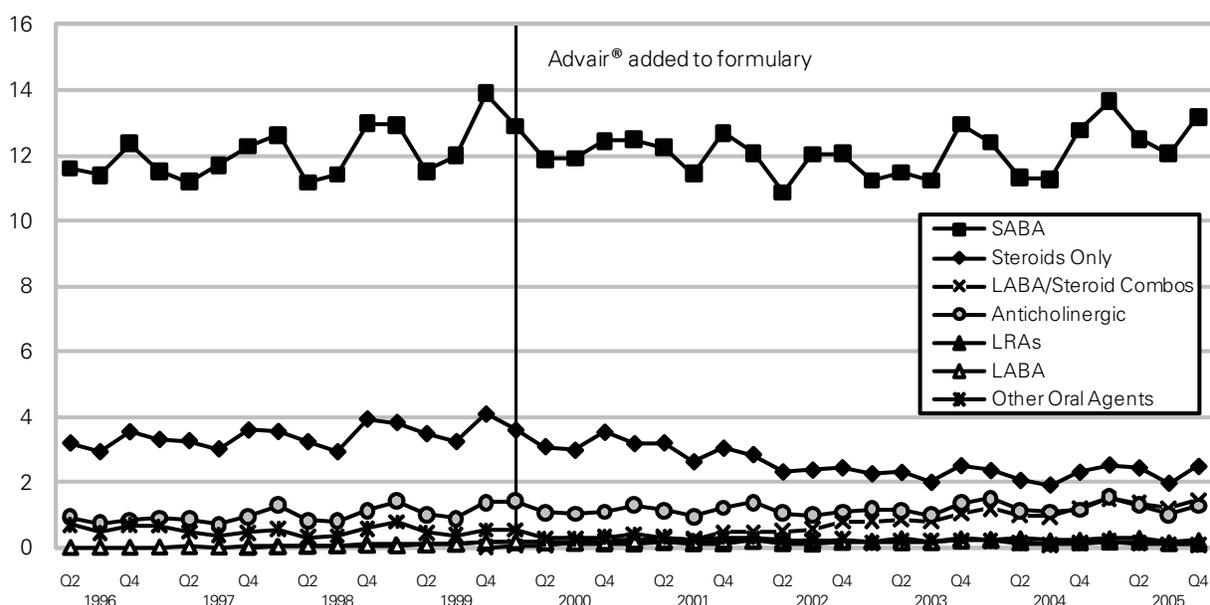
Incidence

Adults

Similar to prevalent use, we observed the greatest incident use of SABA overall for adults in the entire population and adults with asthma and chronic lung disease. Overall incident SABA use increased from 11.6 to 13.2 users per 1,000 residents per quarter, while incident SABA use in the adult population with asthma and chronic lung disease decreased from 196.7 to 142.2 users per 1,000 residents per quarter over the same period. Incident inhaled corticosteroid users decreased from 3.2 to 2.5 users per 1,000 residents per quarter, while incident corticosteroid use in the adult population with asthma and chronic lung disease decreased from 59.5 to 33.6 users per 1,000 residents per quarter. Incident users of LABA/inhaled corticosteroid combinations increased from 0.01 to 1.5 users per 1,000 residents per quarter, while incident LABA/inhaled corticosteroid combination use in the adult population with asthma and chronic lung disease increased from 0.07 to 15.6 users per 1,000 residents per quarter.

Figure 9.12: Medications for Asthma and Chronic Lung Disease Quarterly Incidence, Adults

Crude rates of new users with no use of asthma or chronic lung disease medication in prior year per 1,000 adults, Q2 1996–Q4 2005



'Q2' indicates incidence for the 2nd quarter (April to June)

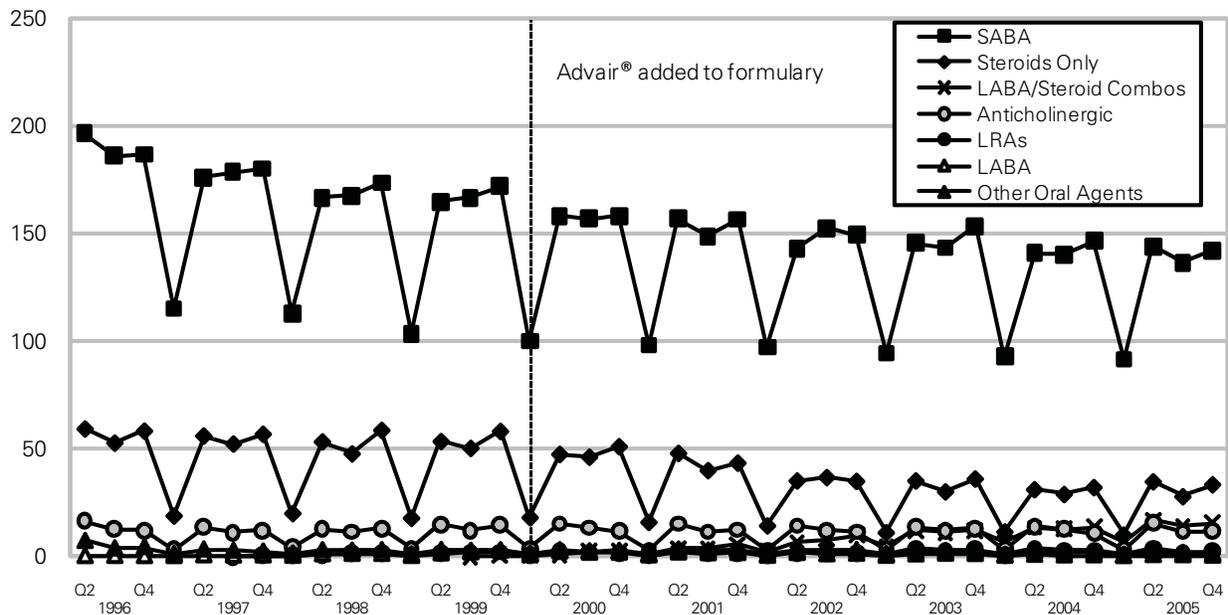
'Q4' indicates incidence for the 4th quarter (October to December)

'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Figure 9.13: Medications for Asthma and Chronic Lung Disease Quarterly Incidence, Adults with Asthma and Chronic Lung Disease

Crude user rates per 1,000 adults with asthma and chronic lung disease with no use of medications for asthma or chronic lung disease (except SABA) for 1 year, Q2 1996–Q4 2005



'Q2' indicates incidence for the 2nd quarter (April to June)
'Q4' indicates incidence for the 4th quarter (October to December)
'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

In adults with asthma and chronic lung disease, the rate of incident use of inhaled corticosteroid medications was 58 per 1,000 prior to the introduction of LABA/inhaled corticosteroid combinations in the first quarter of 2001 (Figure 9.13), or 53 per 1,000 when adjusted for sociodemographic characteristics (Table 9.3).

Prior to the introduction of LABA/inhaled corticosteroid combinations, the rate of new users of inhaled corticosteroids in adults with asthma and chronic lung disease was declining at a rate of 1% per quarter over the previous quarter's rate ($p < 0.05$) (Table 9.3). Independent of sociodemographic characteristics, incident use of inhaled corticosteroids in adults with asthma and chronic lung disease continued to decline after the introduction of LABA/inhaled corticosteroid combinations ($p < 0.05$). Additionally, the slope of the rate of decline of new users of inhaled corticosteroids was steeper after the introduction of LABA/inhaled corticosteroid combinations ($p < 0.05$).

When adults with asthma and chronic lung disease were evaluated by age, an age gradient was observed, with the greatest utilization occurring in the youngest age group for SABA and inhaled corticosteroids (see Appendix 2, Figures A.9.6 and A.9.7).

Table 9.3: Incident Use (New Users/1,000 Adults with Asthma or Chronic Lung Disease) of Inhaled Corticosteroids, 1995-2005

	Before LABA/steroid combination on Formulary (1996Q2-1999Q4)		LABA/steroid combination on Formulary (2000Q1-2005Q4)
	First Quarter 1996Q2	Last Quarter 1999Q4	Last Quarter 2005Q4
Crude rate	59.5	58.3	33.6
Adjusted rate*		53.0	30.7
Adjusted rate of change* per quarter		0.99**	0.98**†

* Adjusted for age, prescription cost sharing, region and time

Rate of change results are presented as relative rates

** Indicates a slope significantly different from zero (p<.05)

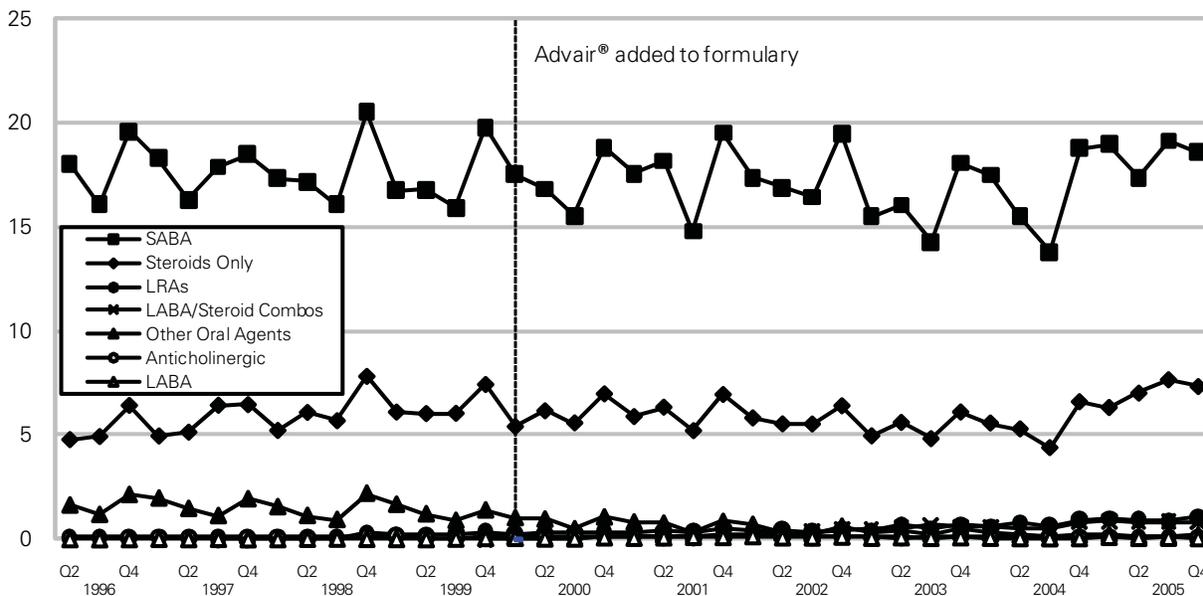
† Indicates a significant change in the slope after the intervention (p<.05)

Source: Manitoba Centre for Health Policy, 2009

Children

For the pediatric population, we observed the greatest incident use of SABA overall for children in the entire population and children with asthma. Overall incident SABA use increased from 18.0 to 18.6 pediatric users per 1,000 residents per quarter, while incident SABA use in the pediatric population with asthma decreased from 198.5 to 153.0 users per 1,000 residents per quarter over the same period. Incident inhaled corticosteroid use increased from 4.8 to 7.3 pediatric users per 1,000 residents per quarter, while incident inhaled corticosteroid use in the pediatric population with asthma increased from 71.1 to 92.9 users per 1,000 residents per quarter. Incident LABA/inhaled corticosteroid combinations use increased from 0.01 to 0.8 users per 1,000 residents per quarter, while incident LABA/inhaled corticosteroid combinations use in the pediatric population with asthma increased from 0.06 to 7.4 users per 1,000 residents per quarter.

Figure 9.14: Medications for Asthma and Chronic Lung Disease Quarterly Incidence, Children
 Crude user rates per 1,000 children with asthma with no use of medications for asthma or chronic lung disease (except SABA) for 1 year, Q2 1996–Q4 2005

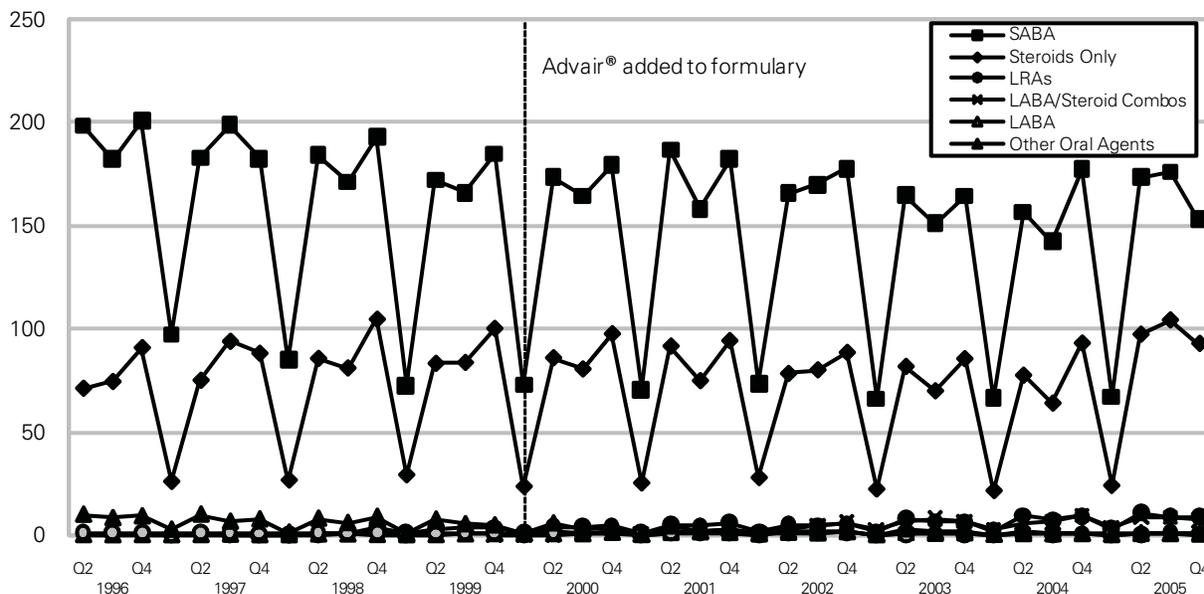


'Q2' indicates incidence for the 2nd quarter (April to June)
 'Q4' indicates incidence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Figure 9.15: Medications for Asthma and Chronic Lung Disease Quarterly Incidence, Children with Asthma

Crude rates of new users with no use of asthma or chronic lung disease medications in prior year per 1,000 children with asthma, Q2 1996–Q4 2005



'Q2' indicates incidence for the 2nd quarter (April to June)
 'Q4' indicates incidence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Table 9.4: Incident Use (New Users/1,000 Children with Asthma) of Inhaled Corticosteroids, 1996-2005

	Before LABA/steroid combination on Formulary (1996Q2-1999Q4)		LABA/steroid combination on Formulary (2000Q1-2005Q4)
	First Quarter 1996Q2	Last Quarter 1999Q4	Last Quarter 2005Q4
Crude rate	71.1	100.1	92.9
Adjusted rate*		95.4	93.2
Adjusted rate of change* per quarter		1.01**	1.01**

* Adjusted for age, prescription cost sharing, region and time

Rate of change results are presented as relative rates

** Indicates a slope significantly different from zero ($p < 0.05$)

† Indicates a significant change in the slope after the intervention ($p < 0.05$)

Source: Manitoba Centre for Health Policy, 2009

Quarterly incident rates of SABA and inhaled corticosteroids for children with asthma are presented in Appendix 2, Figures A.9.8 and A.9.9.

Just prior to the introduction of LABA/inhaled corticosteroid combinations in the fourth quarter of 1999, new use of inhaled corticosteroids was 100 per 1,000 children with asthma, or 95 per 1,000 when adjusted for sociodemographic characteristics and 93 per 1,000 children at the end of the period after LABA/inhaled corticosteroid combinations were introduced (Table 9.4). Prior to the introduction of LABA/inhaled corticosteroid combinations, the rate of new users of inhaled corticosteroids in children with asthma and chronic lung disease was increasing at a rate of 1% per quarter over the previous quarter's rate ($p < 0.05$). Independent of sociodemographic characteristics, incident use of inhaled corticosteroids in children with asthma and chronic lung disease continued to increase after the introduction of LABA/inhaled corticosteroid combinations ($p < 0.05$). The slope of the rate of increase of new users of inhaled corticosteroids was the same after the introduction of LABA/inhaled corticosteroid combinations as before.

9.3 Discussion

We generally observed an increase prevalent and incident utilization of LABA/inhaled corticosteroid combinations. This finding is consistent with prescribing trends over time observed in other studies in adult general populations and populations with asthma and chronic lung disease (Allen-Ramey, Samet, Rand, & Joseph, 2004; Boyter & Steinke, 2005; Dormuth et al., 2006; DiSantostefano, Davis, Yancey, & Crim, 2008). Changes in prescribing of inhaled corticosteroids (1999-2002, as well as pediatric populations (Cohen, Taitz, & Jaffe, 2007; Turner, Thomas, von Ziegenweidt, & Price, 2009; Phillips & McDonald, 2008; Bollinger, Smith, LoCasale, & Blaisdell, 2007). We also observed an overall decline in utilization of single-entity inhaled corticosteroids, as their use was replaced by LABA/inhaled corticosteroid combinations. This pattern has been observed in a population-based study of prescriptions dispensed for inhaled corticosteroid and salmeterol containing products (DiSantostefano et al., 2008). Also consistent with other studies, SABAs were the most commonly utilized class of medications in all groups studied, followed by inhaled corticosteroids (Allen-Ramey et al., 2004). These trends are consistent with asthma management guidelines, as well as guidelines for the management of chronic obstructive lung disease (Becker et al., 2005; Lemiere et al., 2004; O'Donnell et al., 2007).

We observed a statistically significant decrease in the incident utilization of inhaled corticosteroids upon the availability of LABA/inhaled corticosteroid combinations for adults with asthma or chronic lung disease. However, we did not observe a significant decline in the rate of incident utilization of inhaled corticosteroids in children with asthma upon the availability of LABA/inhaled corticosteroid combinations. LABA/inhaled corticosteroid combinations are add-on therapies for patients whose asthma is not optimally controlled with inhaled corticosteroids alone (Lemiere et al., 2004), and as combination therapy with anticholinergics for patients with moderate to severe chronic obstructive lung disease with persistent dyspnea (O'Donnell et al., 2007). For pediatric asthma, LABAs are considered safe and effective medications for improving asthma control in older children whose asthma is not optimally controlled despite regular maintenance therapy with inhaled corticosteroids (Becker et al., 2005). The greater uptake of LABA/inhaled corticosteroid combinations in adults, as compared to children with asthma, likely resulted in greater switching from inhaled corticosteroids or decline in new prescribing of the single-entity inhalers.

CHAPTER 10: STIMULANTS

Stimulants are a class of medications used to treat **attention deficit hyperactivity disorder (ADHD)** and other related conditions. Medications in this class include methylphenidate and long acting amphetamines. Generic short acting methylphenidate was introduced onto the Manitoba formulary (Part 2, utilization for established criteria) in the first quarter of 1996. Short acting brand (Ritalin[®]) and generic methylphenidate are Part 2 on the Manitoba formulary. Long acting brand name methylphenidate (Concerta[®]) and long acting brand name amphetamine (Adderall XR[®]) were not covered by the Manitoba formulary during the study period. Long acting (once daily) brand name methylphenidate (Concerta[®]) was launched in the third quarter of 2003.

We evaluated the utilization of stimulants in children over a 10-year period and determined how the Pharmacare formulary addition of long-acting brand name methylphenidate, Concerta[®], impacted the utilization of all stimulants in school aged children.

10.1 Methods

This analysis focused only on children; the population was stratified by age groups birth to four, five to eight, nine to 12, and 13–18 years. In addition, since very young children do generally not consume stimulants, an analysis was conducted for school-aged children (five to 18 years). Prevalent and incident users were identified for the population of Manitoba for the following medication groups: short acting brand name methylphenidate, short acting generic methylphenidate, long acting brand name methylphenidate, and long acting brand name amphetamine. For a detailed list of the medications included in the categories, please refer to Appendix Table 1.

Incident users were those users of a stimulant who had not used any prior stimulant in the one year prior to this first stimulant prescription. Incident and prevalent utilization of stimulants was compared before and after the market availability of Concerta[®] using GEE modeling.

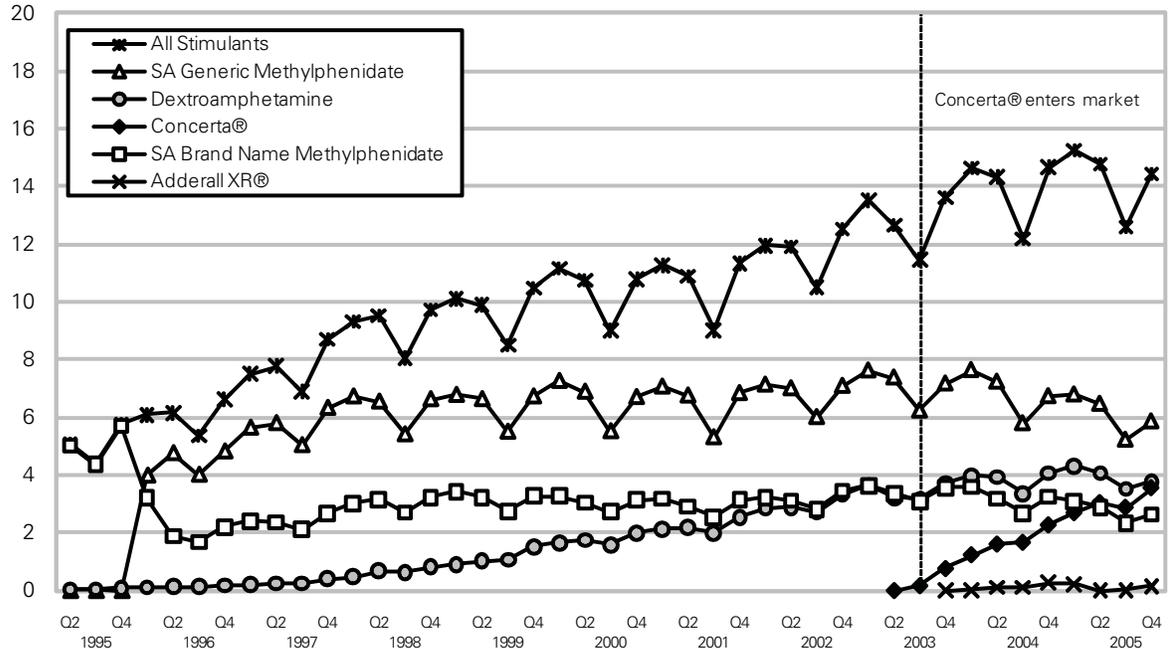
10.2 Results

Prevalence

Overall, we observed a general increase in prevalent utilization of stimulants over time, with greater utilization of short acting generic methylphenidate after it was introduced in early 1996. Total prevalent utilization of stimulants in the pediatric population increased from 5.0 to 14.4 users per 1,000 children over the study period. When Concerta[®] came onto the market in the third quarter of 2003, its utilization increased dramatically from 0.2 to 3.5 users per 1,000 residents by the end of the study period. There were relatively few users of Adderall XR[®] since its market availability at the beginning of 2004. The prevalent utilization of stimulants demonstrated a seasonal pattern, with the lowest utilization in the third quarter of each year.

Figure 10.1: Stimulants Quarterly Prevalence

Crude user rates per 1,000 children, Q2 1995–Q4 2005

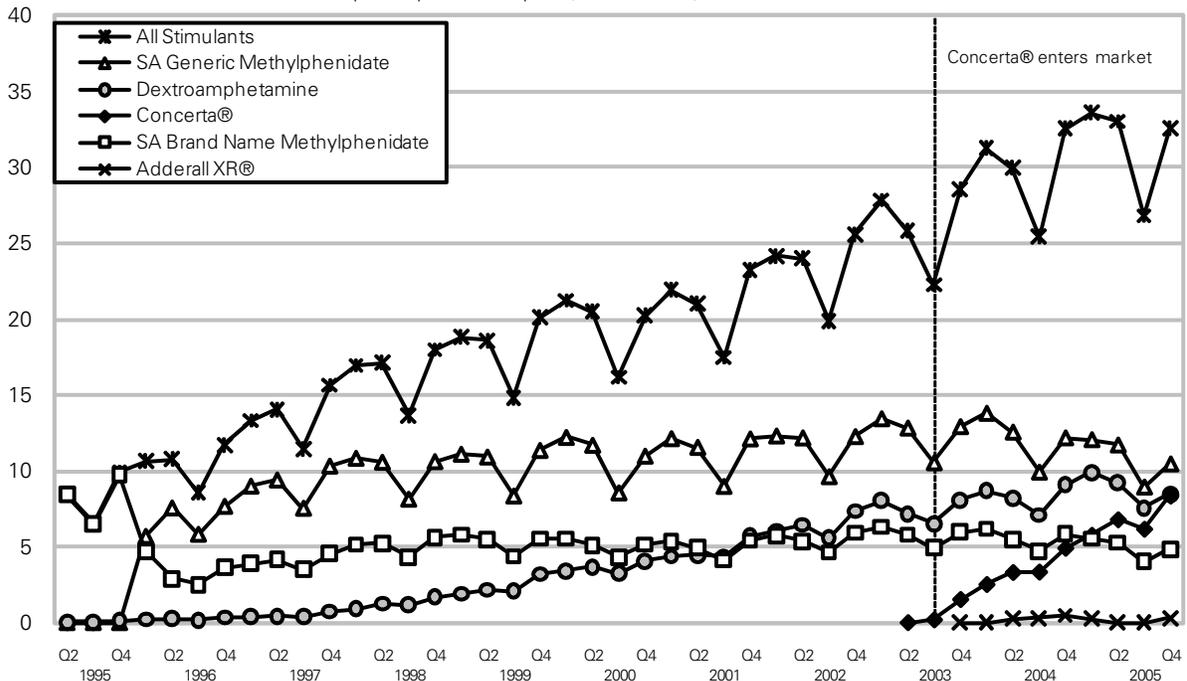


'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Figure 10.2: Stimulants Quarterly Prevalence

Crude prescription rates per 1,000 children, Q2 1995–Q4 2005



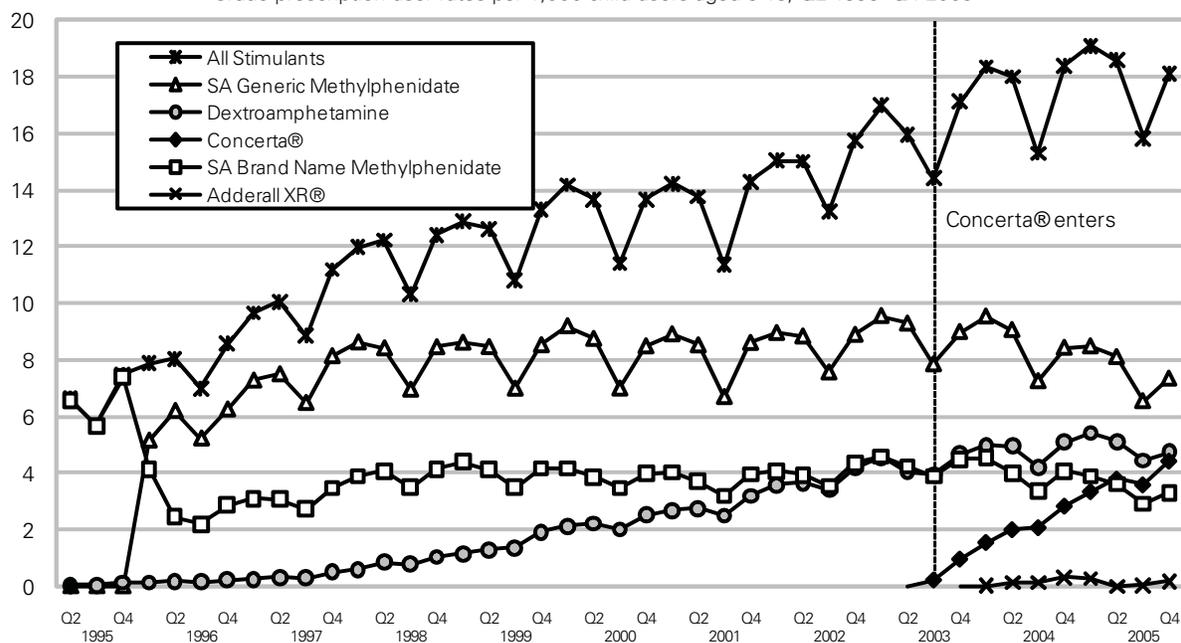
'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

For the population aged five to 18 only, the utilization of all stimulants increased from 6.6 to 16.0 users per 1,000 just prior to the launch of Concerta® to 18.1 per 1,000 by the end of the study period. Independent of sociodemographic characteristics, prevalent use of stimulants did not increase (the rate of prevalent users was not statistically different from zero) after the timing of the launch of Concerta® (Table 10.1).

Figure 10.3: Stimulants Quarterly Prevalence

Crude prescription user rates per 1,000 child users aged 5-18, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Table 10.1: Prevalent Use (Users/1,000 Children aged 5-18) of Stimulants, 1995-2005

Medication	Baseline rate/1,000§	Change in rate* in rate*	Before		Change in rate* in rate*	End 2005 users/1,000	Age effect* Age 5-8 vs 13+	Prescription cost sharing* No cost vs high income	Region effect* Rural vs Urban
			Concerta® rate/1,000 2003Q2	launched rate/1,000 2003Q2					
All stimulants	6.61	1.03 + 3% **	15.96	1.00 -0.4% F16	18.12	0.87 -13%	0.92 -8%	0.21 -79% †	

* Results are presented as relative rates (adjusted for age, prescription cost sharing, region and time) and then, for ease of interpretation, as percentages

** Indicates a slope significantly different from zero (p<.05)

†: Indicates a statistically significant effect (p<.05)

§ Baseline rates are users per 1,000 adults at the second quarter of 1995

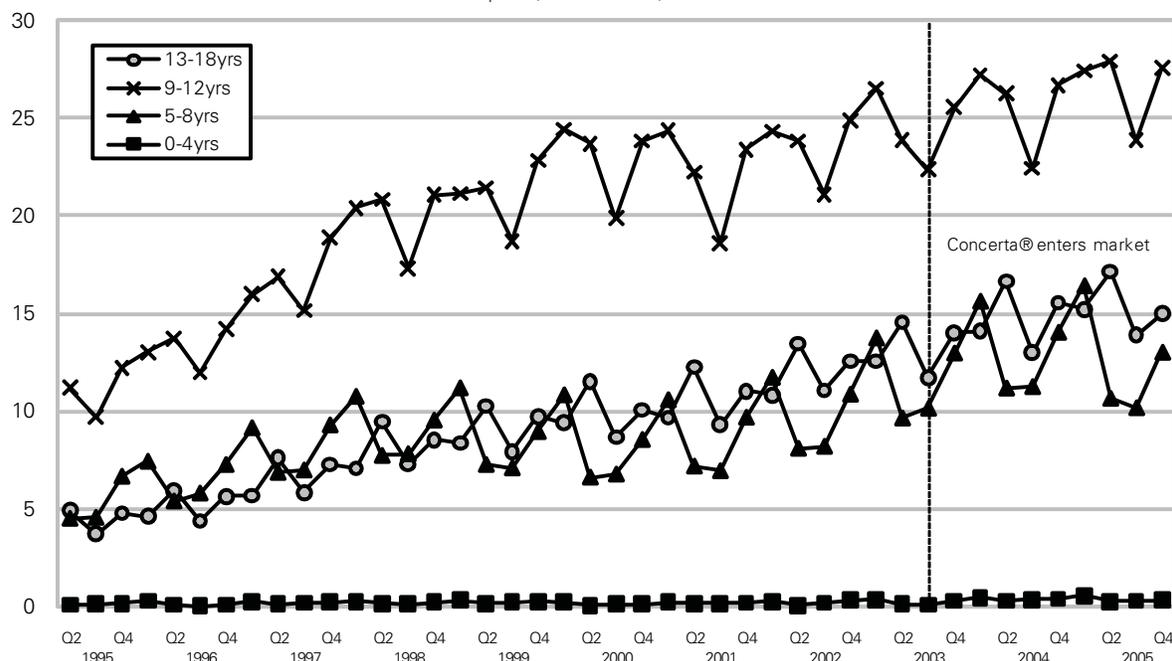
or when prescriptions were first filled for a drug

Source: Manitoba Centre for Health Policy, 2009

When evaluated by age, the greatest utilization of all stimulants was in children aged nine to 12 (11.2 to 27.5 per 1,000 over the study period), followed by children aged 13–18 (4.9 to 15.0 per 1,000) and children aged five to eight (4.5 to 13.0 per 1,000). Utilization was minimal in children younger than four years old (increased from 0.07 to 0.30 users per 1,000 residents over the study period).

Figure 10.4: Stimulants Quarterly Prevalence by Age

Crude user rates per 1,000 children, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)
'Q4' indicates prevalence for the 4th quarter (October to December)
'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

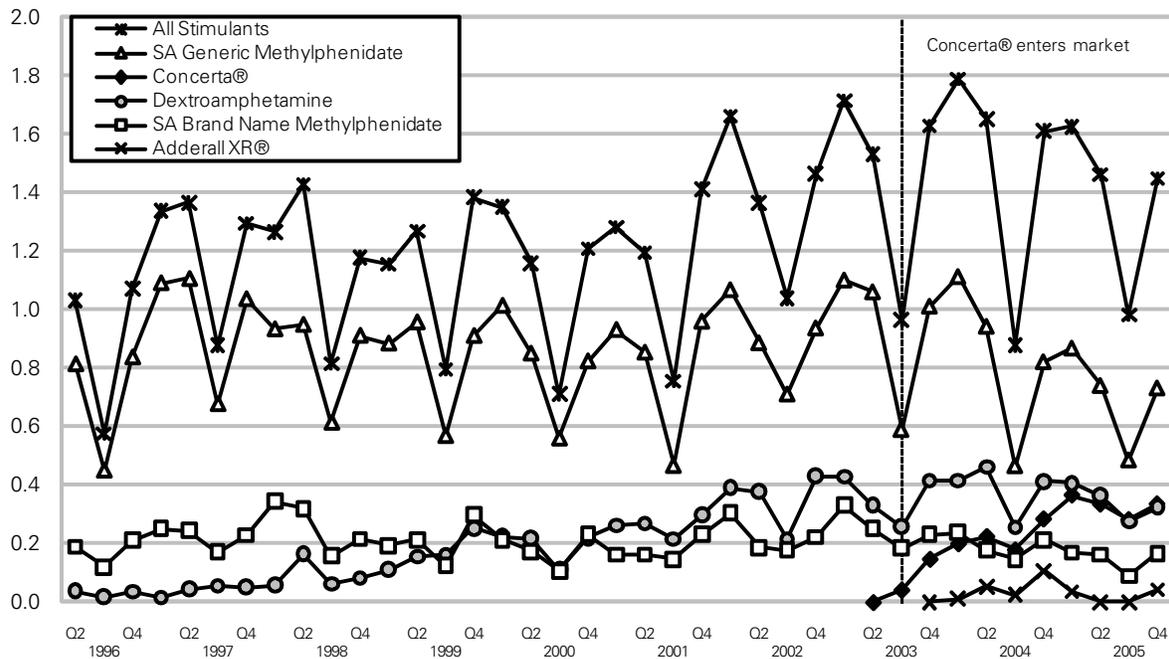
Children (aged five to 18) receiving no cost prescriptions were as likely to be treated with stimulants as children in the highest income Pharmacare group (Table 10.1). Independent of age, prescription cost sharing, and prescribing trend over time, children living in rural areas were 80% less likely to receive a stimulant prescription (Table 10.1).

Incidence

Incident utilization of stimulants was seasonal and increased over the study period from 1.0 to 1.5 users per 1,000 residents per quarter. Similar to the patterns observed with prevalent use, incident utilization of short acting generic methylphenidate was greater than all other medications. Incident use in the entire pediatric population fell from 0.81 to 0.73 users per 1,000 residents per quarter over the study period.

Figure 10.5: Stimulants Quarterly Incidence

Crude rates of users with no use of psychostimulants in prior year per 1,000 children, Q2 1996–Q4 2005



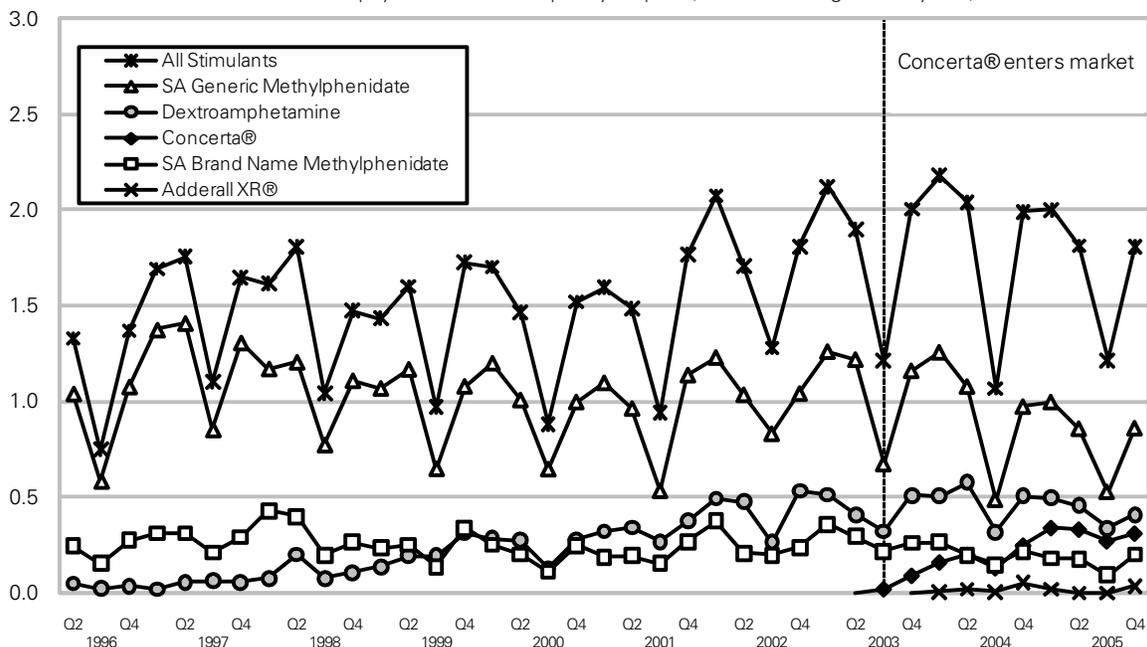
'Q2' indicates incidence for the 2nd quarter (April to June)
 'Q4' indicates incidence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

In the seven-year period before the introduction of Concerta® in the third quarter of 2003, the rate of new use of stimulants for children aged five to 18 increased from 1.33 to 1.81 per 1,000.

Figure 10.6: Stimulants Quarterly Incidence

Crude rates of users with no use of psychostimulants in prior year per 1,000 children aged 5-18 years, Q2 1996–Q4 2005



'Q2' indicates incidence for the 2nd quarter (April to June)
 'Q4' indicates incidence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Independent of sociodemographic characteristics, the rate of increase of new use of all stimulants became less steep after the launch of Concerta® ($p < 0.05$). In addition, incident use of all stimulants leveled off to a constant rate (the rate of new prescriptions was not statistically different from zero) (Table 10.2).

Table 10.2: Incident Use (New Users/1,000 Children aged 5-18) of Stimulants, 1996-2005

	Before Concerta® launched (1996Q2-2003Q2)		Concerta® marketed (2003Q3-2005Q4)
	First Quarter 1996Q2	Last Quarter 2003Q2	Last Quarter 2005Q4
Crude rate	1.33	1.90	1.81
Adjusted rate*		1.99	1.87
Adjusted rate of change* per quarter		1.01**	0.99†

* Adjusted for age, prescription cost sharing, region and time

Rate of change results are presented as relative rates

** Indicates a slope significantly different from zero ($p < .05$)

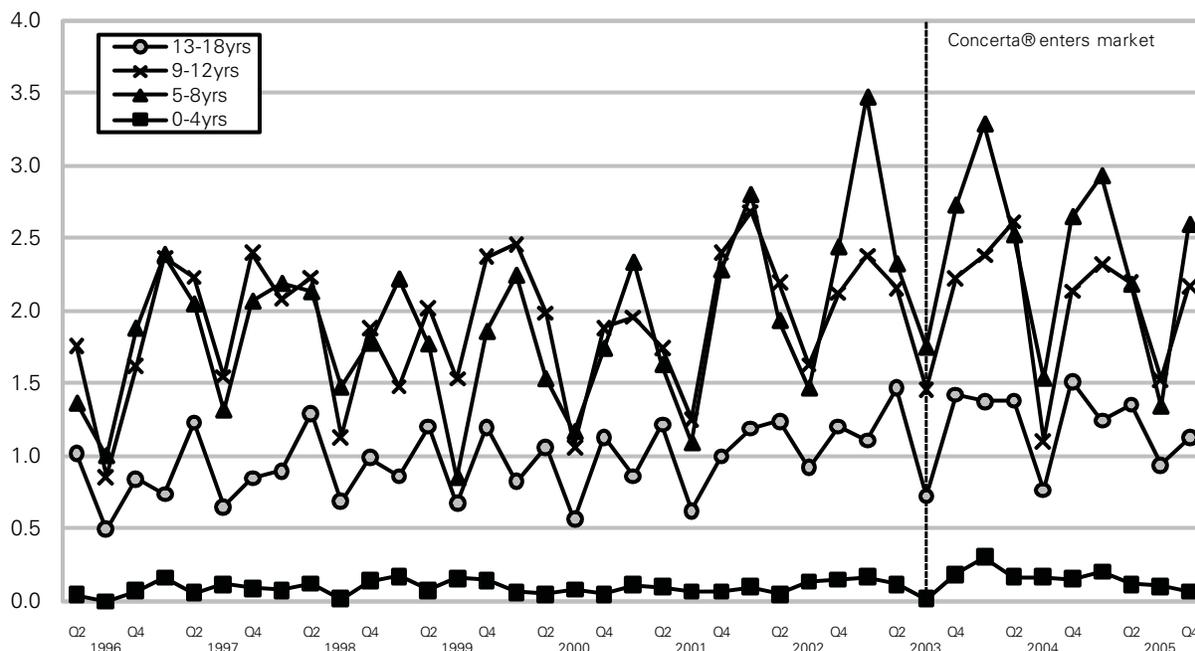
† Indicates a significant change in the slope after the intervention ($p < .05$)

Source: Manitoba Centre for Health Policy, 2009

When evaluated by age groups, the rate of new prescriptions of all stimulants was similar in those aged nine to 12 and five to eight, with very minimal utilization in those younger than four years.

Figure 10.7: All Stimulants Quarterly Incidence by Age

Crude rates of users with no use of psychostimulants in prior year per 1,000 children, Q2 1996–Q4 2005



'Q2' indicates incidence for the 2nd quarter (April to June)

'Q4' indicates incidence for the 4th quarter (October to December)

'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

10.3 Discussion

Overall, we observed an increase in prevalent and incident utilization of all stimulants in Manitoba over the study period. Short-acting generic methylphenidate was the most commonly prescribed stimulant. In a comparative study of stimulant prescribing for children in 2000, amphetamines and methylphenidate were prescribed equally among children in the US; while in the Netherlands and France, more than 95% of stimulant utilization was for methylphenidate (Zito et al., 2008). The second most commonly utilized stimulant for a large part of the study period was short-acting brand name methylphenidate. This category includes sustained-release Ritalin SR[®] that continued to be available as brand name medication throughout the study period.

Despite lack of Pharmacare formulary reimbursement for the long-acting brand name methylphenidate (Concerta[®]), we observed a rapid uptake of this newly marketed agent. The uptake of Concerta[®] and subsequent decline in prevalent utilization of the short-acting brand name methylphenidate suggests that Concerta[®] may have replaced the prescription of short-acting brand name methylphenidate to some extent. The timing of the launch of Concerta[®] did not further increase overall utilization of stimulants in children. In fact, utilization of all stimulants stabilized thereafter.

We found prevalent users of a stimulant to be 14.4 per 1,000 children (from birth to 18 years) in Manitoba by the end of 2005. American studies suggest that the prevalence use of stimulants may be as high as 29 per 1,000 in 2002 (Zuvekas, Vitiello, & Norquist, 2006). A Manitoba study in the mid 1990s reported that stimulant medications were used by nine children per 1,000 (Brownell & Yogendran, 2001). In British Columbia, prevalent methylphenidate use was 11 per 1,000 in 1996 (Miller, Lalonde, McGrail, & Armstrong, 2001). A Canadian survey study estimated utilization to be 16 per 1,000 [95% CI 14.2–17.8] in 1998/99 (Romano et al., 2005). Differences in study methodology likely account for the variation in rates. The seasonality we observed, with the lowest utilization in the third quarter, likely corresponds with school summer holidays.

Several other studies have described the increase in utilization of stimulants in children over time (Winterstein et al., 2008; Knellwolf et al., 2008; Miller et al., 2001; Zito et al., 2003; Berbatis, Sunderland, & Bulsara, 2002; Romano et al., 2002; Charach, Cao, Schachar, & To, 2006; Robison, Skaer, Sclar, & Galin, 2002; Brownell et al., 2008). A recent Manitoba analysis of children aged five to 19 observed an increase in the annual rate of children with at least one stimulant prescription from 19.1 per 1,000 in 2000/01 to 26.8 in 2005/06 (Brownell et al., 2008). We measured quarterly utilization in two time periods—before and after market availability of Concerta[®] in 2003, which may account for the difference in prevalent use between the two studies. Further, some studies such as the large study of stimulant medication utilization in the United States did not demonstrate a significant increase in utilization from 1997 to 2002 (Zuvekas et al., 2006).

We observed the greatest utilization of stimulants to be in children aged nine to 12, consistent with some studies (Zuvekas et al., 2006; Knellwolf et al., 2008), but not others (Winterstein et al., 2008; Miller et al., 2001; Zito et al., 2008). We noted that the utilization of stimulants among children birth to four years was low. Whereas some authors have observed an increase in utilization amongst U.S. children aged two to four (Zito et al., 2000), others did not observe this trend in Canadian children (Charach et al., 2006).

We did not find higher stimulant use in children receiving prescriptions at no cost relative to children in higher income groups. Others have also noted the lack of variation in stimulant utilization by socioeconomic status (Charach et al., 2006) but a study conducted on Manitoba children did document differences by socioeconomic status (Brownell, Mayer, & Chateau, 2006). The same study reported no rural or urban differences in stimulant utilization (Brownell et al., 2006). Differences in study methodology, age groupings, and definitions for socioeconomic status among children prescribed stimulants likely account for these differences.

CHAPTER 11: ANTIBIOTICS

Antibiotics are effective pharmacotherapeutic agents in the treatment and prevention of infectious diseases caused by bacteria. We evaluated how the utilization of newer and older antibiotics in adults and children has changed over time. In particular, we were interested in the utilization of azithromycin, a newer macrolide antibiotic used for the treatment of **upper respiratory tract infections**, community acquired **pneumonia**, chronic bronchitis, genitourinary infections, and other infectious diseases caused by susceptible microorganisms (Peters, Friedel, & McTavish, 1992). Following market release, both azithromycin and clarithromycin (another newer macrolide) were added to Part 2 (utilization for established criteria) of the Manitoba Pharmacare formulary and have remained in Part 2, as have the fluoroquinolones.

11.1 Methods

Prevalent and incident users were identified for the population of Manitoba (both adults and children) for the following groups of oral antibiotics:

- Penicillins: amoxicillin, cloxacillin, amoxicillin/clavulanate
- Fluoroquinolones: ofloxacin, ciprofloxacin levofloxacin, gatifloxacin, moxifloxacin
- Macrolides: azithromycin, clarithromycin, erythromycin
- Cephalosporins: cefalexin, cefuroxime, cefprozil, cefaclor, cefixime
- Trimethoprim and sulfonamides
- Tetracyclines: doxycycline, tetracycline, minocycline
- Other: clindamycin and metronidazole

For a list of the medications included in the categories, please refer to Appendix Table 1. In addition, to more closely examine the prescribing trends over times for the macrolides, separate analyses of the individual medications included in this category were performed (azithromycin, erythromycin, clarithromycin).

Incident users were those users of an antibiotic in one of the above groups who had not filled any prescriptions for systemic antibiotics (oral or intravenous) in the one year prior to this antibiotic prescription. For this chapter, only prevalent utilization of antibiotics is presented due to the generally episodic nature of use of antibiotics. Prevalent utilization of antibiotics adjusted for age, region, and prescription cost-sharing, was determined over time using GEE modeling.

11.2 Results

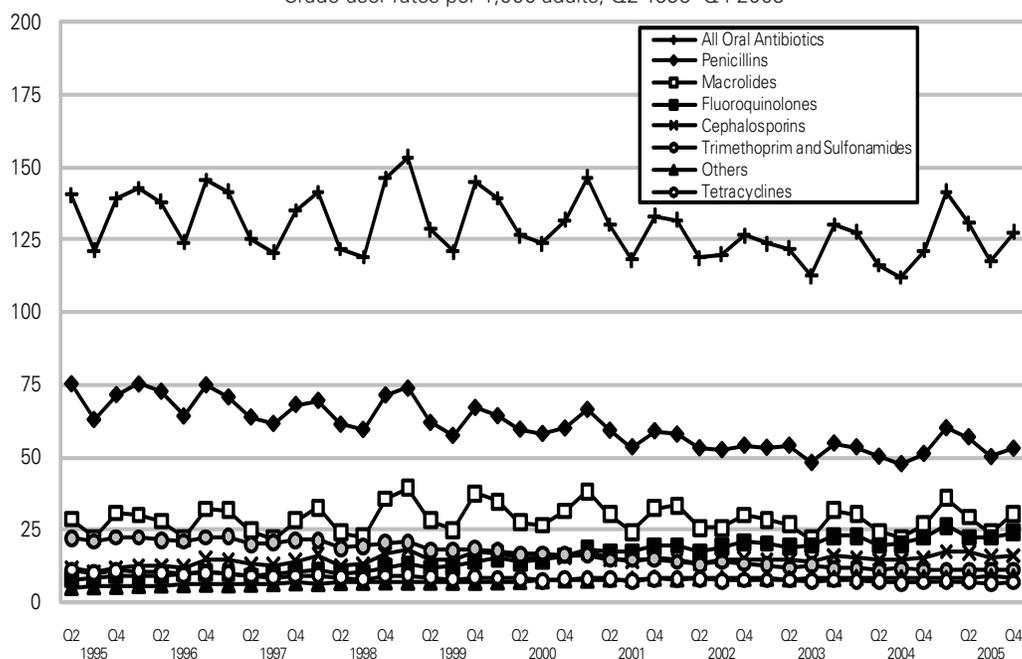
Prevalence

Adults

Overall, utilization of oral antibiotics in adults declined from 140.5 users per 1,000 residents in 1995 to 127.6 users in 2005 (prescriptions decreased from 186.6 to 173.5 per 1,000).

Figure 11.1: Antibiotics Quarterly Prevalence

Crude user rates per 1,000 adults, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)

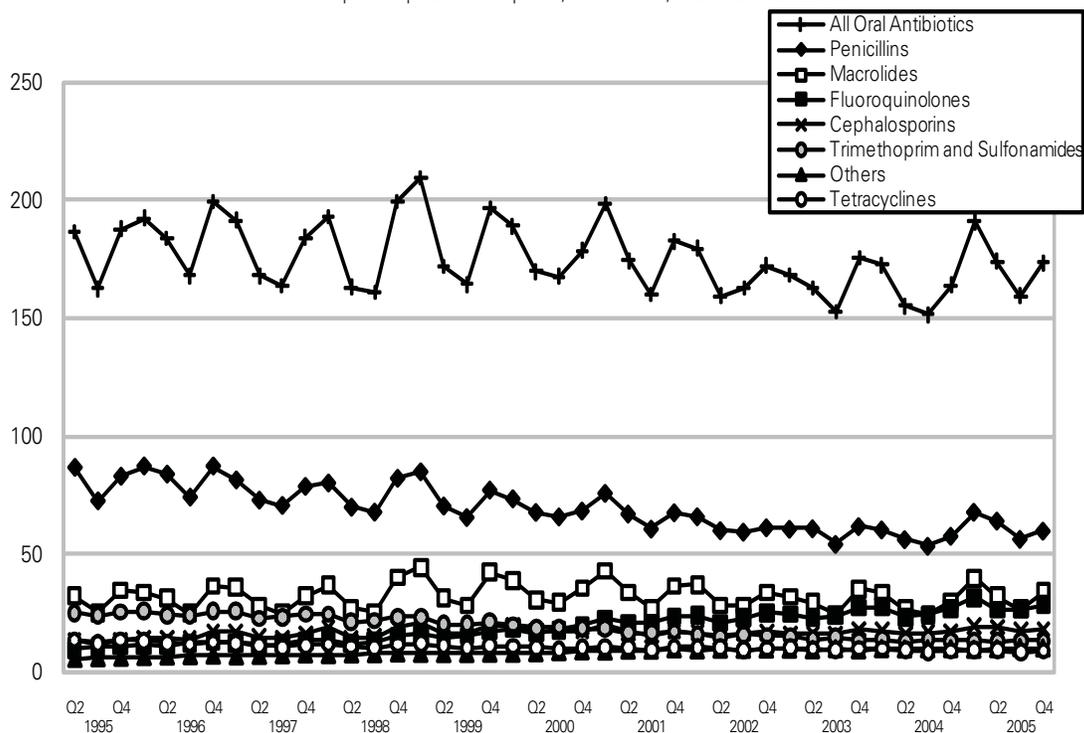
'Q4' indicates prevalence for the 4th quarter (October to December)

'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Figure 11.2: Antibiotics Quarterly Prevalence

Crude prescription rates per 1,000 adults, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Statistically significant rates of decline were observed for the penicillins, the tetracyclines and trimethoprim and sulfonamides. In contrast, utilization of macrolides increased over time from 28.7 to 30.6 users per 1,000 residents population.

Table 11.1: Prevalent Use (Users/1,000 Adults) of Antibiotics, 1995-2005

Medication	Baseline users/1,000§	End 2005 users/1,000	Change in rate*	Age effect* Age 45-64 vs 85+	Prescription cost sharing* No cost vs high income	Region effect* Rural vs urban
Penicillins	75.39	52.95	0.99 -1% **	0.79 -21%	1.76 2 fold higher †	0.94 -6%
Fluoroquinolones	7.87	23.91	1.03 + 3% **	0.32 - 68% †	2.17 2 fold higher †	1.03 + 3%
Macrolides	28.67	30.61	1.00 + 0.3% **	1.02 + 2%	1.78 2 fold higher †	0.87 - 13% †
Cephalosporins	11.61	16.00	1.00 + 0.3% **	0.55 - 45% †	2.14 2 fold higher †	1.25 + 25% †
Trimethoprim and sulphonamides	22.07	11.20	0.98 - 2% **	0.50 - 50% †	2.01 2 fold higher †	1.15 + 15%
Tetracyclines	11.22	6.89	0.99 - 1% **	1.71 + 71% †	1.52 + 52% †	0.89 - 11% †
Others	4.96	8.65	1.01 + 1% **	0.87 - 13%	2.05 2 fold higher †	1.03 + 3%

* Results are presented as relative rates (adjusted for age, prescription cost sharing, region and time) and then, for ease of interpretation, as percentages

** Indicates a slope significantly different from zero (p<.05)

† Indicates a statistically significant effect (p<.05)

§ Baseline rates are users per 1,000 adults at the second quarter of 1995 or when prescriptions were first filled for a drug

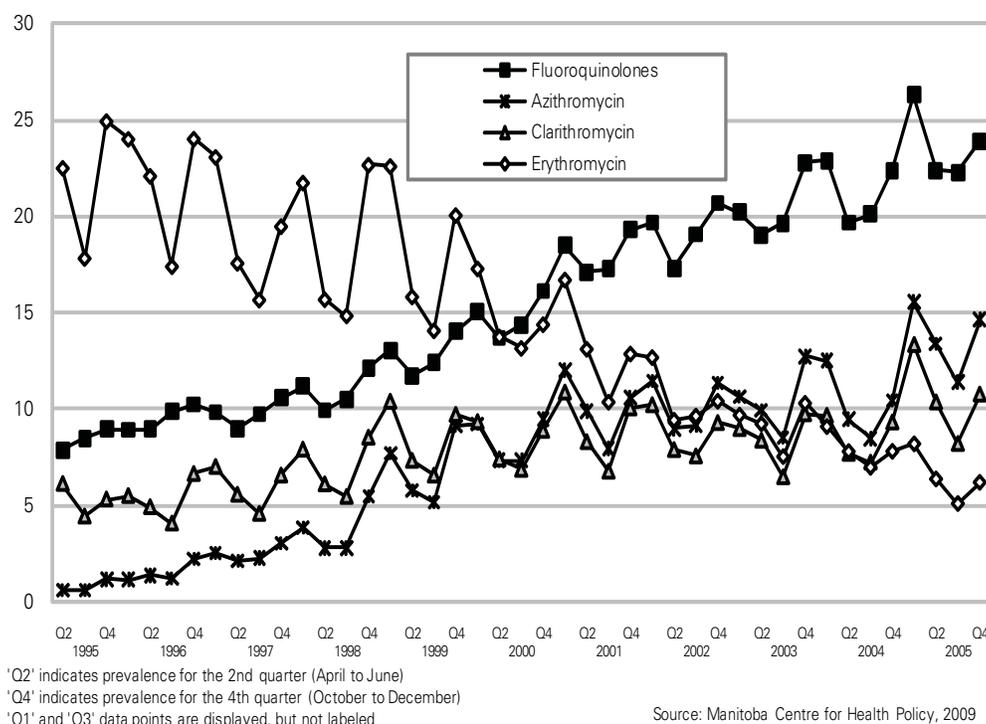
|| Regional analysis for the Fluoroquinolone model compares Point Douglas to Fort Garry

Source: Manitoba Centre for Health Policy, 2009

When each macrolide was examined separately, a pattern of declining utilization of erythromycin was observed over the study period (from 22.5 to 6.2 users per 1,000 residents), along with increasing utilization of azithromycin and clarithromycin (0.6 to 14.6 and 6.8 to 10.8 users per 1,000 residents, respectively). The rate of increase in prevalent azithromycin use was higher in adults than any other class of medications evaluated; with each successive quarter, there was an increase of 6.4% over the previous quarter's rate ($p < 0.05$). For clarithromycin, this increase was 1.5% ($p < 0.05$). The shift towards utilization of newer agents was also observed with fluoroquinolones (users per population increased from 7.9 to 23.9). With each successive quarter, there was a 3% increase in their use as compared to the previous quarter's rate (Table 11.1).

Figure 11.3: Antibiotics Quarterly Prevalence

Crude user rates per 1,000 adults, Q2 1995–Q4 2005



When evaluated by age, different patterns were observed for the utilization of individual oral antibiotics. Generally, older adults were more likely to receive prescriptions for the macrolides (azithromycin and clarithromycin), but less likely to be treated with penicillins and erythromycin.

For fluoroquinolones, greatest utilization was amongst the oldest age groups. Use among persons aged 45–64 was 68% lower than those aged 85 and older (Table 11.1).

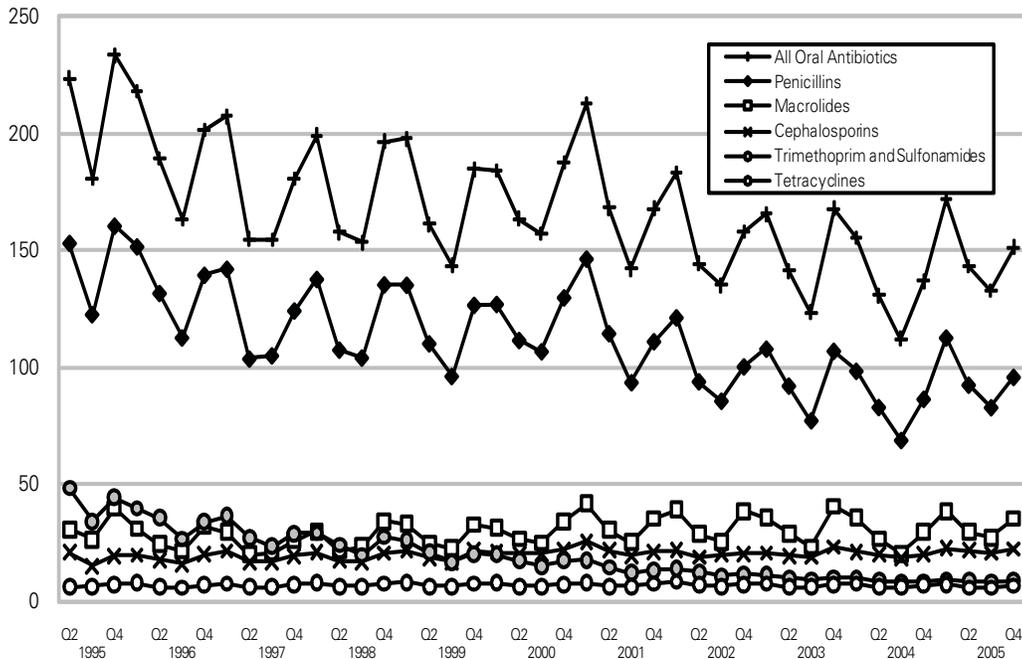
For most antibiotics, utilization was twice as likely amongst persons receiving prescriptions at no cost than in the higher income Pharmacare group, even when adjusted for age, region, and prescribing trend over time (Table 11.1). There were no regional differences in utilization for many antibiotic classes. However, when adjusted for other factors, persons living in rural areas were 25% more likely than urban dwellers to receive prescriptions for cephalosporins, but 13% less likely to receive macrolides.

Children

Similar to adults, fewer children were treated with oral antibiotics in 2005 than 1995 (users per 1,000 residents declined from 223.6 to 151.4). The number of prescriptions per 1,000 decreased from 310.3 to 197.0 per 1,000 over this time period. The penicillins, namely amoxicillin, were the most commonly prescribed antibiotic, followed by the macrolide category (largely due to erythromycin).

Figure 11.4: Antibiotics Quarterly Prevalence, Children

Crude user rates per 1,000 children, Q2 1995–Q4 2005

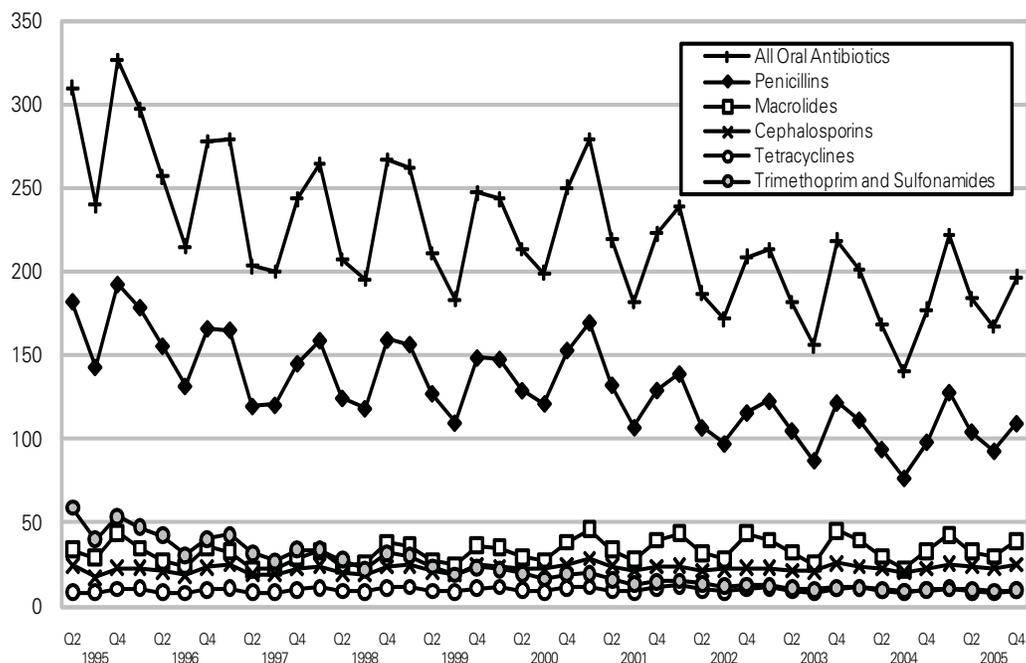


'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Figure 11.5: Antibiotics Quarterly Prevalence, Children

Crude prescription rates per 1,000 children, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

While utilization of all macrolides had increased over the study period, when each macrolide was examined separately, utilization of erythromycin had decreased from 28.7 to 5.6 users per 1,000 residents, but azithromycin and clarithromycin were prescribed increasingly more often (0.1 to 19.3 and 2.0 to 11.4 users per 1,000 residents, respectively). The rate of increase in prevalent azithromycin use was higher in children than any other class of medications evaluated; with each successive quarter, there was an increase of 10% over the previous quarter's rate ($p < 0.05$). For clarithromycin, this increase was 3.6% ($p < 0.05$).

The trend towards declining utilization of older agents was also observed with the penicillins and the trimethoprim–sulphonamides. On the other hand, cephalosporin use rose; with each successive quarter, there was an increase of 0.6% as compared to the previous quarter's rate (Table 11.2).

Table 11.2: Prevalent Use (Users/1,000 Children) of Antibiotics, 1995-2005

Medication	Baseline users/1,000§	End 2005 users/1,000	Change in rate*	Age effect* Age 0-4 vs 13+	Prescription cost sharing* No cost vs high income	Region effect* Rural vs urban
Penicillins	153.09	95.91	0.99 - 1% **	2.08 2 fold higher †	1.21 + 21% †	0.82 - 18% †
Macrolides	30.65	35.18	1.00 + 0.4% **	1.76 2 fold higher †	1.15 + 15%	0.78 - 22% †
Cephalosporins	20.67	22.37	1.01 + 0.6% **	3.30 3 1/2 fold higher †	1.38 + 38% †	1.28 + 28% †
Trimethoprim and sulphonamides	48.39	8.58	0.97 - 3% **	4.55 4 1/2 fold higher †	1.06 + 6%	0.97 - 3% lower
Tetracyclines	6.05	6.63	0.99 - 1% **	0.001 - 99.9% †	0.47 - 53% †	0.89 - 11%

* Results are presented as relative rates (adjusted for age, prescription cost sharing, region and time) and then, for ease of interpretation, as percentages

** Indicates a slope significantly different from zero (p<.05)

† Indicates a statistically significant effect (p<.05)

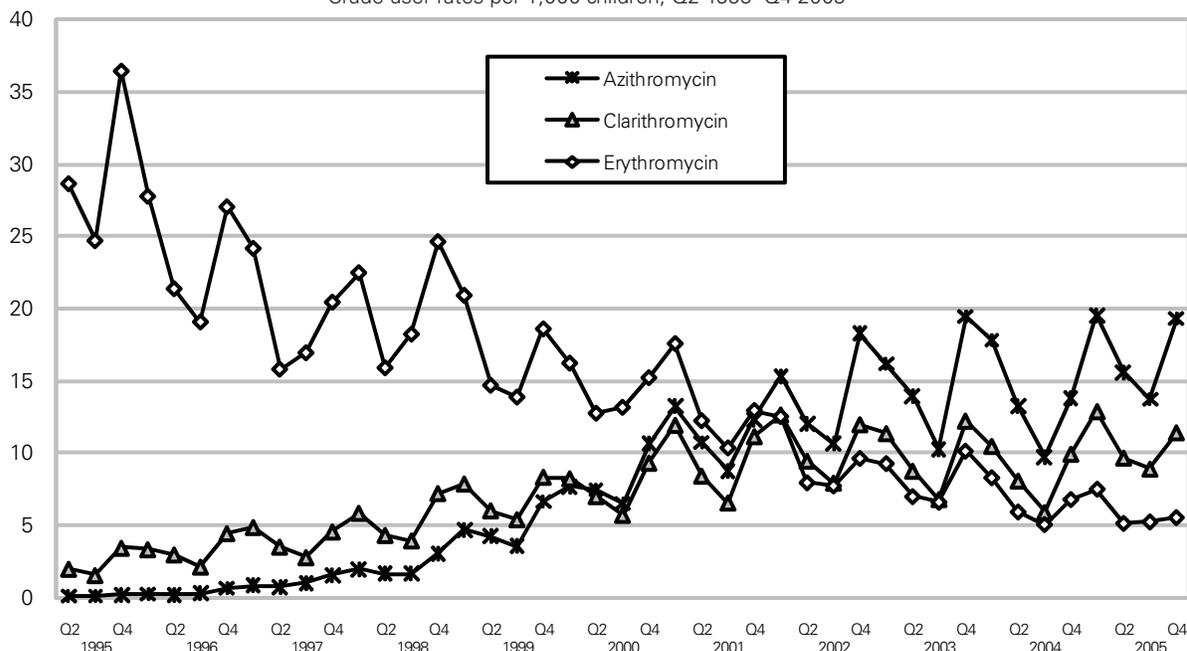
§ Baseline rates are users per 1,000 children at the second quarter of 1995

or when prescriptions were first filled for a drug

Source: Manitoba Centre for Health Policy, 2009

Figure 11.6: Antibiotics Quarterly Prevalence, Children

Crude user rates per 1,000 children, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)

'Q4' indicates prevalence for the 4th quarter (October to December)

'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

When evaluated by age, azithromycin, clarithromycin, erythromycin, and penicillins were used more frequently in the younger age groups, especially when adjusted for other factors (Table 11.2). See Appendix 2, Figures A.11.6 to A.11.9 for illustrations of prevalence by age. Compared to children in higher income groups, children receiving prescriptions at no-cost were more likely to be treated with penicillins and the cephalosporins. This finding could not be attributed to age, region, or prescribing trend over time (Table 11.2). Region of residence also had an independent effect on antibiotic choice: children in rural areas received cephalosporins more often (Table 11.2).

11.3 Discussion

Overall, we observed a reduction in the utilization of antibiotics in both adult and pediatric populations, a phenomenon that has been observed in North American (McCaig, Besser, & Hughes, 2003; Roumie et al., 2005; Patrick et al., 2004; Marra, Patrick, Chong, & Bowie, 2006; Kozyrskyj et al., 2004b; Banthin & Miller, 2006), but not consistently in Europe (Ferech et al., 2006; Elseviers, Ferech, Vander Stichele, & Goossens, 2007; de Jong, van den Berg, de Vries, & de Jong-van den Berg LT, 2008). Oral antibiotics with open formulary listing (especially amoxicillin and erythromycin) dominated antibiotic utilization throughout the study period. These patterns have been observed by others (McCaig et al., 2003; Petersen & Hayward, 2007; Ferech et al., 2006; Rossignoli, Clavenna, & Bonati, 2007; Marra et al., 2006; Kozyrskyj et al., 2004b). Further, utilization of more recently-marketed antibiotics rose throughout the study period, while utilization of older agents decreased. Again, these patterns are consistent with other studies that have evaluated trends in prescribing in adult (McCaig et al., 2003; Roumie et al., 2005) and pediatric populations

(McCaig et al., 2003; Elseviers et al., 2007; de Jong et al., 2008; Marra et al., 2006; Kozyrskyj et al., 2004b; Stille et al., 2004). Our findings are also similar to reported use by age (Blix, Engeland, Litleskare, & Ronning, 2007; Marra et al., 2006; Kozyrskyj et al., 2004b) and regional differences in antibiotic prescribing (Patrick et al., 2004; Ferech et al., 2006; Elseviers et al., 2007; Rossignoli et al., 2007).

In general, the newer, more costly and Part 2 antibiotics (such as azithromycin) were used less frequently than older agents (such as penicillins). Evaluations of formulary listings for antimicrobials have shown an impact on prescribing in other Canadian provinces (Sketris et al., 2004; Marra et al., 2005). However, we observed that use of Part 2 agents was increasing at the same time that use of older antibiotics was declining, suggesting a substitution effect. It may be that this pattern of utilization is appropriate, as newer antibiotics with broader spectrum antimicrobial activity are generally prescribed as second-line agents or for more serious infections. However, our study did not include data on indication for the antibiotic use or on the sequence of prescribing. Kozyrskyj et al. (2004b) found evidence of inappropriate utilization of antibiotics for viral respiratory tract infections and of first line prescribing in children. These types of studies are needed to evaluate the appropriateness of antibiotic prescribing.

CHAPTER 12: ANALYSIS STRENGTHS AND CHALLENGES

This report provides a complete picture of prescribing across several categories of medications for all adult Manitobans over a 10-year period. It assessed a range of societal influences on medication use, such as that of provincial drug program policies, federal agency warnings on safety, and published evidence of medication effectiveness. The influence of provincial drug program policies on medication utilization was the direct outcome of questions submitted by the Manitoba Pharmacare program. Further, as costs are a consideration in the decision to fill a prescription and Manitoba has an income-based Pharmacare deductible, medication utilization in Manitoba varies by prescription cost sharing. Many Manitobans receiving medications at no charge are covered by federal drug plans, such as the First Nations and Inuit Health Branch plan. While these formularies may not have the same formulary restrictions as Manitoba Pharmacare, our grouping of prescription medication users by type of drug plan and household income accounted for the effect of medication cost on utilization.

Limitations of the analyses are the same as those limitations of other studies using prescription and health care administrative databases. Prescription use was derived from records of dispensed prescriptions. Not everyone who seeks medical attention and receives a prescription for a medication fills the prescription. This may underestimate the number of medications actually used and incompletely capture the intent of physician prescribing in Manitoba. Physician sampling of medications are also not captured in the prescription medication records in the Population Health Research Data Repository in Manitoba, also contributing to underestimation the number of users of medications, particularly, newer medications. Alternately, individuals may fill prescriptions, but not actually take the medication, thus overestimating the number of users of medications in Manitoba. Finally, medical histories were derived from diagnosis data on physician claims and hospitalization data. These medical histories may underestimate the prevalence of a given condition in the population because they require contact with the health care system and were dependent on physician reimbursement records, which do not completely record all underlying **comorbidities**. It is very likely that several unmeasured factors also had an influential role on use of medications. These include, but are not limited to: physician access, prescriber characteristics, prescriber-patient interactions, pharmaceutical marketing, physician sampling of newly marketed medications, and patient perception of benefits and safety of medications. The impact of these factors on prescribing at a population level in Manitoba deserves further investigation.

12.1 Conclusions and Recommendations

This study evaluated the impact of Manitoba's Pharmacare Formulary policies and other societal factors on the utilization of prescription medications in Manitoba. We describe incident and prevalent utilization of prescription medications by sociodemographic characteristics within the province of Manitoba. Ten years of prescription drug data (1995 – 2005) have been employed to describe, using previously developed population based indicators of medication utilization, Manitoban's use of pharmacotherapy in 11 different medication categories.

The rates of utilization and increases in utilization of these categories of commonly prescribed medications are consistent with those in other Canadian provinces and with other studies employing Manitoba's prescription drug data.

In a national comparison of spending on pharmaceuticals in Canada, it was found that age adjusted overall spending on prescription medications in Manitoba was 7.6% below the national average in 2007; the cost driver most associated with this was a lower volume of prescriptions (Morgan et al., 2008). This value was between the highest age adjusted spending in Quebec (13.4% above national average) and the lowest in British Columbia (27.7% below national average). However, age standardized average annual rate of change in inflation—adjusted per capita spending by province from 1998–2007—increased in Manitoba by 8.0%, which was higher than the national average of 5.1% (Morgan et al., 2008). So, although overall prescription drug spending was lower in Manitoba in 2007 than in other provinces, the increase in spending over time was greater in Manitoba than other provinces.

The main focus of this deliverable, however, is on the impact of Manitoba Pharmacare Formulary policies on pharmaceutical utilization.

12.1.1 Key Findings and Recommendations

With the exception of oral antibiotics, prevalent and incident utilization of medications in the population of Manitoba had risen from 1995 to 2005. Many societal factors contribute to population trends in medication utilization. We documented the impact of Pharmacare prescription policies, such as change in formulary listing category (COX 2 inhibitors) and formulary addition of newly-marketed medications (Oxycontin®, LABA/corticosteroid inhalers) and generic drugs (bisphosphonates, proton pump inhibitors, stimulants). As observed in other jurisdictions, we found evidence for the influence on medication use, of large randomized controlled trials (bisphosphonates and hormone replacement therapy, antipsychotics, antihypertensives, statins) or newly-emerging literature and Health Canada warnings of harm (antipsychotics in elderly). Other factors such as age, prescription cost sharing, and region of residence, as well as many other unmeasured factors, also affected the utilization of medications.

Impact of change in Pharmacare formulary status from Part 1 to Part 2

- *COX 2 inhibitors.* Less than two years after being listed as an unrestricted benefit in Part 1 of the Pharmacare formulary, 4% of all adult Manitobans had been prescribed a COX 2 inhibitor. During Part 1 listing, the rate of new use climbed at 20% per quarter for celecoxib (Celebrex®) and 84% for rofecoxib (Vioxx®). Following a change in their formulary listing to Part 2 (reimbursement for prescribing according to established criteria) in 2000, a reduction in use of COX 2 inhibitors was observed. New use of both agents fell until the end of 2004, at which time rofecoxib was withdrawn from the market and COX 2 formulary listing was further modified to Part 3 (prior approval required for reimbursement). The decline in use after the transition in listing from Part 1 to Part 2 was slightly greater for celecoxib than for rofecoxib. These changes were independent of sociodemographic and regional differences, strongly suggesting that the change to Part 2 formulary restricted reimbursement curtailed their prescribing.

Impact of Pharmacare formulary addition or launch of a newly marketed medication

- *Oxycontin*[®]. The utilization of *Oxycontin*[®] increased rapidly in adults upon addition to the Manitoba formulary. However, chronic use of *Tylenol #3*[®] and its generics did not decrease after the formulary addition of *Oxycontin*[®], which indicates that *Oxycontin*[®] was not being prescribed as a replacement for *Tylenol #3*[®]. In fact, the timing of the formulary addition of *Oxycontin*[®] was associated with a slight increase in new chronic use of *Tylenol #3*[®]. In 2005, 2% of Manitoba residents had received three or more prescriptions for *Tylenol #3*[®] or its generics; the use of *Oxycontin*[®] was 0.2%.
- *LABA corticosteroid inhalers (Advair*[®], *Symbicort*[®]). In 2005, 19% of adults with asthma and chronic lung disease had received a LABA corticosteroid inhaler, such as *Advair*[®]. Five percent of children with asthma had received this type of combination inhaler. New use of single–entity inhaled corticosteroids in adults with asthma or chronic lung disease had declined since 1996; and following the formulary addition of *Advair*[®], utilization declined at a faster rate. In asthmatic children however, new use of inhaled steroid medications had risen prior to *Advair*[®] and continued to do so afterwards. These findings suggest that LABA corticosteroid products were being prescribed in place of single–entity inhaled corticosteroids for adults but not children. LABA corticosteroid combination inhalers are currently recommended as add–on therapies for children and adults whose asthma is not optimally controlled with single–entity inhaled corticosteroids. In adults, they are also recommended as combination therapy with anticholinergics in moderate to severe chronic obstructive lung disease, which may explain the switching to these products for adults but not children.
- *Long–acting methylphenidate (Concerta*[®]). Close to 2% of schoolchildren had received a prescription for a stimulant in 2005, almost triple the rate from 10 years previous. In that year, less than 0.5% of children had received the newly marketed stimulant *Concerta*[®], which was not listed on the Pharmacare formulary. In the seven–year period before the introduction of *Concerta*[®] in 2003, new use of stimulants had been rising at a rate of 1% per quarter. Afterwards, independent of changes to sociodemographics, new use of all stimulants leveled off. Overall use of stimulants did not increase following the introduction of *Concerta*[®] and stabilization in new use may be the outcome of societal concern over the inappropriate prescribing of stimulants.

Impact of Health Canada warnings and clinical trial publications

- *Bisphosphonates*. In 2005, almost 2% of Manitoba adults had received a bisphosphonate; among those 85 years and older, it was 9%. Prior to the publication of the Women’s Health Initiative (WHI) trial results about hormone replacement therapy in 2002, new use of bisphosphonates had risen 4% every quarter since 1996. In the period after the publication of the WHI trial, hormone replacement therapy dropped dramatically and new use of bisphosphonates leveled off. The lack of subsequent increases to the rate of new prescribing for bisphosphonates after the publication of the WHI trial suggests that they did not replace hormone replacement therapy in Manitoba.

- *Atypical antipsychotics.* Prior to the first Health Canada (2002) warning about the possible association of risperidone with an increased risk of strokes in patients with dementia, atypical antipsychotics were being prescribed at an increasing rate in the elderly, such that by end of 2002, 2% of elderly Manitobans had received these medications. Following the first Health Canada warning, new use of atypical antipsychotics in the elderly leveled off. This change was independent of age and other sociodemographic factors and indicates an impact of the warnings. Despite this suggested impact, almost 3% of elderly Manitobans were prescribed atypical antipsychotics in 2005, indicating the need for further study of their use.

Utilization trends of commonly prescribed medications

- *Medications to treat Diabetes Mellitus.* The most dramatic increase in the use of medications to treat diabetes was for the first-line therapy metformin, such that metformin was the most commonly prescribed medication for diabetes by 2005 in adults, followed by sulfonylureas and insulins. However, independent of sociodemographic characteristics, new use of glitazones (whose reimbursement required prior approval under their Part 3 listing) increased the most (11% per quarter). In 2005, their use was comparable to that for insulin. In addition, there was evidence of more aggressive treatment of diabetes over the study period. The new prescription of triple therapy (three medications for diabetes) rose at a higher rate than that for dual and monotherapy.
- *Antihypertensives.* The use of all commonly prescribed antihypertensive medications in adults increased over the study time. Angiotensin-converting enzyme (ACE) inhibitors were used the most often, followed by beta blockers, calcium channel blockers, and thiazide diuretics. At a rate of 9%, increases in prevalent use were the highest for the angiotensin receptor blockers (ARBs). For adult Manitobans with uncomplicated hypertension, the recommended first-line agents, thiazide diuretics, were the most commonly prescribed, followed by ACE inhibitors. The use of ACE inhibitors for uncomplicated hypertension declined after 2002, coinciding with an increase in thiazide and ARB use. These changes can potentially be attributed to the publication of the ALLHAT trial and require further study to determine if they were sustained.
- *Statins.* Large increases in prevalent and new use of statins were observed over the 10-year study period. In 2005, 8% of adult Manitobans had received a statin prescription, more so for atorvastatin than any other statin. Just over half of new statin users had evidence of a high cardiovascular risk medical condition. Independent of sociodemographic factors, statin use for high cardiovascular risk rose at a quarterly rate of 3%, marginally greater than new use in persons with low cardiovascular risk.
- *Proton pump inhibitors (PPI).* Prevalent use of all PPIs increased from less than 1% of Manitoba adults in 1995 to 6% of adults in 2005. Omeprazole was used the most commonly prescribed PPI. The majority of new PPI users had received these medications for less than

three months of treatment. However, independent of sociodemographic characteristics, new use of PPIs that resulted in three months or more of treatment had increased at a significantly greater rate than short-term use.

- *Antibiotics.* Overall, a reduction in the use of antibiotics was observed for adults and children from 1995 to 2005. In adults and children, penicillins were prescribed the most often, followed by the macrolide antibiotics. The macrolides and cephalosporins were used increasingly more often over the study period. In adults, increases were also observed for the fluoroquinolones. The rise in use of the Part 2 restricted macrolides over the same time that use of erythromycin declined indicates a substitution effect. As a result of the potential for newer antibiotics to increase antibiotic resistance in Manitoba, further study is needed to determine the appropriateness of this substitution.

12.1.2 Data Recommendations

Data for the use of pharmaceuticals is limited to prescriptions filled in community pharmacies. Medication supplied to personal care homes from hospital based pharmacies and patients admitted to hospitals are not available to Manitoba Health for analysis. As hospitals are likely important places for initiating new therapies after important medical events or procedures, this data would be useful to further understand how pharmaceuticals are used and initiated in Manitoba.

Studies of appropriateness, effectiveness, and persistence with therapies will be facilitated by enhanced by merging clinical and/or survey based data with administrative data.

12.1.3 Recommendations for Future Research

This report is one of several in the continued series on pharmaceutical use in Manitoba and lays the foundation for others that will incorporate assessments of the appropriateness and health outcomes of medication use in the analysis. In addition, this report lags behind changes in Pharmacare policy that have been implemented since its completion. As such, these questions for further study include:

New Pharmacare policy changes

Evaluate the impact of the change in Manitoba Pharmacare listing for bisphosphonates from Part 2 to Part 3. This change occurred in 2005. The impact of this formulary restriction on pharmaceutical utilization as well as on patient outcomes (for example, bone density or fractures) is an area for further investigation.

Evaluate the impact of the change in Manitoba Pharmacare listing for proton pump inhibitors from Part 1 to Part 3. This switch occurred in early 2006. The impact of this formulary restriction on both medication utilization and patient outcomes (for example, gastrointestinal bleeding) is an area of further research.

Other classes of medications

Several other commonly prescribed classes of medications were not included in this deliverable could be considered for further population based analysis. Examples of such medications include antidepressants, newer anticonvulsants (e.g., gabapentin), and antithrombotics (e.g., clopidogrel).

Persistence

This deliverable did not evaluate persistence with therapies, which is known to be suboptimal for many classes of important medications. Persistence with medications contributes to utilization. Examples of categories of medications where persistence with therapy could impact clinical outcomes include the statins and the antihypertensives.

Appropriateness

This research has provided an initial assessment of drug utilization patterns in Manitoba. Follow-up research should include specific indicators of appropriate use of therapy. Classes where appropriateness of use of therapy could include proton pump inhibitors, antihypertensives, antibiotics, and inhaled medications for respiratory conditions.

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GLOSSARY

Acronyms used in this report:

ACE – Angiotensin–Converting Enzyme
ADHD – Attention Deficit Hyperactivity Disorder
ARB – Angiotensin Receptor Blockers
ARIMA – Autoregressive Integrated Moving Average
ATC – Anatomical Therapeutic Chemical Classification
CA – Community Area
COX 2 – Cyclo–Oxygenase type 2
EDS – Exception Drug Status
GEE – Generalized Estimating Equations
HRT – Hormone Replacement Therapy
ICD – International Classification of Diseases
LABA – Long–Acting Beta–Agonist
M3P – Multiple Prescribing Practices Program
NSAIDS – Non–Steroidal Anti–Inflammatories
PPI – Proton Pump Inhibitors
SABA – Short Acting Beta Agonist
WHI – Women’s Health Initiative

Anatomical Therapeutic Chemical (ATC) Classification

A drug classification system widely used in Europe. The drugs are divided into different groups at five levels according to the organ or system on which they act and/or therapeutic and chemical characteristics: 1) anatomical group; 2) therapeutic main group; 3) therapeutic/pharmacological subgroup; 4) chemical/therapeutic/pharmacological subgroup; and 5) subgroup for chemical substance. ATC classifications are available online and are updated and published once a year by the World Health Organization Collaborating Centre for Drug Statistics Methodology. The ATC system is becoming used more commonly in Canada.

Asthma

A chronic lung disorder that is marked by recurring episodes of airway obstruction (as from bronchospasm) manifested by labored breathing accompanied especially by wheezing and coughing and by a sense of constriction in the chest, and that is triggered by hyperreactivity to various stimuli (as allergens or rapid change in air temperature).¹

Attention Deficit Hyperactivity Disorder (ADHD)

A neurobehavioral developmental disorder that is characterized by inattention, hyperactivity, and impulsivity. The disorder is often identified during school ages and symptoms may continue into adulthood (American Psychiatric Association, 2000).

¹ <http://www.merriam-webster.com/medical/Asthma>

Body Mass Index (BMI)

A measure of health risk that is correlated with body fat based on height and weight that applies to both adult men and women. BMI is calculated as follows: weight in kilograms divided by height in metres squared.

Community Areas (CA)

The 12 planning districts within the Winnipeg Regional Health Authority (WRHA), which have similar populations to the rural and northern Regional Health Authorities (RHAs). The 12 CAs include: St. James–Assiniboia, Assiniboine South, Fort Garry, St. Vital, St. Boniface, Transcona, River East, Seven Oaks, Inkster, Point Douglas, Downtown, and River Heights.

Comorbidities

Presence of one or more medical conditions known to increase risk of death that exist in addition to the most significant condition which causes a patient's stay in the hospital (usually recorded as the "most responsible diagnosis" on hospital discharge abstracts). The number of comorbid conditions is used to provide an indication of the health status (and risk of death) of patients. In other words, comorbidity is an indicator of the differential utilization of hospital care.

Contraindication

Any circumstances (e.g., a disease) which render some particular line of treatment improper or undesirable.

Dementia

"... a group of [progressive] illnesses that involve memory, behavior, learning, and communicating problems." (from MedlinePlus®).

Diabetes Mellitus

A chronic disease associated with abnormally high levels of the sugar glucose in the blood. Diabetes is due to one of two mechanisms

- Inadequate production of insulin (which is made by the pancreas and lowers blood glucose)
- or**
- Inadequate sensitivity of cells to the action of insulin

The two main types of diabetes correspond to these two mechanisms and are called insulin dependent (type 1) and non–insulin dependent (type 2) diabetes. In type 1 diabetes there is no insulin or not enough of it. In type 2 diabetes, there is generally enough insulin, but the cells upon it should act are not normally sensitive to its action.²

Generalized Estimating Equation (GEE)

A method of estimation used in the analysis of longitudinal data, which consists of repeated measures of an individual or cluster of individuals over time. These repeated measures from any one individual or cluster are correlated with each other and are, therefore, no longer independent. GEEs use the data to estimate the correlation between a single individual or cluster's response and provide a correct estimate of each effect's variance.

²<http://www.medterms.com/script/main/art.asp?articlekey=2974>

Generic

Chemically equivalent competitors of brand name pharmaceuticals, which often enter the market following the expiry of patents held on the brand name product. These drugs typically cost less than the brand name products.

Hormone Replacement Therapy (HRT)

Hormone Replacement Therapy is medication (in the form of a pill, patch or cream) containing one or more female hormones. HRT is most often used to treat symptoms of menopause.

Hypertension

High blood pressure.

Incidence

The number of new cases of a specific disease/condition/event over a specified time period. The incidence rate uses new cases in the numerator; individuals with a history of the disease/ condition are not included. The denominator for incidence rates is the population at risk. Even though individuals who have already developed the condition should be eliminated from the denominator, incidence rates are often expressed based on the average population rather than the population at risk.

Income Quintile

A method to measure the average (mean) household income of residents, ranking them from poorest to wealthiest, and then grouping them into five income quintiles (“1” being poorest and “5” being wealthiest). Each quintile contains approximately 20% of the population. The income quintile measure is derived from Statistics Canada Census data by aggregating household income to the dissemination area (note: as of 2001 Census data, dissemination area replaces enumeration area as a basic unit for dissemination) and then ranking neighbourhoods by income quintile. Income quintiles are available for both urban and rural populations. Income quintiles are often used as a proxy measure of socio-economic status.

International Classification of Diseases (ICD) Codes

A classification system of diseases, health conditions, and procedures developed by the World Health Organization (WHO), which represents the international standard for the labeling and numeric coding of diseases and health related problems. Within this system, all diseases/ conditions are assigned numbers in hierarchical order. There are several versions of the ICD coding system, including ICD-8, ICD-9, ICD-9-CM (Clinical Modifications), ICD-O (Oncology), ICD-10, and ICD-10-CA (Canadian Enhancements).

Ischemic Heart Disease

Ischemia is a condition in which the blood flow (and thus oxygen) is restricted to a part of the body. Cardiac ischemia is the name for lack of blood flow and oxygen to the heart muscle. Thus, the term “ischemic heart disease” refers to heart problems caused by narrowed heart arteries. When arteries are narrowed, less blood and oxygen reaches the heart muscle. This is also called coronary artery disease and coronary heart disease. It can ultimately lead to heart attack.

Medicaid

A United States jointly funded, Federal–State health insurance program for certain low–income and needy people, covering approximately 36 million individuals, including children, the aged, blind, and/or disabled, and people who are eligible to receive federally assisted income maintenance programs.

Morbidity

Any departure, subjective or objective, from a state of physiological or psychological well–being (i.e., sickness or illness).

Myocardial Infarction

A heart attack (myocardial infarction) occurs when an area of heart muscle dies or is permanently damaged because of an inadequate supply of oxygen to that area

Pneumonia

Pneumonia is an inflammation of the lungs caused by a bacterial, viral, or fungal infection. Bacterial pneumonia in adults is commonly caused by a bacterium called *Streptococcus pneumoniae* or *Pneumococcus*. (from MedlinePlus®)

Population Health Research Data Repository

A comprehensive collection of administrative, registry, survey, and other databases primarily comprised of residents of Manitoba. This repository is housed at the Manitoba Centre for Health Policy. It was developed to describe and explain patterns of health care and profiles of health and illness, facilitating inter–sectoral research in areas such as health care, education, and social services. The administrative health database, for example, holds records for virtually all contacts with the provincial health care system, the Manitoba Health Services Insurance Plan (including physicians, hospitals, personal care homes, home care, and pharmaceutical prescriptions), of all registered individuals. MCHP acts as a steward of the information in the Repository for agencies such as Manitoba Health and Healthy Living (MHHL).

Prescription

Any prescription dispensed in a retail pharmacy and recorded in the provincial prescription database (Drug Programs Information Network (DPIN)). This includes prescriptions paid out–of–pocket and prescriptions reimbursed by Manitoba’s Pharmacare and Family Services drug insurance programs, federal drug insurance programs such as Health Canada and Veteran Affairs, and private drug insurance programs.

Prevalence

The term prevalence refers to the proportion of the population that 'has' a given disease at a given time. The measure of a condition in a population at a given point in time is referred to as point prevalence. A second type of prevalence is called period prevalence. Over a period of time, such as five years, this measures the number of individuals with a particular condition in the population during that time period. Period prevalence is the most common measure of prevalence used in MCHP studies. Prevalence data provide an indication of the extent of a condition and may have implications for the provision of services needed in a community. Both measures of prevalence are proportions – as such, they do not describe changes over time and should not be described as rates.

Renal Failure

Renal failure is the loss of the kidneys ability to remove wastes, concentrate urine, and maintain electrolytes levels in the blood.

Rural

Statistics Canada defines an area as rural if it has a population density less than or equal to 400 persons per square km.

Sociodemographic

One of three categories of risk factors related specifically to the sociodemographic factors that may impact discharge outcomes for long stay patients. The risk factors include: age, gender, living alone/living with someone, Winnipeg/non–Winnipeg residence, and neighbourhood income

Upper Respiratory Tract Infections

The upper respiratory tract consists of the nose, nasal cavity, larynx, and trachea, as well as some of the sinuses and air cells. Upper respiratory tract infections include the common cold (rhinitis), influenza, laryngitis (inflammation of the voice box), pharyngitis (sore throat), sinusitis, tonsillitis, and croup (in children).³

Urban

Statistics Canada defines an area as urban if it has a population density greater than 400 persons per square km.

Glossary References

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: American Psychiatric Association; 2000.

Medline Plus Web site. 2009. <http://medlineplus.gov/>. Accessed on September 22, 2009.

³ <http://www.hmc.psu.edu/healthinfo/uz/uprt.htm>

APPENDIX ONE: MODELING APPROACH

This deliverable uses extended segmented time series modeling approach and adopts the works of Wagner, Soumerai, Zhang, & Ross–Degnan (2002). Segmented or interrupted times series model can be used in modeling and evaluating the effects of policy changes. An introduction of a policy change introduces a segmentation of the time series; the first segment is the series before policy introduction and the second segment is the series after policy introduction.

Each segment of the time series is defined by two parameters namely: level and trend. The level is the value of the series at the beginning of each segment (i.e., the intercept) and the trend is the slope during a segment. Mathematically, a segmented times series model can be expressed as:

$$Y_t = \beta_0 + \beta_1 * time_t + \beta_2 * warning_t + \beta_3 * time\ after\ warning_t + e_t \quad (1)$$

Where, Y_t is the rate of the number of drug prescriptions in a quarter; the variable time is a continuous one coded as “1, 2, 3, etc.” with 1 representing the first quarter; the warning variable is code as a dummy (0/1) with 0 representing the time before Health Canada warnings and 1 for the time after Health Canada warnings; the time warning variable is a continuous variable that takes the value of 0 for all times before Health Canada Warnings and “1, 2, 3, etc.” for times thereafter. The estimate of the parameter β_0 is considered the baseline level of the outcome or the intercept at the start of the series, that is, at time zero; the estimate of β_1 is the slope before Health Canada warnings; the estimate of β_2 measures the change in intercept immediately after Health Canada warnings, that is, from the end of the last segment; and the estimate of β_3 is measure of the change in slope or trend after Health Canada warning as compared to before warning.

An assumption of the above model is that the outcome is continuous and normally distributed. The model also assumes a linear relationship between the outcome and the independent variable, time. Hence, the least squares regression method can be used to fit the parameters. The use of least squares method in estimating the above model also assumes independence of error terms.

Autoregressive integrated moving average (ARIMA) models can be used to fit the above models when one assumes non-independence of the error terms and there is a particular interest in the in understanding the nature of the error terms.

Now consider the following model:

$$Y_t = \beta_0 + \beta_1 * time_t + \beta_2 * warning_t + \beta_3 * time\ after\ warning_t + age_t + sex_t + e_t \quad (2)$$

The above model is what would normally be expected in any modeling of health services data because of the adjustment by age and sex, which are always risk factors. The stratification of the data by the variables in Equation 2 reduces the aggregation of the outcome variable Y and therefore makes Y to be less normal. Thus, the use of ARIMA to model the above model will produce invalid results. Besides, in order to use ARIMA and ARMA errors one needs to build different models for different age and sex stratification and then focus on the errors. This concept means no more adjusting for age and sex in the model.

Based on these limitations of ARIMA, we propose what we call the extended segmented times series modeling approach. Here, instead of assuming that Y is normally distributed, we assume that Y is a member of the generalized linear models (GLM) and then model the expected value of Y as a function of the linear predictors ($X\beta$). In this case, we can now use either the Poisson distribution or the negative binomial distribution to model the rate of our outcome. If the nature of correlation is not of interest as is in the case of this project, one can then use generalized estimating estimation (GEE) to adjust for the standard errors.

Appendix Table 1.1: Medication List for Drug Categories

Chapter	Drug Category	Group ATC	Drug	Drug ATC or DIN
1	Narcotic analgesics	N02A	Tylenol #3 [®] : acetaminophen + caffeine +codeine 30 mg (brand and generics)	N02AA59
		Methodone N07BC02	Oxycodone: all products containing oxycodone (except Oxycontin [®])	N02AA05
			Oxycontin [®] sustained release oxycodone	N02AA05 2202441 2202468 2202476 2202484
			Morphine	N02AA01
			Hydromorphone	N02AA03
			Meperidine	N02AB02
			2	COX2
NSAIDs	Rofecoxib	M01AH02		
	Valdecoxib	M01AH03		
	Meloxicam	M01AC06		
	Naproxen	M01AE02		
Diclofenac	M01AB05			
Ibuprofen	M01AE01			
3	Bisphosphonates	M05B	Alendronate	M05BA04
			Alendronate, brand name: Foxamax [®]	M05BA04
			Alendronate, generic: all brands except Foxamax [®]	M05BA04
			Alendronate, weekly dosing 70 mg strength	M05BA04
			Aendronate, daily dosing others strengths	M05BA04
			Etidronate	M05BA01
			Risedronate	M05BA07
			Risedronate, weekly dosing 35 mg strength	M05BA07
			Risedronate, daily dosing other strengths	M05BA07
			Selective Estrogen Receptor Modulator	
	Calcitonin		Calcitonin	H05BA01
	Hormone replacement therapy	G03	Systemic estrogens	G03C
			Progestens	G03D

Appendix Table 1.1: Medication List for Drug Categories (continued)

4	Antipsychotic, non-atypical: except olanzapine, risperidone, quetiapine and clozapine	N05A	Chlorpromazine	N05AA01
			Flupenthixol	N05AF01
			Fluphenazine	N05AB02
			Haloperidol	N05AD01
			Loxapine	N05AH01
			Mesoridazine	N05AC03
			Methotrimeprazine	N05AA02
			Pericyazine	N05AC01
			Perphenazine	N05AB03
			Pimozide	N05AG02
			Pipotiazine	N05AC04
			Prochlorperazine	N05AB04
			Thioridazine	N05AC02
			Thiotixene	N05AF04
			Trifluoperazine	N05AB06
			Zuclopenthixol	N05AF05
			Antipsychotic, atypical	N05A
		Risperidone	N05AX08	
		Quetiapine	N05AH04	
		Clozapine	N05AH02	
5	Angiotensin Converting Enzyme Inhibitor (ACEI) (includes combination with thiazides)	C09A	Captopril	C09AA01
			Enalapril	C09AA02
			Ramipril	C09AA05
			Perindopril	C09AA04
			Quinapril	C09AA06
			Cilazapril	C09AA08
			Lisinopril	C09AA03
			Trandolapril	C09AA10
			Benazepril	C09AA07
			Fosinopril	C09AA09
	Angiotensin Receptor Blocker (ARB) (includes combination with thiazides)	C09C	Losartan	C09CA01
			Valsartan	C09CA03
			Candesartan	C09CA06
			Eprosartan	C09CA02
			Telmisartan	C09CA07
			Irbesartan	C09CA04
	Calcium channel blockers	C08C C08D	Amlodipine	C08CA01
			Felodipine	C08CA02
			Nicardipine	C08CA04
Nifedipine			C08CA05	
Nimodipine			C08CA06	
Verapamil			C08DA01	
Diltiazem			C08DB01	

Appendix Table 1.1: Medication List for Drug Categories (continued)

5 continued	Beta blockers (includes combinations with thiazides) (includes combination with other diuretics)	C07A C07B C07C	Propranolol	C07AA05 C07BA05
			Sotalol	C07AA07
			Oxprenolol	C07AA02
			Pindolol	C07AA03 C07CA03
			Metoprolol	C07AB02
			Atenolol	C07AB03 C07CB03
			Carvediolol	C07AG02
			Timolol	C07AA06 C07BA06
			Nadolol	C07AA12 C07BA12
			Acebutolol	C07AB04
	Labetalol	C07AG01		
	Bisoprolol	C07AB07		
	Thiazides (includes combination with other diuretics only)	C03	Hydrochlorothiazide	C03AA03 C03EA01
Chlorthalidone			C03BA04	
Indapamide			C03BA11	
Alpha Blockers	C02C	Prazosin	C02CA01	
		Doxazosin	C02CA04	
		Terazosin	C02CA05	
6	Statins	C10A	Atorvastatin	C10AA05
			Cerivastatin	C10AA06
			Fluvastatin	C10AA04
			Lovastatin	C10AA02
			Pravastatin	C10AA03
			Rosuvastatin	C10AA07
			Simvastatin	C10AA01
7	Insulins	A10A		
	Sulfonylureas	A10BB	Tolbutamide	A10BB03
			Glimepiride	A10BB12
			Glyburide	A10BB01
			Chlorpropamide	A10BB02
			Gliclazide	A10BB09
			Acetohexamide	A10BB31
	Glitazones (Thiazolidenediones)	A10BG	Rosiglitazone	A10BG02
			Pioglitazone	A10BG03
	Metformin	A10BA	Rosiglitazone/metformin combination Avandamet®	A10BD03
Meglitinides	A10BX	Nateglinide	A10BX03	
		Repaglinide	A10BX02	
Acarbose	A10BF	Acarbose	A10BF01	

Appendix Table 1.1: Medication List for Drug Categories (continued)

8	Proton pump inhibitors	A02BC	Rabeprazole	A02BC04
			Omeprazole	A02BC01
			Lansoprazole	A02BC03
			Esomeprazole	A02BC05
			Pantoprazole	A02BC02
			Omeprazole, brand name: Losec®	A02BC01
			Omeprazole, generic – omeprazole, all brands except Losec®	A02BC01
9	Steroids, inhaled	R03B	Inhaled budesonide	R03BA02
			Fluticasone	R03BA03
			Beclomethasone	R03BA01
	Short acting beta agonists	R03A	Inhaled salbutamol	R03AC02
			Fenoterol	R03AC04
			Terbutaline	R03AC03
	Long acting beta agonists	R03C	Isoproterenol	R03AB02
			Inhaled salmeterol	R03AC12
	Steroid, inhaled in combination with long acting beta agonists	R03K	Formoterol	R03AC13
			Salmeterol/fluticasone	R03AK06
	Anticholinergic, inhaled	R03B	Formoterol/budesonide	R03AK07
			Ipratropium	R03BB01
			Ipratropium in combination with salbutamol	R03AK04
	Leukotriene receptor antagonists	R03D	Ipratropium in combination with tiotropium	R03BB04
			Monteleukast	R03DC03
	Asthma and chronic obstructive lung disease medications, oral	R03D	Zafirlukast	R03DC01
			Aminophylline	R03DA05
Theophylline			R03DA04	
Oxtriphylline			R03DA02	
Orciprenaline			R03AB03	
10	Psychostimulants	N06B	Ketotifen	R06AX17
			Methylphenidate, short acting, brand: Ritalin®	N06BA04
			Methylphenidate, long acting, brand: Concerta®	N06BA04
			Methylphenidate, short acting, generic: all brands except Ritalin® and Concerta®	N06BA04
			Amphetamine, long acting, brand: Adderall®	N06BA01

Appendix Table 1.1: Medication List for Drug Categories (continued)

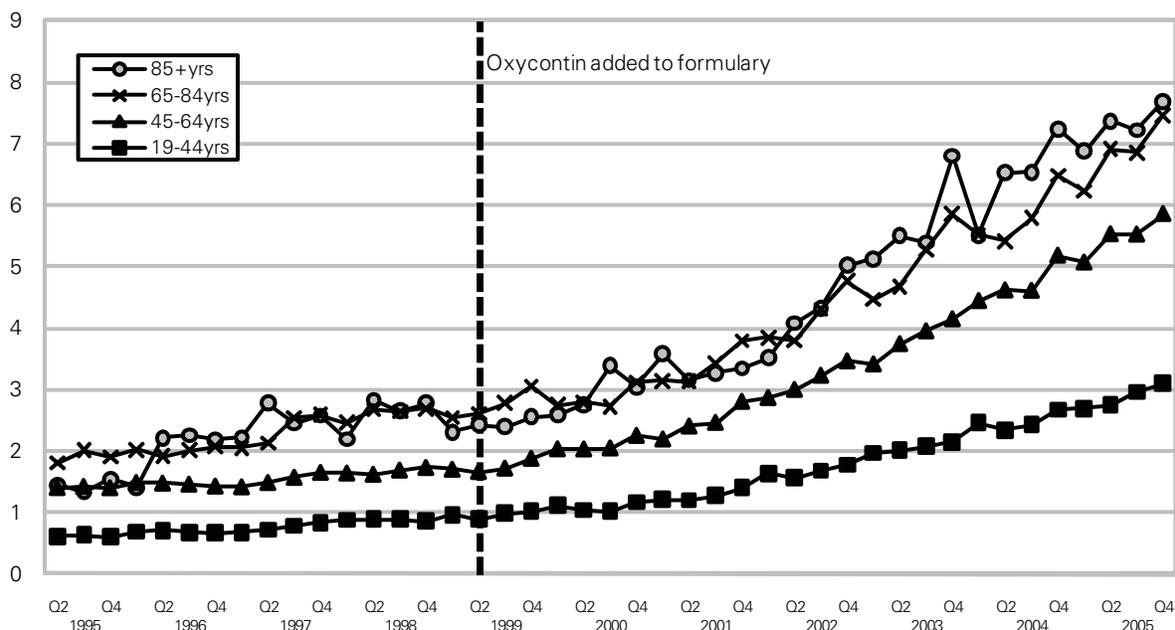
11	Antibiotics: oral or intravenous dosage forms	J01		J01XX
	Floroquinolones, oral dosage forms	J01MA	Levofloxacin	J01MA12
			Gatifloxacin	J01MA16
			Moxifloxacin	J01MA14
			Ciprofloxacin	J01MA02
			Ofloxacin	J01MA01
	Cephalosporins, oral dosage forms	J01DA	Cefalexin	J01DA01
			Cefuroxime	J01DA06
			Cefprozil	J01DA10
			Cefaclor	J01DA08
			Cefixime	J01DA23
	Macrolides, oral dosage forms	J01FA	Erythromycin	J01FA01
			Clarithromycin	J01FA09
			Azithromycin	J01FA10
	Penicillins, oral dosage forms	J01C	Penicillin	J01CE10
			Amoxicillin	J01CA04
			Amoxicillin / clavulanate	J01CR02
			Cloxacillin	J01CF02
			Flucloxacillin	J01CF05
	Trimethoprim and sulphonamides, oral dosage forms	J01E	Trimethoprim	J01EA01
Sulfamethoxazole / Trimethoprim			J01EE01	
Tetracyclines, oral dosage forms	J01AA	Doxycycline	J01AA02	
		Tetracycline	J01AA07	
		Minocycline	J01AA08	
Other		Clindamycin	J01FF01	
		Metronidazole	J01XD01	

APPENDIX TWO: APPENDIX FIGURES

Note: The first number in Appendix Figure Numbers refers to the related subject's chapter number.

Appendix Figure A.1.1: Oxycodone Quarterly Prevalence by Age

Crude user rates per 1,000 adults, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)

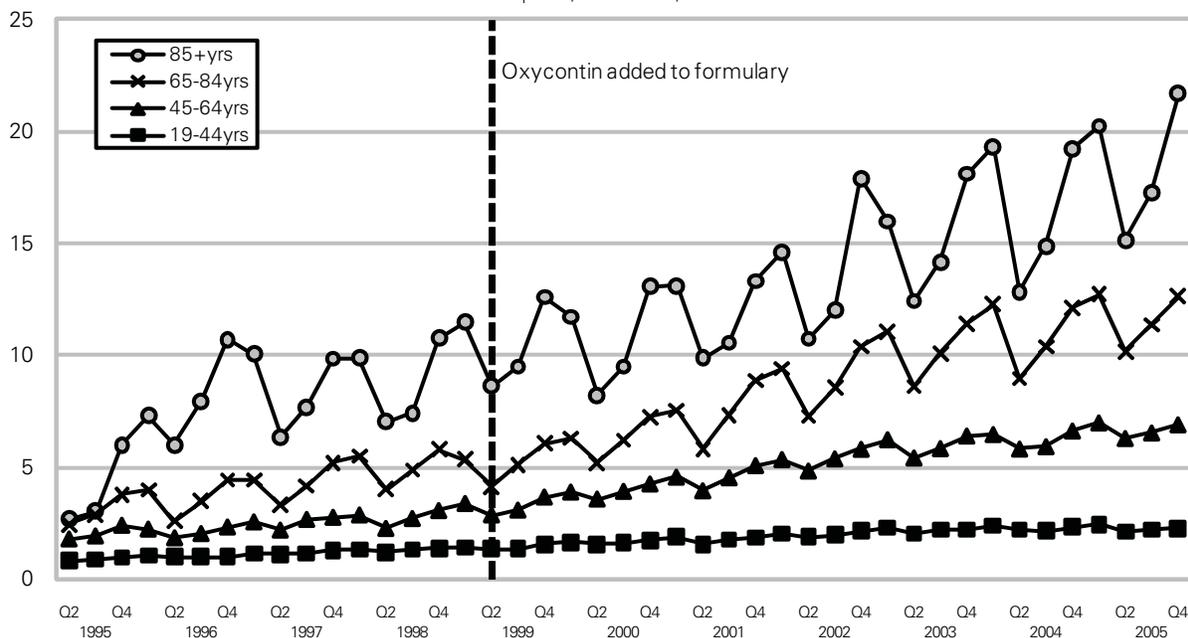
'Q4' indicates prevalence for the 4th quarter (October to December)

'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Appendix Figure A.1.2: Hydromorphone, Meperidine & Morphine Quarterly Prevalence by Age

Crude user rates per 1,000 adults, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)

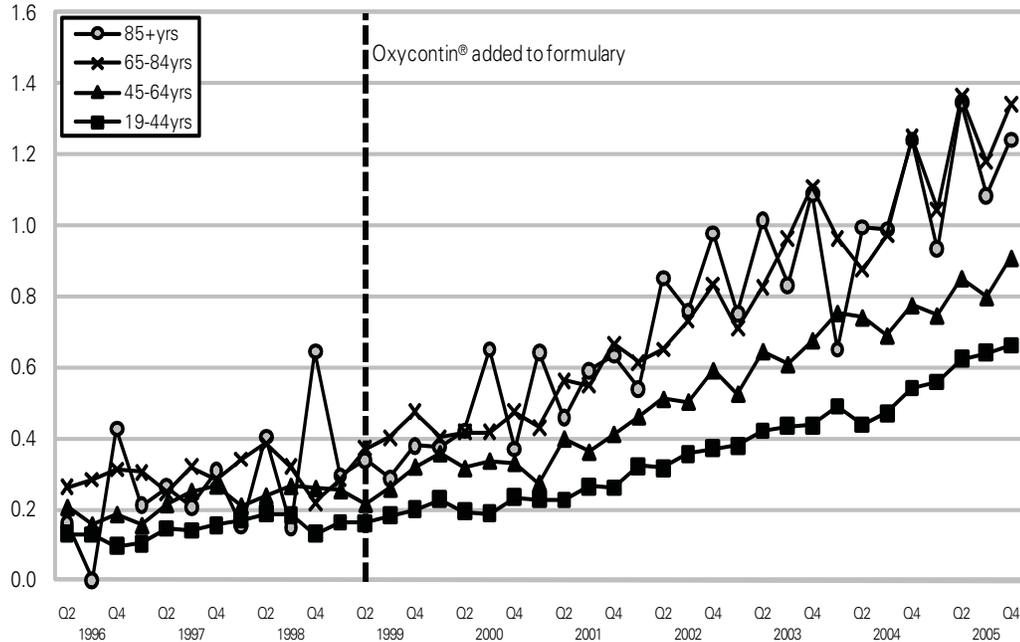
'Q4' indicates prevalence for the 4th quarter (October to December)

'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Appendix Figure A.1.3: Oxycodone Quarterly Incidence by Age

Crude rates of new users with no use of any narcotics (N02A or N07BC02) in prior year per 1,000 adults, Q2 1996–Q4 2005

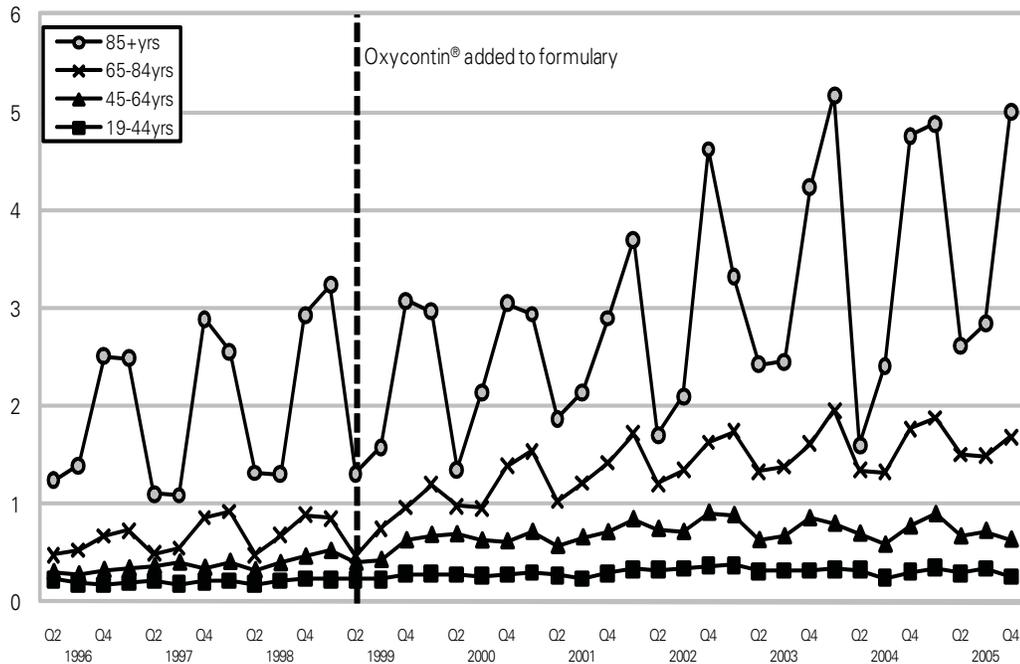


'Q2' indicates incidence for the 2nd quarter (April to June)
 'Q4' indicates incidence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Appendix Figure A.1.4: Hydromorphone, Meperidine & Morphine Quarterly Incidence by Age

Crude rates of new users with no use of any narcotics (N02A or N07BC02) in prior year per 1,000 adults, Q2 1996–Q4 2005

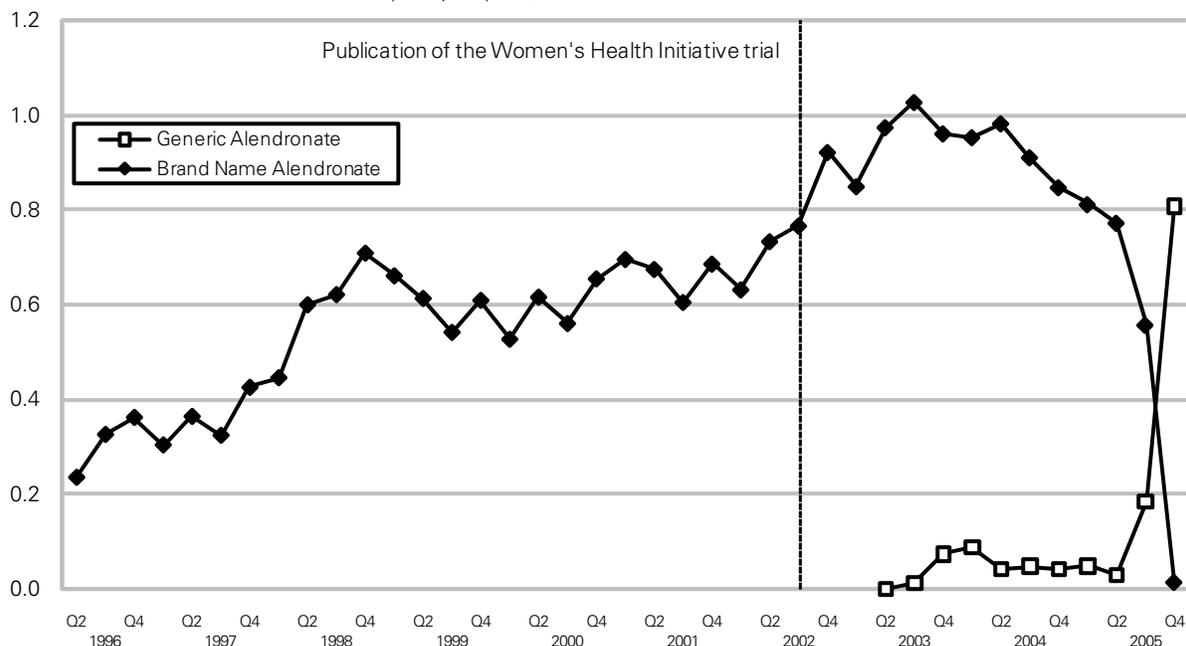


'Q2' indicates incidence for the 2nd quarter (April to June)
 'Q4' indicates incidence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Appendix Figure A.3.1: Alendronate Quarterly Incidence

Crude rates of new brand name and generic alendronate users with no use of HRT, bisphosphonates, raloxifene or calcitonin in prior year per 1,000 adults, Q2 1996–Q4 2005



'Q2' indicates incidence for the 2nd quarter (April to June)

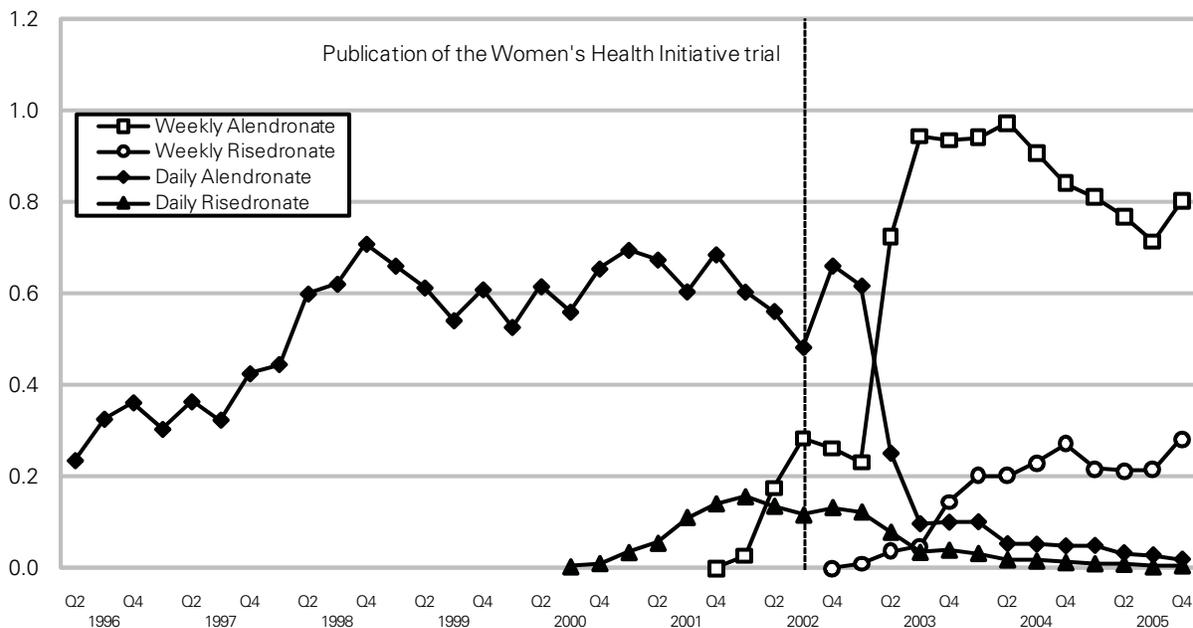
'Q4' indicates incidence for the 4th quarter (October to December)

'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Appendix Figure A.3.2: Alendronate and Risedronate Dosing, Quarterly Incidence

Crude weekly and daily dosing rates of new users with no use of HRT, bisphosphonates, raloxifene or calcitonin in prior year per 1,000 adults, Q2 1996–Q4 2005



'Q2' indicates incidence for the 2nd quarter (April to June)

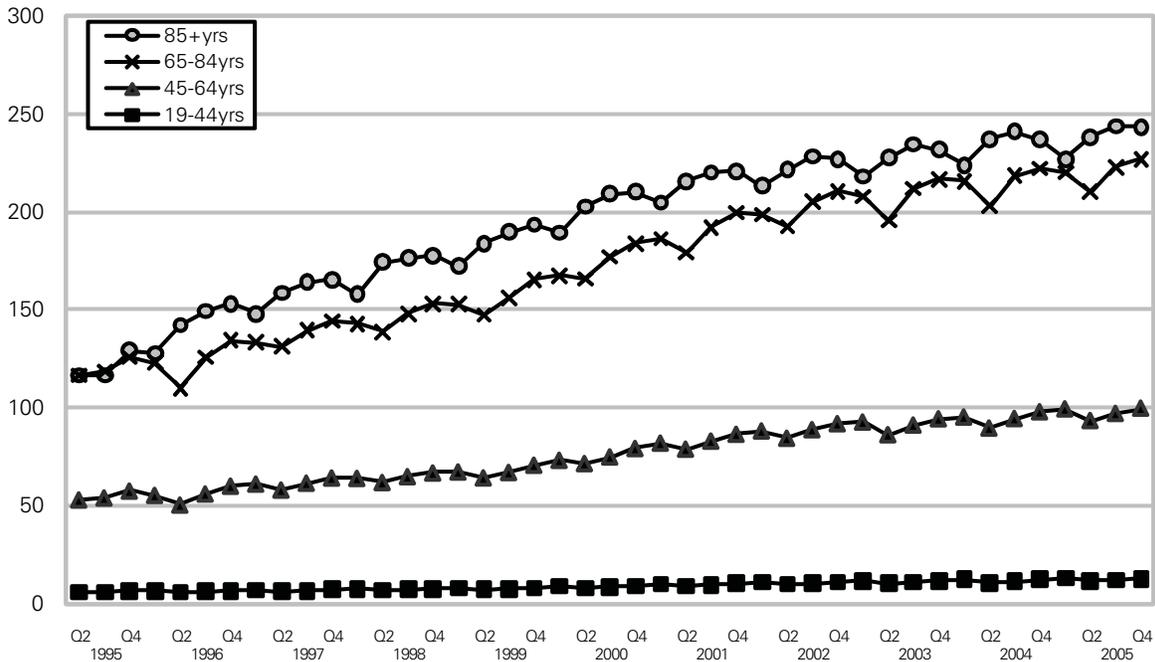
'Q4' indicates incidence for the 4th quarter (October to December)

'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Appendix Figure A.5.1: ACE Inhibitors Quarterly Prevalence by Age

Crude user rates per 1,000 adults, Q2 1995–Q4 2005

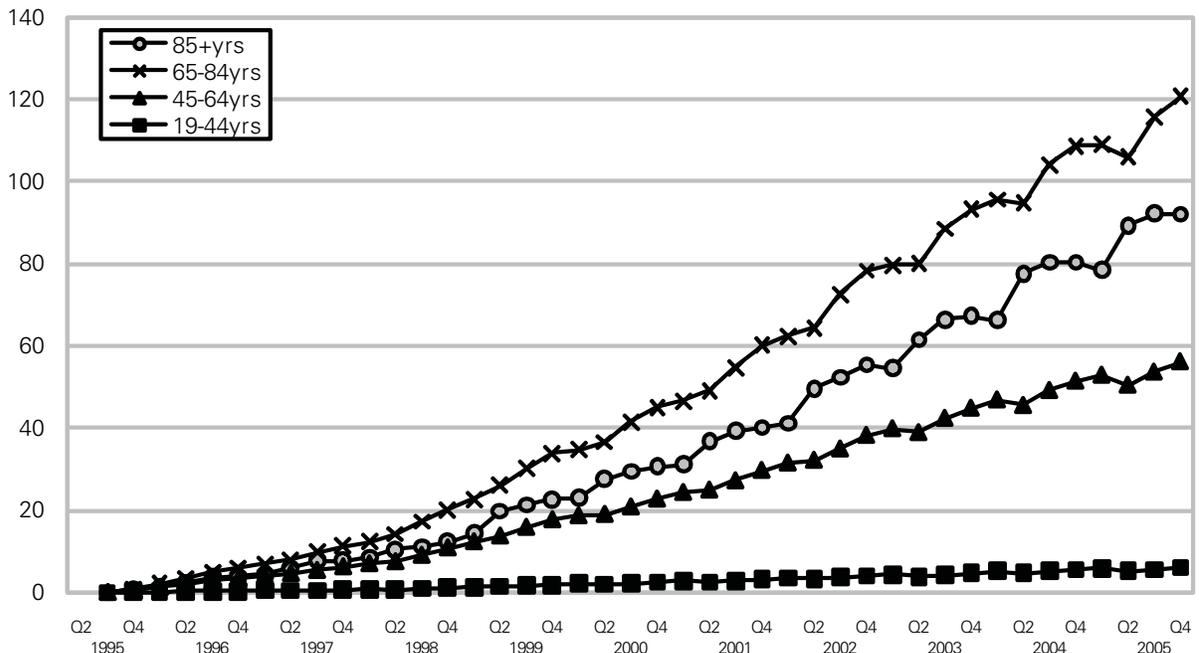


'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Appendix Figure A.5.2: Angiotensin Receptor Blockers Quarterly Prevalence by Age

Crude user rates per 1,000 adults, Q2 1995–Q4 2005

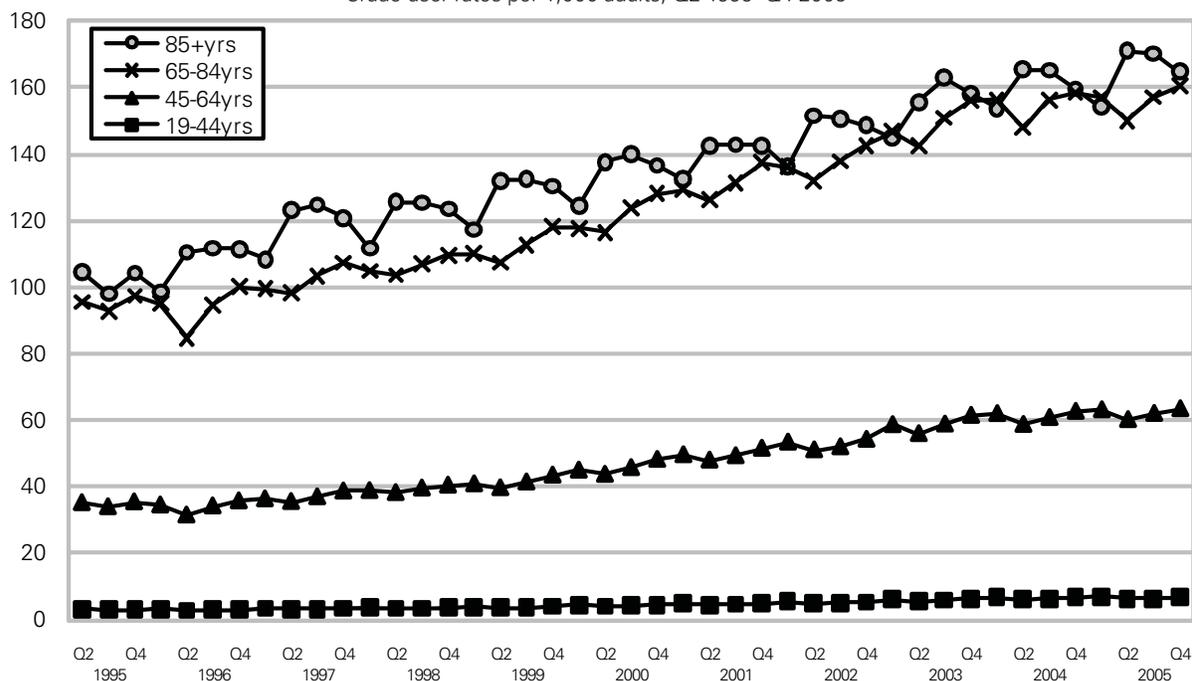


'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Appendix Figure A.5.3: Thiazides Quarterly Prevalence by Age

Crude user rates per 1,000 adults, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)

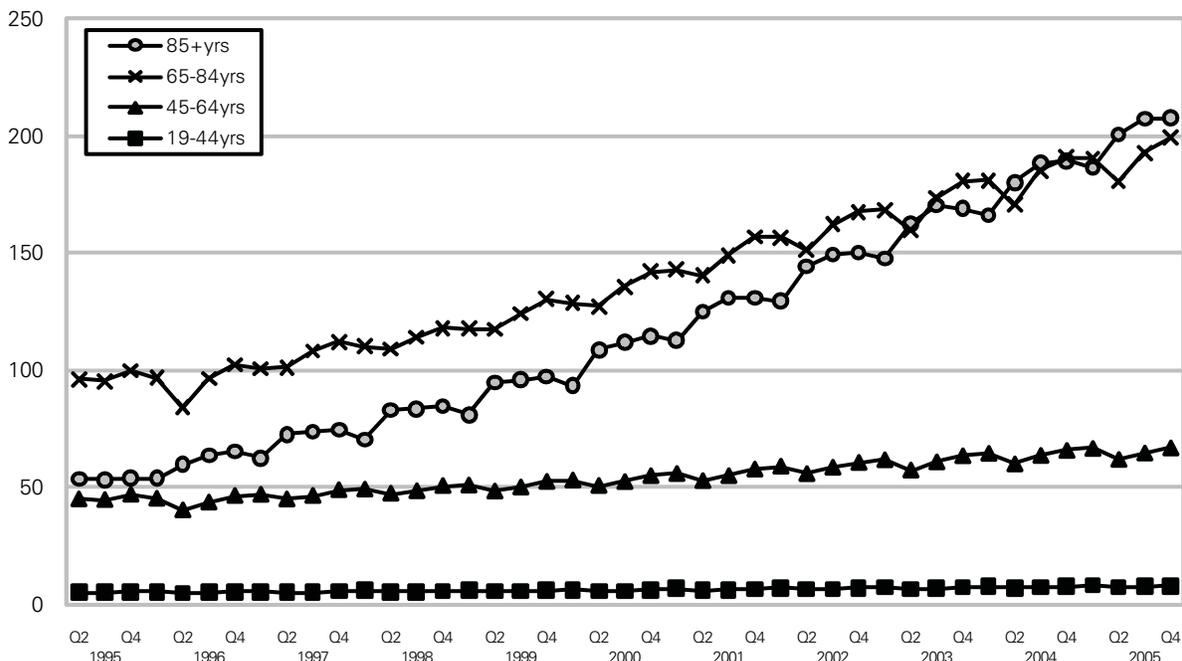
'Q4' indicates prevalence for the 4th quarter (October to December)

'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Appendix Figure A.5.4: Beta Blockers Quarterly Prevalence by Age

Crude user rates per 1,000 adults, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)

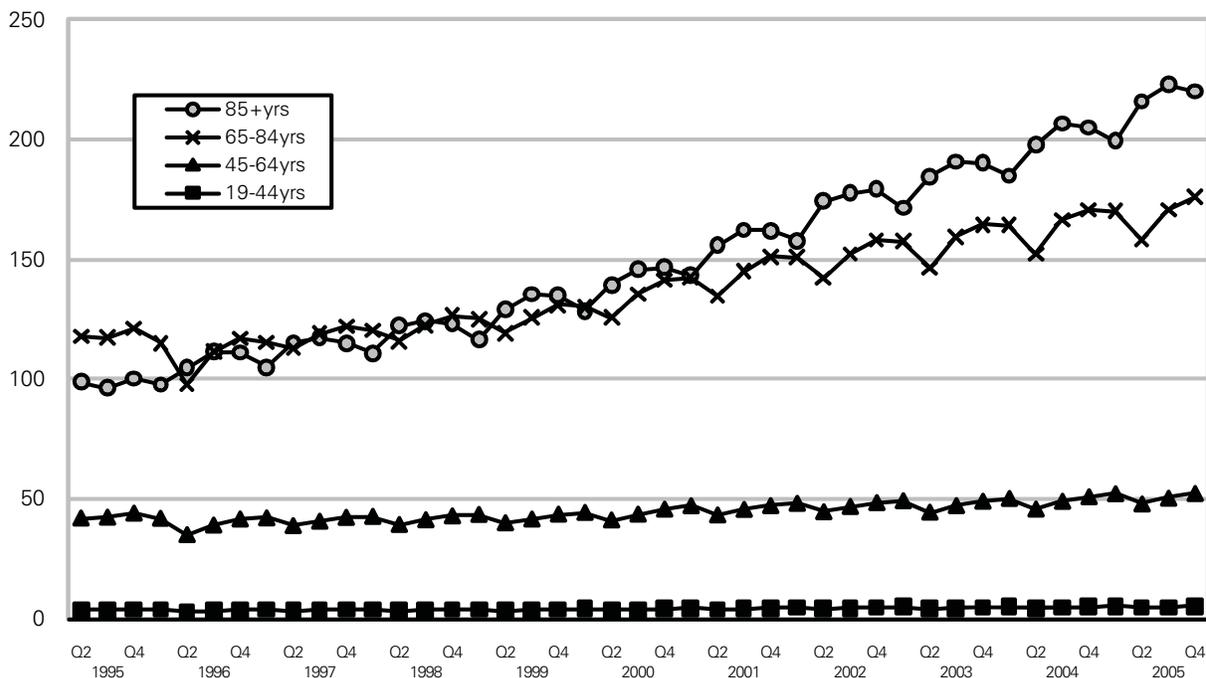
'Q4' indicates prevalence for the 4th quarter (October to December)

'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Appendix Figure A.5.5: Calcium Channel Blockers Quarterly Prevalence by Age

Crude user rates per 1,000 adults, Q2 1995–Q4 2005

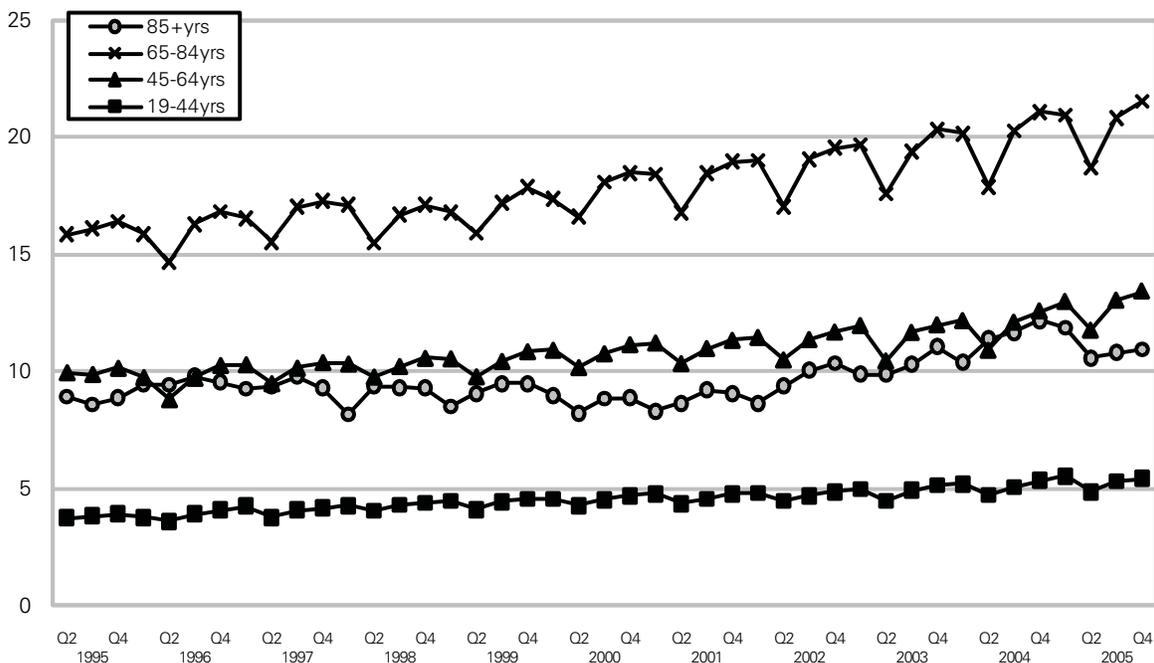


'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Appendix Figure A.7.1: Insulins Quarterly Prevalence by Age

Crude user rates per 1,000 adults, Q2 1995–Q4 2005

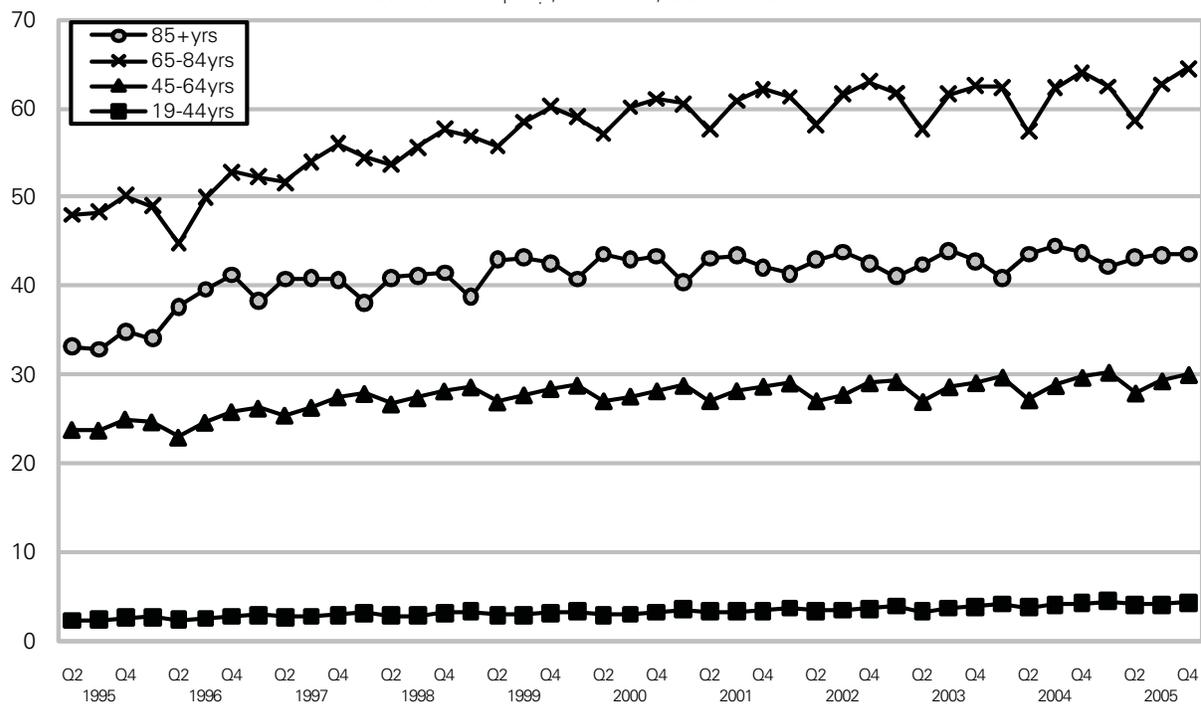


'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Appendix Figure A.7.2: Sulfonylureas Quarterly Prevalence by Age

Crude user rates per 1,000 adults, Q2 1995–Q4 2005

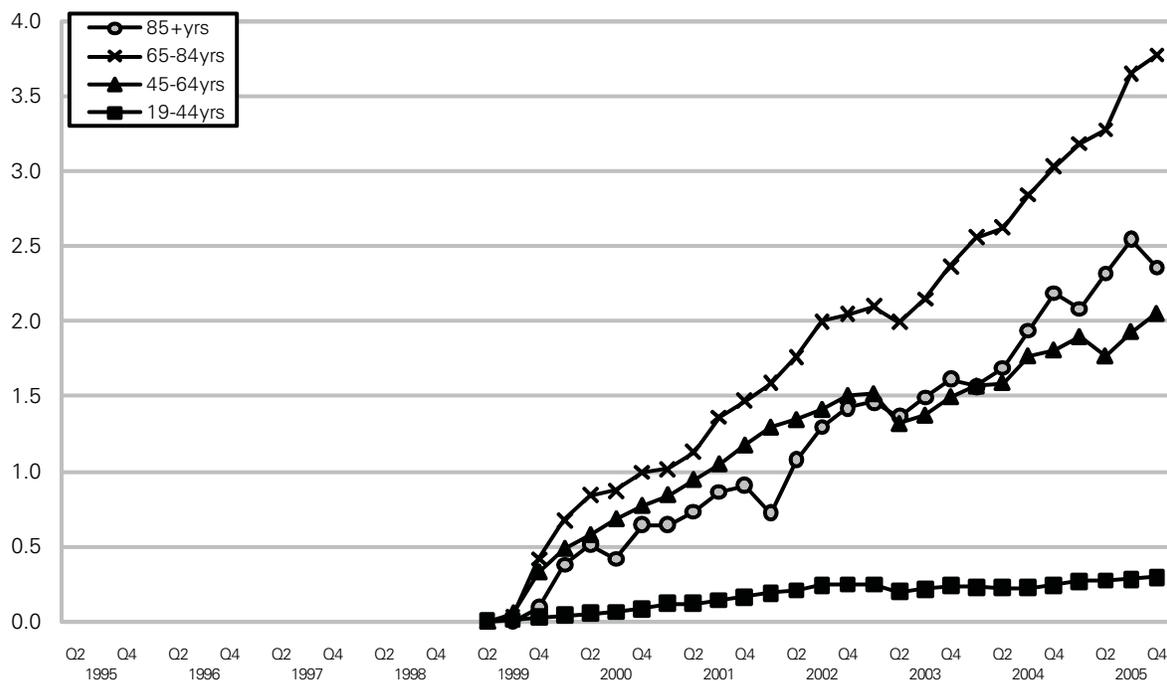


'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Appendix Figure A.7.3: Meglitinides Quarterly Prevalence by Age

Crude user rates per 1,000 adults, Q2 1995–Q4 2005

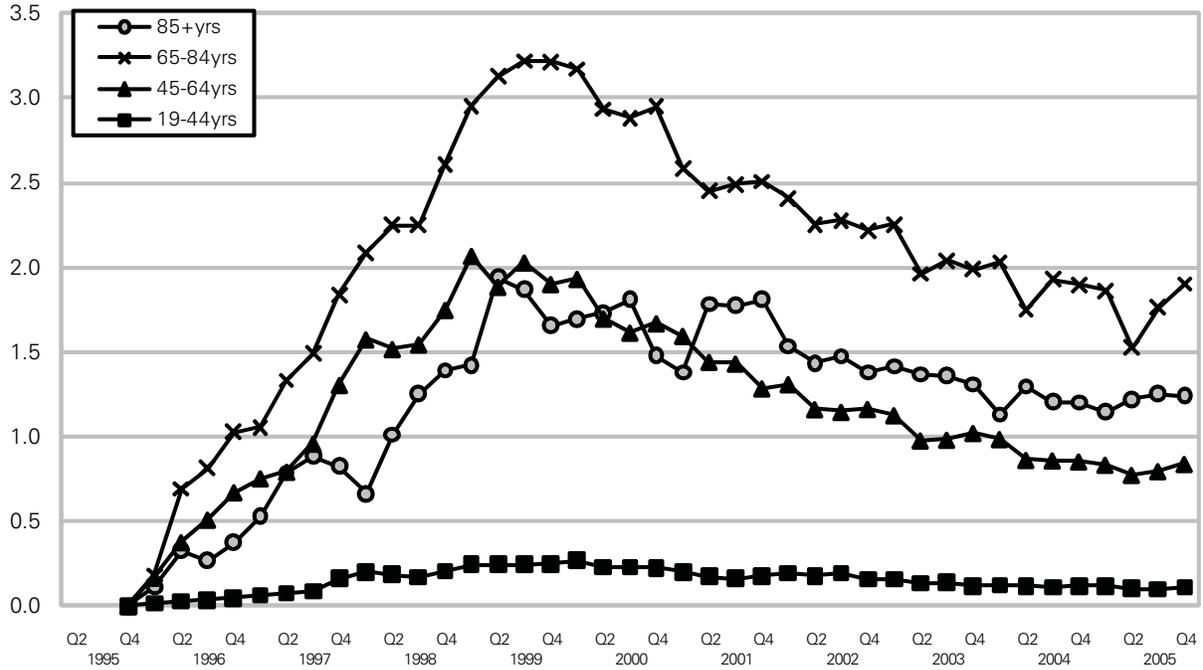


'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Appendix Figure A.7.4: Acarbose Quarterly Prevalence by Age

Crude user rates per 1,000 adults, Q2 1995–Q4 2005

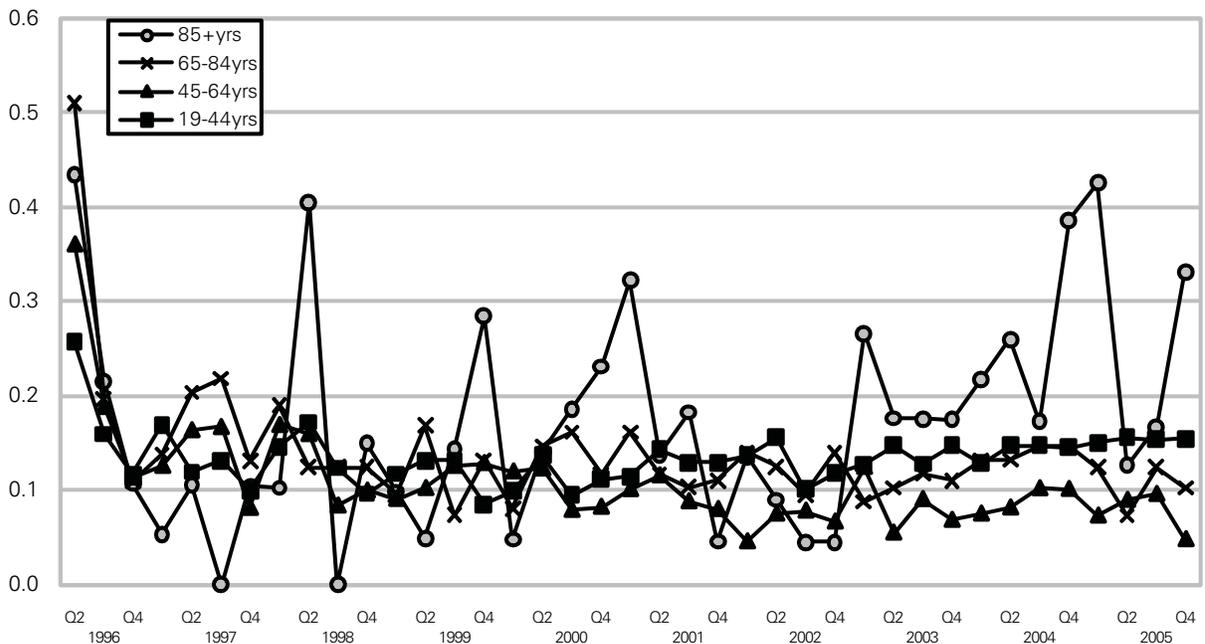


'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Appendix Figure A.7.5: Insulins Quarterly Incidence by Age

Crude rates of new users with no use of medications for diabetes in prior year per 1,000 adults, Q2 1996–Q4 2005

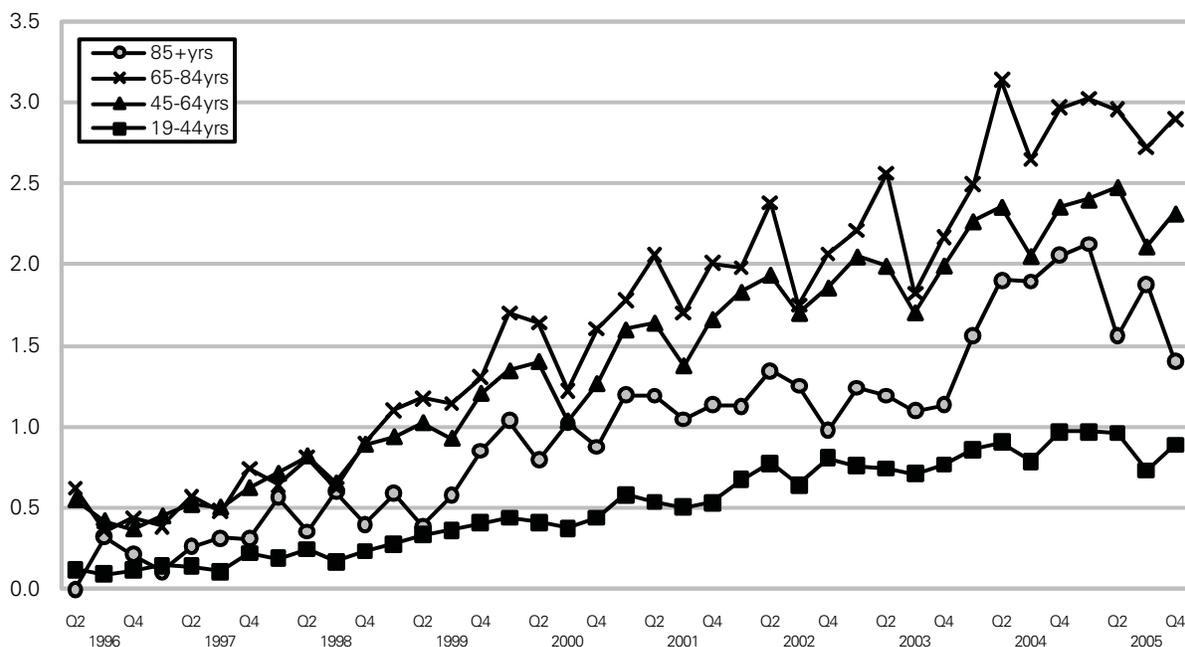


'Q2' indicates incidence for the 2nd quarter (April to June)
 'Q4' indicates incidence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Appendix Figure A.7.6: Metformin Quarterly Incidence by Age

Crude rates of new users with no use of medications for diabetes in prior year per 1,000 adults, Q2 1996–Q4 2005



'Q2' indicates incidence for the 2nd quarter (April to June)

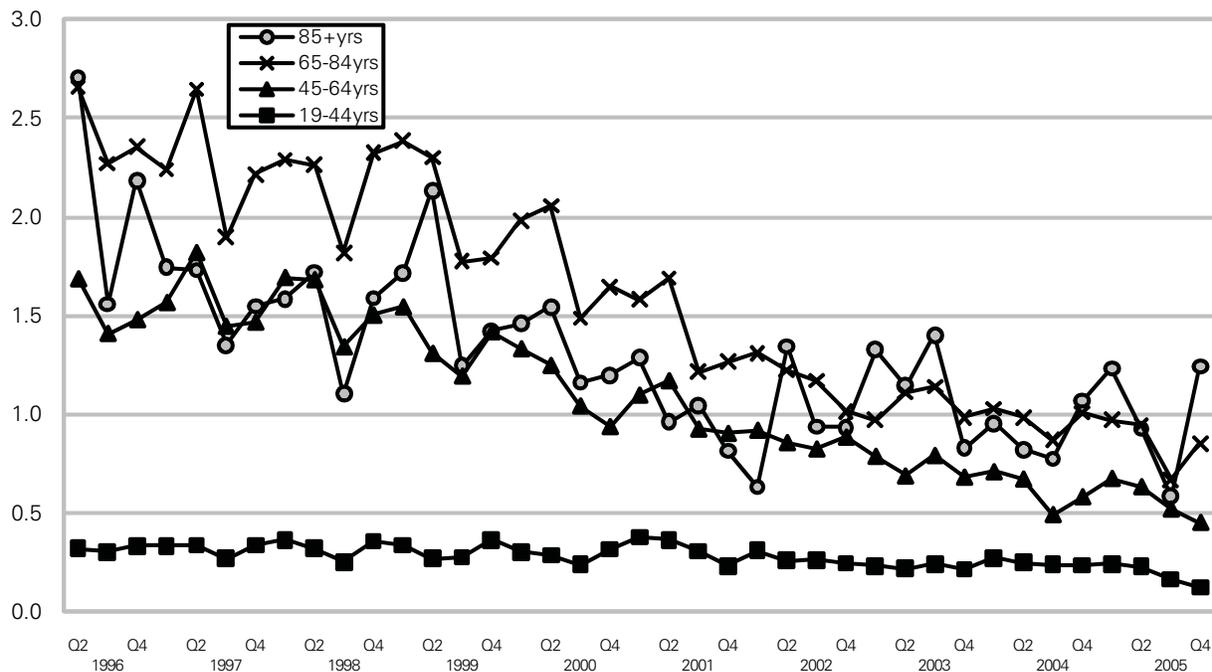
'Q4' indicates incidence for the 4th quarter (October to December)

'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Appendix Figure A.7.7: Sulfonylureas Quarterly Incidence by Age

Crude rates of new users with no use of medications for diabetes in prior year per 1,000 adults, Q2 1996–Q4 2005



'Q2' indicates incidence for the 2nd quarter (April to June)

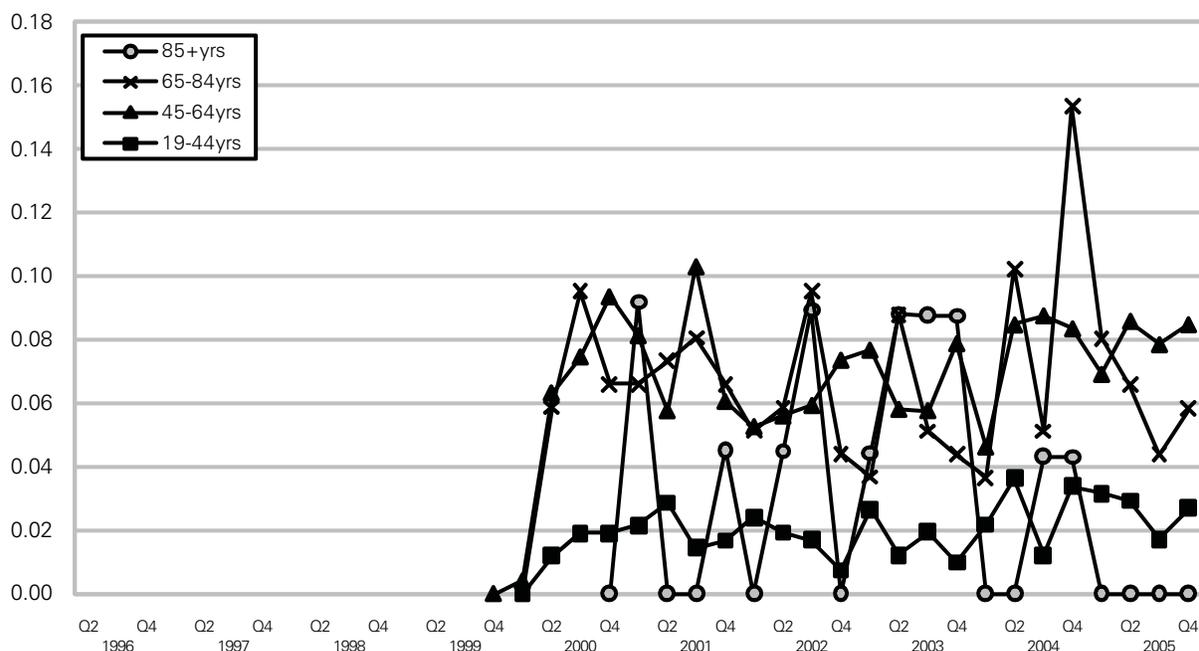
'Q4' indicates incidence for the 4th quarter (October to December)

'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Appendix Figure A.7.8: Glitazones Quarterly Incidence by Age

Crude rates of new users with no use of medications for diabetes in prior year per 1,000 adults, Q2 1996–Q4 2005

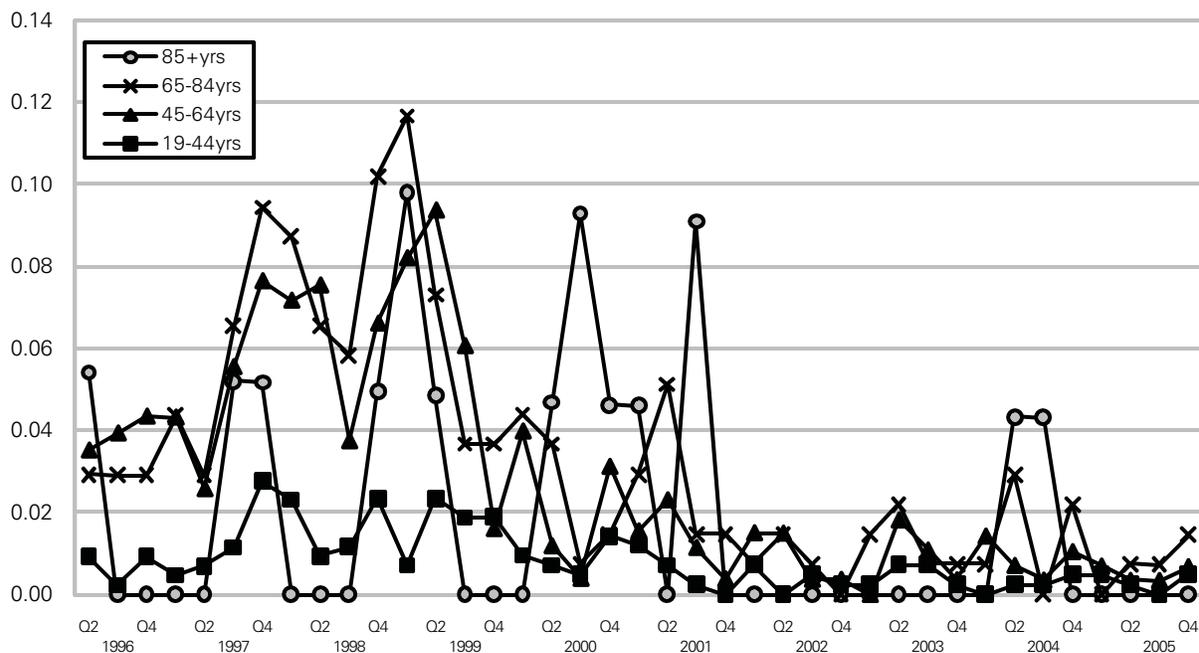


'Q2' indicates incidence for the 2nd quarter (April to June)
 'Q4' indicates incidence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Appendix Figure A.7.9: Acarbose Quarterly Incidence by Age

Crude rates of new users with no use of medications for diabetes in prior year per 1,000 adults, Q2 1996–Q4 2005

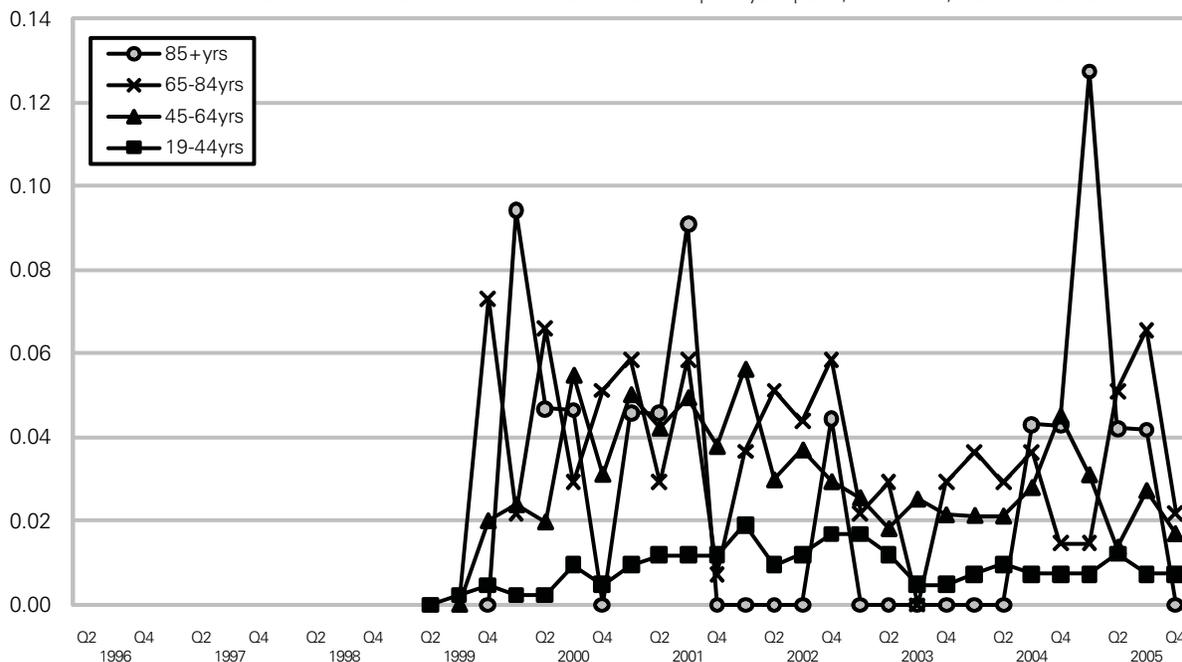


'Q2' indicates incidence for the 2nd quarter (April to June)
 'Q4' indicates incidence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Appendix Figure A.7.10: Meglitinides Quarterly Incidence by Age

Crude rates of new users with no use of medications for diabetes in prior year per 1,000 adults, Q2 1996–Q4 2005

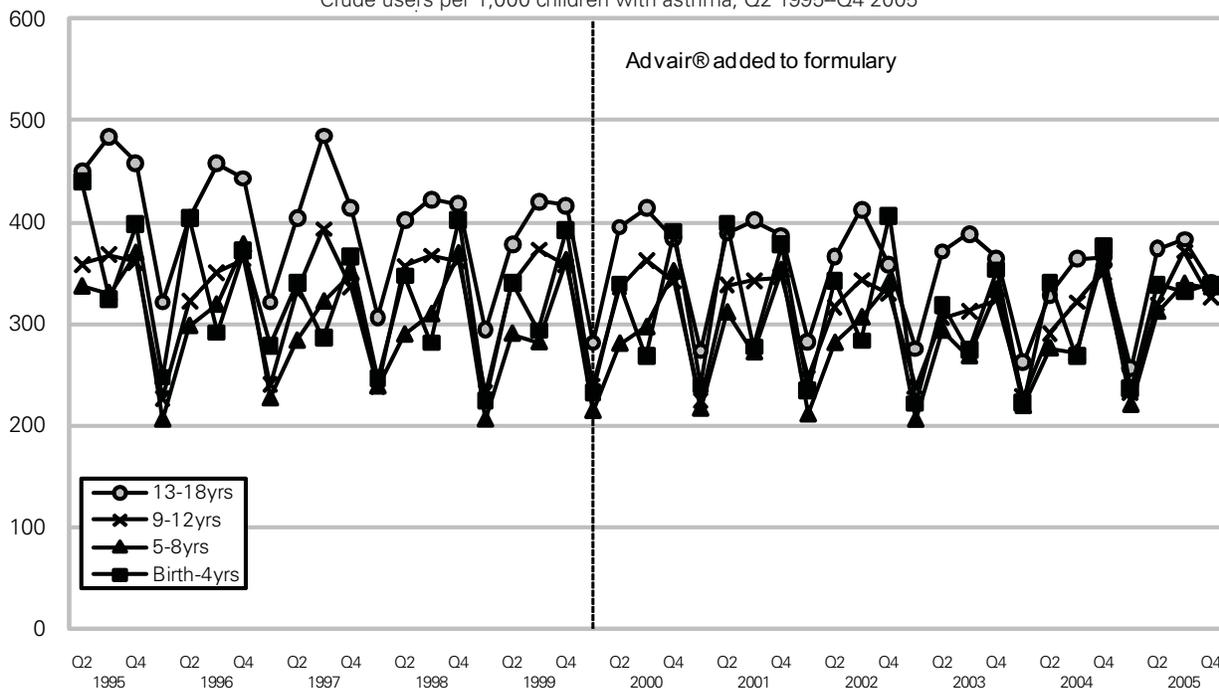


'Q2' indicates incidence for the 2nd quarter (April to June)
 'Q4' indicates incidence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

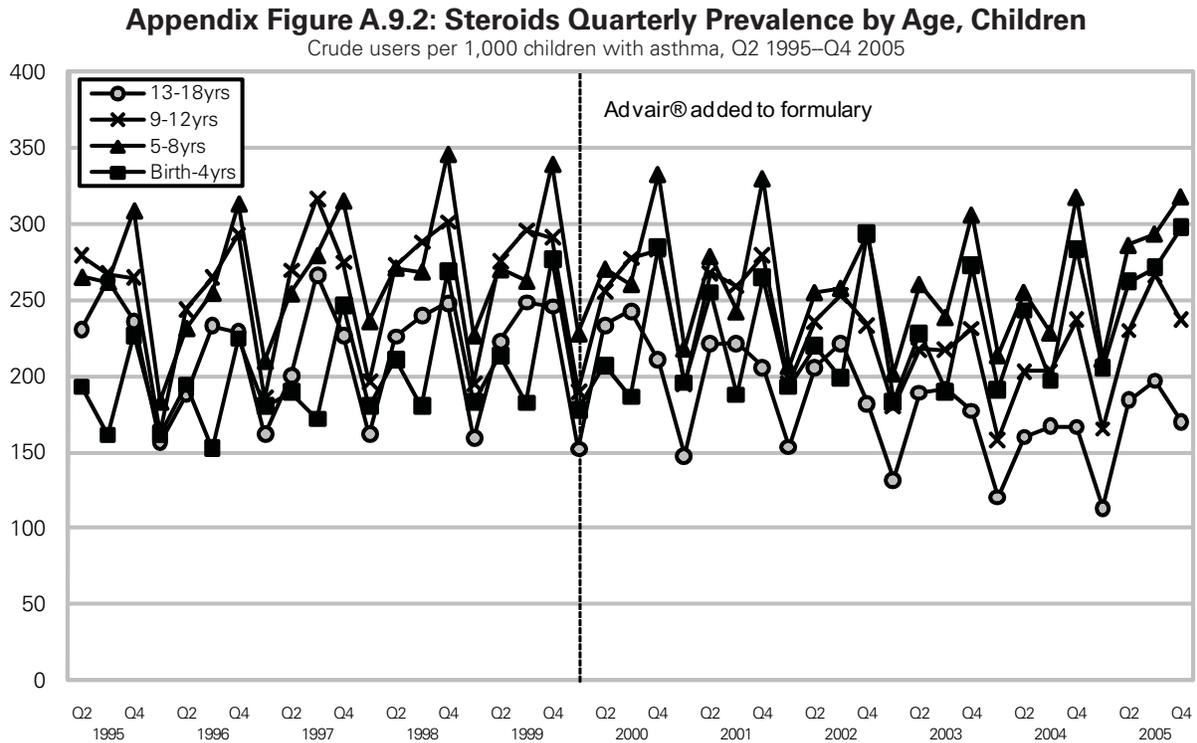
Appendix Figure A.9.1: SABA Quarterly Prevalence by Age, Children

Crude users per 1,000 children with asthma, Q2 1995–Q4 2005



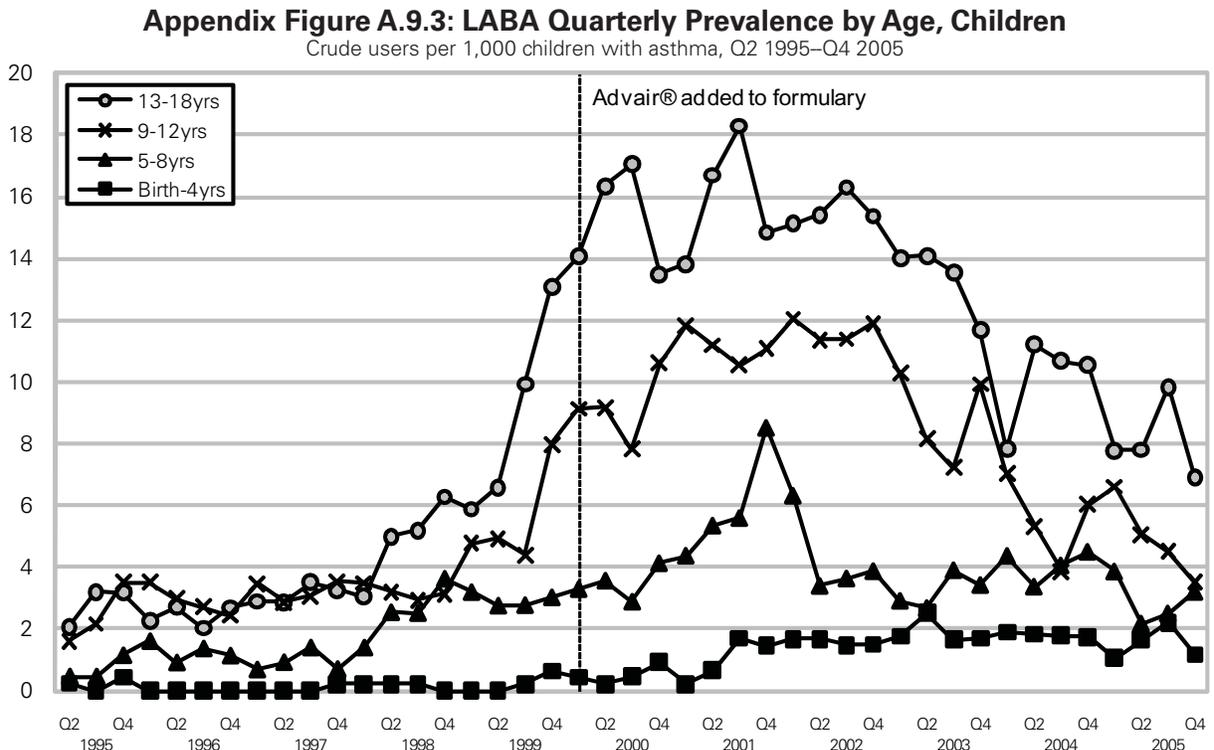
'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009



'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

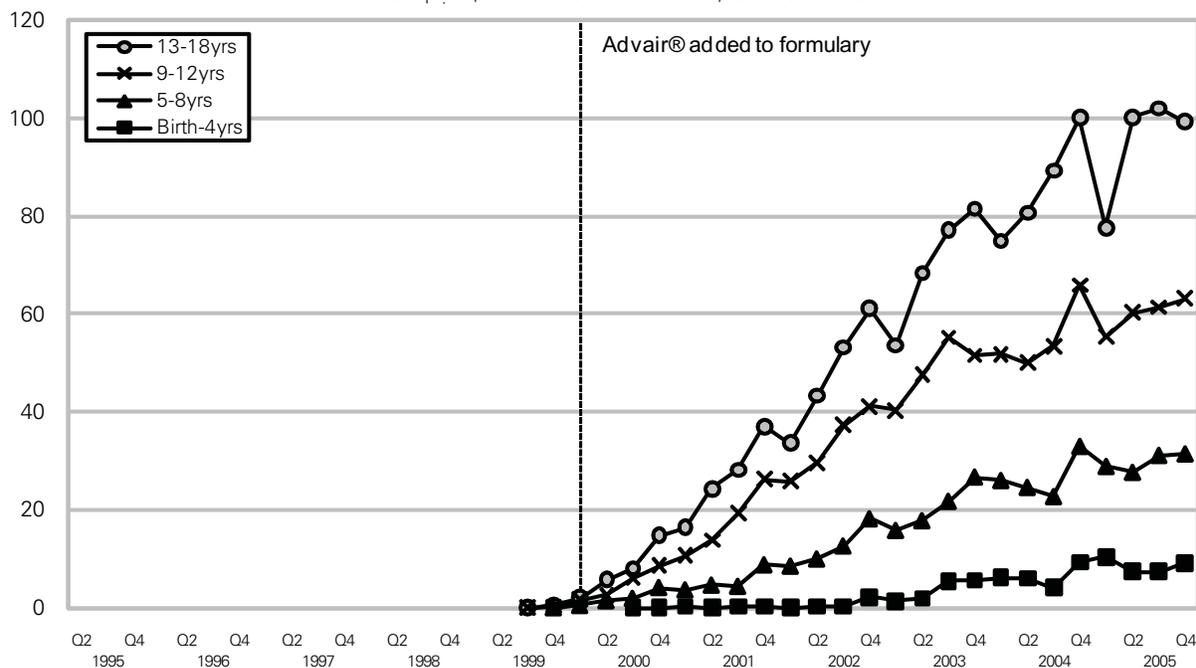


'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Appendix Figure A.9.4: LABA/Steroid Combinations Quarterly Prevalence by Age, Children

Crude users per 1,000 children with asthma, Q2 1995–Q4 2005

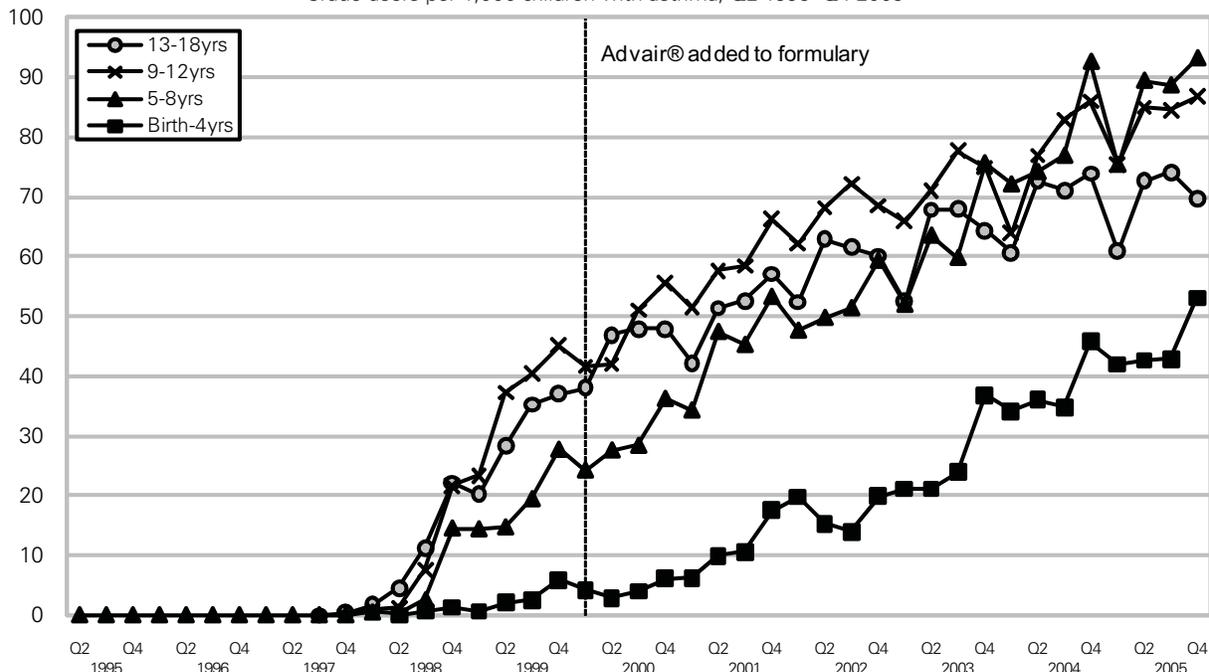


'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Appendix Figure A.9.5: Montelukast & Zafirlukast Quarterly Prevalence by Age, Children

Crude users per 1,000 children with asthma, Q2 1995–Q4 2005

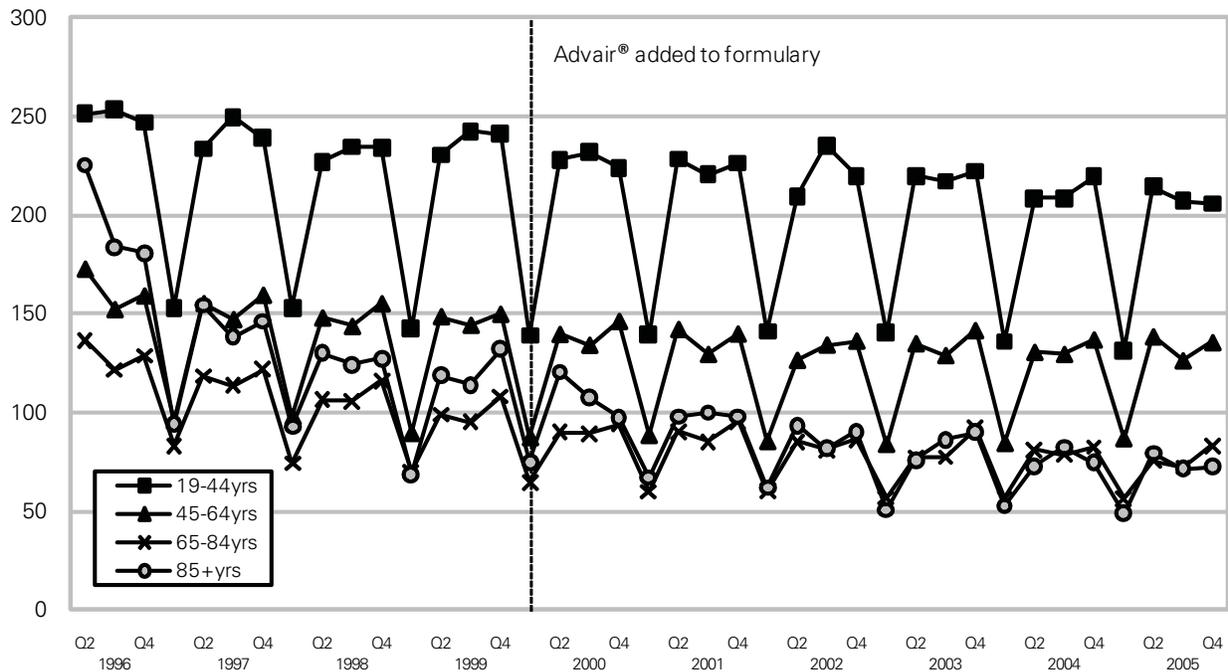


'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Appendix Figure A.9.6: SABA Quarterly Incidence by Age, Adults

Crude rates of new users with no use of SABA in prior year per 1,000 adults with chronic lung disease, Q2 1996–Q4 2005

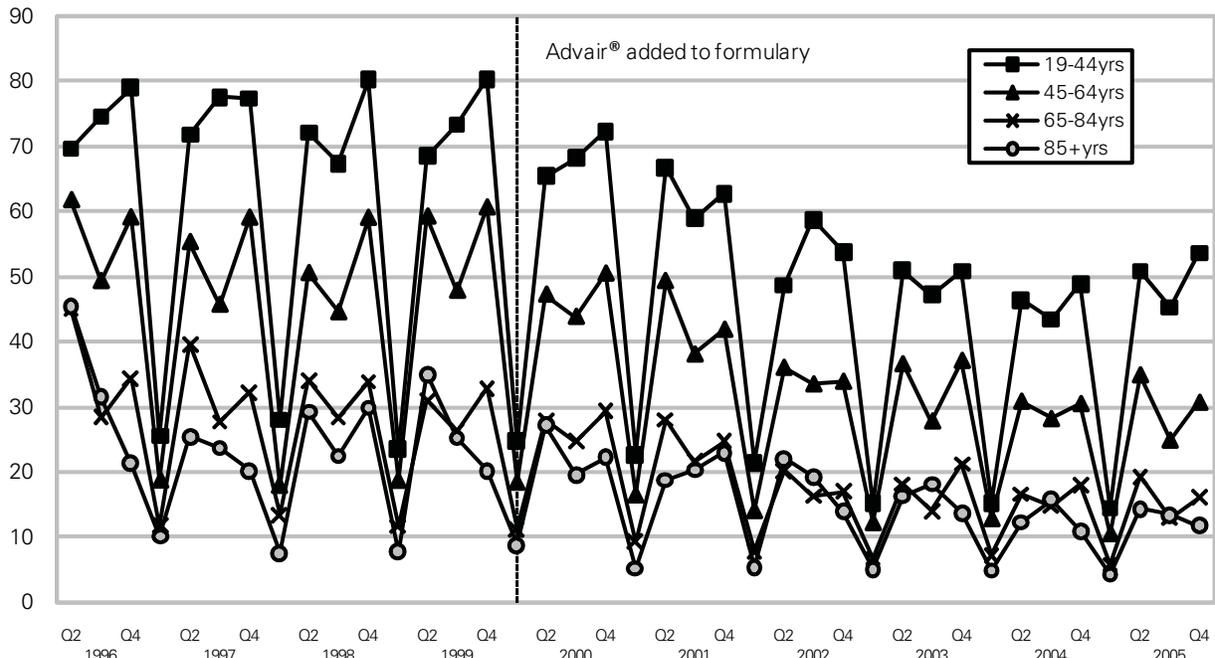


'Q2' indicates incidence for the 2nd quarter (April to June)
 'Q4' indicates incidence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Appendix Figure A.9.7: Steroids Quarterly Incidence by Age, Adults

Crude rates of new users with no use of steroids in prior year per 1,000 adults with chronic lung disease, Q2 1996–Q4 2005

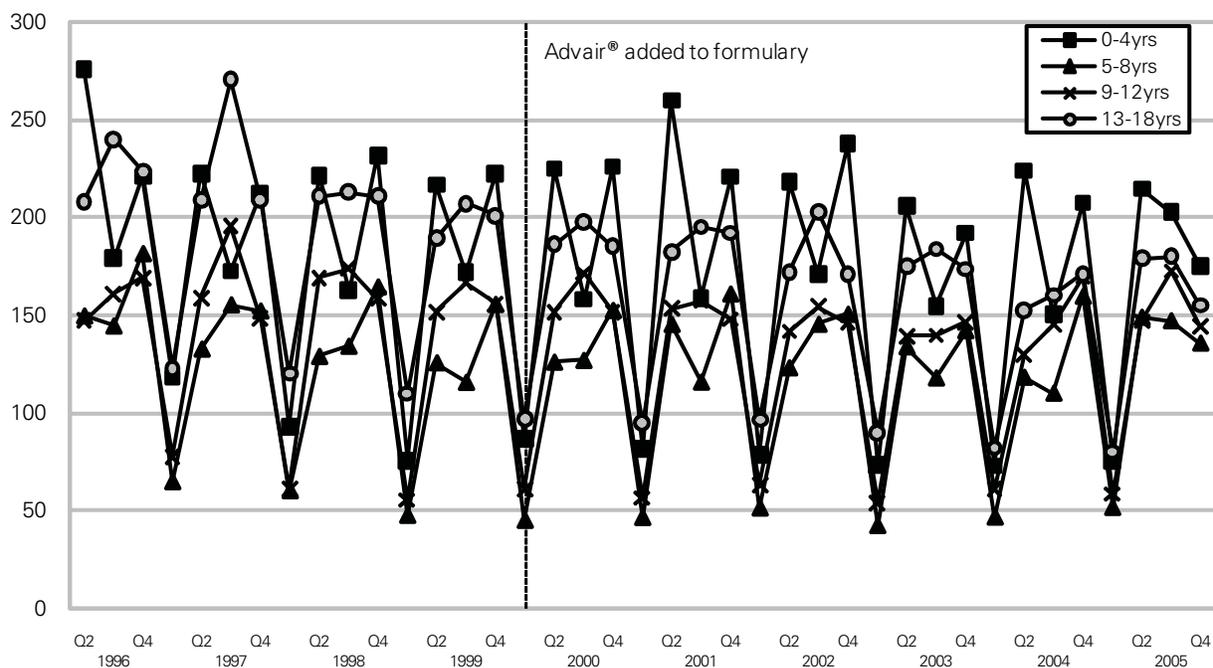


'Q2' indicates incidence for the 2nd quarter (April to June)
 'Q4' indicates incidence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Appendix Figure A.9.8: SABA Quarterly Incidence by Age, Children

Crude rates of new users with no use of SABA in prior year per 1,000 children with asthma, Q2 1996–Q4 2005

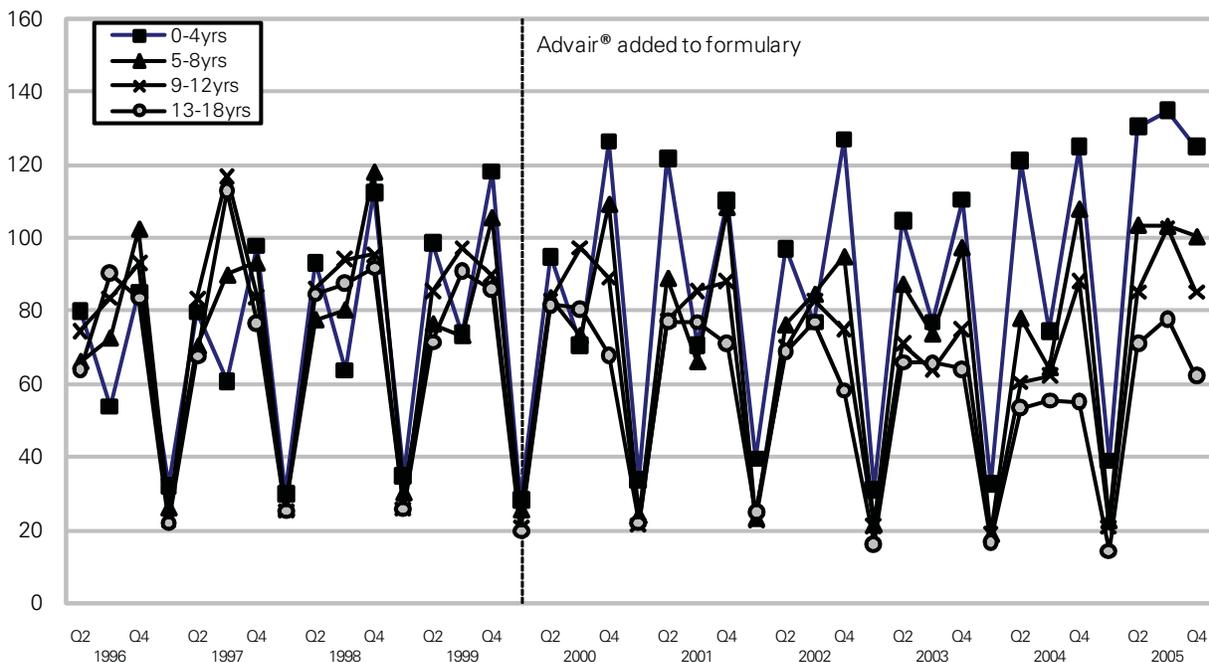


'Q2' indicates incidence for the 2nd quarter (April to June)
 'Q4' indicates incidence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Appendix Figure A.9.9: Steroids Quarterly Incidence by Age, Children

Crude rates of new users with no use of steroids in prior year per 1,000 children with asthma, Q2 1996–Q4 2005

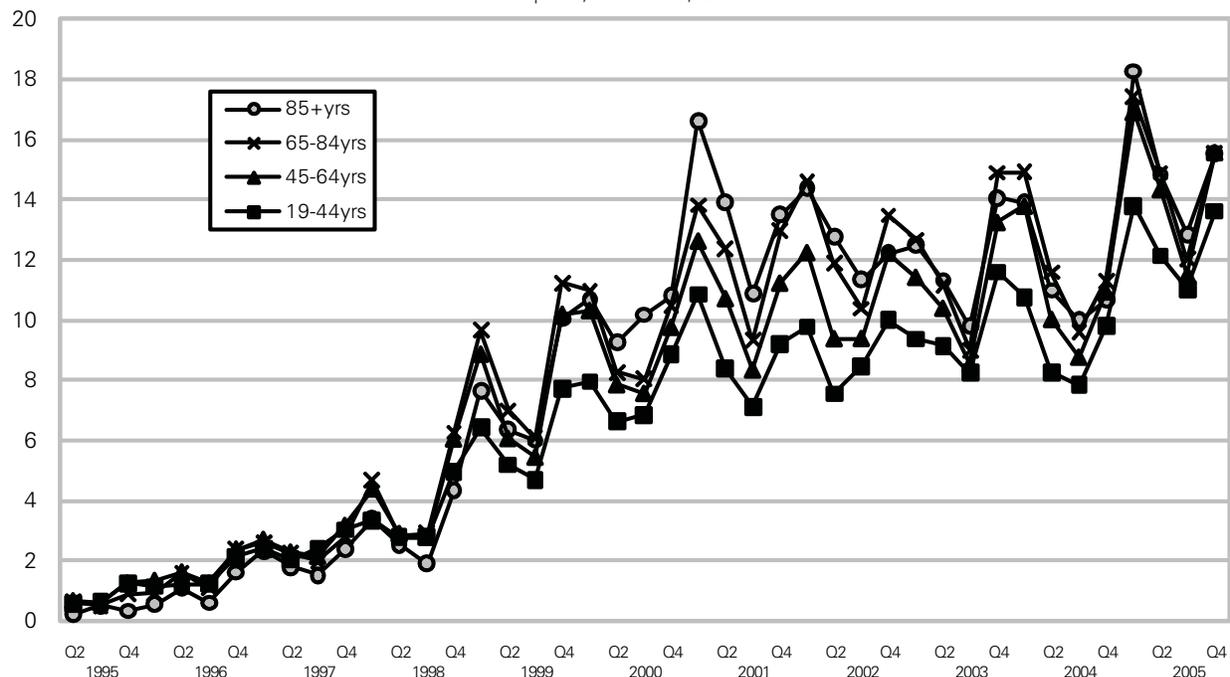


'Q2' indicates incidence for the 2nd quarter (April to June)
 'Q4' indicates incidence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Appendix Figure A.11.1: Azithromycin Quarterly Prevalence by Age

Crude user rates per 1,000 adults, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)

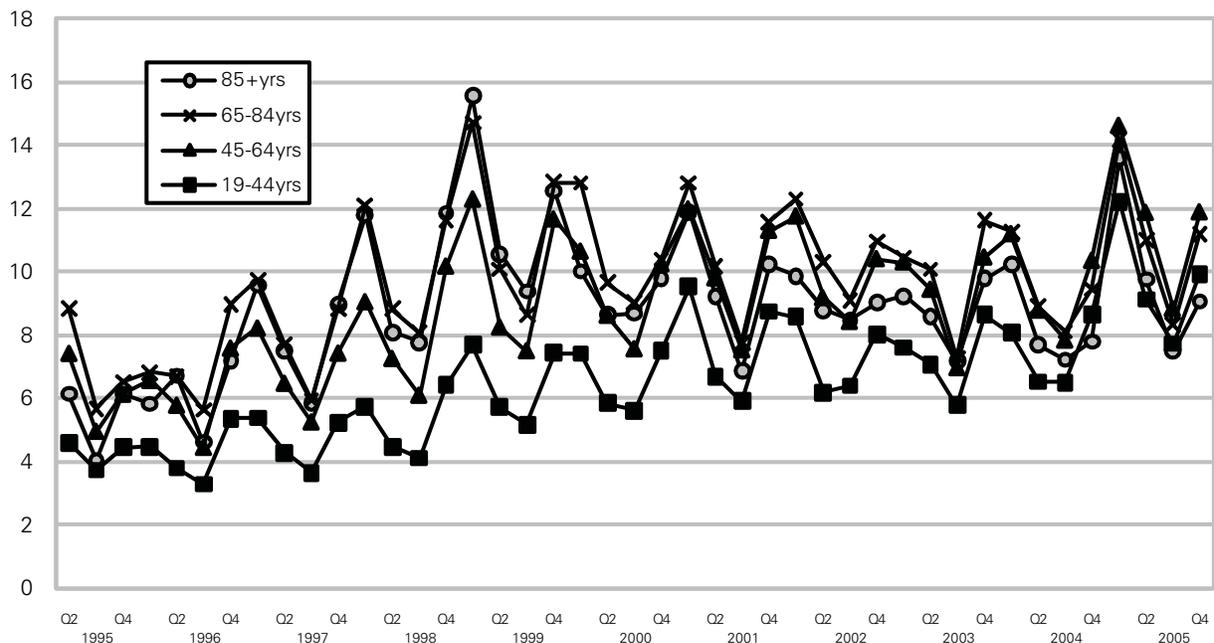
'Q4' indicates prevalence for the 4th quarter (October to December)

'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Appendix Figure A.11.2: Clarithromycin Quarterly Prevalence by Age

Crude user rates per 1,000 adults, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)

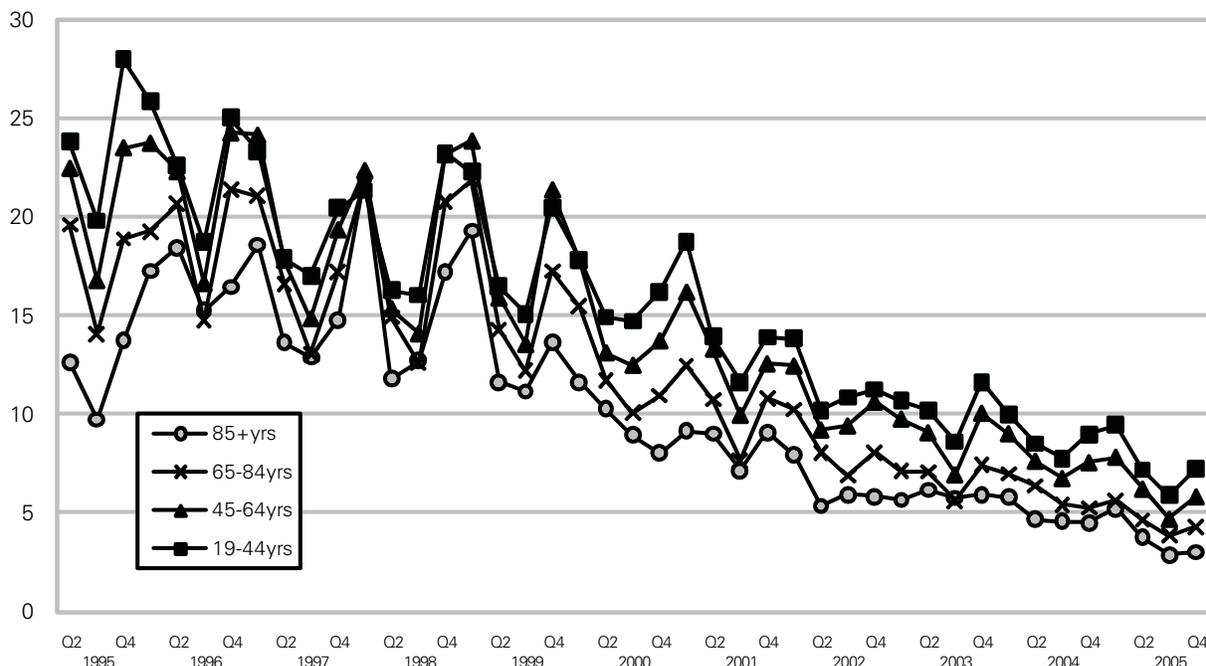
'Q4' indicates prevalence for the 4th quarter (October to December)

'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Appendix Figure A.11.3: Erythromycin Quarterly Prevalence by Age

Crude user rates per 1,000 adults, Q2 1995–Q4 2005

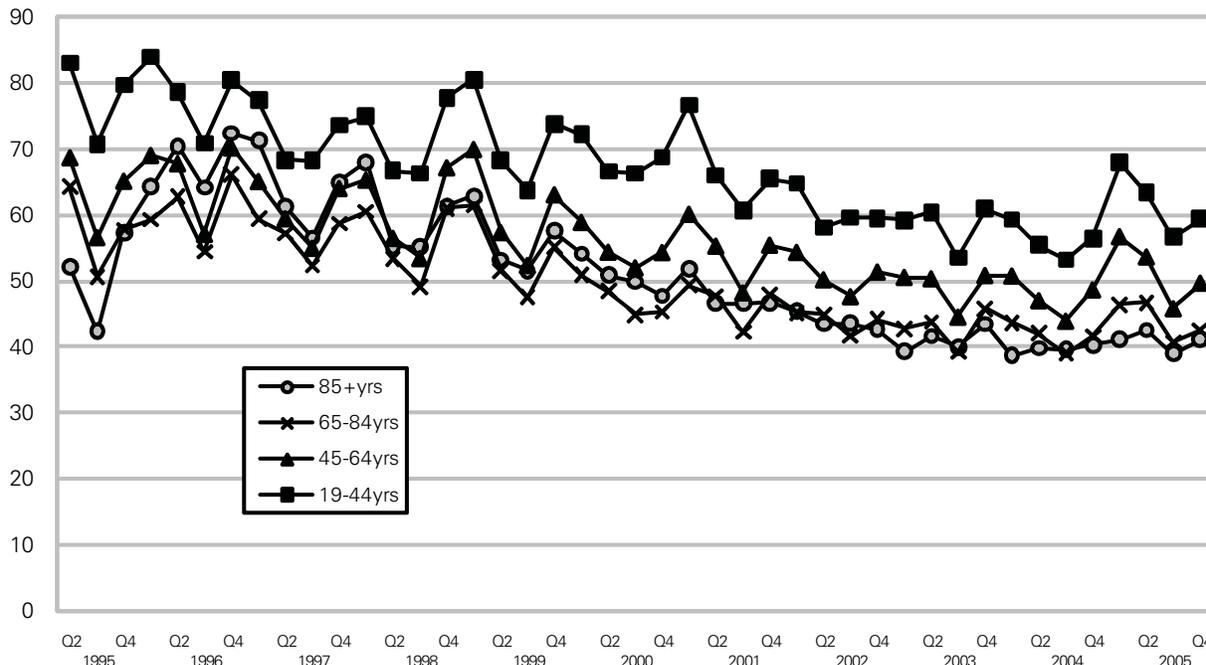


'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Appendix Figure A.11.4: Penicillins Quarterly Prevalence by Age

Crude user rates per 1,000 adults, Q2 1995–Q4 2005

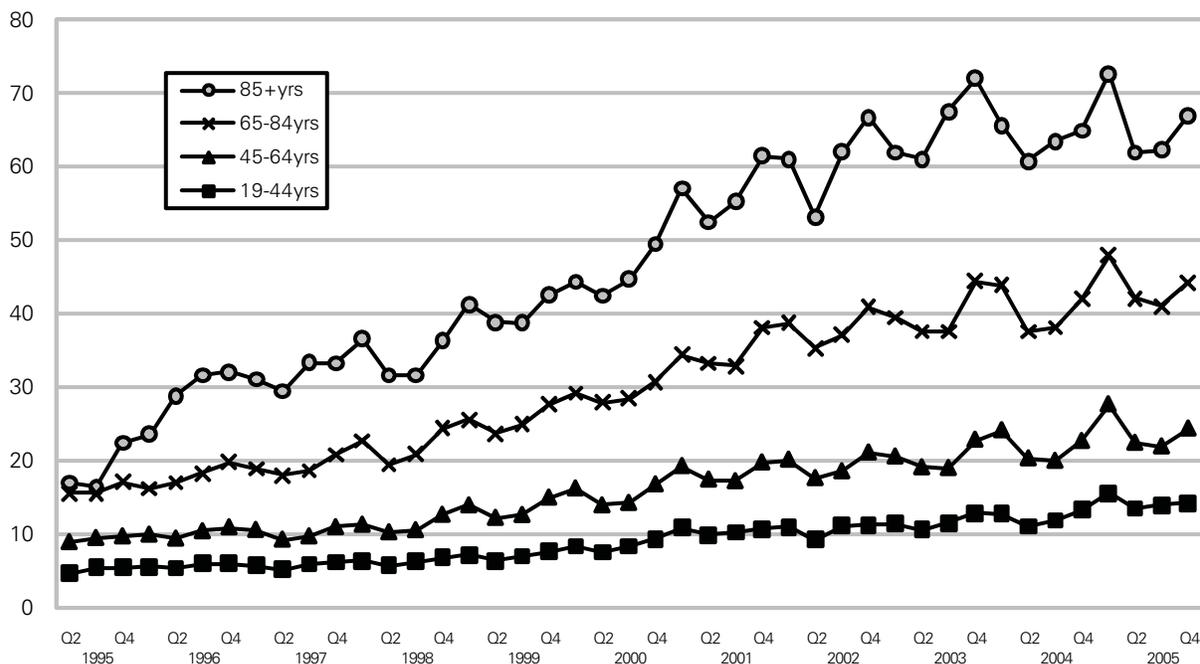


'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Appendix Figure A.11.5: Fluoroquinolones Quarterly Prevalence by Age

Crude user rates per 1,000 adults, Q2 1995–Q4 2005

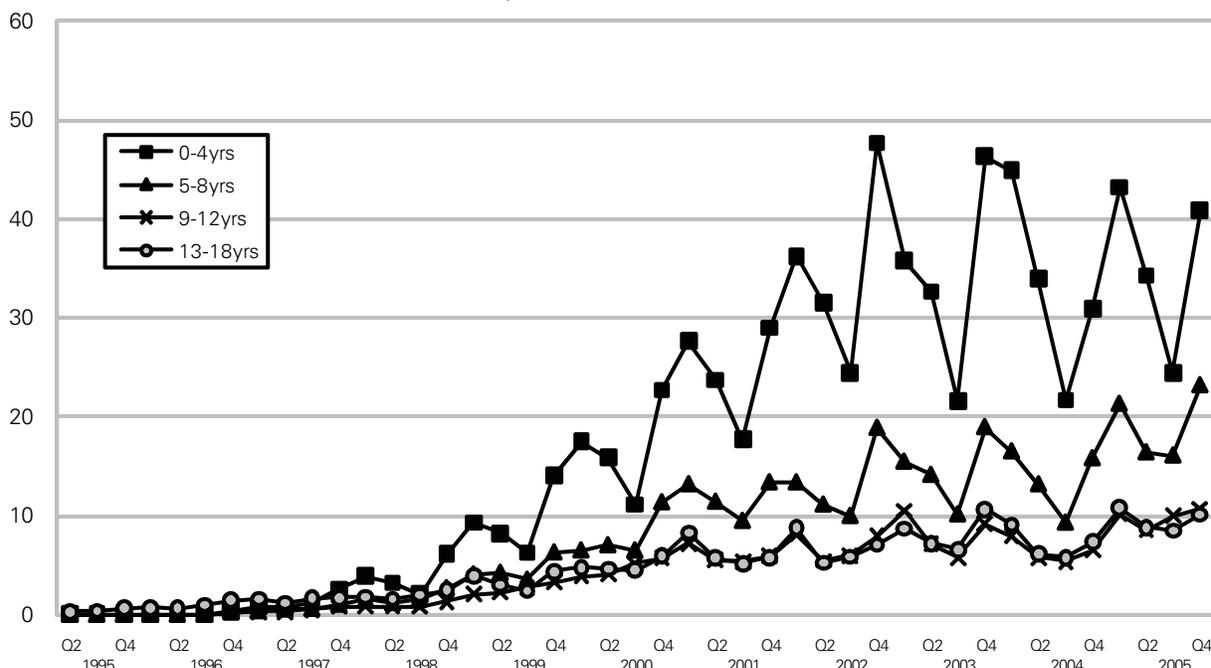


'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Appendix Figure A.11.6: Azithromycin Quarterly Prevalence by Age, Children

Crude user rates per 1,000 children, Q2 1995–Q4 2005

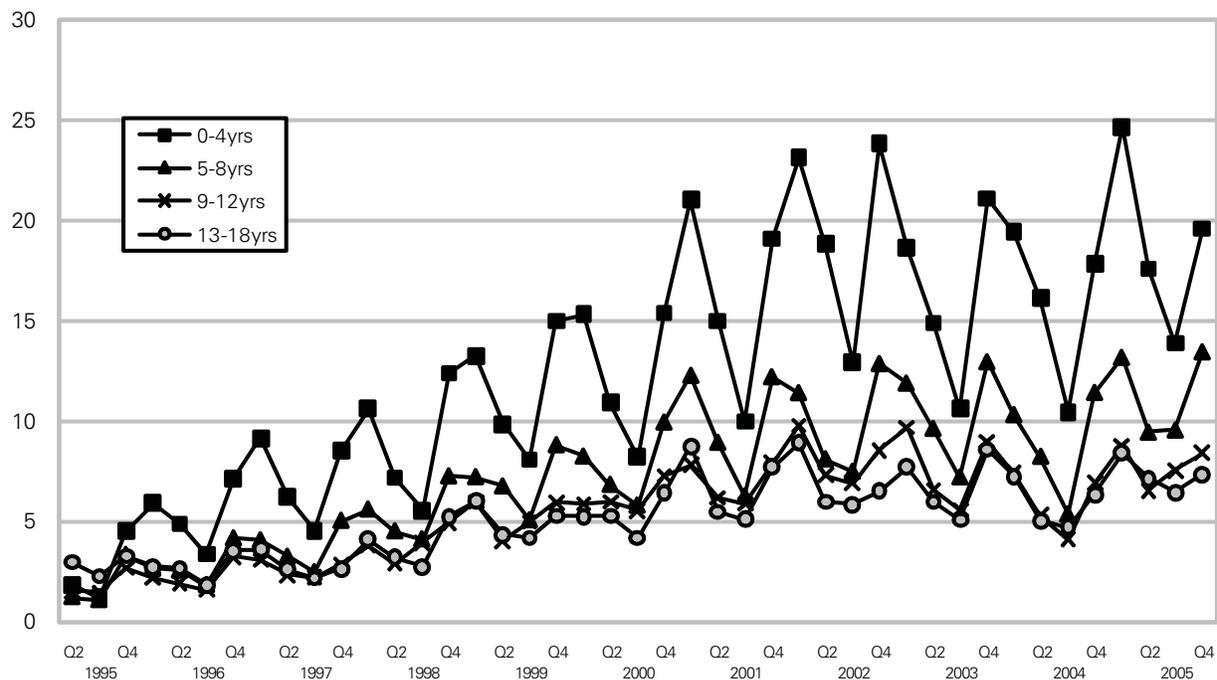


'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Appendix Figure A.11.7: Clarithromycin Quarterly Prevalence by Age, Children

Crude user rates per 1,000 children, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)

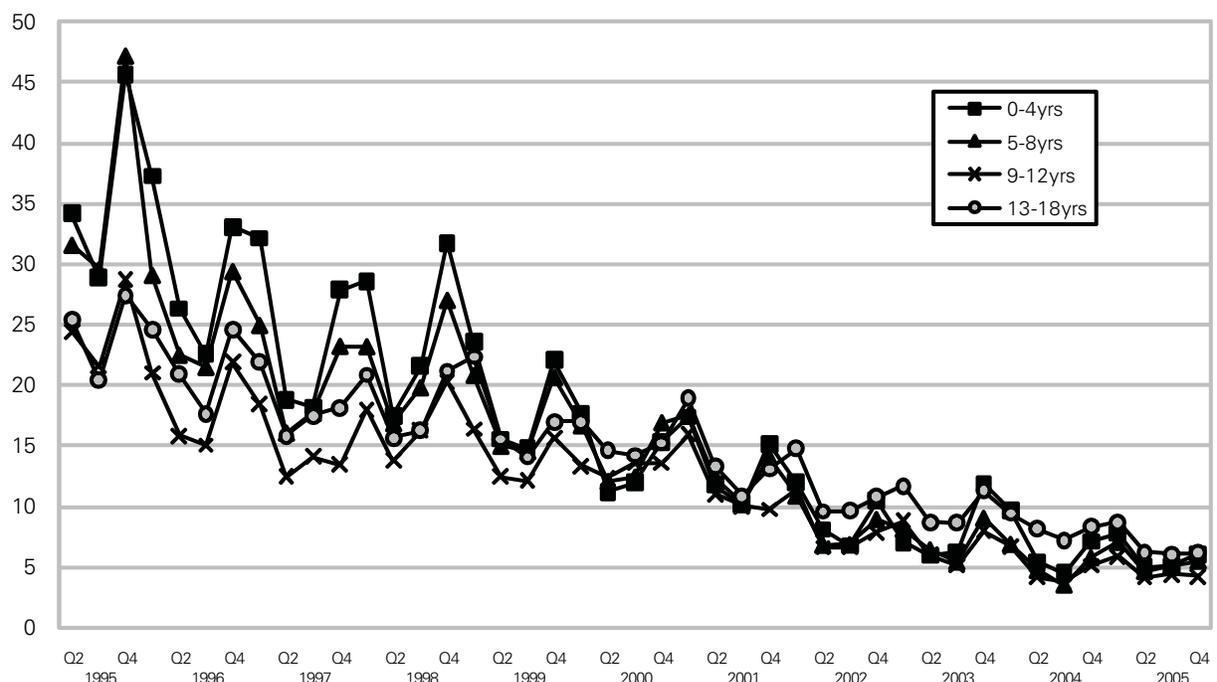
'Q4' indicates prevalence for the 4th quarter (October to December)

'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Appendix Figure A.11.8: Erythromycin Quarterly Prevalence by Age, Children

Crude user rates per 1,000 children, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)

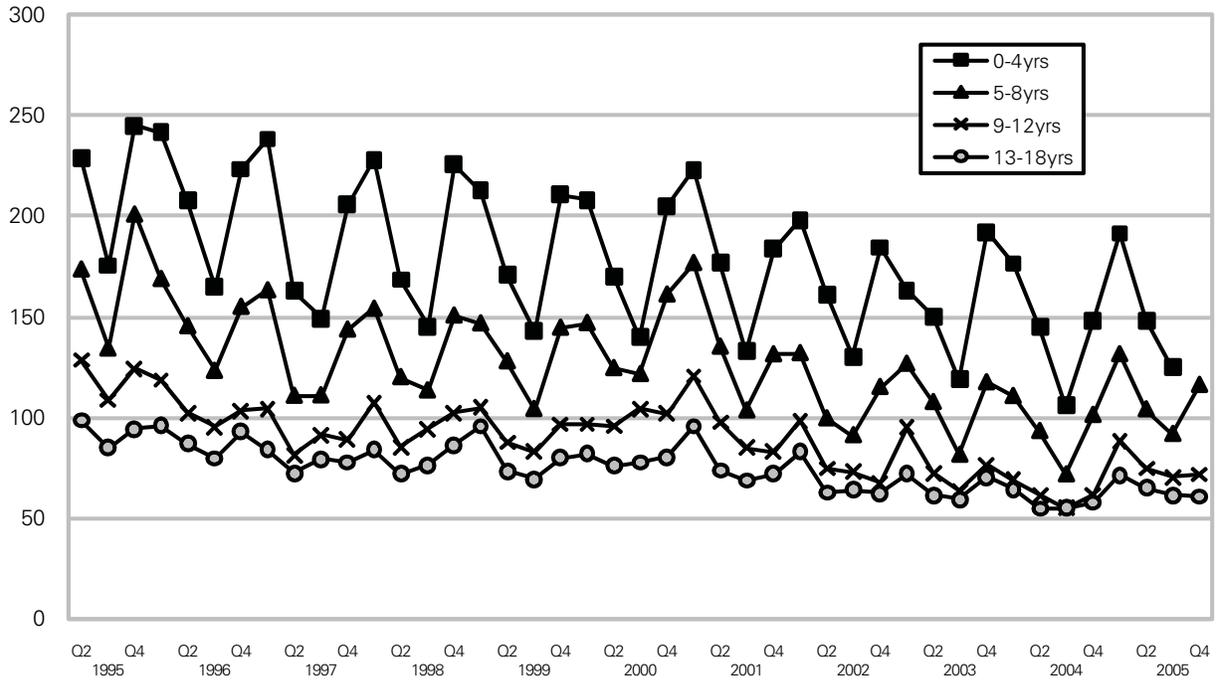
'Q4' indicates prevalence for the 4th quarter (October to December)

'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

Appendix Figure A.11.9: Penicillins Quarterly Prevalence by Age, Children

Crude user rates per 1,000 children, Q2 1995–Q4 2005



'Q2' indicates prevalence for the 2nd quarter (April to June)
 'Q4' indicates prevalence for the 4th quarter (October to December)
 'Q1' and 'Q3' data points are displayed, but not labeled

Source: Manitoba Centre for Health Policy, 2009

APPENDIX THREE: ICD CODES FOR MEDICAL CONDITIONS

Individuals with uncomplicated hypertension could not have any hospital or physician billing records for the following medical conditions: diabetes, peripheral vascular disease, cerebrovascular disease, ischemic heart disease, atherosclerosis, arrhythmias, or cardiomyopathy, hyperlipidemia, congestive heart failure, or renal failure in the three years before date of the incident antihypertensive prescription {258}.

Congestive heart failure: During three years at least one physician visit or hospitalization (any diagnosis field) for heart failure (428), hypertensive heart disease (402)

Renal Failure: During three years at least one physician visit or hospitalization (any diagnosis field) for hypertensive renal disease (403), hypertensive heart and renal disease (404), chronic renal failure (585), dialysis (V451, procedure: 3995, 5498)

Diabetes: During three years at least one prescription for insulin or hypoglycemic drug (A10) or during three years at least one hospitalization or two physician visits for diabetes (250)

Arrhythmias or cardiomyopathy: During three years at least one physician visit or hospitalization (any diagnosis field) for cardiomyopathy (425), conduction disorders (426), cardiac dysrhythmias (427) or one prescription for anti-arrhythmic (C01B)

Peripheral Vascular Disease: During three years at least one physician visit or hospitalization (any diagnosis field) for peripheral vascular disease (443, 440.2, 440.3)

Ischemic Heart Disease: During three years at least one physician visit or hospitalization (any diagnosis field) for acute myocardial infarction (410), acute/subacute forms of ischemic heart disease (411), old myocardial infarction (412), angina pectoris (413), chronic ischemic heart disease (414), arterio-sclerotic cardiovascular disease (4292) or coronary artery bypass graft (procedure 361), or angioplasty (procedure: 360, 362, 363).

Cerebrovascular Disease: During three years at least one physician visit or hospitalization (any diagnosis field) for subarachnoid hemorrhage (430), intracerebral hemorrhage (431), other intracranial hemorrhage (432), occlusion of precerebral arteries (433), occlusion of cerebral arteries (434), transient cerebral ischemia (435), acute cerebrovascular disease (436), other cerebrovascular disease (437), late effects of cerebrovascular disease (438).

Hyperlipidemia: During three years at least one prescription for cholesterol-lowering drug (C10A) or ICD9 272 (disorders of lipid metabolism).

Atherosclerosis: During three years at least one physician visit or hospitalization (any diagnosis field) for procedure code 440.

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An Initial Analysis of Emergency Departments and Urgent Care in Winnipeg by Malcolm Doupe, Anita Kozyrskyj, Ruth-Ann Soodeen, Shelley Derksen, Charles Burchill, and Shamima Huq.

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Next Steps in the Provincial Evaluation of the BabyFirst Program: Measuring Early Impacts on Outcomes Associated with Child Maltreatment by Marni Brownell, Rob Santos, Anita Kozyrskyj, Noralou Roos, Wendy Au, Natalia Dik, Mariette Chartier, Darlene Gerard, Okechukwu Ekuma, Monica Sirski, Nadine Tonn, and Jennifer Schultz.

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How do Educational Outcomes Vary With Socioeconomic Status? Key Findings from the Manitoba ChildHealth Atlas 2004 by Marni Brownell, Noralou Roos, Randy Fransoo, Anne Guèvremont, Leonard MacWilliam, Shelley Derksen, Natalia Dik, Bogdan Bogdanovic, and Monica Sirski.

Using Administrative Data to Develop Indicators of Quality in Family Practice by Alan Katz, Carolyn De Coster, Bogdan Bogdanovic, Ruth-Ann Soodeen, and Dan Chateau.

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