THE HEALTH RESOURCE UTILIZATION AND ECONOMIC BURDEN OF SYSTEMIC AUTOIMMUNE RHEUMATIC DISEASES

by

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Abstract

Background: SARDs (Systemic Autoimmune Rheumatic Diseases) are a group of rare, chronic conditions (systemic vasculitis, systemic lupus erythematosus, scleroderma, Sjogren's disease, and poly/dermatomyositis) associated with high health resource consumption. However, estimates of their healthcare burden are sparse, with most determined at tertiary centres over short periods. Studying them separately has also limited research progress. Here we grouped the SARDs, for the first time ever, to quantify their collective, longitudinal (twelve-year) burden at the population-level.

Methods: A population-based cohort of SARDs cases was identified from the administrative database of BC's single-payer health system (PopDataBC). A detailed algorithm, with time and specialist parameters, was used to enhance diagnostic specificity. From PopDataBC, all provincially-funded health services, and all prescriptions (regardless of funding source), consumed from 1996 -2007 were captured. Costs for outpatient services and prescriptions were summed directly from paid claims; case-mix methodology was used for most hospitalizations. To quantify their net burden, costs were summed for claims attributable (under broad and narrow definitions) to SARDs. Costs are reported in 2007 Canadian dollars.

Results: 18,741 SARDs cases were identified, contributing 82,140 patient-years(PY). After inflation adjustments, the annual mean per-PY direct medical costs of SARDs averaged $6,954/PY, with $1,882/PY(27%) from outpatient, $3,551/PY(51%) from hospital, and $1,521/PY(22%) from prescriptions. Over twelve years, annual costs decreased by 32%, from $8,901/PY in 1996 to $6,087/PY in 2007. Outpatient costs and encounters decreased by 26% ($2,205-$1,641/PY) and 19% (34-27/PY), respectively. Mean annual hospital costs decreased by half ($5,579-$2,776/PY), and admissions by 46% (0.89-0.48/PY). Despite these decreases, the annual mean number of dispensed prescriptions increased by 49% (23-34/PY), and their costs by 50% ($1,117-$1,670/PY). The annual net per-PY costs of SARDs, mainly from hospitalizations(18-43% of costs) and prescriptions(48-76%), averaged $2,011-$3,202/PY.

Conclusions: SARDs impart a substantial healthcare burden at the population level, and in 2007 were directly responsible for ≥44% of cases' gross mean annual healthcare costs ($6,087/PY). Most costs have decreased over twelve years; however, medication costs are rising (by 4% annually, on-average), which suggests comorbidity burdens are too. As demand grows for expensive but potentially-better SARDs therapies, research to assess their impact on long-term comorbidity risk is needed.

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ACE-II	Angiotensin-II Converting Enzyme
ALC	Alternate Level of Care
ANA	Anti-Nuclear Antibody
ANCA	Anti-Neutrophil Cytoplasmic Antibody
ATC-2	Anatomical Therapeutic Chemical Classification System, Second Level
BAFF	B-Cell Activating Factor
BC	British Columbia
BCLHD	British Columbia Linked Health Database
B-Lys	B-Lymphocyte Stimulator Protein
CI	Confidence Interval
CIHI	Canadian Institute for Health Information
CMG	Case-Mix Group
CPI	Consumer Price Index
CPWC	Cost-Per-Weighted-Case
CSD	Churg-Strauss Syndrome
CTD	Connective Tissue Disorders
DAD	Discharge Abstract Database
DIN	Drug Identification Number
DM	Dermatomyositis
DPG	Day Procedure Group
DPG-RIW	Day Procedure Group Resource Intensity Weight
FFS	Fee-For-Service
GC	Systemic Glucocorticoids
GCA	Giant Cell Arteritis
GERD	Gastrooesophageal Reflux Disease
H_2RA	Histamine-II Receptor Antagonist

HAQ	Stanford Health Assessment Questionnaire
ICD	International Classification Of Diseases
ICD-10	International Classification Of Diseases, 10th Revision
ICD-9	International Classification Of Diseases, 9th Revision
IL	Interleukin
JIA	Juvenile Idiopathic Arthritis
LN	Lupus Nephritis
LNN	Lupus Nephritis-Negative
LOS	Length-Of-Stay
MSP	Medical Services Plan
NSAID	Non-Steroidal Anti-Inflammatory Drug
OA	Osteoarthritis
PAH	Pulmonary Arterial Hypertension
PAN	Polyarteritis Nodosa
PDE-5	Phosphodiesterase-Five
PHN	Personal Health Number
PM	Polymyositis
PM/DM	Poly/Dermatomyositis
PopDataBC	Population Data BC
PPI	Proton Pump Inhibitor
PPP	Purchasing Power Parity
PY	Person-Year/Patient-Year
RA	Rheumatoid Arthritis
RAAS	Renin Angiotensin Aldosterone System
RIW	Resource Intensity Weight
SARDs	Systemic Autoimmune Rheumatic Diseases
SARDs-CTD	Connective Tissue Disorders

SARDs-VD	Vasculitic Disorders/Systemic Vasculitides
SjD	Sjogren's Disease
SLE	Systemic Lupus Erythematosus
SMR	Standardized Mortality Ratios
SSc	Systemic Sclerosis/Scleroderma
STD	Standard Deviation
TA	Takayasu's Arteritis
TNF-α	Tumour Necrosis Factor-Alpha
UK	United Kingdom
USA	United States Of America
VD	Vasculitic Disorders/Systemic Vasculitides
Wegener's	Wegener's Granulomatosus

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1 Introduction

1.1 Systemic Autoimmune Rheumatic Diseases

Systemic Autoimmune Rheumatic Diseases, or SARDs, refers to a group of related chronic rheumatic disorders. They are divided, on the basis of the affected tissues, into connective tissue (SARDs-CTD) and vasculitic (SARDs-VD) disorders. SARDs-CTD includes systemic lupus erythematosus (SLE), systemic sclerosis/scleroderma (SSc), Sjogren's disease (SjD), polymyositis (PM), and dermatomyositis (DM). SARDs-VD, known collectively as systemic vasculitides, are characterized by inflammation in one or more types of blood vessels throughout the body – ranging from the smallest capillaries to the aorta. This results in fibrosis, narrowing, stenosis, and restricted blood flow (2). SARDs-VD includes polyarteritis nodosa (PAN), Wegener's granulomatosis (Wegener's), giant cell arteritis (GCA), Takayasu's arteritis (TA), and Churg-Strauss syndrome (CSD).

1.1.1 Epidemiology

SARDs are seen in those of all ages, including children, but the incidence of most SARDs peaks in the fourth and fifth decades. Two exceptions are TA and SLE, which arise during the childbearing years (3,4). All SARDs-CTD predominantly affect females: in a recent population-based Canadian study SARDs-CTD affected about four-to-six times more females overall, and 1-in-100 females over 45 years (5). SARDs-VD affect males more than females, with male-to-female incidence ratios of 1.09 (6) and 1.43 (7) reported. More sex-stratified incidence and prevalence estimates are listed in Table 1.1. Within Canada SARDs are more prevalent among those of Asian and Aboriginal ethnicities (8,9), as compared to Caucasians. Two Canadian population-based studies have shown that Aboriginals, particularly females over 45 years of age (9), may be affected twice as often as non-Aboriginals (10).

SARDs are considered rare - a widely-used definition of rare disorders includes those affecting less than one per-2,000 (11), or 50 per-100,000, individuals – and as illustrated in Table 1.2, most SARDs meet this definition. Because of this rarity prevalence estimates for Canada are limited (8). However in the first and only (known to-date) population-based investigation of the epidemiology of each SARD in adults, the prevalence of SLE, SSc, SjD, PM, and DM in the province of British Columbia (BC), Canada, was 113.9, 21.3, 21.3, 5.4, and 9.2, respectively, per-100,000 adult in 2007(1). While these estimates are low, they were determined with high sensitivity and case

capture was not limited to a single algorithm or institution. This investigation showed how SARDs-VD are even rarer, with their prevalence ranging from just 0.2 per-100,000 for TA to 17.3 per-100,000 for GCA in BC (1). In comparison, the prevalence of rheumatoid arthritis (RA) in Canada is approximately 1,000 per-100,000 adults (12) while the adult prevalence of osteoarthritis (OA) in BC is ten-times greater at approximately 11,000 per-100,000 (13,14).

1.1.2 Pathogenesis

The aetiology and exact pathogenesis of most SARDs is unknown; however, they do share an autoimmune origin. All SARDs elicit an immune response against the body's own cells and tissues, instead of a foreign body or pathogen, that lead to inflammation and potentially to organ failure. There may be shared aetiologies or environmental triggers too, with solvents linked to the development of SSc and SARDs-VD (8), silica dust to SLE, SSc, and SARDs-VD (8), and Epstein-Barr virus to SLE and SjD (15). This abnormal immune activity can be cell-mediated or humoral, though these two mechanisms work hand-in-hand. When cell-mediated, B-lymphocytes (B-cells) produce antibodies (auto-antibodies in this case) against antigen proteins on the surface of body's own cells (16). Antibodies may be produced against nuclear components like DNA (referred to as antinuclear antibodies, or ANA) (15) or against the cytoplasmic components of white blood cells (referred to as antineutrophil cytoplasmic antibodies, or ANCA) (17). These are present in multiple SARDs: ANA in SLE and PM/DM (15,17), and ANCA in PM/DM (15,17) CSD (18), and Wegener's (19). Cases diagnosed with one SARD, such as SjD, may even test positive for auto-antibodies usually produced in other SARDs (20).

When these auto-antibodies bind to 'self'-antigens, immune complexes are formed and deposited in sites around the body (4,15). When they deposit in organs – like the skin and kidneys in SLE (4) – injury occurs directly at those sites. They can also deposit in blood vessels where they promote further systemic inflammation and damage by activating the complement pathway (15). Humoral immunity involves another type of white blood cell, the T-cell, which stimulate B-cells to produce antibodies. T-cells enhance the immune response by releasing pro-inflammatory substances called cytokines (16), most often interleukins (IL) (15). One T-cell of particular importance in autoimmunity and chronic inflammation is the T_H17 cell, which produces IL-17 (15). Usually T-cells are only

activated by foreign antigens, but in autoimmune disorders they are activated by the body's own antigens, and carry out and mediate the attack of its own cells and tissues (16).

Different cytokines may be involved in this process depending on the specific SARD, such as type-I interferons in SLE (15), IL-4 in SSc (21), and IL-2 and IL-6 in GCA (22). Still, this general process of autoimmune-mediated attack, followed by systemic inflammation and dysfunction and damage in organs, blood vessels, and connective tissues, links all the SARDs together (15). The individual SARDs-VD are differentiated by the size and/or type of blood vessel affected, but all result from autoimmune-mediated inflammation and degradation of these vessels, often from the formation of lesions (2). Different tissues may be targeted amongst SARDs-CTD (15) – the epithelia of the salivary and lachrymal glands in SjD (20), muscle fibres in PM (23), and blood vessels in DM (15,24) – but the clinical implications of this chronic inflammation are similar throughout the spectrum of SARDs. On top of this, many individuals are actually afflicted with more than one SARD: SjD often develops in those with SLE or PAN (20,25), and about 25% of SSc cases also have PM/DM (23). These commonalties amongst the SARDs will be emphasized in the next section when describing their many clinical manifestations.

1.1.3 Clinical Manifestations

We have just described how a similar autoimmune-mediated mechanism underlies the pathology of all the SARDs. The systemic inflammation characterizing these disorders leads to a diverse spectrum of manifestations. SLE is one of the most well-known SARDs and considered the "prototypic systemic autoimmune rheumatic disease" (15). In addition to systemic symptoms and haematological problems - like anaemia and thromboses (17,26) - a multitude of organ-specific effects are seen. SLE can affect nearly every organ system, but the skin, and renal, central nervous (CNS), and musculoskeletal systems (particularly the joints) are affected most (17,26). Renal disease (or lupus nephritis (LN)), which is very common, can result in hypertension (4,26) that further increases the already elevated risk of coronary artery disease and stroke (27,28) in these patients.

Given their common pathology all SARDs share some generalized or systemic features. These include headache (4,29,30), fatigue (2,4), fever (2,4), muscle pain (18,23-25), joint swelling and/or pain (2,4,18,19,25,29), peripheral neuropathy (18,20,25), hair loss (4,24), and rashes (4,24,25) and other skin ulcerations (19,24,25). Many different

SARDs can damage the same internal organs, including those of the cardiovascular, respiratory, gastrointestinal, renal, and nervous systems, via inflammation. Some of the adverse cardiovascular effects include stroke (4,29), heart failure (4,18), and cardiomyopathy (23), while the respiratory morbidities include reactive airway disease (18), interstitial lung disease/fibrosis (20,29), and pulmonary hypertension (21,29). In addition to LN, renal failure (19,25) is common in other SARDs too, as are impaired digestion and gastrooesophageal reflux disease (GERD) (20,21). Some of these manifestations (ie. neuropathy and nephritis) are quite progressive and others can resolve, but each of the SARDs generally relapse and remit over the patient's lifetime. It is proposed these relapses stem from the immune system encountering the same self-antigen that first triggered the disease and, often in conjunction with an environmental trigger, launching another damaging autoimmune response (15). Unfortunately these subsequent responses tend to be stronger than the initial ones (15). Particularly in SLE, these relapses are referred to as flares.

1.2 SARDs Treatment

1.2.1 Current Therapies

Consistent with their shared pathogenesis and manifestations, the different SARDs are treated with many of the same medications, the details of which are outlined in Table 1.3. Systemic glucocorticoids (GC), as they decrease both inflammation and the abnormal immune response (4), are a mainstay for treating every SARD (4,18-21,23-25,29,31). However their long term use is associated with multiple adverse effects including weight gain/obesity, cataracts, glaucoma, adrenal suppression, glucose intolerance/hyperglycaemia/diabetes, hyperlipidaemia, hypertension, and avascular necrosis of bone (17,26,27,32). Because of these, GC are often given in conjunction with an immune-modulating or -suppressing agent to minimize the dose required and therefore the associated side effects (32). The powerful but toxic immunosuppressants include cyclophosphamide, methotrexate, azathioprine, cyclosporine, and mycophenolate (19). Methotrexate has anti-inflammatory and immune-modulating properties while azathioprine works to reduce the number of immune cells (4). Cyclophosphamide, being associated with infertility, an increased susceptibility to infections, and bladder and haemotologic cancers (19,25), is considered the most toxic of these; therefore, it is generally reserved for severe or unresponsive cases (4,20). Because of this, mycophenolate has become a popular alternative to cyclophosphamide and azathioprine. It has been used successfully in many studies as an induction (33-37) and maintenance therapy in LN (38-52) with fewer adverse

events like opportunistic infections (33,40,41,53,54). It appears to be well tolerated (55) and unlike cyclophosphamide, does not decrease fertility although it cannot be taken during pregnancy (56). The antimalarial hydroxychloroquine, an immune-modulator, is also less toxic than the conventional immunosuppressants (32). It is employed in SLE (4), SjD (20), and DM (24). Some other drugs used for multiple SARDs include non-steroidal anti-inflammatory drugs (NSAIDs) to alleviate joint and muscle pain (4,20,28,57), aspirin to improve blood flow (29,57) and prevent stroke and vision loss (22,28), and calcium channel blockers for vasospasm in SSc (21,57), calcinosis in DM (24), and hypertension (29). Angiotensin-II converting enzyme (ACE-II) inhibitors, which are anti-hypertensives with additional renal benefits, are used to manage LN (27) and prevent renal disease in SSc (17), amongst other SARDs. Immune globulins are another option for SLE flares (4), and in PM/DM (23,24), Wegener's (19), and CSD (18).

These drugs are intended to treat the manifestations of SARDs and have definitely improved survival (26). Immunosuppressants have been credited with improving the five-year survival rate in LN from close to zero in the 1950's (before these therapies were available) to around 85% now (27). Amongst more than 9,500 SLE cases in seven countries (including Canada), standardized mortality ratios (SMRs) decreased by over 60% from 1970-1979 to 1990-2001. In this study longitudinal mortality decreases specifically for many lupus-related causes, like infections and renal disease (58), further illustrate the positive impact of these therapies and other improvements in care. In another Canadian SLE cohort, SMRs not only decreased from 1970-1994, but these decreases were 3-10 times greater than those in the general population (59).

However despite their benefits these drugs can lead to further morbidities requiring additional therapy. GC are associated with myopathy (23), a particular problem for PM/DM cases (17). They can cause gastrointestinal haemorrhage, so histamine-II receptor antagonists (H_2RAs) and proton-pump inhibitors (PPIs) are prescribed both to prevent this adverse effect (18) and address GERD, a primary SARD symptom (21,23). GC can also cause osteoporosis, so calcium, vitamin D, and bisphosphonates are needed as preventive therapies (22,23,25). Prophylactic antibiotics may also be prescribed to prevent opportunistic infections, like pneumonia, that can develop during corticosteroid and/or cyclophosphamide treatment (19,25). Since cyclophosphamide is also associated with haemorrhagic cystitis, an agent called mesna is given before and following infusion as a preventive measure (17)

1.2.2 Emerging Therapies

In addition to these longstanding regimens, there are a variety of other treatments being introduced to market or otherwise increasingly indicated for SARDs. Of particular note are mycophenolate and the biologic immune modulators rituximab and belimumab. Some vasodilators with other treatment indications, including bosentan, sildenafil, and epoprostenol, are increasingly being used to address symptoms of SSc. For many of these emerging therapies, more and larger-scale studies of their safety and efficacy are required for their use to become widespread in SARDs. But they are also much more expensive than conventional treatments (as shown in Table 1.4, about ten-to-fifty times greater) which presents another barrier to their use.

Mycophenolate

Mycophenolate inhibits the production of lymphocytes and antibodies, suppressing both humoral and cell-mediated immunity (60,61). Its lower toxicity when compared to cyclophosphamide and azathioprine is likely from it targeting T- and B-cells more selectively than the older therapies (62). It is officially indicated to prevent organ rejection after transplant (63) but has become a common treatment for LN. Now, its use in SLE is expanding from renal manifestations to treating those of the dermatological, haematological, and musculoskeletal systems (56,60,61,64-67). Studies have suggested it may be more effective than azathioprine (68) and at least as effective as cyclophosphamide (37) for inducing remission in these systems and reducing the number of new SLE flares. Mycophenolate is emerging as an option for other SARDs too, showing promise in SjD (69), DM (70-73) and SARDs-VD (49,74-87). With it increasingly recommended as a treatment for SLE and other SARDs, some may no longer consider mycophenolate - which costs approximately $1,000-$2,000 CDN per-patient annually (88) - as an emerging therapy. However, though available in Canada since 1995 (89) it is still not approved in BC for the management of SARDs.

Rituximab

Rituximab modulates cell-mediated immunity by reducing the number of B-lymphocytes. Specifically, it induces B-cell death by binding to the CD20 antigen on its surface (90). It was first approved in Canada in 2000 as a cancer therapy (89) but with evidence from many published reports (91-115) of its efficacy, it was officially indicated for

use in Wegener's in late 2011 (116). Some investigations and reviews have concluded rituximab – which costs about $9,500 per-patient (32) - to be beneficial for SLE, often inducing good renal responses(117-123) and partial or complete disease remission (92,93,114,124-135) or other benefits (91,115,136-163). Initial studies suggest it may also be beneficial in SSc (91,136,164-166), SjD (91,93,125,167-175), PM/DM (93,176-184), and, along with Wegener's, other SARDs-VD (185-193) including CSD (92,194-197), PAN (198), and GCA (136).

Etanercept (a fusion protein (17)) and infliximab (a monoclonal antibody (17)) are two other biologics that were approved in Canada in 2001 (89). There is evidence etanercept may be useful in GCA (199-202) and PM/DM (203). Infliximab has been associated with improvements in PM/DM (203-206) and SjD (207,208), and has been shown to reduce inflammation and induce disease remission in SARDs-VD (209), including GCA (201,202,210-213) and Wegener's (214-224). Still interest in these two very expensive therapies (the annual per-patient cost for etanercet is approximately double that of rituximab (225)) is very guarded Although both bind and inhibit tumour necrosis factor (TNF)-α, but one cytokine whose levels are elevated in SLE (226), its role in the pathogenesis of SLE is not well-defined, with suggestions it may actually be protective or otherwise beneficial in these patients (227,228). Shockingly, etanercept and infliximab may even induce SLE (17,226-228)! They have been used extensively in other forms of arthritis such as RA, ankylosing spondylitis, and psoriatic arthritis (229), but there are reports of such cases developing auto-antibodies and SLE or a lupus-like syndrome after exposure to these therapies (230-243).

Belimumab

Belimumab is brand new and has generated much publicity since it is considered to be the first specific SLE treatment to come out in nearly 50 years (244). It is a monocolonal antibody that binds the B-lymphocyte stimulator protein (B-LyS), also known as B-cell activating factor (BAFF), which SLE patients often have higher levels of (245). This action prevents the usual binding of B-LyS to B-cells, thus indirectly inhibiting their survival and differentiation into antibody-producing plasma cells (245). Being so new – it was only formally approved in the United States of America (USA) in March 2011 (246), and just four months later in Canada (244), fewer studies have been published on it, but its efficacy, particularly in relation to standard therapy, has been demonstrated in some clinical trials (247-249). Even more, these trials also suggest the drug is well-tolerated (226,250,251), but any

benefits from this therapy will come at a significant price, with annual Canadian per-patient costs for belimumab estimated at $20,000 (32).

Vasodilators

When, in SSc, excess collagen is deposited in blood vessel walls these become narrowed and spastic (57) which increases blood pressure and can lead to pulmonary arterial hypertension (PAH) (17). Blood flow to the fingers, toes, and skin is also restricted (this is referred to as Raynaud's phenomenon (21)), causing ulcers (252), reduced oxygenation to these tissues, and potentially even more fibrosis (57). Calcium channel blockers have traditionally been employed to reverse this spasticity but interest is growing in several other classes of vasodilators (253). Bosentan (an endothelin-1 receptor antagonist) prevents this peptide from binding to vascular smooth muscle cells (252), and may also directly inhibit collagen production (57). It was approved in Canada in 2001 (89) and though officially indicated to treat PAH (254), is used off-label to treat digital ulcers and Raynaud's phenomenon too (255). Of these emerging SARDs therapies, bosentan is by-far the most expensive (Table 1.4), costing over $40,000 CDN per-patient each year (256). Still, its efficacy for treating and preventing digital ulcers has been demonstrated in studies (257-259), including some RCTs (260,261), and it is approved in Europe for this purpose (252).

Epoprostenol, a prostaglandin analogue, also costs about $40,000 CDN per-year (256), but both it and bosentan may be better treatments for PAH since they are more selective than calcium channel blockers for regulating pulmonary blood flow (57). Sildenafil promotes vascular smooth muscle dilation by inhibiting the phosphodiesterase (PDE)-5 enzyme (262). It was approved in Canada for erectile dysfunction (262) in 1999 (89) but this agent and other PDE-5 inhibitors may be useful for Raynaud's (263,264), digital ulcers (265,266), and PAH (267). It is cheaper than the vasodilators just described but still five-to-fifteen times more expensive than calcium channel blockers used for this purpose (Table 1.4). Currently its use in PAH is recommended by the European League Against Rheumatism (EULAR) and it has been officially approved in the US for this purpose (253) but not Canada.

Implications

These emerging therapies are not suitable for all patients, and may induce further morbidities. Because the biologics are proteins themselves, the body may recognize them as foreign bodies and launch an acute immune response. This

is referred to as an infusion reaction, and can result in fever and rash (17). Not only may infliximab and etanercept actually induce SLE, but by inhibiting TNF, these therapies also make patients more vulnerable to infections, especially tuberculosis, and sepsis (17). Rituximab may only be a superior therapy in cases of severe refractory SLE (226) with two very recent RCTs finding it not efficacious in LN (268,269). Rituximab may also increase susceptibility to infections and has been associated with the development of a rare but disabling CNS disorder called progressive multifocal leukoencephalopathy (PML) (226,251). More studies are needed before belimumab can be used in those with CNS lupus or LN (245,250,270) and although SLE is more common in those of black African descent, the efficacy of this drug in such patients was *not* demonstrated in the initial studies (245,246,270,271). The new vasodilators carry risks as well: bosentan is associated with liver toxicity and being a teratogen (253) cannot be taken during pregnancy.

Aside from their clinical limitations, there are significant costs associated with these therapies. We have just described how the prices of these drugs alone are very high – at least five-to-fifty-times those of longstanding therapies - with some costing $10,000 or more per-patient each year (Table 1.4). On top of this, some (infliximab, rituximab, belimumab, and epoprostenol) must be administered by intravenous infusion, an additional expense not required for oral formulations of hydroxychloroquine, calcium channel blockers, GC, or methotrexate (32,272). Plus the administration of epoprostenol requires the implantation of a central venous line (272), increasing costs and the risk of infection. Still, given the adverse effects we described for some current therapies, and their limited ability to control the progression of these diseases and development of complications, both clinicians and patients are excited at the prospect of these new options.

1.3 SARDs as a Group of Diseases

In sections 1.1 and 1.2 of this chapter we established how SARDs have shared pathogenesis, manifestations, and treatments, but despite these commonalities they have traditionally been studied as separate disorders. Now there is increasing recognition, particularly following the Canadian Arthritis Society's multinational Consensus Conference on SARDs in 2005, of the benefits that could come from studying them together (8). In section 1.1.1 we described how SARDs are quite rare, with most of the individual disorders affecting less than 50 per-100,000 adults. This means focussing on a single disorder severely limits the number of cases available for study: to illustrate, the

aforementioned BC SARDs prevalence study identified only 711 SSc cases and 710 SjD cases in 2007 (1). These numbers are miniscule when compared to BC's entire adult population, with each disorder affecting only 0.02% of it (273), but with 12,966 collective SARDs-CTD cases identified in 2007 (1), the SARDs-CTD together affected twenty-times more BC adults (0.4%) (273). When conducting research, small samples limit the ability to identify trends, and attribute these trends to actual phenomena instead of chance alone. But when the SARDs are grouped, larger samples are available and statistical power is gained.

Apart from this methodological advantage, grouping the SARDs also emphasizes the public health impact of these disorders. It was noted at the Consensus Conference these individually-rare disorders can be considered "common" when grouped (8), and this is evident when comparing the single-SARD prevalence estimates in BC with the combined: the prevalence of SARDs-CTD together was 388.6 per-100,000 adults (more than three-times the prevalence of SLE alone), and the prevalence of the SARDs-VD combined was 31.9 per-100,000 adults (1). Being rarer, this transformation is especially important for SARDs-VD. There were only 135 diagnoses of PAN, and 58 diagnoses of TA, located in BC in 2007 (1), and researchers, sponsors, and the general public may see little benefit in studying a disorder that affects just one hundred or-so individuals. But they may think differently when thousands (all SARDs-VD combined) and tens-of-thousands (all the SARDs combined) (1) are affected.

Increasing the public profile of SARDs is important because of the high economic costs, both direct (in terms of actual medical costs) and indirect (the value of productivity losses from time spent seeking healthcare or unable to work) incurred annually by the average SARD patient in Canada. In 2007 the annual costs of SSc averaged $18,543 CDN (95% CI: $16,598-$20,308) per-patient (274). Canadian estimates for SLE are also high, costing approximately $60,590 2007 CDN (275) per-patient cumulatively over four years, and approximately $22,352 2007 CDN (276) per-patient in 1990. Per-patient cost estimates of the direct medical costs of many SARDs are detailed in section 1.5 and Table 1.5-1.6 of this chapter. Combined, SARDs-CTD and SARDs-VD affect about 0.4% of the adult population (1) while RA affects more than twice as many adults, about 1% (12). However these annual per-patient cost estimates for SARDs have exceeded multiple Canadian estimates for RA (all in 2007 Canadian dollars): $8,248 (277) annually from 1990-1994, $13,029 (278) in 2000, and $16,552 (279) in 2002. Therefore the total

economic burden of SARDs in Canada is clearly disproportionate to the number of individuals affected, and may be similar to that of RA, a more well-known disorder.

1.4 Significance of the Health Resource Utilization and Economic Burden of SARDs

As detailed in section 1.2, the health resources consumed in the management of SARDs are vast and diverse. Their diagnosis and follow-up entail many diagnostic radiologic and laboratory tests, and consultations with multiple physicians such as rheumatologists, respirologists, gastroenterologists, nephrologists, pathologists, and dermatologists, among others. Along with the complex medication regimens, frequent monitoring laboratory tests (for example, monthly during mycophenolate treatment (63), and every three months in SLE (4,21)) and other consultations - annual ophthalmologist visits when taking anti-malarials (32) - are needed to monitor for adverse effects and track disease activity and progression. As SARDs are chronic and often relapse, this heavy utilization can be lifelong. If renal involvement progresses to end-stage renal disease (ESRD), dialysis or renal transplant are required (4). Additionally, cases face an increased risk of comorbidity either as complications of the disease itself or secondary to the treatments used in their management. For example cancer can be directly associated in SSc (21), SjD (20), PM/DM (23,24), and SLE (280-282), or could be related to the use of immunosuppressive therapy (19,20,25), such that vigilant screening is required. Any malignancies that do develop naturally impart an additional burden on the healthcare system. Altogether the health care needs of SARDs patients are great and this high health resource consumption entails considerable costs, particularly in a publically-funded healthcare system. With the number of new SARDs diagnoses increasing, and many SARDs disproportionally affecting seniors (Table 1.7), the very population that is currently expanding, the overall burden of these disorders on the healthcare system may continue to grow. When combined with the very expensive drugs emerging for SARDs, the cost of treating all these cases could be considerable.

1.4.1 Rising Case Numbers

As large as the burden of SARDs may be now, it may even get larger since the incidence of SARDs, or number of new diagnoses relative to the total population, may actually be increasing. This is supported by epidemiological evidence from many countries, as listed in Table 1.8. We must emphasize that each increase listed in Table 1.8 occurred within the context of the same investigation. This means they cannot be wholly explained by differences in

the makeup of the study populations or methods of case ascertainment between different investigations. Although increases in clinical recognition (283,284) and the sensitivity of diagnostic tests (285) have likely contributed to these additional diagnoses, this may not explain 100% of the rise. A true increase in the incidence of CSD is biologically plausible since it may be triggered by one asthma therapy, leukotriene receptor antagonists, whose use has recently increased (18). As exposure to environmental pollutants may contribute to the development of SARDs-VD (286), longitudinal rises in pollution levels may also have led to a true rise in case numbers. Whatever the reason for the increasing incidence rates, the implications for the health care system are great: more diagnoses, even if just of milder or earlier-onset cases, could equate to health resource consumption that would not have occurred otherwise.

With the Canadian population growing older - by 2036, those 65 years and older are expected to make up 24% of BC the population, versus 15% in 2010 (287) - a further increase in the number of new SARDs diagnoses over and above general population growth is anticipated. Plus with survival improving (58,59,288,289) the prevalence of many SARDs is likely to increase too. National healthcare spending on seniors (44% of total healthcare spending in 2009 (290)) is already disproportionate to their share of the Canadian population (14% in 2009 (290)), and when combined with the additional healthcare consumption necessitated by SARDs, a great demand may be imparted on the healthcare system going forward.

1.4.2 Increasing Drug Costs

It is exciting to think the therapies emerging for SARDs could improve outcomes and cause fewer adverse effects. However as shown in Table 1.4, their annual per-patient costs (around $10,000 CDN) are about twenty-times greater than those of established therapies. Being so new (244), the cost of belimumab in Canada is less certain but is predicted to be $20,000 CDN (32). Already, biologics are believed responsible for a substantial increase in the direct medical costs of RA in Canada (278), and as their use in SARDs grows, they could certainly impact the costs for SARDs in the same way (26). With the complications of SARDs also having the potential to strain healthcare budgets (291), these additional costs may be worthwhile over the long-term, but detailed breakdowns of the current healthcare costs of SARDs and types of health resources consumed in these disorders are needed for such an analysis.

1.5 Review of Available Literature

We have established that the diagnosis, treatment, and ongoing care for SARDs mandate a large and diverse consumption of healthcare resources. However, details of this consumption and the associated costs are difficult to find. Therefore a comprehensive literature review was undertaken to locate and evaluate such estimates, and identify gaps in the literature and ongoing research needs in this area.

1.5.1 Methods

An extensive literature search was undertaken to locate any studies reporting on the direct health care costs and/or health resource utilization for the SARDs as a whole, or for any group of SARDs or individual disorder. The MEDLINE database (1948 to present with daily update) was searched in July 2011. Keywords and MeSH subject headings relating to either SARDs (including each disorder individually) or health care costs were compiled by mapping the associated subject headings and perusing those assigned to a preliminary set of SARDs costing studies we had located. The disease terms included "Lupus Erythematosus, Systemic", "Lupus Nephritis", "Sjogren's Syndrome", "Scleroderma" (localized, systemic, limited, and diffuse), "CREST Syndrome", "Polymyositis", "Dermatomyositis", "Connective Tissue Diseases", "Vasculitis", "Polyarteritis Nodosa", "Giant Cell Arteritis", "Takayasu Arteritis", "Wegener Granulomatosis", "Churg-Strauss Syndrome", and "Microscopic Polyangitis". Some of the terms for healthcare costs included "Costs and Cost Analysis", "Health Care Costs", "Health Expenditures", "Direct Service Costs", "Hospital Costs", "Hospital Charges", "Drug Costs", "Fees, Pharmaceutical", and "Prescription Fees". This allowed us to collect all possible search terms relating to each of these two concepts (SARDs and healthcare costs), and searches combining the two concepts were executed.

Additional studies were located through the "Cited By" and "Find Similar" features in MEDLINE, Web of Science, and Google Scholar. Economic and Canadian search parameters were also used to increase the specificity of our results. The reference lists of publications initially located, including systematic reviews, were also examined. Studies exclusively involving paediatric patients were excluded, as were those reporting on arthritis or musculoskeletal conditions in general but not any SARD specifically. Commentaries, editorials, and materials with previously presented work, including subgroup and secondary analyses, were also excluded. Foreign currencies

were converted to Canadian dollars based upon the historical exchange rate on December 30-31 of the reporting year (292). From this, all Canadian costs were inflated to 2007 Canadian dollars using the BC Health Care Component of the Canadian Consumer Price Index (293).

1.5.2 Results

The MEDLINE searches retrieved a total of 91 records, of which 13 were duplicates. After their removal, 6 additional non-English records were excluded, as were 18 that were not primary research articles. The titles and abstracts of the remaining records were screened for relevance, and 23 studies reporting primary data on the direct health care costs and/or utilization of at least one SARD were selected from MEDLINE for review. An additional 10 articles were located through handsearch, for a final total of 33. Some overlap existed between cohorts and investigative groups – such as longitudinal follow-ups of cross-sectional studies, and the cost and utilization reports from one investigation being split between two papers – but only papers with a unique primary objective, and/or those with otherwise unavailable primary data were included.

There were many inconsistencies amongst these 33 studies, which illustrated many limitations in the current knowledge. For one, no studies were found that reported on the SARDs collectively. Instead, almost all examined just a single SARD, with the exception of one analysis of PM and DM (294), two very similar disorders, and an abstract reporting on the costs of SARDs-VD together (295). Not only have the SARDs never been studied together, but with more than two thirds (23 of the 33) of the selected papers reporting on SLE, the other disorders have been practically ignored. Amongst most studies, the period of follow-up for each patient was brief, often twelve months or less. Only three of the studies were longitudinal analyses, and just two of these produced annual cost estimates.

Most reports, 24 of the 33, concerned North America (Canada, USA, and Puerto Rico) and/or the United Kingdom (UK), with five for Canada alone (274,276,294,296,297), thirteen for the US alone (295,298-309), one for Puerto Rico alone (310), two for the UK alone (311,312), one comparing Canada and the US (313), and two (314,315) reporting on all three countries. There were four reports from Europe (316-319), and five from Asia (320-324). As detailed in section 1.7.1 many factors, including currency conversion, and transnational differences in health

insurance, health care delivery, and unit prices, limit the applicability of international estimates in informing Canadian health care policy.

This large group of studies can first be divided based on the data source, either clinic-based or from administrative databases. With clinic-based sources, utilization data are obtained directly from patients (usually by completion of a questionnaire, often a modified version of the economic portion of the Stanford Health Assessment Questionnaire (HAQ)) and/ or from their actual medical records. The cost of each health care service/resource is then estimated from multiple sources. With administrative databases, utilization data are obtained through the healthcare claims collected for billing purposes by governments or health insurance providers. Cases are identified on the basis of having a health encounter with an International Classification of Diseases, 9th (ICD-9) or 10th (ICD-10) revision, diagnostic code for the SARD in question recorded with it, and all claims billed for that case are included. Such studies are population-based since investigators have no direct contact with the patients, or their records or healthcare providers.

1.5.3 Results from Clinic-Based Studies

The majority of the publications located (21 of 33), including all but one of the Canadian studies, used clinic-based data. Cases consisted of patients admitted to the study hospital, attending specialty clinics, and/or enrolled in a regional or national disease registry. Clinical examinations were conducted to confirm the diagnosis in accordance with disease-specific criteria. For instance SLE cases needed to meet at least four of the American College of Rheumatology criteria (276,302,309,312-314,317,322,323). The characteristics of these studies and their main findings are listed in Tables 1.5a, 1.6a, and 1.9a. The annual mean overall direct per-patient healthcare costs ranged, in 2007 Canadian dollars, from $5,038 (274) – in a Canadian SSc study – to $17,413 (313) – in a US study on SLE. All estimates referenced in this section pertain to gross healthcare costs – the costs for all health resources consumed by SARDs cases, and not just those resources related to SARDs care. Gross mean annual outpatient costs ranged from $223 per-patient for SSc cases in Hungary (319) to $8,098 per-patient for the same US SLE cases that accounted for the highest overall estimate (313). Annual per-patient gross medication costs spanned $241 for SjD cases in the UK (311) to $4,979 for Canadian LN cases (297). Hospital costs were provided inconsistently, with some studies only reporting per-patient estimates for total hospital costs ($1,670-$8,723), which included day

surgeries, ER visits, and/or rehabilitation stays, as well as inpatient admissions. Other studies just reported average annual inpatient costs, ranging from $951-$7,996 per-patient.

1.5.4 Results from Population-Based Studies

The literature search found 12 population-based studies. From these only one was conducted in Canada, where administrative data was used to study PM/DM. The characteristics of these studies and their main cost and utilization findings are listed in Tables 1.5b, 1.6b, and 1.9b. In these, the mean annual overall direct per-patient gross healthcare costs ranged from $1,399 (324) to $28,312 (304) per-year for SLE cases in Taiwan and the USA, respectively. The Taiwanese study did not include medications. The minimum average annual per-patient gross cost estimate for any SARD amongst those studies that included all three components (outpatient, hospital, and medication) was $8,685 (300). This was the primary estimate in a US study on SSc. Gross mean outpatient costs for SARDs ranged from $713 per-patient for SLE cases in Taiwan (324) to $18,183 per-patient for LN cases each year in the USA (301). Drug costs ranged from $1,882 for US SSc cases (300) to $7,256 per-patient for US LN cases (301) but were only reported in three of these population-based studies. Again, there were inconsistencies when reporting hospital costs: total hospital costs were $2,964-$3,871, with inpatient costs of $682-$11,067 (all in 2007 Canadian dollars). In general the population-based studies produced higher annual per-patient estimates of gross costs, but five of the seven costing studies were from the USA. One explanation may lie in the healthcare prices found in this nation which, as outlined in section 1.7.1 of this chapter, are typically higher than other countries'.

1.5.5 Results from SARDs-Attributable Costs

Of course SARDs are not the responsible for every health resource a SARD case consumes, and the per-patient estimates cited above definitely encompass some costs incurred by individuals without a SARD. To accurately quantify the net burden imparted by these disorders on the healthcare system we sought published estimates of direct medical costs that could be attributed to SARDs. Unfortunately we only found eight studies providing any estimate of the incremental costs of SARDs or reporting on some aspect of attributable costs or utilization (Table 1.9). Three compared the gross healthcare costs of SARDs cases to those of a matched control group (299,304,311), one population-based study separately tabulated the costs of just claims with an SLE diagnostic code (301), and another

collected data on SARDs-attributable utilization exclusively (316). From these, the annual incremental direct medical costs of SARDs (being the additional healthcare costs that SARDs are responsible for, above baseline consumption) ranged (in 2007 Canadian dollars) from $2,964 per-patient (301) to $14,964 per-patient (299). Both of these estimates were for SLE in the USA. The proportion of gross medical costs that were attributable to SARDs ranged from 15% to 63%. In a sixth study, the gross per-patient cost estimates for SLE cases were compared to the average per-capita healthcare costs amongst the general US population. Here, 66% of costs, or $10,566 per-patient annually, could be attributed to SLE (302). Incremental utilization, which was only measured by four groups, is listed in Table 1.9b. In one report, 70% of hospital admissions for SLE cases could be attributed to SLE either directly or indirectly (325). In another it was determined SLE cases made an average of 4.9 additional outpatient visits each year than did the general Quebec population (276).

1.5.6 Summary of Current Cost Estimates

Estimates for the annual healthcare costs of SARDs clearly run a wide spectrum, with mean per-patient estimates of overall costs ranging (in 2007 Canadian dollars) from nearly $1,400 to over $28,000 per-year. In Canada we found the annual per-patient costs for PM/DM cases were $4,006 (294) and for SSc cases they were $5,038 , while the annual per-patient costs of SLE cases ranged from $6,210 (315) to $12,122 (297). With some of these estimates exceeding Canadian reports of the direct medical costs of other forms of arthritis (Table 1.10), the burden of SARDs is clearly significant, and potentially greater than that of these better-studied disorders. Additional reports from the UK (311), USA (299), and Hungary (319) comparing the direct costs of RA to some SARDs further supports this revelation.

1.5.7 Research Gaps

Our review showed that SARDs potentially impart an outstanding healthcare burden but also revealed many gaps in the current knowledge of this burden, particularly pertaining to Canada. For one there are no Canadian estimates concerning any of the SARDs-VD, let alone the SARDs together. As two of the SLE estimates (276,315) were calculated in the 1980's and 90's, they are unlikely to reflect current healthcare prices and utilization patterns. As well nearly every estimate was cross-sectional, allowing little context in which to interpret the results, and neither of the two longitudinal investigations we located had produced annual Canadian cost estimates. Greatly needed are

estimates of the net medical costs stemming from SARDs but there are few available from any country, and again, none from Canada. Most importantly, the Canadian estimates were limited by all but one (294) being clinic-based, since population-based administrative health databases permit the study of a much larger and unbiased sample of cases over many years. They also provide detailed data on each health encounter and its cost, making cost estimates more precise. The one population-based Canadian estimate did not even include medication costs. We intend to fill these gaps in our forthcoming research by using population-based Canadian data to produce the largest, longest, and most comprehensive estimates of the healthcare burden (including the net burden) of SARDs to-date

1.6 Research Objectives

The primary objective of this study is **estimate the health resource utilization and direct medical costs of SARDs at the population level, and longitudinally**.

This will be accomplished using twelve years of patient-level, administrative health claims data from the Canadian province of British Columbia (BC). The quantities and types of health care services consumed by a cohort of SARDs cases in each year will be captured. These include all provincially-funded hospitalizations, surgeries, outpatient visits and investigations, and all prescription medications, regardless of funding. We will sum the costs of these services, annually and cumulatively, and with these sums calculate the average annual healthcare costs incurred by each case.

Once these estimates are obtained, subsequent study objectives are to:

a) Determine the net health resource utilization and economic burden that SARDs impart on the provincial healthcare system

b) Identify any longitudinal trends in cost and utilization

1.7 Study Significance

This study will be like no other. Our literature review confirmed the paucity of estimates available, particularly from Canada, of the direct medical costs of SARDs, with none determined for the SARDs as a group. Even fewer were the number of population-based or longitudinal estimates for any SARD, and with many SARDs including SLE following an "unpredictable course" (26) and characterized by periods of flares and remissions, cross-sectional estimates may not encompass the long-term burden of disease. Instead our analysis will be population-based and longitudinal, and by spanning twelve-years, be the longest of any previous. This will add another dimension to our work, enabling us to identify trends and observe the impact of any new technologies, drugs, or policies in this time. Multiple years of study can also help predict areas of future consumption and costs, which could be used by healthcare administrators to better prepare for ongoing healthcare needs.

We located no incremental cost estimates from Canada in our review, and of the just eight studies reporting on attribution, all but one (311) reported on SLE alone. The reports themselves were inconsistent and limited (Table 1.9). By quantifying the additional costs incurred by SARDs patients, which for most SARDs are currently unknown, we shall emphasize the impact of these disorders and provide more incentive for reducing their costs and morbidities.

1.7.1 Importance of Canadian Estimates

Only eight studies have reported cost and/or utilization estimates from Canada and unfortunately many factors limit the usefulness of foreign estimates in Canadian health policy decisions. In addition to different currencies, these include transnational differences in health insurance, and health care prices and delivery. Precision is always lost when converting cost estimates between currencies, but this was a bigger problem with investigations from Taiwan (324) and Hong Kong (322,323) that reported their estimates in US dollars instead of their respective national currencies. It meant two currency conversions took place between the original calculations and final Canadian dollar estimates we used for comparison, making these less reliable. Even when expressed in the same currency, there are variations in the unit prices for health services between countries, which reduces the comparability of total cost estimates. As shown in Tables 1.5 and 1.6, the annual per-patient estimates from the US, where health care costs are usually high, were generally the largest. However, in the two investigations where US cost estimates were

calculated with Canadian unit prices (314,315), these estimates were much lower and differed little from the Canadian. In contrast, other countries may have lower health care prices that drive down the totals, and reliance on these would underestimate the burden of SARDs in Canada. This may explain the comparatively low hospital per-patient estimate from Taiwan (at most, $835 2007 CDN annually (324)), and overall per-patient estimate from Hungary ($5,177 2007 CDN) (319).

Purchasing power parity (PPP) can help standardize international estimates by adjusting for transnational differences in the unit prices of the same goods and services. In theory, after conversion, any residual difference in average per-patient cost estimates would be from the patients in each country consuming different quantities of the same health service, and not the unit price of each service (314). However, PPP conversions do not make international estimates fully comparable to Canadian ones: the conversion factors are general, and may not sufficiently standardize healthcare expenditures (314).

Costs of care are also influenced by practice patterns within various countries. In the Hungarian study, over 98% of SSc cases were hospitalized in one year while outpatient costs made up only 4% of the total. The authors attributed this to national reimbursement practices that favour inpatient care over outpatient, and transportation inefficiencies that make day trips difficult for patients (319). Even utilization estimates from the US may not be applicable to Canada, with reports indicating Canadian SLE cases consume more hospital resources (313,315) but see fewer specialists (276) and undergo fewer diagnostic tests (276,314,315) than American. This implies that strategies to reduce hospitalizations in SARDs would have a greater financial impact in Canada, and this would not be as apparent if only examining US figures. These differences in practice patterns are another limitation of PPP conversion. As Clarke *et al* note, this procedure assumes transnational price differences are just due to macroeconomics, but medical care is not provided identically throughout the world. They propose that PPP adjustment makes the actual costs of smaller-scale, more basic services - like blood tests - comparable between countries, but not necessarily more complex ones like hospitalizations (315). For example, between two countries an admission for the same purpose may use different resources and entail a different length-of-stay (LOS), and thus a different cost (315).

A final difference relates to health insurance, as Canada has a single-payer, public system, while there are multiple providers in the US, some of them for-profit. US health care costs are higher than Canada's, regardless of the insurance provider, but the added influence of for-profit companies, whose costs are often higher than those from government-based insurance (302), can further reduce the comparability of any cost estimates. In addition to the provider (302,306,308,326,327), the type of plan (capitated versus fee-for-service) can also influence health care costs in the US (299,301,309), but is not relevant in Canada. This makes comparing cohort mixes and cost estimates between the two countries even more difficult.

1.7.2 Advantages of Administrative Data

Most estimates of the healthcare costs of SARDs were produced using clinic-based data. This limited their accuracy and external validity. Below we describe the many advantages of population-based data and how it will help us overcome these earlier limitations. Population-based data has only been used in only one other Canadian SARDs costing study. In that study, the costs of only two disorders (PM/DM) were investigated and medication use was not included, which will make ours the first in Canada to include all three health resource components: outpatient encounters, hospitalizations, and *every* dispensed prescription.

Large and Minimally-Biased Study Population

With clinic-based data, cases are recruited from patient populations attending at these tertiary rheumatology clinics, but population-based data allows for study on a much larger scale. Retrospective data from multiple years can be accessed, thus permitting the identification of trends. While recruitment from tertiary centres may bias the study population toward cases whose disease is severe enough (326) to warrant referral there, using population-based data allows nearly every case in the province to be followed. Considering the well-documented association between greater disease activity and/or lesser health status (including nephritis) in SARDs and greater healthcare costs (274,276,291,294,297,299,301,302,304,305,311-314,316,322,323,328) the healthcare costs of tertiary-clinic patients would not reflect that of milder cases. Patients attending specialized rheumatology clinics may also consume more resources than patients treated in other settings (297) simply as a result of being seen by specialists with specific interest in, and knowledge of, their disorder (311). Therefore estimates derived from these clinic populations may misrepresent actual mean per-patient costs.

In contrast, Canadian databases like ours provide a less-biased and more representative cohort regardless of the urban/rural residence, income level, employment status, or race of cases. Since these factors have also been shown to impact costs (297-299,308), this source will make our cost estimates even more reliable and representative of most cases. Selection bias aside, the generalizability of the results from clinic-based studies is often limited by the small number of cases available for study (this ranged from 67 to 812 in our review). These cases may not adequately reflect the full spectrum of disease severity and health resource utilization in SARDs (304), but since we identified approximately 13,000 SARDs cases in just one year of our data (1), we expect to overcome this limitation.

Comprehensive and Precise Health Resource Utilization

The questionnaires used to collect utilization data from clinic patients, especially the HAQ, have been used extensively in costing studies. However the onus is on the patient to report their utilization and they may do so inaccurately (329), leading to incomplete and potentially biased estimates of health resource use. This is more likely the longer the recall period, with some investigations inquiring, at one time, about all consumption in the previous twelve months (302). Instead administrative databases record every health encounter in a centralized and systematic manner, which eliminates this problem. A particular advantage of BC data are its records of all dispensed prescriptions, regardless of funding source, which are not available in many other Canadian provinces. Together, this shall equate to more accurate cost estimates and more detailed and comprehensive accounts of utilization.

Precise Costing

With clinic data, a unit price is assigned to each service that is consumed, but these prices may not reflect the actual unit costs. Prices derived from the fee schedule at an urban, tertiary care hospital, as used in one study (312), would not reflect the lower costs of care seen in a smaller hospital or town. Prescription prices have particularly lacked precision in previous studies, with some investigators using wholesale prices (thus omitting dispensing fees), or approximating a therapy duration of three (311,312) , six (302), or nine (316) months in their calculations when details were not available. This incorporates some uncertainty into the final cost estimates from these studies, but our estimates will be more precise since each outpatient and prescription claim in the BC database specifies what the

health ministry reimbursed for it. Given the longitudinal nature of our study, with payment arrangements and actual fees changing over time, having these precise costs is especially valuable.

1.8 Study Implications

SARDs impart a tremendous physical and psychological impact on patients and their families. A complex medication regimen is required to alleviate symptoms, slow disease progression, and prevent complications, but the current treatments remain suboptimal. The clinical manifestations can significantly limit participation in family life and career opportunities, while the associated health resource consumption imparts a great economic burden on government and society. But given the rarity of these disorders, the role they play in driving healthcare costs, especially compared to other forms of arthritis, is not well recognized. This has limited the research funding and support they receive, and in turn, the quality of care available to people living with these conditions.

We hope to turn this around and establish SARDs as a research priority by producing comprehensive estimates of their current health resource utilization and economic burden at the population-level. Our analysis will be the first of its kind in the world, allowing us to fill many existing gaps in research on the direct medical costs of SARDs. In undertaking this innovative work we hope other researchers will follow in our footsteps and investigate the health outcomes and pharmacoeconomics of these disorders in more detail. With the number of SARDs cases rising, and some very expensive therapies emerging to treat these disorders, their healthcare burden is expected to rise. As such, current estimates of these costs are especially needed by health policymakers.

This chapter has provided an introduction to the SARDs, including the current and emerging treatment options, and described the potential benefits of studying them together. A review of the literature available on the direct health care costs of SARDs was also presented, and gaps in current knowledge identified. From this, the current study and its objectives were outlined, along with its significance and potential impact. The next chapter will detail the data source and methods that were used in undertaking this analysis.

1.9 Tables

Table 1.1 Prevalence and Incidence of SARDs, Stratified by Sex

Disorder	Study	Location	Year(s)	Prevalence (95% CI) per-100,000		Incidence (95% CI) per-100,000	
				Female	Male	Female	Male
SARDs-CTD (all)	Avina-Zubieta 2011 (1)	British Columbia	2007	591.9	176.3	67.5	20.1
	Bernatsky 2011 (5)	Manitoba Nova Scotia Quebec	2003	690 (660-720) 420 (360-570) 420 (410-440)	120 (110-130) 100 (80.0-140) 80.0 (80.0-90.0)	-	-
SLE	Alamanos 2003 (330)	Greece	1982-2001	69.27 (65.90-72.64)	9.46 (6.14-12.78)		
	Alonso 2011 (331)	Italy	1987-2006	29.2 (20.0-40.7)	5.8 (2.0-12.0)	5.9 (4.9-7.0)	1.1 (0.7-1.7)
	Avina-Zubieta 2011 (1)	British Columbia	2007	193.9	30.4	24.2	3.6
	Chakravarty 2007 (332)	Pennsylvania California	2000	253 (248.3-257.7) 184.2 (181.4-187.0)	38.7 (36.8-40.7) 25.5 (24.5-26.6)		
	Govoni 2006 (333)	Italy	1996-2002	100.1	12.0		
	Gudmundsson 1990 (334)	Iceland	1975-1984	62	7.2	5.8	0.8
	Hochberg 1987 (335)	UK	1981-1982	12.5 (7.6-19.3)	2.0	-	-
	Hopkinson 1993 (336)	UK	1989-1990	45.4 (37.6-53.1)	3.7 (1.5-6.0)	6.5 (3.5-9.4)	1.5 (0.02-2.9)
	Lopez 2003 (337)	Spain	1998-2002	57.91 (51.61-64.21)	8.33 (5.84-10.82)	3.64 (2.93-4.35)	0.54 (0.26-0.82)
	McCarty 1995 (338)	Pennsylvania	1985-1990			3.5 (whites) 9.2 (blacks)	0.4 (whites) 0.7 (blacks)
	Naleway 2005 (339)	Wisconsin	1991-2001	131.5 (95.5-167.5)	24.8 (9.4-40.2)	8.5 (5.5-10.9)	1.9 (0.6-3.3)
	Nightingale 2006 (340)	UK	1992-1998	-	-	5.30 (4.75-5.86)	0.65 (0.45-0.85)
	Nived 1985 (341)	Sweden	1981-1982	64.8	11.7	7.6	2.0
	Nossent 1992 (342)	Curaco	1980-1990	83.8 (65.8-101.8)	8.5(2.8-14.2)	7.86 (2.3-13.2)	1.13 (0.9-3.1)
	Nossent 2001 (343)	Norway	1978-1996	89.3 (78.9-100.2)	9.7 (6.9-12.6)	4.6 (3.6-5.8)	0.6 (0.3-1.3)
	Uramoto 1999 (288)	Minnesota	1950-1992	-	-	5.11	0.91

Disorder	Study	Location	Year(s)	Prevalence (95% CI) per-100,000		Incidence (95% CI) per-100,000	
				Female	Male	Female	Male
SLE	Voss 1998 (344)	Denmark	1995	37.9 (29.8-47.5)	4.7 (2.2-9.0)	-	-
	Ward 2004 (345)	USA	2000	100 (19.8-179.3)	Females and males combined: 53.6 (12.2-95.0)		
SSc	Alamanos 2005 (346)	Greece	1981-2002	2.5	28.2	1.9	0.2
	Allcock 2004 (347)	UK	2000	14.17	2.98	-	-
	Arias-Nunez 2008 (348)	Spain	1988-2006	22.2 (14.2-33.1) - 44.4 (32.8-58.9)	7.0 (2.4-14.4) – 9.9 (4.8-18.2)	1.8 (1.2-2.5) - 3.5 (2.3-3.9)	0.7 (0.3-1.2) - 1.0 (0.5-1.4)
	Avina-Zubieta 2011 (1)	British Columbia	2007	35.6	6.4	5.6	1.5
	Bernatsky 2009 (349)	Quebec	2003	-	-	74.4 (69.3-79.7)	13.3 (10.2-14.8)
	Geirsson 1994 (350)	Iceland	1975-1990	11.9	1.5	0.7	0.05
	Mayes 2003 (351)	Michigan	1989-1991	38.98 (35.3-43.0)	8.41 (6.8-10.4)	2.85 (1.97-4.11)	0.90 (0.47-1.73)
	Rosa 2011 (352)	Buenos Aires, Argentina	1999-2004	47.7 (30.9-70.4)	2.8 (0.7-15.7)	-	-
	Steen 1997 (353)	Pennsylvania	1963-1972 1973-1982			1.33 (1.09-1.56) 2.76 (2.39-3.13)	0.55 (0.38-0.71) 0.88 (0.66-1.1)
	Valter 1997 (354)	Estonia	?	54.0 (7.0-197.0)	females and males: 35.0 (4.0-127.0)		
SjD	Alamanos 2006 (355)	Greece	1982-2003	8.4	177.4	10.1	0.5
	Avina-Zubieta 2011 (1)	British Columbia	2007	36.4	5.5	6.8	1.7
	Birlik 2009 (356)	Turkey	2000?	300 (110-660) – 490 (220-930)	0-50 (0-280)	-	-
	Miyasaka 1995 (357)	Japan	1993	25.6	1.9	-	-
	Pillemer 2001 (358)	Minnesota	1976-1992			6.9 (5.0-8.8)	0.5 (0.0-1.2)
	Thomas 1998 (359)	UK	?	4100 (3000-5500)	2500 (1600-3700)	-	-
SjD	Weng 2011 (360)	Taiwan	2005-2007	-	-	11.0 (10.6-11.4)	1.1 (1.0-1.2)

Disorder	Study	Location	Year(s)	Prevalence (95% CI) per-100,000		Incidence (95% CI) per-100,000	
				Female	Male	Female	Male
PM only	Avina-Zubieta 2011 (1)	British Columbia	2007	10.3	8.0	1.8	1.1
	Oddis 1990 (361)	Pennsylvania	1963-1982			whites: 0.61 (0.037-1.183) blacks: 1.71 (0.292-3.128)	whites: 0.29 (0.008-0.572) blacks: 1.14 (0.13-2.15)
DM only	Avina-Zubieta 2011 (1)	British Columbia	2007	7.5	3.2	1.6	0.4
PM/DM	Bernatsky 2009 (362)	Quebec	2003	older urban: 70.0 (61.3-79.3)	young rural: 2.7 (1.6-4.1)	-	-
SARDs-VD (all)	Avina-Zubieta 2011 (1)	British Columbia	2007	42.2	21.1	6.9	3.7
	Gonzalez-Gay 2003 (6)	Spain	1988-2001			1.25 (0.84-1.85)	1.36 (0.94-1.98)
	Mohammad 2007 (363)	Sweden	2003	29.0 (20.2-37.8)	30.7 (21.7-40.0)	-	-
	Mohammad 2009 (364)	Sweden	1997-2006	-	-	2.26 (1.74-2.77)	2.10 (1.60-2.61)
	Reinhold-Keller 2000 (365)	Germany	1994	25.6 (18.9-32.2) - 27.5 (20.7-34.2)	12.8 (7.9-17.7) – 15.2 (10.0-20.4)	-	-
	Reinhold-Keller 2002 (366)	Germany	1998 1999	-	-	4.84 (2.7-7.0) – 5.12 (2.9-7.3)	4.03 (2.1-5.9) – 5.29 (3.1-7.5)
	Reinhold-Keller 2005 (367)	Germany	1998-2002			4.20 (2.90-5.50) - 5.94 (4.40-7.40)	3.70 (2.50-4.90) - 4.89 (3.50-6.30)
	Watts 2000 (7)	UK	1988-1997	-	-	1.64 (1.14-2.28)	2.35 (1.73-3.13)
Wegener`s	Avina-Zubieta 2011 (1)	British Columbia	2007	10.7	10.0	2.5	2.0
	Gonzalez-Gay 2003 (6)	Spain	1988-2001			0.335 (0.165-0.68)	0.27 (0.13-0.55)
	Mohammad 2007 (363)	Sweden	2003	13.8 (7.7-19.8)	18.2 (11.2-25.2)	-	-
	Mohammad 2009 (364)	Sweden	1997-2006	-	-	0.93 (0.60-1.26)	1.04 (0.68-1.39)
	Watts 2001 (368)	UK Spain	1981-1998	-	-	0.98 (0.62-1.47) 0.61 (0.24-1.26)	1.14 (0.74-1.68) 0.36 (0.10-0.93)
CSD	Gonzalez-Gay 2003 (6)	Spain	1988-2001			0.13 (0.09-0.21)	0.13 (0.09-0.18)

Disorder	Study	Location	Year(s)	Prevalence (95% CI) per-100,000		Incidence (95% CI) per-100,000	
				Female	Male	Female	Male
CSD	Mohammad 2009 (364)	Sweden	1997-2006	-	-	0.12 (0.00-0.24)	0.06 (0.00-0.15)
	Watts 2001 (368)	UK Spain	1981-1998	-	-	0.21 (0.07-0.50) 0.09 (0.00-0.49)	0.41 (0.19-0.77) 0.09 (0.00-0.51)
PAN	Avina-Zubieta 2011 (1)	British Columbia	2007	5.0	3.0	0.8	0.4
	Gonzalez-Gay 2003 (6)	Spain	1988-2001			0.10 (0.09-0.10)	0.08 (0.05-0.14)
	Mohammad 2007 (363)	Sweden	2003	13.8 (7.7-19.8)	18.2 (11.2-25.2)	-	-
	Mohammad 2009 (364)	Sweden	1997-2006	-	-	0.12 (0.00-0.24)	0.06 (0.00-0.15)
	Watts 2001 (368)	UK Spain	1981-1998	-	-	0.72 (0.42-1.16) 0.61 (0.24-1.26)	1.23 (0.81-1.78) 0.64 (0.25-1.31)
GCA	Avina-Zubieta 2011 (1)	British Columbia	2007	25.6	8.5	3.8	1.6
	Baldursson 1994 (369)	Iceland	1984-1990			36.0 (29.3-44.3)	18.0 (12.8-24.5)
	Boesen 1987 (370)	Denmark	1982	all ages: 35.7 50+ years: 120.8	all ages: 7.4 50+ years: 28.0	all ages: 55.5 50+ years: 188.6	all ages: 20.4 50+ years: 77.1
	Gonzalez Gay 2001 (371)	Spain	1981-1998	-	-	11.00 (8.97-13.54)	9.57 (5.56-13.58)
	Gonzalez Gay 2007 (372)	Spain	1981-2005	-	-	10.23 (8.60-12.08)	9.92 (8.19-11.89)
	Gonzalez-Gay 1997 (373)	Spain	1986-1990 1991-1995	6.33 8.94	10.53 12.14	-	-
	Gran 1997 (374)	Norway	1987-1994			all ages: 53.4 50+ years: 177.6	all ages: 27.7 50+ years: 99.5
	Petursdottir 1999 (375)	Sweden	1976-1995	-	-	29.8	12.5
	Reinhold-Keller 2000 (365)	Germany	1994	urban: 54.5 (49.9-59.1) – 60.2 (55.4-65.0) rural: 14.1 (11.8-16.4) – 29.6 (8.26-33.0)	urban: 8.2 (6.4-10.0) – 8.6 (6.8-10.4) rural: 8.4 (6.6-10.2) – 12.5 (10.3-13.7)	-	-

Disorder	Study	Location	Year(s)	Prevalence (95% CI) per-100,000		Incidence (95% CI) per-100,000	
				Female	Male	Female	Male
GCA	Reinhold-Keller 2002 (366)	Germany	1998 1999	-	-	4.58 (3.2-5.9) 3.54 (2.4-4.7)	3.24 (2.3-4.2) 1.76 (1.1-2.5)
	Reinhold-Keller 2005 (367)	Germany	1988-2002	-	-	2.82 (1.40-4.20) – 6.90 (4.60-7.60)	1.09 (0.70-1.50) – 2.56 (1.60-3.60)
	Salvarani 1995 (376)	Minnesota	1950-1991	-	-	24.2 (19.5-28.9)	8.2 (4.8-11.6)
	Salvarani 2004 (377)	Minnesota	1950-1999			24.4 (20.3-28.6)	10.3 (6.9-13.6)
	Sonnenblick 1994 (378)	Jerusalem	1980-1991			12.1 (8.8-15.4)	7.7 (5.0-10.5)
TA	Avina-Zubieta 2011 (1)	British Columbia	2007	2.8	0.6	0.5	0.2

Table 1.2 Prevalence of SARDs

Disorder	Study	Location	Year	Prevalence (95% CI) per 100,000
SARDs-CTD (all)	Avina-Zubieta 2011 (1)	British Columbia	2007	388.6
	Bernatsky 2011 (5)	Manitoba Nova Scotia Quebec	2003	410 (390-430) 270 (230-340) 260 (250-270)
SLE	Alamanos 2003 (330)	Greece	2001	39.51 (37.70-41.62)
	Al-Arfaj 2002 (379)	Saudi Arabia	?	19.28
	Alonso (331)	Spain	2006	17.5 (12.6-24.1)
	Anagnostopoulos 2010 (380)	Greece	2007-2008	110
	Avina-Zubieta 2011 (1)	British Columbia	2007	113.9
	Bernatsky 2007 (381)	Quebec	2003	44.7 (37.4-54.7)
	Bossingham 2003 (382)	Australia	1996-1998	45.3
	Chakravarty 2007 (332)	California Pennsylvania	2001	107.6 (106.1-109.2) 149.5 (146.9-152.2)
	Gourley 1997 (383)	Northern Ireland	1993	21.7 (19.7-23.8) – 25.4 (22.1-28.7)
	Govoni 2006 (333)	Italy	2002	57.9
	Gudmundsson 1990 (334)	Iceland	1984	35.9
	Hart 1983 (384)	New Zealand	1980	17.62
	Helve 1985 (385)	Finland	1978	28.0
	Hochberg 1987 (335)	UK	1981-1982	6.5
	Hopkinson 1993 (336)	UK	1989-1990	24.6 (20.6-28.7)
	Hopkinson 1994 (386)	UK	1991	24.7 (20.7-28.8)
	Johnson 1995 (387)	Birmingham, UK	1992	27.7 (24.2-31.2)
	Laustrup 2009 (388)	Denmark	2002	28.3 (23.2-34.2)
	Lopez 2003 (337)	Spain	2002	34.12 (30.63-37.61)
	Maskarinec 1995 (389)	Hawaii	1989	41.8
	Naleway 2005 (339)	Wisconsin	2001	78.5 (59.0-98.0)
	Nived 1985 (341)	Sweden	1982	39.0 (30.0-48.0)
	Nossent 1992 (342)	Curaco	1990	47.0 (34.1-54.1)
	Nossent 2001 (343)	Norway	1996	49.7 (44.3-55.0)
	Serdula 1979 (390)	Hawaii	1970-1975	15.3
	Stahl-Hallengren 2000 (391)	Sweden	1986 1991	42.0 68.0
	Uramoto 1999 (288)	Minnesota	1993	122.0 (97.0-147.0)
	Voss 1998 (344)	Denmark	1995	21.7 (17.3-26.8)
	Ward 2004 (345)	USA	2000	53.6 (12.2-95.0) – 241 (130-152)

Disorder	Study	Location	Year	Prevalence (95% CI) per 100,000
SSc	Airo 2007 (392)	Italy	?	33.9 (15.5-52.3)
	Alamanos 2005 (346)	Greece	2002	15.4 (12.0-18.8)
	Allcock 2004 (347)	UK	2000	8.21 (6.35-10.07)
	Arias-Nunez 2008 (348)	Spain	2006	14.9 (10.1-21.2) - 27.7 (21.1-35.84)
	Arnett 1996 (393)	Oklahoma	1990-1994	9.5 (5.8-14.6) - 469.0 (203.0-930.0)
	Avina-Zubieta 2011 (1)	British Columbia	2007	21.3
	Bernatsky 2009 (349)	Quebec	2003	44.3 (41.1-47.6)
	Geirsson 1994 (350)	Iceland	1990	7.1
	Kaliterna 2010 (394)	Croatia	2007-2009	15.6 (11.8-19.4)
	Le Guern 2004 (395)	Paris, France	2001	15.83 (12.9-18.7)
	Lo Monaco 2011 (396)	Italy	1999-2007	25.4 (22.2-28.6) - 34.1 (30.4-37.8)
	Maricq 1989 (397)	South Carolina	1985	28.6-113.0
	Mayes 2003 (351)	Michigan	1989-1991	24.2 (21.3-27.4) - 27.6 (24.5-31.0)
	Robinson 2008 (398)	USA	2001-2002	30.0-50.0
	Rosa 2011 (352)	Buenos Aires, Argentina	1999-2004	23.8 (22.0-25.7)
	Thompson 2002 (399)	Ontario	1996?	7.1 (3.4-10.8) – 28.0 (9.7-46.4)
	Valter 1997 (354)	Estonia	?	35.0 (4.0-127.0)
SjD	Alamanos 2006 (355)	Greece	2003	58.0
	Alamanos 2006 (355)	Greece	2003	92.8 (83.8-102.5)
	Anagnostopoulos 2010 (380)	Greece	2007-2008	230 (220-750)
	Avina-Zubieta 2011 (1)	British Columbia	2007	21.3
	Birlik 2009 (356)	Turkey	2000?	160 (60-350) – 280 (130-510)
	Bowman 2004 (400)	UK	?	140 (17-510) - 400 (40-1320)
	Dafni 1997 (401)	Greece	1992	women: 600 (190-1390)
	Goransson 2011 (402)	Norway	2009	50.0 (48.0-52.0)
	Jacobsson 1989 (403)	Sweden	?	2700 (1000-4500)
	Kabasakal 2006 (404)	Turkey	2001-2002	women: 720 (330-1570) - 1560 (920-2660)
	Thomas 1998 (359)	UK	?	3500 (2500-4800)
	Tomsic 1999 (405)	Slovenia	?	600 (70-2160)

Disorder	Study	Location	Year	Prevalence (95% CI) per 100,000
SjD	Whaley 1972 (406)	UK	?	elderly: 3300
	Zhang 1995 (407)	China	?	330-700
PM only	Avina-Zubieta 2011 (1)	British Columbia	2007	9.2
DM only	Avina-Zubieta 2011 (1)	British Columbia	2007	5.4
PM/DM	Bernatsky 2009 (362)	Quebec	2003	21.5 (19.4-23.9)
SARDs-VD (all)	Avina-Zubieta 2011 (1)	British Columbia	2007	31.9
	Haugeberg 1998 (408)	Norway	1996	43.9
	Mahr 2004 (409)	Paris, France	2000	9.03 (7.4-10.6)
	Mohammad 2007 (363)	Sweden	2003	29.9 (23.6-36.2)
	Ormerod 2008 (410)	Australia	1995-1999 2000-2004	9.5 (7.69-11.61) 14.8 (12.5-17.4)
	Reinhold-Keller 2000 (365)	Germany	1994	19.5 (15.3-23.6) - 21.6 (17.3-25.9)
	Watts 2000 (7)	UK	1997 1988-1997	14.45 (11.04-18.53) 22.14 (17.92-27.02)
Wegener's	Avina-Zubieta 2011 (1)	British Columbia	2007	10.3
	Cotch 1995 (295) 1996 (411)	New York	1986-1990	2.6 (99%CI: 1.7-3.5)
	Gibson 2006 (412)	New Zealand	2003 1999-2003	9.35 (6.6-12.1) - 11.2 (8.3-14.2) 13.1 (9.9-16.3) - 15.2 (11.7-18.6)
	Haugeberg 1998 (408)	Norway	1996	5.3
	Koldingsnes 2001 (413)	Norway	1988 1993 1998 1984-1988 1989-1993 1994-1998	3.04 (1.66-5.10) 4.93 (3.12-7.39) 9.51 (6.91-12.90 3.01 (1.65-5.06) 6.29 (4.21-9.04) 10.90 (8.11-14.33)
	Mahr 2004 (409)	Paris, France	2000	2.37 (1.6-3.1)
	Mohammad 2007 (363)	Sweden	2003	12.9 (8.7-17.0) - 16.0 (11.4-20.6)
	Ormerod 2008 (410)	Australia	1995-1999 2000-2004	6.43 (4.93-8.17) 9.50 (7.69-11.61)
	Reinhold-Keller 2000 (365)	Germany	1994	4.2 (2.3-6.2) – 5.8 (3.6-8.0)
	Watts 2000 (7)	UK	1997 1988-1997	6.29 (4.15-9.16) 10.64 (7.73-14.28)
GCA	Avina-Zubieta 2011 (1)	British Columbia	2007	17.3
	Boesen 1987 (370)	Denmark	1982	all ages:37.8 50+ years: 135.4
	Cotch 1995 (295)	New York	1986-1990	19.6

Disorder	Study	Location	Year	Prevalence (95% CI) per 100,000
GCA	Reinhold-Keller 2000 (365)	Germany	1994	50+: 24.0 (16.4-31.5) - 30.0 (20.7-39.3)
PAN	Avina-Zubieta 2011 (1)	British Columbia	2007	4.0
	Cotch 1995 (295)	New York	1986-1990	2.7
	Haugeberg 1998 (408)	Norway	1996	3.3
	Mahr 2004 (409)	Paris, France	2000	3.07 (2.1-4.0)
	Mohammad 2007 (363)	Sweden	2003	3.1 (1.1-5.2)
	Ormerod 2008 (410)	Australia	1995-1999 2000-2004	2.05 (1.30-3.21) 2.23 (1.38-3.33)
	Reinhold-Keller 2000	Germany	1994	0.2 (0-0.7) – 0.9 (0-1.8)
CSD	Haugeberg 1998 (408)	Norway	1996	1.3
	Mahr 2004 (409)	Paris, France	2000	1.07 (0.5-1.7)
	Mohammad 2007 (363)	Sweden	2003	1.4 (0.03-2.7)
	Ormerod 2008 (410)	Australia	1995-1999 2000-2004	1.17 (0.62-2.96) 2.23 (1.34-3.33)
	Reinhold-Keller 2000 (365)	Germany	1994	0.2 (0.0-0.7) – 0.7 (0.0-1.4)
TA	Avina-Zubieta 2011 (1)	British Columbia	2007	1.7

Table 1.3 Drugs Used in the Treatment of SARDs

Drug Class	Examples	Disorder	Role
non-steroidal anti-inflammatory drugs (NSAIDs)	ibuprofen, naproxen, diclofenac	SLE (4), SSc (57), SjD (20)	alleviate joint pain
corticosteroids	prednisone, methylprednisone, prednisolone	SLE (4), SSc (21), SjD (20), PM (23), DM (24), PAN (25), Wegener's (19), CSD (18), TA (29), GCA (31)	decrease inflammation and immune response
anti-malarials	hydroxychloroquine	SLE (4), SjD (20), DM (24)	modulate immune response
immunosuppressants	cyclophosphamide, methotrexate, azathioprine, mycophenolate, chlorambucil, thalidomide	SLE, SSc (21), PM (23), DM (24), PAN (hepatitis B-negative cases) (25), Wegener's (19), CSD (18), TA (29), GCA	inhibit cell growth, reduce inflammation
B-cell depletors	rituximab	SLE (4), SjD (20), PM (23), DM (24), Wegener`s (19)	reduce number of B cells
B-cell-stimulator inhibitor	belimumab	SLE (4)	inhibit B-cell differentiation
tumour necrosis factor (TNF) - inhibitors	etanercept, infliximab	PM (23), TA (29)	inhibit pro-inflammatory cytokines
chelating agents	penicillamine	SSc (21,57)	reduce collagen metabolism and fibrosis (21,57)
vasodilators	sildenafil, bosentan	SSc (21,414)	address pulmonary hypertension, alleviates vasospasm and fibrosis (57,414)
proton-pump inhibitors (PPIs)	omeprazole (21)	SSc (21), PM (23), DM (24), GCA	alleviate GERD, prevent corticosteroid-associated gastrointestinal damage
histamine-II receptor antagonists (H_2RAs)	cimetidine, ranitidine	SSc (21), PM (23), DM (24), CSD (18)	alleviate GERD, prevent corticosteroid-associated gastrointestinal haemorrhage (18)
calcium channel blockers	diltiazem, nifedipine (29)	SSc (21), PM, DM (24), TA (29)	reduce vasospasm and fibrosis in SSc (57), calcinosis in PM/DM (24), hypertension in TA (29)
parasympathetic agonists	pilocarpine	SjD (20)	alleviate oral dryness
immune globulins		SLE (4), PM (23), DM (24), Wegener`s (19), CSD (18)	

Drug Class	Examples	Disorder	Role
anticoagulants	warfarin, heparin	SLE (28), PM/ DM (24), TA (29)	improve renal function (29), calcinosis (24),
anti-platelet agents	aspirin, clopidogrel	SLE (28)SSc (21)TA (29), GCA (22)	enhance blood flow in SSc (57), prevent stroke and vision loss in GCA (22), improve renal function in TA (29)
anti-virals (25)	vidarabine, lamivudine, interferon (25)	PAN (hepatitis B-positive cases) (25)	clear hepatitis B (HBV) infected cells, as HBV often leads to PAN (25)
antibiotics (19)	trimethoprim-sulfamethoxazole (TMP-SMZ) (19)	Wegener's (19)	prevent opportunistic pneumonia, may reduce inflammation (19)
bisphosphonates (19)	pamidronate (24)	SLE (28), PM (23), DM (24), Wegener's (19), GCA	reduce calcinosis (24), prevent glucocorticoid-associated osteoporosis (19,28)

Table 1.4 Estimated Annual Per-Patient Costs of Standard and Emerging SARDs Therapies in Canada

Standard Therapies	Cost (CDN)	Emerging Therapies	Cost (CDN)
corticosteroids	$240 (32)	mycophenolate	$1020-$2040 (88)
hydroxychloroquine	$240 (32)	infliximab	$13,000 (225)
methotrexate	$240-480 (32)	rituximab	$9500 (32)
cyclophosphamide	$240-480 (32)	belimumab	$20,000 (32)
azathioprine	$600 (12)	etanercept	$22,000 (225)
calcium channel blockers	$360 (255)	sildenafil	$1825-$5475 (415)
		epoprostenol	$40,515 2003 CDN (256)
		bosentan	$43,800 2003 CDN (256)

Table 1.5a Study Characteristics for Included Studies using Clinic-Based Data – Mean Annual Direct Medical Costs, Per-Patient

Study	Year	Disease	Country	Study Years	Number of Subjects	Data Collection / Recall Period	Mean Total Annual Direct Medical Costs	Mean Annual Outpatient Costs	Mean Annual Total Hospital Costs	Mean Annual Inpatient Hospital Costs	Mean Annual Medication Costs
Aghdassi *et al* (297)	2011	SLE	Canada	2004-2009	141: 79 LN, 62 LNN	4 weeks	LN=$12,122 LNN=$10,186	LN=$3,578 LNN=$3,390	n/a	LN=$951 LNN=$1,476	LN=$4,979 LNN=$2,865
Bernatsky *et al*(a) (274)	2009	SSc	Canada	?	457	12 months	$5,038	$1,492	$1,670	$1,448	$1,575
Callaghan *et al* (311)	2007	SjD	UK	2001	129	6 months	$5,443	$3848	$1221	n/a	$241
Clarke *et al* (276)	1993	SLE	Canada	1989, 1990	1989=164 1990=155	6 months	1989=$8,667 1990=$10,752	1989=$3,165 1990=$2922	1989=$4,183 1990=$6649	1989=$3,385 1990=$6,242	1989=$1,452 1990=$1,181
Clarke *et al* (315)	1999	SLE	Canada, USA, UK	1995-1997	Canada= 229 USA=268 UK=211	6 months	Canada=$6210 USA=$6,753 UK=$6,084 (adjusted)	Canada=$1902 USA=$2,106 UK=$1,677 (unadjusted)	Canada=$3238 USA=$2,271 UK=$2753 (unadjusted)	Canada=$2946 USA=$1,176 UK=$1,649 (adjusted)	Canada=$1296 USA=$1,562 UK=$1,478 (adjusted)
Clarke *et al* (314)	2004	SLE	Canada, USA, UK	1995-2001	Canada= 231 USA=269 UK=215	6 months – 4 years	Canada=$16,570 USA=$22,090 UK=$18,927 (4-year cumulative)	Canada=$4266 USA=$5,497 UK=$4,265 (4-year cumulative)	n/a	Canada=$4172 USA=$6,296 UK=$6,682 (4-year cumulative)	Canada=$5454 USA=$6,599 UK=$6,510 (4-year cumulative)
Finn *et al* (305)	1993	SLE	USA	1988-1992	74	5 years	$11,705	$4,155	$7,128 (same)	$7,128	$1,150
Gironimi *et al* (313)	1996	SLE	USA	1990-1991	174	6 months	$17,413	$8,098	$4,754	$4367	$1713
Krulichova *et al* (318)	2004	TA	Italy	1998-2000	67	12 months	$6,801	$1,607	$3,700		$1,494
Minier *et al* (319)	2010	SSc	Hungary	2006	80	12 months	$5,177	$223	$4,322	$4,322 (same)	$395
Panopalis *et al* (302)	2008	SLE	USA	2003-2005	812	12 months	$16,368 (sensitivity analysis: $13,411-$17,925)	$2,967	$8,723	$7,966	$4,200

Study	Year	Disease	Country	Study Years	Number of Subjects	Data Collection / Recall Period	Mean Total Annual Direct Medical Costs	Mean Annual Outpatient Costs	Mean Annual Total Hospital Costs	Mean Annual Inpatient Hospital Costs	Mean Annual Medication Costs
Sutcliffe *et al* (312)	2001	SLE	UK	1995-1996	105	2 x 6 months	$7,253	$3,059	$2,784	n/a	$1,252
Zhu *et al*(a, b) (322,323)	2009	SLE	Hong Kong	2005-2007	306	12 months	$9,765	$2,551	n/a	$5,116	$389

Table 1.5b Study Characteristics for Included Studies using Clinic-Based Data –Mean Annual Health Resource Utilization, Per-Patient

Study	Aghdassi *et al* (297)	Bernatsky *et al* (b) (274, 296)	Clarke *et al* (276)	Clarke *et al* (315)	Edwards *et al* (320)	Gironimi *et al* (313)	Krulichova *et al* (318)	Minier *et al* (319)	Panopalis *et al* (302)	Petri and Genovese (325)	Sutcliffe *et al* (312)	Teh *et al* (321)	Yelin *et al* (309)	Zhu *et al*(a,b) (322, 323)	Zink *et al* (317)
Year	2011	2009	1993	1999	2003	1996	2004	2010	2008	1992	2001	2008	2007	2009	2004
Disease	SLE	SSc	SLE	SLE	SLE	SLE	TA	SSc	SLE	SLE	SLE	SLE	SLE	SLE	SLE
Country	Canada	Canada	Canada	Canada, USA, UK	Singapore	USA	Italy	Hungary	USA	USA	UK	Malaysia	USA	Hong Kong	Germany
Study Years	2004-2009	2004-2005	1989, 1990	1995-1997	2000	1990-1991	1998-2000	2006	2003-2005	1989-1990	1995-1996	2006	2001-2005	2005-2007	2001
Number of Subjects	141: 79 LN 62 LNN	352	1989=164 1990=155	Canada=229 USA=268 UK=211	1698	174	67	80	812	261	105	79		306	1248
Data Collection/ Recall Period	4 weeks	12 months	6 months	6 months	12 months	6 months	12 months	12 months	12 months	24 months	2 x 6 months	12 months	12 months	12 months	12 months
# Outpatient Visits	LN=3.0 LNN=2.5 (4 weeks)	7.3	11.8	Canada=19 USA=20 UK=19 (unadjusted)	n/a		22.2	17.4	30.6		17.4	n/a		7.25	21.9
Annual Hospitalization Rate	LN=6.5% LNN=5.0% (4 weeks)	n/a	1989=18% 1990=15% (6 months)	Canada=18% USA=11% UK=12%	13.10%		n/a	98+%	21.10%	1989=37% 1990=39%	1st 6-months=13.66%; 2nd 6-months=8.78%	n/a		27%	~25%
Annual # Hospitalizations (whole cohort)	n/a	n/a			0.2		0.5		0.3	1989=0.705 1990=0.669 Overall=0.69		n/a		n/a	
Annual # Hospitalizations (hospitalized cases)	n/a	n/a	1989=1.13 1990=1.09 (6 months)		1.56		n/a	4.9	1.5			1.58		n/a	
Mean LOS per Hospitalizo	LN=2.8 LN=5.7 (4 weeks)	n/a			median=4		n/a	n/a	n/a	9.6		median=6	n/a	n/a	

Study	Aghdassi *et al* (297)	Bernats-ky *et al* (b) (274, 296)	Clarke *et al* (276)	Clarke *et al* (315)	Edwards *et al* (320)	Gironi-mi *et al* (313)	Krulicho-va *et al* (318)	Minier *et al* (319)	Panopal-is *et al* (302)	Petri and Genovese (325)	Sutcliffe *et al* (312)	Teh *et al* (321)	Yelin *et al* (309)	Zhu *et al*(a,b) (322, 323)	Zink *et al* (317)
Mean LOS per Patient		n/a	1989=9.5 1990=18.0 (6 months)	Canada=12 USA=8 UK=11 (6 months)	n/a		n/a	n/a	n/a		1st 6-months=8 2nd 6-months=9	n/a	n/a	21	
Proportion Dispensed Medication	LN=99% LNN=100%	n/a			n/a		n/a		99%		95%	n/a	4.9	97%	
Mean # Prescriptions (recipient cases)		n/a			n/a		n/a		6.1			n/a	n/a	n/a	

Table 1.6a Study Characteristics for Included Studies using Administrative Databases – Mean Annual Direct Medical Costs, Per-Patient

Study	Year	Disease	Country	Study Years	Number of Subjects	Data Collection Period	Mean Total Annual Direct Medical Costs	Mean Annual Outpatient Costs	Mean Annual Total Hospital Costs	Mean Annual Inpatient Hospital Costs	Mean Annual Medication Costs
Bernatsky *et al* (294)	2011	PM/DM	Canada	2003	1,102	12 months	$40,06	~$1,042	~$2,964	~$,2964 (same)	n/a
Carls *et al* (299)	2009	SLE	USA	2000-2005	6,269	12 months	$23,847	$10,391	n/a	$9831	$3238
Chiu and Lai (324)	2010	SLE	Taiwan	2000-2007	22,182	maximum 8 years	$1,399-$1,727	$713-$908	n/a	$682-$835	n/a
Cotch *et al* (295) Cotch (416)	1995 2000	PAN, Wegener's GCA, TA	USA	1986-1990	PAN=480 Wegener's= 571 GCA=3519 TA=154 (New York State)	5 years	n/a	n/a	n/a	PAN: NY=$4879, USA=$4896; Wegener's: NY=$5324, USA=$7198; GCA: NY=$2820, USA=$2817; TA: NY=$3631, USA=$3710	n/a
Li *et al* (304)	2009	SLE	USA	2000-2005	2,298	5 years	$18,206-$28,312	n/a	n/a	n/a	n/a
Pelletier *et al* (301)	2009	SLE	USA	2007-2008	15,590: LN=1,068 LNN=14,522	12 months	LN=$36,507 LNN=$14,327 overall= $15,846	LN=$18,183 LNN=$7,387	n/a	LN=$11,067 LNN=$3,140	LN=$7,256 LNN=$3,799
Wilson (300)	1997	SSc	USA	1994	77	12 months	$8,685 (main) $5,699 ($2^{o}$)	$1,835	$3,871 ($3,819-$4,296)	n/a	$1,882

Table 1.6b Study Characteristics for Included Studies using Administrative Databases – Mean Annual Health Resource Utilization, Per-Patient

Study	Bernatsky *et al* (294)	Chiu and Lai (324)	Chung *et al* (307)	Cotch *et al* (295) Cotch (416)	Krishnan (306)	Li *et al* (304)	Molina *et al* (310)	Nietert *et al* (308)	Pelletier *et al* (301)	Wilson (300)
Year	2011	2010	2007	1995, 2000	2006	2009	2008	2001	2009	1997
Disease	PM/DM	SLE	SSc	PAN, Wegener's GCA, TA	SLE	SLE	SLE	SSc	SLE	SSc
Country	Canada	Taiwan	USA	USA	USA	USA	Puerto Rico	USA	USA	USA
Study Years	2003	2000-2007	2002-2003	1986-1990	1998-2002	2000-2005	2003	1995	2007-2008	1994
Number of Subjects	1102	22,182	n/a	PAN=480 Wegener's=571 GCA=3519 TA=154 (New York State)	n/a	2298	RH=665 GP=92	n/a	15,590: LN=1068 LNN=14,522	77
Data Collection/ Recall Period	maximum 12 months	maximum 8 years	12 months	5 years	5 years	5 years	12 months	12 months	12 months	12 months
# Outpatient Visits	n/a	12	n/a	n/a	n/a	5.6-6.9	n/a	n/a	LN=20.49 LNN=18.93	10.8
Annual Hospitalization Rate	24.20%	n/a	n/a	n/a	n/a	year 1=24% years 2-5=18%	n/a	n/a	LN=30.3% LNN=13.6%	
Annual # Hospitalizations (whole cohort)	n/a	0.4	n/a	n/a	n/a	year 1=0.5 years 2-4=0.3 year 5= 0.4	RH=0.2 GP=0	n/a	n/a	
Annual # Hospitalizations (hospitalized cases)	n/a	n/a	n/a	PAN=1.39 Wegener's=1.71 GCA=1.28 TA=1.55 (New York State) (5 years)	n/a		n/a	n/a	LN=2.08 LNN=1.55	

Study	Bernatsky *et al* (294)	Chiu and Lai (324)	Chung *et al* (307)	Cotch *et al* (295) Cotch (416)	Krishnan (306)	Li *et al* (304)	Molina *et al* (310)	Nietert *et al* (308)	Pelletier *et al* (301)	Wilson (300)
Mean LOS per Hospitalization	n/a	9.6	6.6	PAN=20 Wegener's=17 GCA=13 TA=11 (New York State)	6	4.4-6.0	n/a	7.5	LN=6.93 LNN=5.32	
Mean LOS per Patient	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	LN=16.52 LNN=9.69	1.6
Proportion Dispensed Medication	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Mean # Prescriptions (recipient cases)	n/a	n/a	n/a	n/a	n/a	54.5-62.9	n/a	n/a	LN=60.62 LNN=42.68	n/a

Table 1.7 Studies Reporting a Greater SARDs Burden in Older Individuals

Disorder	Study	Location	Year	Report
SARDs-CTD (all)	Avina-Zubieta 2011 (1)	British Columbia	2007	incidence in 45+ years=52.9 vs. <45 years=33.8
	Bernatsky 2011 (5)	Canada	2003	greatest prevalence in those aged 45 years and over, age a significant predictor of prevalence; rural Manitoba females: 1250 (1160-1340) for >45 years vs. 200 (170-230); urban Nova Scotia females: 1150 (920-1670) for >45 years vs. 110 (80-170)
SLE	Avina-Zubieta 2011 (1)	British Columbia	2007	incidence in 45+ years=16.8 vs. <45 years=10.8
	Bernatsky 2007 (381)	Quebec	1994-2003	highest incidence and prevalence rates in those aged 45-64 years
	Hopkinson 1993 (336)	UK	1989-1990	highest incidence rates in those aged 50-59 years, median age at diagnosis=55.5 for males and 47.0 for females
	Naleway 2005 (339)	Wisconsin	2001	highest incidence rate in those aged 60-79 years: 11.5 vs. 5.1 (3.6-6.6) overall; highest prevalence rate in those aged 80+ years: 252.7 vs. 78.5 (59.0-98.0) overall
	Stahl-Hallengren 2000 (391)	Sweden	1981-1991	highest incidence rates in 65-74 years: females=14.1 and males=3.2 vs. 4.5-4.8 overall
SSc	Arias-Nunez 2008 (348)	Spain	1988-2006	highest incidence rates in those 45 years : 3.1 (2.0-4.1) for 45-64 years and 3.0 (2.1-4.1) for 65+ years vs. 2.3 (1.6-2.5) overall
	Avina-Zubieta 2011 (1)	British Columbia	2007	incidence in 45+ years=4.9 vs. <45 years=1.9

Disorder	Study	Location	Year	Report
SSc	Steen 1997 (353)	Pennsylvania	1963-1972	highest incidence rate in black women aged 45-54 years (2.12 (0.40-3.83) vs. 0.19 (0.01-0.36) in white women aged 15-24 years
SjD	Alamanos 2006 (355)	Greece	1982-2003	highest incidence rate for males 46-55 years and females 56-65 years
	Avina-Zubieta 2011 (1)	British Columbia	2007	incidence in 45+ years=5.8 vs. <45 years=2.4
	Haugen 2008 (417)	Norway	1997-1999	prevalence for 71-74 years: 1400 (95%CI: 1020-1920) - 3390 (95%CI: 2770-4140); prevalence for 40-44 years: 220 (95%CI: 150-320) – 440 (95%CI: 340-570)
	Pillemer 2001 (358)	Minnesota	1976-1992	peak incidence for females aged 55-64 years, no cases in males <75 years
	Thomas 1998 (359)	UK	?	highest prevalence in 55 years+: 4900 (3700-6400) vs. 3100 (2100-4400)
	Weng 2011 (360)	Taiwan	2005-2007	highest incidence in females aged 55-64 years (23.4 (21.6-25.1)) and males aged 65-74 years (4.0 (3.1-4.9))
PM only	Avina-Zubieta 2011 (1)	British Columbia	2007	incidence in 45+ years=2.2 vs. <45 years=0.5
	Oddis 1990 (361)	Pennsylvania	1963-1982	highest incidence in those 65 years+: 1.05 (0.11-1.99) vs. 0.55 (0.03-1.07) overall
DM only	Avina-Zubieta 2011 (1)	British Columbia	2007	incidence in 45+ years=1.3 vs. <45 years=0.7
PM/DM	Benbassat 1980 (418)	Israel	1960-1976	highest incidence in those 70-79 years (0.63 vs. 0.22 overall)
SARDs-VD (all)	Avina-Zubieta 2011 (1)	British Columbia	2007	incidence in 45+ years=8.1 vs. <45 years=2.0

Disorder	Study	Location	Year	Report
SARDs-VD (all)	Gonzalez-Gay 2003 (6)	Spain	1988-2001	highest incidence in those 55-64 years: 3.49 (2.86-4.26) vs. 1.31 (0.89-1.92) overall
	Herlyn 2008 (419)	Germany	1998-2005	greater incidence in those 50+ years: 6.94 (5.3-8.5) – 11.43 (9.3-13.5) vs. 1.24 (0.6-1.9) - 2.48 (1.5-3.5) for <50 years
	Koldingsnes 2001 (413)	Norway	1984-1998	for males, highest incidence in males aged 65-74 years 2.90 (1.25-5.71) vs. 1.22 (0.84-1.70) for all adult males
	Mohammad 2009 (364)	Sweden	1997-2006	highest incidence in those aged 75 years+ (7.91 (5.52-10.30) vs. 2.18 (1.82-2.54) overall
	Reinhold-Keller 2000 (365)	Germany	1994	prevalence 5x higher in those 50+ (44.2 (34.0-54.5) – 45.0 (33.63-56.4) vs. 7.8 (4.6-11.1) - 8.7 (5.3-12.1) for <50 years
	Reinhold-Keller 2002 (366)	Germany	1998 1999	greater incidence in those 50+ years: 8.18 (5.9-10.5) - 10.47 (7.8-13.1) vs. 2.32 (0.7-4.0) - 2.36 (0.7-4.1)
	Reinhold-Keller 2005 (367)	Germany	1988-2002	incidence 2-5x higher in those aged 50 years: 7.40 (5.70-9.10) - 11.43 (9.30-13.50) vs. 1.24 (0.06-1.90) – 2.48 (1.50-3.50)
	Watts 2000 (7), 2001	UK	1988-1997	highest incidence in those aged 65-74 years : 6.01 (4.08-8.53)
Wegener's	Avina-Zubieta 2011 (1)	British Columbia	2007	incidence in 45+ years=2.9 vs. <45 years=1.4

Disorder	Study	Location	Year	Report
Wegener's	O'Donnell 2007 (420)	New Zealand	1999-2003	highest incidence in those 70-79 years, approximately 25.0 vs. 3.9 overall
PAN	Avina-Zubieta 2011 (1)	British Columbia	2007	incidence in 45+ years=0.8 vs. <45 years=0.4
	Gonzalez-Gay 2003 (6)	Spain	1988-2001	highest incidence in those 55-64 years: 0.93 (0.58-1.49)
GCA	Avina-Zubieta 2011 (1)	British Columbia	2007	incidence in 45+ years=4.8 vs. <45 years=0.2
	Bengtsson 1981 (421)	Sweden		incidence for 50+ years: 28.6 vs. 9.3 overall
	Boesen 1987 (370)	Denmark	1982	incidence for 70-79 years: 142.9 incidence for 50+ years: 76.6 overall incidence: 21.5
	Friedman 1982 (284)	Israel	1960-1978	highest incidence of temporal arteritis in those 70-79 years: 1.16 vs. 0.49 for whole 50+ population
	Friedman 1982 (284)	Israel	1960-1978	greatest incidence in those 70+ years: 1.16 (0.69-1.63) vs. 0.49 (0.35-0.63) for all 50+ years and 0.02 (0.00-0.11) for those 50-59 years
	Gonzalez-Gay 2001 (371)	Spain	1981-1998	highest average annual incidence in those aged 70-79 years: 20.78 (13.33-28.23) vs. 10.24 (8.13-12.58) overall
	Gonzalez-Gay 2007 (372)	Spain	1981-2005	incidence rate for 70-79 years: 23.16 (19.52-27.28) vs. 10.13 (8.93-11.46) overall
	Gran 1997 (374)	Norway	1987-1994	highest incidence in those 75-79 years: 308.6 vs. 141.7 for all 50+ years and 41.1 overall
	Petursdottir 1999 (375)	Sweden	1976-1995	incidence for 50+ years: 22.2 vs. 7.7 overall

Disorder	Study	Location	Year	Report
GCA	Reinhold-Keller 2000 (365)	Germany	1994	higher prevalence in those aged 50 years and older: 24.0 (16.4-31.5) - 30.0 (20.7-39.3) vs. 8.7 (5.9-11.4) - 9.4 (6.5-12.3) overall
	Salvarani 1995 (376)	Minnesota	1950-1991	highest incidence in those 70-79 years 48.9 (33.9-68.3) vs. 17.8 (14.7-21.0) for all 50+ years
	Salvarani 2004 (377)	Minnesota	1950-1999	highest incidence in those aged 80+ years: 51.9 (37.6-65.3) vs. 18.8 (15.9-21.6) for all those 50+ years
	Sonnenblick 1994 (378)	Jerusalem	1980-1991	highest incidence in those aged 75+ years 28.4 (21.0-35.7) vs. 2.2 (0.8-5.2) in those aged 50-64
TA	Avina-Zubieta 2011 (1)	British Columbia	2007	incidence in 45+ years=0.5 vs. <45 years=0.2

Table 1.8 Studies Reporting an Increase in the Incidence of SARDs

Disorder	Study	Location	Initial		Subsequent	
			Years	Incidence (95% CI) per-100,000	Years	Incidence (95% CI) per 100,000
SARDs-CTD (all)	Avina-Zubieta 2011 (1)	British Columbia	1996	16.2	2007	44.3
SLE	Alamanos 2003 (330)	Greece	1982-1986	1.41 (0.99-1.83)	1997-2001	2.19 (1.78-2.60)
	Avina-Zubieta 2011 (1)	British Columbia	1996	4.7	2007	14.1
	Laustrup 2009 (388)	Denmark	1995	0.52 (0.05-1.90)	2002	1.04 (0.27-3.69)
	Uramoto 1999 (288)	Minnesota	1950-1979	1.51 (0.85-2.17)	1980-1992	5.56 (3.93-7.19)
	Voss 1998 (344)	Denmark	1980	1.1 (0.3-2.9)	1994	3.6 (2.0-6.1)
SSc	Arias-Nunez 2008 (348)	Spain	1988-1992	1.4 (0.6-2.3)	2003-2006	2.5 (1.4-4.1)
	Avina-Zubieta 2011 (1)	British Columbia	1996	1.8	2007	3.6
	Steen 1997 (353)	Pennsylvania	1963-1967	0.97 (0.75-1.18)	1978-1982	1.82 (1.50-2.13)
SjD	Avina-Zubieta 2011 (1)	British Columbia	1996	0.6	2007	4.3
PM only	Avina-Zubieta 2011 (1)	British Columbia	1996	0.3	2007	1.4
DM only	Avina-Zubieta 2011 (1)	British Columbia	1996	0.6	2007	1.0
PM/DM	Benbassat 1980 (418)	Israel	1960-1964	0.13	1970-1974	0.26
	Oddis 1990 (361)	Pennsylvania	1963-1972	all: 0.25 females: 0.32 males: 0.17	1973-1982	all: 0.89 females: 1.16 males: 0.58
SARDs-VD (all)	Avina-Zubieta 2011 (1)	British Columbia	1996	2.4	2007	5.3
	Watts 2001 (368)	UK	1988-1993	1.55 (1.06-2.19)	1994-1998	2.10 (1.56-2.74)

Disorder	Study	Location	Initial		Subsequent	
			Years	**Incidence (95% CI) per-100,000**	**Years**	**Incidence (95% CI) per 100,000**
Wegener's	Avina-Zubieta 2011 (1)	British Columbia	1996	0.6	2007	2.2
	Koldingsnes 2001 (413)	Norway	1984-1988	0.52 (0.27-0.90)	1994-1998	1.20 (0.80-1.73)
GCA	Avina-Zubieta 2011 (1)	British Columbia	1996	1.4	2007	2.7
	Franzen 1992 (422)	Finland	1984-1987 (44 months)	overall= 22.5 50+ years=69.8	1987-1988 (16 months)	overall= 30.4 50+ years= 94.4
	Friedman 1982 (284)	Israel	1960-1964	0.16 (0.00-0.32)	1975-1978	0.86 (0.51-1.22)
	Gonzalez-Gay 1997 (373)	Spain	1986-1990	annual average: 8.26 5-year average: 41.30	1991-1995	annual average: 10.49 5-year average: 51.99
	Gonzalez-Gay 2007 (372)	Spain	1981-1985	3.18 (1.82-5.16)	2001-2005	12.92 (9.97-16.46)
	Petursdottir 1999 (375)	Sweden	1976	9.6	1995	30.1
	Salvarani 2004 (377)	Minnesota	1950-1954	6.7 (0.0-14.3)	1995-1999	18.5 (11.3-25.7)
PAN	Avina-Zubieta 2011 (1)	British Columbia	1996	0.2	2007	0.6
TA	Avina-Zubieta 2011 (1)	British Columbia	1996	0.03	2007	0.4

Table 1.9a Study Characteristics for Included Studies Reporting Incremental/Attributable Mean Annual Direct Medical Cost Data, Per-Patient

Study	Callaghan *et al* (311)	Carls *et al* (299)	Huscher *et al* (316)	Li *et al* (304)	Panopalis *et al* (302)	Pelletier *et al* (301)
Year	2007	2009	2006	2009	2008	2009
Disease	SjD	SLE	SLE	SLE	SLE	SLE
Country	United Kingdom	USA	Germany	USA	USA	USA
Study Years	2001	2000-2005	2002	2000-2005	2003-2005	2007-2008
Number of Controls	92	6,269	844	2,298	n/a: US national average	n/a
Data Collection/Recall Period	6 months	12 months	3 months	12 months	12 months	12 months
Mean Total Annual Direct Medical Costs (Controls)	$2,361	$8,882	n/a	$10,920-$19,181	$5,802	n/a
Total Mean Annual Attributable Direct Medical Costs	$3,085 (57%)	$14,964 (63%)	$5,878 (n/a)	$4,475-$9,569 (15-42%)	$10,566 (66%)	LN=$8,326 (23%) LNN=$2,964 (31%)
Mean Annual Outpatient Costs (Controls)	$1,903	$5,839	n/a	n/a	n/a	n/a
Mean Annual Attributable Outpatient Costs	$1,943 (50%)	$5,659 (54%)	$680 (n/a)	n/a	n/a	LN=$2,332 (13%) LNN=$1,000 (14%)
Mean Annual Hospital Costs (Controls)	$358	n/a	n/a	n/a	n/a	n/a
Mean Annual Attributable Hospital Costs	$863 (71%)	n/a	n/a	n/a	n/a	n/a

Study	Callaghan *et al* (311)	Carls *et al* (299)	Huscher *et al* (316)	Li *et al* (304)	Panopalis *et al* (302)	Pelletier *et al* (301)
Mean Annual Attributable Inpatient Hospital Costs	n/a	$7,576 (77%)	$2,853 (n/a)	n/a	n/a	LN=$3,829 (35%) LNN=$1,096 (35%)
Mean Annual Medication Costs (Controls)	$67	$1,777	n/a	n/a	n/a	n/a
Mean Annual Attributable Medication Costs	$174 (72%)	$1,500 (46%)	$1,566 (n/a)	n/a	n/a	LN=$1,818 (25%) LNN=$868 (23%)

Table 1.9b Study Characteristics for Included Studies with Incremental/Attributable Health Resource Utilization Data, Per-Patient

Study	Clarke *et al* (276)	Li *et al* (304)	Pelletier *et al* (301)	Petri and Genovese (325)
Year	1993	2009	2009	1992
Disease	SLE	SLE	SLE	SLE
Country	Canada	USA	USA	USA
Study Years	1989, 1990	2000-2005	2007-2008	1989-1990
Number of Controls	n/a: Quebec average	2,298	n/a	n/a
Data Collection/Recall Period	6 months	12 months	12 months	24 months
Mean # Outpatient Visits (Controls)	6.9	3.4-3.8	n/a	n/a
Mean Attributable Outpatient Visits	4.9	2.2-3.2	n/a	n/a
Annual Hospitalization Rate (Controls)	n/a	10.4-12.0%	LN=16.1% LNN=5.9%	n/a
Annual Attributable Hospitalization Rate	n/a	6.3-14.4%	LN=14.2% LNN=7.7%	70% of hospitalizations
Mean Annual Admissions (whole cohort)	n/a	0.2	n/a	n/a
Annual Attributable Admissions	n/a	0.1-0.3	n/a	n/a
Mean LOS per Hospitalization (Controls)	n/a	4.2-5.8	n/a	n/a
Mean Attributable LOS	n/a	-2.4	n/a	n/a
Mean LOS per Patient (controls)	1.16	n/a	n/a	n/a
Mean Attributable LOS	3.69	n/a	n/a	n/a
Mean # Prescriptions (Controls)	n/a	37.4-47.2	n/a	n/a
Mean # Attributable Prescriptions	n/a	15.0-17.1	n/a	n/a

Table 1.10 Mean Annual Direct Medical Costs of Other Arthritides in Canada, Per-Patient

Disease	Canadian Prevalence (per 100,000 adults)	Location	Study	Year	Mean Annual Per-Patient Costs (2007 CDN)
Rheumatoid Arthritis (RA)	1,000 (12)	Saskatchewan & Quebec	Clarke *et al* (277)	1983-1989 1990-1994	$4,997 $6,142
		Ontario	Maetzel *et al* (279)	2000	$7,414
		Quebec	Fautrel *et al* (278)	2002	$11,436
Juvenile Idiopathic Arthritis (JIA)	1,000 per-100,000 children and teenagers (423)	British Columbia & Quebec	Bernatsky *et al* (424)	mid-2000's	gross=$3,143 incremental=$1,765
Osteoarthritis (OA)	10,000 (425)	Ontario	Maetzel *et al* (279)	2000	$5,690
Fibromyalgia	2,000-4,000 (426)	Canada	Penrod *et al* (427)	2001	$5,269
		Ontario	White *et al* (428)	1994	$1,386 (outpatient only)

2 Methods

In the previous chapter we presented our study objectives – to determine the health resource utilization and economic burden of SARDs – and explained how we will employ provincial administrative health data while meeting them. The many advantages of this data source were presented, including large and less-biased patient samples, comprehensive capture of health resource utilization, and more precise costing of this utilization. In this chapter we will detail our case and data sources and the methods we will use for identifying cases, costing services, and producing these estimates of mean direct per-capita medical costs.

2.1 Case and Data Source-British Columbia Linked Health Database

Data on the health resource utilization and demographics of the cohort were obtained from the British Columbia Linked Health Database (BCLHD). These are administrative datasets containing the claims for health care services consumed by BC residents. BCLHD was administered by the provincial government (specifically the Ministry of Health) but this data is now made available through a separate organization, Population Data BC (PopDataBC). These claims are linked to the Consolidation File, or vital statistics datasets, through each resident's unique Personal Health Number (PHN). This allows researchers access to health resource utilization data at the patient level. Although the PHN is used to link claims, a separate study identification number (study id) generated by PopDataBC is used to differentiate patients in the research data, rendering it anonymous. Because the data are de-identified, informed consent was not required from the selected cases and ethics approval was not needed.

In BC, health insurance is available through a single provider, the Medical Services Plan (MSP). The Consolidation File mainly contains data collected by MSP to register beneficiaries and collect their annual premiums. The datafields of interest include the birth year and month, and the dates when MSP coverage started and ended (429). Also available are data on all deaths registered in BC (429). It is through these registered deaths and MSP coverage end-dates that we determined the end-of-follow-up date for each case. If there was no record of a case's death or termination of coverage, they were followed through the end of the study period (December 31, 2007).

We used the following health claims datasets: Medical Services Plan Payment Information File (MSP) for outpatient encounters, Discharge Abstract Database (DAD) for hospital separations, and PharmaNet for prescriptions. These are detailed in sections 2.1.1, 2.1.2, and 2.1.3, respectively, of this chapter.

Coverage for the DAD and MSP data extends from April 1, 1985 onwards (429). PharmaNet coverage is from January 1, 1995 onwards (430), but since this dataset is not considered to be well-populated for the first twelve months of this time, our study period began on January 1, 1996. It extended for twelve years, through December 31, 2007, the last full calendar year for which data was available at the time of request.

All BC residents are both eligible for, and required to, enroll for MSP. This entitles them to the use of all medically-necessary outpatient and hospital services (429) without upfront charges. Neither the inability, nor the failure, to pay premiums bars access to health services or the capture of claims in the database (431). Residents cannot opt-out of PharmaNet when dispensed a prescription (430). This means the health care consumption of nearly every BC resident is captured by BCLHD.

Given the publically-operated and funded nature of BC's health care system, where a full range of services are provided to all residents regardless of financial means, the BCLHD's coverage is considered comprehensive and unbiased. Only a small and select group of BC residents (mainly active members of the RCMP and Canadian Armed Forces - but not their dependants - and Status Native and Inuit individuals, all of whom receive federal health benefits) are not covered by MSP (429). There are a small number of private medical and surgical facilities in the province whose services are not captured by BCLHD. However, the quantity and cost of these services are relatively insignificant in relation to provincially-funded consumption, particularly as complex procedures requiring an extended inpatient stay are not provided by these facilities.

2.1.1 Medical Services Plan Dataset

MSP is strictly a BC entity – claims for services provided to BC residents are submitted to and adjudicated by MSP directly within the province. The outpatient services captured in the MSP dataset essentially refer to any medially-necessary services provided, ordered, or interpreted by a physician or some select non-physician fee-for-service

(FFS) practitioners. This includes any eligible physician visits/consultations (including those occurring in a hospital), procedures or operations performed, and laboratory, radiological, and other investigations are ordered or interpreted by them (431). Also included are surgical podiatry services and those provided by a dentist or oral surgeon in a hospital setting (431). Neither routine physical or eye examinations, dental services provided outside hospital, cosmetic procedures, counselling/psychological services (431), nor any services provided through other, non-FFS arrangements are captured in the MSP data. The latter would include physicians reimbursed through a salary (429). Concerning other supplementary-benefit services (those not provided by a physician), the scope of eligible benefits was reduced significantly as-of April 1, 2002. This resulted in the MSP database offering only partial coverage of these encounters over our study period.

Each MSP claim includes datafields for the service date, practitioner number, specialty code (referring to the specialty of the physician or profession of the non-physician practitioner), fee item (referring to the exact service provided), one diagnostic code (using International Classification of Diseases, 9th revision (ICD-9) nomenclature, up to six digits), and the amount paid to the practitioner by MSP. This amount corresponds to the fee item billed and follows the Medical Services Commission payment schedule. The sex and birthdate of the beneficiary are also listed (429). The specialty codes do change over time; for instance, many specialties previously coded under Internal Medicine are now coded more specifically as Respirology or Nephrology (432). This has implications for SARDs in that rheumatology, the primary specialty involved in SARDs care, was not coded separately until January 1, 1998.

2.1.2 Discharge Abstract Database

The hospital separations in the DAD include any discharges, deaths, or transfers – as part of an inpatient or day admission - from any acute-care hospital. These include any separations from an extended or long-term care facility attached to an acute-care hospital (referred to as Alternate Level of Care, or ALC, stays) (429). While the MSP database includes the services provided by physicians during a hospitalization (such as consultations or surgeries), the resource consumption captured by the DAD covers every other medical service and cost involved in providing this care such as nursing costs, consumables, housekeeping, equipment and other overhead. However, the DAD does not capture outpatient emergency room services (429).

Unlike MSP, the DAD is a national entity maintained by the Canadian Institute for Health Information (CIHI). CIHI collects discharge records directly from all BC hospitals, processes and performs further data analysis, and submits this back to the BC Ministry of Health on a monthly basis (429). This centralized structure of data collection and processing is thought to increase the quality of the information contained in the DAD (429). In addition to the sex and birthdate of the beneficiary, each DAD record has fields on the hospital, level of care (inpatient, day, or ALC), admission and separation dates, diagnostic code(s) and type(s) (up to 6-digits each and up to 25 total diagnoses), length of stay (LOS), case-mix group (CMG) and resource intensity weight (RIW). The CMG is a method of grouping together similar diagnoses that should necessitate a similar level of resource consumption. The RIW is a weighted measure of the actual resource consumption was necessitated by that hospitalization (429). More detail about the RIW is provided in section 2.6.3.

2.1.3 PharmaNet

PharmaNet contains the records for all prescriptions dispensed by any community pharmacy in BC. The Ministry of Health subsidizes some prescription costs through the PharmaCare program, but all prescriptions are recorded in PharmaNet regardless of the payment arrangement. PharmaNet does not capture medications provided in hospital. Each PharmaNet record has fields for the dispensing date, drug identification number (DIN), drug quantity, number of days supplied, drug cost, and professional fee charged.

2.2 Inclusion Criteria

Any BC resident who, at any point during the study period (January 1, 1996 through December 31, 2007) was registered with MSP, and was at least 18 years of age, was eligible for inclusion. There was no minimum follow-up period. The MSP dataset and the DAD were searched from January 1, 1990 onwards for potential cases. These were individuals with a claim containing a diagnostic code for any SARD. The specific International Classification of Diseases (ICD) codes, for both the ninth (ICD-9) and tenth (ICD-10) revisions, that this included are listed in Appendix A.

To be eligible for inclusion cases had to meet one of the three definitions below:

a) ≥2 codes by any non-rheumatologist physician on an outpatient encounter, >60 days apart but within a single two-year period;

b) ≥1 code by a rheumatologist on an MSP encounter;

c) ≥1 hospital discharge code as either the primary or one of the 24 secondary discharge diagnoses;

Definition a) required two visits to increase diagnostic specificity. The intention was to exclude individuals who did not actually have a SARD, but had a single SARD-coded encounter to rule-out this diagnosis, or where a non-SARDs-specialist (non-rheumatologist) was uncertain of the SARDs diagnosis. The 61-day (two-month) minimum timeframe was implemented to exclude those with transient, inflammatory, undifferentiated connective tissue diseases that did not meet the criteria for a SARD.

2.2.1 Rationale

Similar case definitions have been used to identify cases from US administrative databases for several SLE costing studies (299,301,304). High sensitivity (0.85(95%CI: 0.73-0.97)) and specificity (0.90(95%CI: 0.81-0.99)) values for ICD-9-CM 710.0 (SLE) have been reported for rheumatology billings in a US Medicare database (433). But of particular importance for our work, these same ICD-9 codes and nearly-identical case definitions have been applied to Canadian provincial administrative data when measuring the incidence and prevalence of SARDs-CTD (5,349,362,381). The one Canadian population-based study of SARDs costs also used a similar definition (294). The accuracy of these (and SARDs-VD) diagnoses in Canadian data was assessed in a subsequent validation study (434) which compared them to cases' medical records. The diagnosis was confirmed for 83% of cases. Among cases with a false-positive diagnosis for one SARD, most were deemed to still have a SARD (or similar disorder), only a different one, upon chart review (5,434).

Using multiple datasets and definitions helps maximize case ascertainment and minimize bias. These Canadian studies compared the different sources and definitions and as shown in Table 2.1, they differed in the number of cases detected and their sensitivity and specificity. For instance, the prevalence of PM/DM, when calculated using all three sources (rheumatologist billings, all physician billings, and hospital separations) was nearly twice as large

as when only rheumatologist billings were examined (362). With only 24% of SLE cases identified in both physician and hospital data (381), there is clearly limited overlap in the coverage provided by each source. This means fewer cases will be captured if just one is used, limiting sample size and statistical power. Using multiple sources can increase diagnostic specificity, with the validation study finding this was higher when multiple sets were used (434).

Bias is also minimized since the cases captured by each source can differ in their demographic characteristics, including age (362,381), sex (5), and urban/rural residence (5,349,362,381). As detailed in Chapter 1, these factors can influence healthcare consumption. With hospital-sourced cases more likely to have a greater severity of disease and/or a greater comorbidity burden than others (349,362), using only hospital data could overestimate costs. Instead, by combining the three sources and definitions together, we should obtain the most-representative and least-biased cohort possible.

2.3 Exclusion Criteria

2.3.1 Diagnostic Specificity

After potential SARDs cases were identified, we implemented additional exclusion criteria to increase the reliability of the SARDs diagnosis and specificity of our cost estimates. First, any potential case was excluded if more than five years passed between the dates of the last encounter (MSP claim or hospital separation) coded for the SARD and end-of-follow-up. Given the high rate of SARDs-related consumption expected for true SARDs cases, such a gap in utilization reduced the certainty of the SARDs diagnosis. Potential cases only meeting definition a) were excluded if they had a rheumatologist encounter subsequent to their SARDs index date (the date of the first qualifying visit) which was not coded for a SARD. This was also to increase the reliability of the SARD diagnosis.

2.3.2 Costing Specificity

Even though an individual can legitimately have both a SARD and another form of arthritis, such as RA, due to overlap in the types of health resource utilization necessitated by these two classes of disorders, we excluded these cases. It would otherwise be difficult to attribute any healthcare consumption to SARDs. This meant potential cases that were later diagnosed with another type of inflammatory arthritis (including RA, psoriatic

arthritis, spondyloarthropathy, systemic vasculitis and other non-SARD connective tissue diseases) at any time during the follow-up period were excluded. This was determined through the presence of any diagnostic code corresponding to these disorders (ICD-9 274, 696, 711, 712, 713, 714, or 720; ICD-10 M02, M05, M07, M10, M11, M14, M45, or M148) on a health encounter claim.

Individuals who had originally met definition a) for SARDs were excluded if, after their second qualifying SARD visit, they had ≥2 encounters (MSP claims or hospital separations) ≥61 days apart coded for a different form of arthritis. The two encounters, however, did *not* need to occur within a two-year period. Individuals who originally met either case definition b) or c) were excluded if they had either ≥1 rheumatologist encounter or ≥1 hospital separation coded for one of these arthritides.

Colleagues have used this same cohort to measure the incidence and prevalence of SARDs in BC, and their estimates were consistent with those reported in other jurisdictions (1). This supports the reliability of these case definitions, diagnostic codes, and exclusion criteria for appropriately identifying SARDs cases.

2.4 Index Dates and Subgroups

2.4.1 Index Dates

For cases meeting definition a), the index date was the date of the first visit in the set of two qualifying encounters (the index visit). For cases meeting definitions b) or c), the index date was equal to the date of the single qualifying encounter (again referred to as index visit). When a case met more than one of the above criteria, the *actua*l index date was set to the *earliest* of any of the possible index dates.

2.4.2 Subgroups

Aside from being included in the entire SARDs cohort, cases coded with a SARDs-CTD diagnosis at any index visit were included in a SARDs-CTD subgroup. Similarly cases coded for a SARDs-VD diagnosis at any index visit were included in a SARDs-VD subgroup. Any case with both a SARDs-CTD and SARDs-VD index diagnosis was

included in the main SARDs cohort but not assigned to a subgroup. All subsequent analyses were performed for each group separately: the entire cohort (all-SARDs), and the SARDs-CTD and SARDs-VD subgroups.

2.5 Health Resource Utilization

2.5.1 Follow-Up Parameters

All health resources consumed by cases during their follow-up period were tabulated. For some components, any consumption occurring within 30 days after the end-of-follow-up date was also included. This thirty-day window was implemented to account for errors and inconsistencies in billing dates. We assumed an encounter billed shortly after the end-of-follow-up date likely occurred during the follow-up period, particularly if follow-up ceased due to death. When the index date fell on or after January 1, 1996, follow-up began from that same date (referred to from here-on as the start date). When the index date fell before this time, follow-up began on January 1, 1996 (the start date). For cases that were less than 18 years old in the year of their index date, follow-up did not begin until January 1 of the year in which they turned 18. The last day of follow-up was the earliest date of either death, de-enrollment in MSP (usually from moving out of BC), or December 31, 2007, the last day of the study period. Any resource consumption occurring on this end-of-follow-up date (referred to from here-on as the end date) was included. A summary of the timeframes during which encounters were included is provided in Table 2.2.

We determined the number of unique cases followed each year and during the entire study period. For each year, a case was counted if their start date fell on or before January 1 of that year and their end date fell after December 31 of the previous year. Therefore, a case would be included in the year-2000 cohort if their death date was recorded as January 1, 2000, because they were alive for a portion of the year 2000. Since there was no minimum length of follow-up, many cases were followed for only part of a calendar year. To account for this, the contribution of each case was weighted by the amount of follow-up time they had, rounded up to the nearest month and expressed in patient-years or person-years (PY). For example, a case with a start date of January 1, 1996, and an end date of March 5, 1997, would have contributed a total of 1.25 PY (twelve months in 1996 and three months in 1997).

2.5.2 Outpatient Encounters

For each component, the number of services consumed was summed both annually and for the entire study period. For outpatient encounters, each unique combination of study id, service date, and specialty-type was considered a single encounter. Therefore, only the first of any set of claims made by the same practitioner-type on the same date for the same case was counted. This still allowed an individual to have multiple encounters in one day if they were with different specialists. All claims occurring on or after the start date were considered, as were any occurring within 30 days after the end date (but before 2008). For annual tabulations, encounters were allocated to the year of the service date.

2.5.3 Prescriptions

The prescription tabulations included all those dispensed on or after the start date, and those dispensed within 30 days following the end date (but before 2008). For annual tabulations, prescriptions were allocated to the year of the service/dispensing date.

2.5.4 Hospitalizations

When tabulating the number of admissions, only the first admission per-case, per-day, was considered. This eliminated multiple admissions in a single day that typically resulted from inter-hospital transfers, or multiple day procedures. For annual tabulations, hospitalizations were allocated to the year of the admission date.

Considering that inpatient hospitalizations span multiple days, and therefore could span parts of two calendar years and even fall outside the follow-up period, the eligible inclusion dates were modified slightly. Hospitalizations spanning outside a case's follow-up period were included under the following circumstances:

a) admission *within 30 days* before the start date and separation *during* follow-up

b) separation *within 30 days* after the end date but admission *during* follow-up

c) admission outside of follow-up, but *within 30 days* of the start date, AND separation outside of follow-up, but *within 30 days* of the end date

However, those hospitalizations where the admission occurred *more than 30 days* before the start date AND the separation occurred *more than 30 days* past the end date were excluded. For patients followed through December 31, 2007, any separations occurring *within the first 30 days* of 2008 were included (and allocated to the year 2007) as long as admission occurred before 2008. Similarly, for patients whose start date was January 1, 1996, any admissions occurring *in the last 30 days* of 1995 were included (and allocated to 1996) as long as separation occurred after 1995.

2.6 Cost Calculation

As detailed below, we determined the unit price of each health service consumed. The total direct medical costs were equal to the sum of these prices. Totals were produced for each component (outpatient, hospital, and prescription), and for all health resources combined. Table 2.2 summarizes the methods used to cost each type of encounter.

2.6.1 Outpatient Encounters

Included with each claim was the specific amount paid to the practitioner for that service (the Amount Paid field). Therefore, the cost of each encounter was equal to this figure. All submitted claims were included, even multiple claims pertaining to the same case, specialist, and date. Annual costs were allocated to the year of the service date.

2.6.2 Prescriptions

Costs for the other components were calculated from the provincial government (payer) perspective, but prescription costs were calculated from a societal perspective. This meant the total cost of each prescription was considered, not just the amount subsidized by the provincial government under the PharmaCare program. This total cost was equal to the sum of the total drug cost and the total professional fee, as listed on each PharmaNet record. A secondary analysis of just the subsidized cost of each prescription was also undertaken. The subsidized cost was equal to the Pharmacare Paid field (the sum of the drug cost and professional fees that were subsidized) on the PharmaNet record. Annual costs were allocated to the year of the service/dispensing date.

2.6.3 Hospitalizations

The costs of most hospitalizations, including all acute-care stays and about half of the day surgeries, were calculated using CIHI's established case-mix methodology. In this, the cost of each hospitalization is equal to its RIW multiplied by the cost-per-weighted-case (CPWC) specific to the fiscal year. Both of these figures are calculated by CIHI. This standard method of pricing hospitalizations has been used in many Canadian costing studies for individual SARDs (274,297,313-315) and other disorders. The cost of each hospitalization was allocated to the year of admission whereas inflation adjustments were made according to the year of separation. As with the MSP claims, all admissions were included for costing, even multiple admissions from the same date.

Cost-Per-Weighted-Case

The CPWC is the average cost of an inpatient hospitalization for a 'standard' patient across all hospitals in a particular jurisdiction, and is specific to a fiscal year (435). We used CPWC values specific to BC, and those corresponding to the fiscal year of the separation date.

Provincial CPWC figures for the fiscal years 2004/2005 to 2007/2008 were calculated and provided by CIHI (436) (Table 2.3), but those for the fiscal years prior to 2004/05 were unavailable. Instead, we had to estimate them, and explored several methods of doing so:

a) deflating the earliest-available CPWC figure, that for 2004/05, by the percent-change in the Canadian Consumer Price Index (CPI) between 2004 and each previous year;
b) constructing a line-of-best-fit with the known CPWC values and using it to extrapolate the values for the previous years;
c) using the CPWC for fiscal year 2007/08 for each study year and not making further inflation adjustments;

After some test calculations, the first method was rejected because the CPWC estimates seemed too high. The third method was rejected because it is better to use CPWC figures specific to each year. The methods used in calculating it are "not consistent across years" (437), and year-to-year changes in health services delivery can all drive-up the annual CPWC independent of any inflation increases (438). These changes could include an older or more complex

inpatient caseload, a tendency to treat straightforward and less-expensive cases on an outpatient basis, and the introduction of more expensive technologies and procedures (438). It has also been suggested that using only the most recent CPWC value to calculate previous years' costs can overestimate them (439). Therefore, we decided to extrapolate the earlier values from a line-of-best-fit (method b), which are listed in Table 2.3.

Resource Intensity Weight

The RIW is a measure of the relative resource consumption (or cost) of each hospitalization, taking into account the specifics of the patient and setting, including LOS (435). It is derived from the age of the patient, complexity of the case, and its assigned CMG – a method of grouping cases with similar diagnoses, resource utilization patterns, and clinical characteristics (438). The RIW is expressed as a decimal - either less than, equal to, or greater than 1.00 (depending on whether the hospitalization required the consumption of greater or fewer resources than the average inpatient case). This makes the RIW is a multiplier of the cost of the average hospitalization (the CPWC).

To ensure consistency, the same edition of RIW should be used to price all admissions. However, this was not possible since our study period spanned three editions of the RIW. The first edition, cRIW01, was available for separations through March 31, 2001. It was derived from the ICD-9 system and CMG/Plx case-mix methodology. The second edition, cRIW05, was available for separations spanning April 1, 2001 through March 31, 2007. It was also derived from ICD-9 and CMG/Plx methodology. The third edition, p_RIW07, was available for separations spanning April 1, 2001 through December 31, 2007. This was instead derived from the newer ICD-10-CA system and CMG+ case-mix methodology. Therefore, the only RIW available for the first 63 months (5.25 years) of the study period was derived from one system (ICD-9), while the only RIW available for the last 9 months (0.75 years) was derived from another system (ICD-10), with 72 months (6 years) of overlapping systems in the middle. RIWs calculated using the old methodology are not fully comparable to those from the latest edition, but if we only used separations with a p_RIW07 value, we would have lost 5.25 valuable years of observation. Instead, we stayed as consistent as possible while maximizing the quantity of data available, using the cRIW01 and cRIW05 for most of the study period, and the p_RIW07 for only the 2007 calendar year.

Alternate Level of Care Separations

Case-mix methodology could not be used to price ALC separations since the RIW value was set to 0. Instead, these stays were priced by multiplying the LOS by a provincial per-diem rate specific to extended care beds in acute care hospitals. Such rates were not available for every year of study, so the 2007 rate of $225 CDN - quoted by several BC centres (440,441) - was used, and no further inflation adjustment was needed. Two Canadian studies of the costs of SLE have also a used per-diem rate (one provided by Statistics Canada) to price non-acute hospitalizations (314,315).

Day Procedure Separations

Case-mix methodology could not be used to cost some day procedures either. The RIW calculated by CIHI for day procedures is referred to as the Day Procedure Group Weight (DPG)-RIW, or DPG-RIW. PopDataBC only provided these values through the 2000-01 fiscal year so we investigated several methods of estimating the costs after this time. We decided that using a flat, per-diem rate (as was done for ALC separations) would not reflect the actual costs of care since this would apply an average charge to a wide range of procedures. Also, a Saskatchewan study on diabetes costs found, when compared to other imputation methods, this method produced the highest hospital cost estimates (442). Instead the day procedure costs for the year 2001 and beyond were extrapolated (using the annual change in the CPI) from the actual total costs incurred for the year 2000, the latest full calendar year for which the DPG-RIW data was available. A method presented by Pohar *et al* (439) - a version of which was used in the Saskatchewan diabetes study above - was considered. In this, the mean DPG-RIW value for the year 2000 would be applied to each day case occurring in the subsequent years and multiplied by the corresponding CPWC. However, these authors found that cost estimates obtained this way were higher than those obtained using the cost-inflation method described above. Therefore, we chose the latter method to ensure the most conservative estimates.

2.7 Attribution

Three separate utilization and cost analyses were undertaken, with the primary (gross) analysis encompassing every health resource that a case consumed. However, to estimate the net burden of SARDs we undertook a secondary analysis that only included SARDs-related encounters, which were selected by two rheumatologists (J.A. Avina-

Zubieta, D. Lacaille). We used two definitions for these encounters, one narrow and one broad. Table 2.4 summarizes the encounters included in each analysis.

2.7.1 Narrow Definition.

For outpatient encounters, the narrow definition encompassed two mutually-exclusive types of MSP claims based on the diagnostic code and physician specialty. The first was any claim billed by a *non-rheumatologist* practitioner containing *any SARD* diagnostic code (as listed in Appendix A). The second was any claim billed by a *rheumatologist* (as indicated by Specialty Code '44'), which could contain *any* diagnostic code. Any hospital separation with a *primary* discharge diagnosis for SARDs (as listed in Appendix A) was included. A list of the classes of drugs relating to SARDs was compiled (Appendix A), and all PharmaNet records with a DIN pertaining to these drugs were included.

2.7.2 Broad Definition

We suspected many SARDs-related encounters would not be captured under the narrow definition. Because only one diagnosis is recorded on each MSP claim, the morbidity necessitating the encounter (such as nephritis) may be coded instead of the underlying SARD, particularly for laboratory investigations. Therefore, our broad definition captured an additional set of encounters on the basis of physician specialty, specific SARD diagnosis, drug class, and/or fee item. These additional encounters are listed in Appendix A. The claims captured under the narrow definition were also included under the broad. For hospitalizations, the broad definition included any separation with a SARD code listed in *any* of the twenty-five diagnostic positions. The attributable drugs were the same as under the narrow.

2.8 Statistical Analysis

The number of resources consumed, and cost of each one, was summed annually and cumulatively for the twelve-year period. Crude mean annual per-patient-year (PY) utilization and cost estimates were obtained by dividing these totals by the number of patient-years (PY) contributed each year. For some components, annual mean per-PY estimates were also calculated amongst only users (for example, the mean number of prescriptions dispensed to each

patient calculated only amongst those patients *actually* dispensed a prescription in that year). The annual mean LOS per admission and per-patient was calculated for cases that had an inpatient hospitalization.

Analyses were performed using SAS Software, Version 9.2 of the SAS System for Unix (443). All costs are reported in 2007 Canadian dollars, and were adjusted for inflation using the BC Health Care component of the Canadian Consumer Price Index (CPI) (293).

In this chapter we have described our population-based data source in detail and how we identified the SARDs cases. We detailed the types of health care encounters we included in our cost estimates, the methods employed in calculating these costs, and our rationale for selecting them. These estimates and other important findings from our analysis will be presented in the next chapter.

2.9 Tables

Table 2.1 Comparison of Incidence, Prevalence, Sensitivity, and Specificity Calculated from Different Administrative Sources

		Incidence (per-100,000) (95% CI) Prevalence (per-100,000) (95% CI) Sensitivity (95% CI) Specificity (95% CI)			
Study	**Disease**	**Hospital Separations**	**Rheumatologist Billings**	**All Physician Billings**	**All Sources**
Bernatsky 2007 (381)	SLE	2.8 (2.6-3.0) 31.9 42 (41-43)% – 68 (67-68)% 99.99 (99.98-99.99) % – 99.99 (99.99-100)%	- - - -	3.0 (2.6-3.4) 32.8 45 (43-47)% – 56 (56-57)% 99.99 (99.98-99.99)% – 99.99 (99.99-100)%	- 51.0 - -
Bernatsky 2009 (349)	SSc	- - - -	- - 20% minimum -	- - 73% maximum -	- - ---
Bernatsky 2009 (362)	PM/DM	- 10.5 - -	- 8.1 - -	- 10.2 - -	- 15.6 - -
Bernatsky 2011 (5)	all SARDs -CTD	- - - -	- - 40-70% -	- - 50-90% -	- - - -

Table 2.2 Summary of Included Encounters and Costing Procedures

COMPONENT		SERVICE/SEPARATION DATES ELIGIBLE FOR INCLUSION	UNIT COST CALCULATION
Outpatient		[start date] to [end date +30 days][a]	= [Amount Paid] datafield
Prescription		[start date] to [end date +30 days][a]	= [Drug Cost Paid datafield] + [Professional Fee Paid datafield]
Hospital	Inpatient: fiscal years 1995/1996-2000/2001	[start date -30 days][b] to [end date +30 days][c]	=[cRIW01 x CPWC]
	Inpatient: fiscal years 2001/2002 – December 31, 2006	[start date -30 days][b] to [end date +30 days][c]	=[cRIW05 x CPWC]
	Inpatient: January 1, 2007 – December 31, 2007	[start date -30 days][b] to [end date +30 days][c]	=[p_RIW07 x CPWC]
	Day Case: fiscal years 1995/1996-2000/2001	[start date -30 days][b] to [end date +30 days][c]	=[DPG-RIW x CPWC]
	Day Case: fiscal years 2001/2002-2007/2008	[start date -30 days][b] to [end date +30 days][c]	unit costing n/a; total annual costs= [total costs for 2000] x [annual change in inflation from 2000]
	ALC	[start date -30 days][b] to [end date +30 days][c]	=[LOS x $225]

[a]not including encounters during 2008
[b]where separation occurred on or after the start date
[c]where admission occurred on or before the end date

Table 2.3 Provincial (BC) CPWC Values

Fiscal Year	Extrapolated CPWC	Fiscal Year	Actual CPWC, Obtained from CIHI
1995/96	$2,737.50	2004/05	$4,325.00
1996/97	$2,925.20	2005/06	$4,767.00
1997/98	$3,112.90	2006/07	$4,802.00
1998/99	$3,300.60	2007/08	$4,939.00
1999/00	$3,488.30		
2000/01	$3,676.00		
2001/02	$3,863.70		
2002/04	$4,051.40		
2003/04	$4,239.10		

Table 2.4 Summary of Encounters Considered for Each Utilization and Cost Analysis

COMPONENT	ANALYSIS		
	Gross	**Attribution - Narrow**	**Attribution - Broad**
Outpatient	-all eligible claims	- all eligible claims from a non-rheumatologist practitioner that contained any SARD diagnostic code (as listed in Appendix A) - all eligible claims from a rheumatologist with any diagnostic code	- all eligible claims from a non-rheumatologist practitioner containing any SARD diagnostic code (as listed in Appendix A) - all eligible claims from a rheumatologist with any diagnostic code; -all eligible claims from Appendix A
Hospital	-all eligible separations	-all eligible separations with a primary discharge diagnosis for SARDs	-all separations with a primary or secondary discharge diagnosis for SARDs
Prescriptions	-all eligible prescriptions	-all eligible prescriptions as listed in Appendix A	-all eligible prescriptions as listed in Appendix A

3 Results

3.1 Descriptive Statistics

Over twelve years, 18,741 SARDs cases were identified, contributing 82,140 patient-years (PY) of total follow-up. 16,773 (89%) of SARDs cases had a SARDs-CTD diagnosis and 1,680 had a SARDs-VD diagnosis. The number of cases and patient-years observed each year are listed in Table 3.1. The SARDs-VD group had a lower proportion of females than the SARDs-CTD group (65% vs. 76%) and the mean age of SARDs-VD cases at the start date was higher (70 years) when compared to SARDs-CTD (52 years) (Table 3.2). These differences are consistent with published reports (described in Chapter 1) of SARDs-VD having an older peak age of incidence, and less of a female predominance, than SARDs-CTD.

3.2 Gross Overall Direct Medical Costs

Over twelve years, the entire SARDs cohort incurred over $571,216,780 in direct medical costs. The cumulative costs for the SARDs-CTD and SARDs-VD groups were $469,854,838 and $75,697,339, respectively. With regards to all SARDs cases, the relative contributions of each cost category were $154,580,563 (27%) from outpatient services, $291,664,951 (51%) from hospitalizations, and $124,971,267 (22%) from prescription medications (Figure 3.1a). As illustrated in Figure 3.2 the hospital proportion decreased over the study period (from 63% of costs in 1996 to 46% in 2007) while that for prescriptions increased (from 13% to 27%) and actually equalled the outpatient in the final year of study. For SARDs-VD, the overall proportion of costs from hospital was higher (67%) and that from prescriptions lower (13%) than for SARDs-CTD cases (Figures 3.1b & 3.1c).

SARDs case incurred, on-average, annual per-patient-year (PY) overall direct medical costs of $6,954 per-PY. The mean annual per-PY costs for SARDs-CTD cases were $6,230/PY, while SARDs-VD cases incurred mean annual per-PY costs that were more than double SARDs-CTD at $15,892/PY (Table 3.3). Annual overall mean per-PY costs for all-SARDs decreased by 32% over twelve years, and by 27% for SARDs-CTD (Figures 3.3-3.4). The decrease was even greater (47%) amongst SARDs-VD cases (Figure 3.3c).

3.3 Gross Outpatient Consumption

Over twelve-years, the SARDs cohort had a total of 2,445,748 outpatient claims (Appendix B). On average all-SARDs, SARDs-CTD, and SARDs-VD cases had 30, 28, and 48 outpatient encounters per PY, respectively. For SARDs-CTD cases these diagnostic tests and physician visits accounted for 29% of overall mean annual per-PY costs but for SARDs-VD this was just 20%. Still, at $3,146/PY the mean annual per-PY costs for SARDs-VD were almost twice as high as those for SARDs-CTD ($1,783/PY). Annual mean per-PY costs decreased over the period, by 26%, 25%, and 32% for SARDs, SARDs-CTD, and SARDs-VD, respectively (Figure 3.5). These cost decreases were accompanied by similar decreases (19%, 18%, 21% for the three groups, respectively) in mean per-PY outpatient encounters (Appendix B).

Table 3.4 lists the five most-frequently billed medical specialties that combined for 85% of all encounters. Tests and investigations were a major contributor to outpatient utilization, as 56% of all outpatient encounters by SARDs cases were billings from the specialist physicians associated with these services (Laboratory Medicine, Medical Microbiology, and Radiology). The most frequently visited practitioners were primary care physicians and internists, whose claims combined for another 29% of outpatient encounters. The percents varied slightly, but these practitioners were visited with the same general frequency by each diagnostic group.

3.4 Gross Hospital Consumption

SARDs cases had 48,055 hospital admissions over the twelve years. Nearly two-thirds (64%) were inpatient stays, while 35% were day-case (admissions for surgeries or procedures that did not involve an overnight stay) and just 0.6% were extended or alternate level of care (ALC). Amongst all cases the annual mean number of admissions averaged 0.59 per-PY. Inpatient admissions averaged 0.37 per-PY amongst all cases, but over the study period only half the cohort had such an admission. These admitted cases averaged 1.72 (STD=1.31, range=1-24) annual admissions with a mean LOS of 10.32 days for each (Table 3.5). As compared to SARDs-CTD, SARDs-VD cases consumed more hospital services: more were hospitalized (78% vs. 47%) at any point, and those hospitalized SARDs-VD cases had more annual admissions, on average (1.90 (STD=1.47, range=1-22) vs. 1.68 (STD=1.27, range=1-24) per-PY). These admissions also tended to be longer (12.0 days vs. 9.9 days for SARDs-VD and

SARDs-CTD, respectively), on-average. The annual and twelve-year sums for each type of admission, and all admissions combined, are available in Appendix B.

Averaging $3,551/PY for all-SARDs, hospital care contributed the most toward overall mean per-PY direct medical costs. Not surprisingly inpatient care was disproportionately costly, accounting for 64% of all-SARDs admissions but nearly all (94%) of their total hospital costs. Though SARDs-VD cases averaged more than *twice* as many annual admissions per-PY (1.31/PY) as SARDs-CTD (0.53/PY), their average annual per-PY costs were more than *triple*, at $10,700/PY vs. $2,968/PY.

Mean per-PY hospital costs amongst all SARDs cases decreased by half over twelve years (Figure 2.6). This was accompanied by not only a similar decrease (46%) the mean *number* of admissions per-PY (Appendix B), but also a longitudinal decrease in the *intensity* of hospital use. The annual proportion of cases admitted to hospital decreased from 32% in 1996 to 15% in 2007, while amongst these admitted cases the mean number of annual admissions decreased from 1.87 (STD=1.53, range=1-22) in 1996 to 1.66 (STD=1.29, range=1-15) in 2007. The mean length of these admissions also decreased – by 7% - from 10.3 to 9.6 days (Figure 3.7, Table 3.5).

3.5 Gross Prescription Medication Consumption

Annual mean per-PY medication costs over twelve years were $1,521/PY, $1,479/PY, and $2,046/PY for SARDs, SARDs-CTD, and SARDs-VD, respectively. However Figure 3.9 illustrates our most dramatic finding: while mean per-PY outpatient and hospital costs *decreased* over the study period, mean per-PY prescription medication costs *increased* in this time. For all-SARDs this was a 50% increase, from $1,117/PY in 1996 to $1,670/PY in 2007 (Appendix B), while the increase was 49% for SARDs-CTD and 59% for SARDs-VD. With 86-90% of the cohort dispensed a prescription each year, the annual mean per-PY costs just amongst users were very similar to the crude annual estimates, and increased almost identically (by 54%) over twelve years (Appendix B).

Similarly, while mean per-PY utilization of outpatient and hospital resources decreased over the twelve years, per-PY prescription utilization *increased*, and quite substantially. SARDs cases were dispensed an average of 30 prescriptions per-PY overall, and (as shown in Figure 3.10 and Appendix B) annual per-PY consumption increased

by 49%, nearly as much as per-PY costs did. While SARDs-VD cases had a mean per-PY medication cost increase (59%) that was similar to SARDs-CTD cases (49%), their twelve-year increase in per-PY medication consumption (96%) was much greater than SARDs-CTD (44%), and overall SARDs-VD cases averaged 25 more prescriptions per-PY than SARDs-CTD (53/PY vs. 28/PY). Consistent with what we observed for prescription costs, the annual mean number of prescriptions dispensed per-PY *amongst users* overall - 29 per-PY for all-SARDs - almost matched the crude estimate, as did the twelve-year increase in mean annual per-PY prescriptions (55%) (Appendix B).

3.5.1 Costs and Consumption by Drug and Drug Class

Spending and consumption were examined for each drug (by active generic ingredient) and drug class (according to Anatomical Therapeutic Chemical (ATC) Classification, Second Level). The most common agents and categories within each ATC-2 class are available in Appendix A. Tables 3.6 and 3.8 and Figures 3.11-3.12 illustrate the most dispensed drug classes and medications overall, while the annual breakdowns are available in Appendix B. Even amongst all prescriptions dispensed to the cohort, the heavy burden of SARDs is clear, with many of these therapies used to treat SARDs directly, or to manage the adverse effects of SARDs treatments and comorbidities that frequently arise in these cases. With corticosteroids a mainstay therapy for all SARDs, it was fitting this class made the fifth-largest contribution to cumulative prescriptions and one such GC, prednisone, was almost always the most-frequently prescribed drug each year. The anti-malarial hydroxychloroquine, another common SARDs therapy, was also heavily-prescribed. Considering that many SARDs medications can cause gastritis and osteoporosis, it was also fitting that the proton-pump inhibitors (PPIs) omeprazole and rabeprazole (part of the Antacid class), and, especially for SARDs-VD cases, the bisphosphonates etidronate and alendronate, were prescribed frequently to protect against these adverse effects.

Those drug classes prescribed most frequently generally accounted for the greatest costs as well (Table 3.7, Figure 3.13), though immunosuppressants were disproportionatly costly, making up 7.8% of drug costs but only 1.7% of all prescriptions. Concerning specific drugs, omeprazole and hydroxychloroquine were among both the most dispensed (Table 3.8, Figure 3.12) and most costly (Table 3.9, Figure 3.14) medications overall.

Emerging Vasodilators

In Chapter 1 we described how interest is growing in the use of several vasodilators – that have other indications - to address digital ulcers, Raynaud's phenomenon, and pulmonary arterial hypertension (PAH) in SSc. One is bosentan, approved in Canada in 2001 (89) to treat PAH (254), and after its release it quickly became one of the costliest drugs prescribed to this SARDs cohort (Table 3.9). In 2003 there were only 89 prescriptions filled for bosentan (and none to SARDs-VD cases), but with each costing $4,268 2007 CDN on-average, total costs for bostenan exceeded $379,000 that year. As shown in Appendix B this trend continued with bosentan actually being the most-costly drug in 2007, despite only 250 prescriptions for it. Sildenafil and epoprostenol, two other emerging and expensive vasodilators, did not influence drug costs in the same way. There were relatively few sildenafil prescriptions overall – just 547 in 2007– and its mean unit cost during our study ($153 2007 CDN) was high but nothing compared to that of bosentan. Epoprosentol prescriptions were much more expensive than sildenafil (with each averaging $1,823 2007 CDN) but this drug was rarely dispensed.

Mycophenolate

Mycophenolate, a more expensive but less-toxic immunosuppressant when compared to cyclophosphamide or azathioprine (62), is officially approved for preventing the rejection of transplanted organs (63), and not the management of SARDs. Still it is available for this purpose under special access, and was one of only two new therapies to emerge for SARDs over our study period. With a mean unit cost of $535 2007 Canadian dollars, it heavily influenced the annual drug costs of our cohort. In 2002 it was the eighth-costliest drug prescribed to SARDs cases - even with only 313 prescriptions - and in subsequent years continued to move up the cost rankings (Appendix B). This immense cost contribution continued despite infrequent dispensing: in 2007 only 0.32% of all dispensed prescriptions were for mycophenolate. For context, while the average unit price amongst all drugs over twelve years was $116 2007 CDN, the average unit price of mycophenolate was almost five-times greater this, and about forty-five times greater than the cost of the average prednisone prescription ($12 2007 CDN), which was the most-frequently prescribed drug overall.

Biologic Therapies

We also examined the costs contributed by the newer biologic therapies we detailed in Chapter 1: ritiximab (approved in 2000 (89), this was the second SARDs therapy that emerged during our study period) and etanercept and infliximab (both approved in 2001 (89)). These drugs were prescribed to 88 discrete cases over the twelve years: etanercept to 45 cases, infliximab to 26, and rituximab to 24. Table 3.10 shows these cases had a range of individual SARD diagnoses. While infliximab may actually induce SLE (17), amongst recipient cases with an SLE diagnosis, only one received this drug prior to the first record of that diagnosis (for this case, the first infliximab prescription was filled 16 months prior).

These three very expensive agents (costing approximately $10,000-$20,000 per-patient annually (32,225)) were not prescribed frequently enough to be amongst the top ten costliest drugs in any year for the cohort at large. Still their influence on costs rose in the last three years of our study, and with the exception of rituximab in 2006 total annual costs for these drugs in the final three years exceeded their proportion of total prescriptions by at least ten-times (Table 3.11). Together the three drugs accounted for 1.74% of total costs in 2005 but more than 3% in 2007, when etanercept also became the tenth-costliest drug prescribed to SARDs-CTD cases (Appendix B).

Lipid-Modifying Agents/Atorvastatin

Though lipid-modifying agents - including statins - are not used in the direct treatment of SARDs, they are often dispensed to SARDs cases since they, especially those with SLE, have an elevated risk of cardiovascular disease due to underlying inflammation and exposure to GC (28). As such we were not surprised the volume of prescriptions for this class grew five-fold over the period. Consumption rose for one statin in particular, atorvastatin, which became the twelfth-most prescribed drug in 2007. With a higher-than-average unit price - at $128 2007 CDN, it was almost twice that of hydroxychloroquine ($66 2007 CDN) – and mean per-PY prescriptions rising for it, atorvastatin was another emerging cost contributor and amongst all SARDs cases was actually the third-costliest drug overall (Table 3.9).

3.5.2 Major Contributors Toward Twelve-Year Per-Patient-Year Consumption and Cost Increases

To gain insight into the reasons for the tremendous growth in mean per-PY prescription quantities and costs, we examined which drugs and drug classes contributed most to it. As outlined by the Canadian Institute for Health Information (CIHI) (444) we did so by dividing, for each drug and class, the mean difference in its per-PY consumption and costs from 1996 to 2007, by the mean net increase for all prescriptions. This was the number of additional prescriptions dispensed to, and costs incurred by, the average SARD case in 2007, as compared to 1996. For costs the total mean net increase was $553/PY (from $1117/PY in 1996 to $1670/PY in 2007). Table 3.12a and Figure 3.14a list the five most influential drug classes, with the top-two - immunosuppressants and lipid-modifying agents - combining for one-third ($180) of the entire mean per-PY cost increase.

Looking at specific drugs, the four greatest contributors to the mean per-PY cost increase (Table 3.12b, Figure 3.14b) – bosentan, mycophenolate, atorvastatin, and rabeprazole – were also the four mostly-costly drugs in 2007 (Appendix B), though none were prescribed to the cohort (or even approved in Canada (89)) in 1996. SARDs likely influenced the contribution from these drugs, and from gabapentin: although classified as an anti-epileptic agent, it is also used to relieve neuropathic pain (445) and pain in fibromyalgia, a comorbidity of SLE (28). It must be emphasized that while bosentan and mycophenolate were the greatest contributors, on-average, few cases were actually prescribed them, so for most SARDs cases they would not have been responsible for the increase in drug costs. Still this is another indication of their small but growing influence on overall healthcare costs in SARDs.

Over twelve years, the mean number of prescriptions dispensed per-PY increased by 11 per-PY (from 23/PY in 1996 to 34/PY in 2007). Of interest two of the five classes that contributed most to the increase in annual per-PY prescriptions – lipid-modifying agents and anti-epileptics – and two of the five drugs – rabeprazole and atorvastatin - were also major contributors to the mean increase in per-PY costs (Table 3.13, Figure 3.15). About 6% of SLE cases develop hypothyroidism (28) which may explain levothyroxine being the third-highest contributing drug, on-average. As well, with ramipril (the second-highest contributing drug) having multiple applications in SARDs - from hypertension to renal disease - and bisphosphonates (the fifth-highest contributing class) frequently prescribed as prophylaxis against GC-induced osteoporosis, much of the twelve-year increase in mean per-PY drug consumption and costs can be attributed to SARDs.

3.6 Net Overall Direct Medical Costs

To determine the net healthcare burden of SARDs, or the additional direct medical costs imparted by these disorders, we separately tabulated the costs of just those healthcare services attributable to SARDs. As described in Chapter 2 we used both a narrow and broad definition of SARDs-related consumption. The narrow definition included all SARDs-coded and/or rheumatology-associated outpatient encounters and all hospital discharges where any SARD was the primary diagnosis. We also included these services under the broad definition while adding more SARDs-related outpatient services (Appendix A) and any hospital discharges with a SARD coded in any diagnostic position. A single list of SARDs-related medications was compiled (Appendix A) and employed for both definitions.

3.6.1 Net Overall Costs - Narrow Definition

Approximately 29% of the direct medical costs incurred by the cohort were attributable to SARDs under our narrow definition. These totalled approximately $165,165,682, with $10,316,313 (6%) from outpatient, $29,969,223 (18%) from hospital, and $124,880,146 (76%) from prescriptions (Figure 3.17). The total attributable costs for each year are provided in Appendix B. As illustrated in Figure 3.18, the proportion of attributable costs increased over time. Less of the cumulative costs incurred by SARDs-VD cases were attributable (23%) as compared to SARDs-CTD (30%) though by 2007 this gap had narrowed (Figures 3.18b &c).

Hospitalizations were the largest component of costs in the gross analysis but prescription costs were by-far the largest here for all SARDs cases. This is likely because of the large proportion (99%) of gross dispensed prescriptions that were attributable to SARDs. SARDs-VD was an exception with the hospital proportion exceeding the prescription in most years up to 2004. The hospital proportion decreased substantially over twelve years (Figure 3.19), making up, for SARDs, SARDs-CTD, and SARDs-VD, respectively, 38%, 34%, and 55% of costs in 1996 but only 11%, 8%, and 27% of costs in 2007. The contribution from outpatient services – 6% for all SARDs and 7% for SARDs-CTD, but only 3% for SARDs-VD, changed little over the study period.

Per-capita, the annual mean per-PY overall direct medical costs that we attributed to SARDs averaged $2,011 per-PY over twelve years. These annual mean per-PY costs were almost twice as high ($3,646/PY) for SARDs-VD cases than SARDs-CTD ($1,868/PY). While gross overall annual per-PY costs decreased by 32%, as illustrated in Table 3.15 and Figure 3.20, net annual per-PY costs remained stable for all groups over the study period.

3.6.2 Net Overall Costs - Broad Definition

Under our broad definition we attributed nearly half ($263,040,026, or 46%) of our cohort's gross direct medical costs to SARDs. This cumulative total was 59% greater than the attributable total under the narrow definition. From these costs $23,764,332 (9%) were from outpatient, $114,395,548 (43%) from hospital and $124,880,146 (48%) were from prescriptions (Figure 3.21). The total attributable costs for each year are provided in Appendix B. Unlike what we observed for the narrow, SARDs-VD cases had almost the same percent of attributable costs (47%) as SARDs-CTD (46%). For all groups these annual percents changed little over the study period (Figure 3.18).

The proportion of costs from hospital for all-SARDs (43%) was about two-and-a-half times greater here than under the narrow definition (18%). Still the proportion from hospital decreased over time - making up 68% of costs in 1996 for all-SARDs but just 27% in 2007 – while prescription costs *increased* almost identically, from 27% to 62% (Figure 3.22). Outpatient costs were slightly more influential using this definition (making up 9% of costs overall) when compared to the narrow (6%), and their annual contribution increased slightly, from 6% of costs to 10%, over twelve years.

With this expanded definition the net, or incremental, annual mean per-PY overall direct medical costs of SARDs averaged $3,202 per-PY, about one-and-a-half times (and $1,191) higher than under the narrow. Unlike with the narrow, these annual mean per-PY costs decreased over twelve years by 36% (Figure 3.21), slightly more than by what gross per-PY costs decreased (32%). But as with the narrow, the incremental mean per-PY costs for SARDs-VD ($7,390/PY) were more than double those for SARDs-CTD ($2,866/PY) (Table 3.16).

3.7 Net Prescription Medication Consumption

The impact of SARDs on prescription use was important: our attribution analysis captured nearly every prescription (over 99% for all-SARDs and SARDs-CTD, and 98% for SARDs-VD) dispensed to the cohort (Appendix B). This meant most prescription costs (at least 99.9% in all groups) were captured too (Appendix B). On an annual basis this percentage did decrease slightly: in 1996, only 0.03% of all prescriptions were *not* attributable to SARDs, but this increased to 1.00% of the prescriptions in 2007. The same prescriptions were included under the broad and narrow definitions.

This heavy SARDs-related consumption was widespread amongst the cohort, with an attributable prescription dispensed to every case who received any prescription during the period. The overall net mean per-PY estimates barely differed from the gross, with attributable annual mean per-PY prescription costs averaging $1,520/PY, $1,478/PY, and $2,044/PY for SARDs, SARDs-CTD, and SARDs-VD, respectively (Appendix B). Similar too were the twelve-year mean per-PY cost increases. The average SARDs case was still dispensed 30 prescriptions per-PY, with the same twelve-year increase (from 23 per-PY in 1996 to 34 per-PY in 2007) as under the gross (Appendix B).

3.8 Net Outpatient and Hospital Consumption - Narrow Definition

3.8.1 Net Outpatient Consumption

Outpatient services had little influence on SARDs healthcare consumption under this definition, with only 7% of all outpatient encounters considered attributable. While the annual percent of attributable encounters changed little amongst SARDs-CTD cases, it increased slightly over twelve years (from 2% in 1996 to 4% in 2007) for SARDs-VD cases (Appendix B). Given these low percentages it is not surprising SARDs, SARDs-CTD, and SARDs-VD cases averaged only 2.0, 1.9, and 1.7 attributable outpatient encounters per-PY. Attributable outpatient costs (Appendix B) totalled $10,316,313 and made up 6% of all incremental costs. The annual mean per-PY costs were not tremendous ($126/PY for all-SARDs) and changed little over the period (Appendix B).

3.8.2 Net Hospital Consumption

Just seven percent of the cohort's hospitalizations were attributable to SARDs under this definition, a proportion which decreased from 12% of 1996 hospitalizations to just 3% of those in 2007. There was a decrease in the annual attributable-proportion of hospital costs for SARDs-CTD cases (from 14% to 6%) but a slight increase (from 12% to 14%) for SARDs-VD. SARDs cases had an average of 0.04 attributable admissions per-PY, which decreased by 84% from 0.10-0.02/PY (Appendix B). Over twelve years the average annual per-PY hospital costs ($365/PY for SARDs and $266/PY for SARDs-CTD) decreased by 70% and 76%, respectively - more than gross per-PY costs did. For SARDs-VD cases these costs were considerably higher ($1,477/PY) and decreased less (by 51%) over twelve years (Appendix B).

3.9 Net Outpatient and Hospital Consumption – Broad Definition

3.9.1 Net Outpatient Consumption

With our expanded definition almost all SARDs cases (98%) had an attributable encounter, including 98% of SARDs-CTD and 93% of SARDs-VD cases (as compared to 94% of SARDs-CTD cases and just 59% of SARDs-VD cases under the narrow). More than twice as many (15% vs. 7%) encounters for all-SARDs were attributable here, and this increased slightly over twelve years from 11% of encounters in 1996 to 15% in 2007. The annual mean number of encounters per-PY was still small, but under this definition doubled from the narrow to 4.4 per-PY (Appendix B). The total attributable outpatient costs ($23,764,332) exceeded those under the narrow by 130% and accounted for 15% of gross outpatient costs. Annual mean per-PY costs ($289/PY for all-SARDs, $284/PY for SARDs-CTD, and $315/PY for SARDs-VD) were also more than double those under the narrow. In contrast to the twelve-year decreases we observed in mean per-PY gross outpatient costs, these costs actually increased over time, by 12% for all-SARDs, 6% for SARDs-CTD, and 93% for SARDs-VD (Appendix B).

3.9.2 Net Hospital Consumption

When all twenty-five discharge positions were considered, 25% of the cohort's admissions were attributable to SARDs - more than three-times that under the narrow – and 39% of their gross hospital costs – more than twice that under the narrow (Appendix B). These attributable-percentages did decrease over time, admissions from 42% of the gross in 1996 to 15% in 2007, and costs from 51% of the gross to just 26%. With the percent of attributable costs

exceeding that for attributable admissions in each year and for each diagnostic group, SARDs-related hospitalizations for our cohort may be especially costly.

SARDs cases averaged about four-times more attributable admissions (0.15/PY) annually under this definition than under the narrow (0.04/PY). Still, mean annual per-PY admissions decreased over twelve years, by 81% (from 0.37/PY-0.07/PY). SARDs-VD cases averaged more attributable admissions (0.44/PY) than SARDs-CTD (0.13/PY) but had a similar twelve-year decrease (78%) in these admissions as SARDs-CTD (81%). The average annual per-PY costs ($1,393/PY, $1,104/PY and $5,031/PY for SARDs, SARDs-CTD, and SARDs-VD, respectively) were also about four-times greater here than under the narrow, but decreased by about 74% over twelve years.

In this chapter we have presented the most relevant findings of our analysis. These will be discussed in greater depth in the next chapter, which will conclude with a final summary of our current work and the follow-up analyses we plan to undertake.

3.10 Tables

Table 3.1 Number of Cases and Patient-Years Contributed

	SARDS		SARDs-CTD		SARDs-VD	
Year	**# Cases**	**Patient-Years**	**# Cases**	**Patient- Years**	**# Cases**	**Patient- Years**
1996	3,305	2,925.58	2,967	2,658.42	287	221.58
1997	3,649	3,237.08	3,287	2,942.67	304	242.83
1998	4,224	3,612.50	3,840	3,305.08	315	249.17
1999	4,893	4,217.17	4,471	3,892.67	342	255.08
2000	5,425	4,833.50	4,988	4,480.58	342	271.00
2001	6,054	5,387.67	5,595	5,015.58	351	277.00
2002	6,779	6,052.75	6,302	5,654.42	350	291.83
2003	8,371	7,288.08	7,734	6,787.67	490	368.00
2004	9,856	8,750.50	9,121	8,144.75	572	459.00
2005	11,463	10,373.00	10,608	9,629.00	674	579.17
2006	13,235	12,045.33	12,192	11,156.33	848	708.08
2007	14,372	13,416.83	13,245	12,385.25	928	840.42
Overall	**18,741**	**82,139.99**	**16,773**	**76,052.42**	**1,680**	**4,763.17**

Table 3.2 Cohort Characteristics

	SARDs	SARDs-CTD	SARDs-VD
Total Cases	18,741	16,773	1,680
# Female (%)	13,948 (74.43%)	12,682 (75.61%)	1085 (64.58%)
Mean Age at Index Date (years)	53.97	52.35	69.65
Maximum Age at Index Date (years)	101	101	99
Mean Length of Follow-Up (months)	51.83	53.65	33.18

Table 3.3 Crude Annual Overall Mean Per-Patient-Year Costs (2007 Canadian dollars)

Year	SARDs	SARDs-CTD	SARDs-VD
1996	$8,901.13	$7,699.89	$20,709.78
1997	$9,126.09	$7,913.16	$22,332.14
1998	$8,520.70	$7,511.71	$19,019.20
1999	$8,420.50	$7,263.20	$22,575.60
2000	$7,883.24	$6,813.42	$20,301.37
2001	$7,147.81	$6,254.67	$17,957.15
2002	$7,056.73	$6,402.34	$16,981.82
2003	$6,947.75	$6,208.18	$18,341.26
2004	$6,375.23	$5,883.99	$14,045.00
2005	$6,326.98	$5,790.73	$13,473.23
2006	$6,333.86	$5,704.59	$13,475.82
2007	$6,087.17	$5,603.42	$10,964.38
Overall	**$6,954.19**	**$6,230.17**	**$15,892.23**
%-Change	-31.61%	-27.23%	-47.06%

Table 3.4 Top Five Most-Frequent Outpatient Encounters, by Billing Specialty

	SARDs		SARDs-CTD		SARDs-VD	
Specialty	**Number of Claims**	**% of Total Claims**	**Number of Claims**	**% of Total Claims**	**Number of Claims**	**% of Total Claims**
Laboratory Medicine	2,861,612	47	2,453,581	46	318,743	53
General Practice	1,318,767	22	1,188,155	22	106,167	18
Internal Medicine	416,531	7	344,381	6	58,483	10
Medical Microbiology	387,257	6	342,602	6	31,791	5
Radiology	189,598	3	170,007	3	15,054	3
subtotal	**5,173,765**	**85**	**4,498,726**	**85**	**530,238**	**89**
Other Specialties	916,037	15	822,153	1	68,883	12
Total	**6,089,802**	**100**	**5,320,879**	**100**	**599,121**	**100**

-due to rounding, some percents may not sum to 100% exactly

Table 3.5 Annual Mean Length-of-Stay Per-Year and Per-Admission (amongst hospitalized cases) (days)

	Mean Annual Total LOS						Mean LOS per Admission					
	SARDs		SARDs-CTD		SARDs-VD		SARDs		SARDs-CTD		SARDs-VD	
Year	**Mean**	**STD**	**Mean**	**STD**	**Mean**	**STD**	**Mean**	**STD**	**Mean**	**STD**	**Mean**	**STD**
1996	19.32	29.10	18.19	27.69	24.52	34.45	10.33	15.88	9.95	15.07	11.86	19.36
1997	18.83	32.84	17.73	33.23	23.82	31.47	10.47	19.21	10.05	19.06	12.51	20.59
1998	17.87	26.95	16.85	26.44	22.21	26.53	10.13	17.32	9.78	16.58	11.27	18.06
1999	19.03	29.81	17.74	27.49	25.71	40.23	10.65	19.54	10.26	18.19	12.41	24.97
2000	19.94	32.96	18.62	31.27	24.92	38.62	11.37	21.19	11.13	20.50	11.92	23.89
2001	19.47	30.00	17.68	27.65	27.21	36.35	11.31	20.01	10.50	18.30	14.05	23.85
2002	18.92	30.28	17.57	27.29	26.01	42.85	11.05	18.44	10.40	15.81	13.73	27.65
2003	17.39	26.51	16.38	26.27	21.47	26.59	10.18	16.55	9.78	16.26	11.51	16.89
2004	15.85	25.43	15.57	25.25	18.43	28.10	9.64	16.04	9.49	15.77	11.27	18.73
2005	16.54	26.65	15.72	25.65	21.32	32.24	9.94	17.05	9.68	16.44	11.57	20.35
2006	17.07	30.60	16.08	28.40	20.74	35.64	10.14	18.54	9.75	16.91	11.86	23.75
2007	15.90	28.10	14.90	27.12	21.38	33.07	9.58	15.61	9.29	15.30	10.85	17.29
Overall	**17.72**	**28.99**	**16.66**	**27.67**	**22.74**	**33.80**	**10.32**	**17.88**	**9.93**	**16.94**	**11.97**	**21.31**
%-Change	-17.70%		-18.08%		-12.78%		-7.30%		-6.70%		-8.55%	

Table 3.6 Top-Ten Most Frequently-Prescribed Drug Classes

	SARDs		SARDs-CTD		SARDs-VD	
	Class	**Proportion (%)**	**Class**	**Proportion (%)**	**Class**	**Proportion (%)**
12-year Cumulative	Analgesics	8	Analgesics	9	Systemic Corticosteroids	7
	Psycholeptics	7	Psycholeptics	8	Analgesics	7
	Psychoanaleptics	6	Psychoanaleptics	7	Antacids	6
	Antacids	6	Antacids	6	Psycholeptics	6
	Systemic Corticosteroids	4	Systemic Antibiotics	4	Diuretics	6
	Systemic Antibiotics	4	RAAS Agents	4	RAAS Agents	5
	RAAS Agents	4	Systemic Corticosteroids	4	Psychoanaleptics	5
	Diuretics	4	Diuretics	4	Systemic Antibiotics	4
	Anti-inflammatory Agents	3	Anti-inflammatory Agents	4	Bisphosphonates	4
	Anti-protozoals	3	Anti-protozoals	4	Drugs for Obstructive Airway Diseases	3
	subtotal	**49%**	**subtotal**	**54%**	**subtotal**	**53%**
1996	Analgesics	10	Analgesics	10	Systemic Corticosteroids	10
	Psycholeptics	9	Psycholeptics	9	Analgesics	8
	Systemic Corticosteroids	6	Systemic Antibiotics	6	Antacids	6
	Systemic Antibiotics	6	Antacids	6	Systemic Antibiotics	6
	Antacids	6	Systemic Corticosteroids	6	Psycholeptics	6
	Psychoanaleptics	5	Psychoanaleptics	5	Diuretics	5
	Anti-inflammatory Agents	4	Anti-inflammatory Agents	4	Cardiac therapy	5
	Diuretics	4	Diuretics	4	Drugs for Obstructive Airway Diseases	4
	Drugs for Obstructive Airway Diseases	4	Drugs for Obstructive Airway Diseases	3	RAAS agents	3
	Calcium Channel Blockers	3	Anti-protozoals	3	Diabetes Therapies	3
	subtotal	**57%**	**subtotal**	**56%**	**subtotal**	**56%**
2007	Analgesics	8	Analgesics	9	Antacids	6
	Psychoanaleptics	8	Psychoanaleptics	8	Systemic Corticosteroids	6

	SARDs		SARDs-CTD		SARDs-VD	
	Class	**Proportion (%)**	**Class**	**Proportion (%)**	**Class**	**Proportion (%)**
2007	Psycholeptics	8	Psycholeptics	7	Analgesics	6
	Antacids	6	Antacids	6	Psycholeptics	6
	RAAS Agents	5	RAAS Agents	5	Diuretics	5
	Diuretics	4	Anti-epileptics	4	RAAS Agents	5
	Anti-epileptics	4	Diuretics	4	Psychoanaleptics	5
	Systemic Antibiotics	4	Systemic Antibiotics	4	Bisphosphonates	4
	Systemic Corticosteroids	4	Anti-protozoals	3	Lipid-Modifying Agents	4
	Lipid-Modifying Agents	3	Systemic Corticosteroids	3	Beta-Blockers	3
	subtotal	**54%**	**subtotal**	**53%**	**subtotal**	**50%**

Table 3.7 Top-Ten Most-Costly Drug Classes (2007 Canadian dollars)

	SARDs		SARDs-CTD		SARDs-VD	
	Class	**Proportion (%)**	**Class**	**Proportion (%)**	**Class**	**Proportion (%)**
12-year cumulative	Antacids	10	Antacids	10	Antacids	10
	Immunosuppressants	8	Immunosuppressants	8	Immunosuppressants	9
	Psychoanaleptics	7	Psychoanaleptics	7	RAAS Agents	8
	Analgesics	7	Analgesics	7	Drugs for Obstructive Airway Diseases	7
	RAAS Agents	6	RAAS Agents	6	Lipid-Modifying Agents	6
	Lipid-Modifying Agents	5	Lipid-Modifying Agents	5	Calcium Channel Blockers	5
	Calcium Channel Blockers	4	Calcium Channel Blockers	4	Bisphosphonates	5
	Anti-protozoals	4	Anti-protozoals	4	Psychoanaleptics	5
	Drugs for Obstructive Airway Diseases	3	Anti-inflammatory Agents	4	Analgesics	4
	Anti-inflammatory Agents	3	Psycholeptics	3	Systemic Antibiotics	3
	subtotal	**57%**	**subtotal**	**58%**	**subtotal**	**62%**
1996	Antacids	12	Antacids	12	Antacids	12
	Calcium Channel Blockers	7	Calcium Channel Blockers	7	Calcium Channel Blockers	8
	Psychoanaleptics	6	Psychoanaleptics	7	RAAS Agents	6
	Immunosuppressants	6	Analgesics	6	Drugs for Obstructive Airway Diseases	6
	Analgesics	5	Immunosuppressants	6	Systemic Antibiotics	6
	Drugs for Obstructive Airway Diseases	5	Anti-inflammatory Agents	5	Immunosuppressants	5
	RAAS agents	5	RAAS Agents	5	Cardiac therapy	4
	Anti-inflammatory Agents	5	Drugs for Obstructive Airway Diseases	5	Anti-neoplastic agents	4
	Systemic Antibiotics	4	Anti-protozoals	5	Psychoanaleptics	4
	Anti-protozoals	4	Systemic Antibiotics	4	Anti-thrombotic agents	3
	subtotal	**59%**	**subtotal**	**62%**	**subtotal**	**58%**
2007	Immunosuppressants	10	Immunosuppressants	10	Immunosuppressants	12%
	Antacids	9	Antacids	9	Antacids	9

	SARDs		SARDs-CTD		SARDs-VD	
	Class	**Proportion (%)**	**Class**	**Proportion (%)**	**Class**	**Proportion (%)**
2007	Analgesics	7	Analgesics	7	Drugs for Obstructive Airway Diseases	7
	Psychoanaleptics	7	Psychoanaleptics	7	Lipid-Modifying Agents	7
	Lipid-Modifying Agents	6	Lipid-Modifying Agents	5	RAAS Agents	7
	RAAS Agents	6	RAAS Agents	5	Analgesics	6
	Anti-epileptics	4	Anti-hypertensives	4	Bisphosphonates	5
	Anti-hypertensives	4	Anti-epileptics	4	Psychoanaleptics	5
	Calcium Channel Blockers	4	Calcium Channel Blockers	4	Calcium Channel Blockers	5
	Drugs for Obstructive Airway Diseases	3	Psycholeptics	3	Psycholeptics	3
	subtotal	**60%**	**subtotal**	**58%**	**subtotal**	**66%**

Table 3.8 Top-Ten Most Frequently-Prescribed Drugs Overall

SARDs		SARDs-CTD		SARDs-VD	
Drug	**Quantity**	**Drug**	**Quantity**	**Drug**	**Quantity**
Prednisone	99,302	Prednisone	77,415	Prednisone	18,122
Acetaminophen-codeine(30mg)	76,474	Acetaminophen-codeine(30mg)	71,594	Furosemide	7,274
Hydroxychloroquine	70,095	Hydroxychloroquine	68,963	Levothyroxine	7,066
Levothyroxine	62,641	Levothyroxine	54,393	Ramipril	5,870
Zopiclone	44,698	Zopiclone	40,081	Rabeprazole	5,398
Furosemide	41,408	Ramipril	36,064	Etidronate	4,817
Lorazepam	38,607	Lorazepam	34,780	Hydrochlorothiazide	4,075
Rabeprazole	35,485	Furosemide	33,440	Warfarin	3,688
Methadone	31,556	Methadone	31,292	Alendronate	3,684
Omeprazole	31,472	Rabeprazole	29,421	Zopiclone	3,662

Table 3.9 Top-Ten Most Costly Drugs Overall (2007 Canadian dollars)

SARDs		SARDs-CTD		SARDs-VD	
Drug	**Cost**	**Drug**	**Cost**	**Drug**	**Cost**
Omeprazole	$4,716,312.42	Hydroxychloroquine	$4,544,282.46	Atorvastatin	$ 346,784.88
Hydroxychloroquine	$4,607,507.46	Omeprazole	$ 4,281,761.58	Omeprazole	$ 340,208.82
Atorvastatin	$3,201,112.96	Bosentan	$3,155,985.26	Ramipril	$ 281,443.42
Bosentan	$3,155,985.26	Atorvastatin	$2,793,593.36	Rabeprazole	$ 245,091.38
Mycophenolate mofetil	$2,891,982.68	Mycophenolate mofetil	$2,570,013.53	Alendronate	$ 206,689.58
Ramipril	$2,632,366.36	Ramipril	$2,271,717.88	Cyclosporine	$ 206,282.44
Azathioprine	$2,235,403.73	Azathioprine	$ 2,050,439.81	Prednisone	$ 196,966.25
Rabeprazole	$2,134,508.76	Gabapentin	$1,867,080.09	Mycophenolate mofetil	$ 195,008.65
Gabapentin	$2,049,041.56	Rabeprazole	$1,846,544.82	Pantoprazole	$ 189,677.68
Morphine	$1,916,976.26	Morphine	$ 1,815,148.99	Etidronate	$ 187,880.67

Table 3.10 Distribution of Specific SARD Diagnoses Amongst Cases Dispensed a Biologic Therapy

Biologic	Total Cases	Specific SARD Diagnoses								
		SLE	SSc	SjD	PM	DM	PAN	Wegener's	GCA	TA
Etanercept	**45**	9	4	2	3	4	1	0	3	2
Infliximab	**26**	3	1	0	2	2	0	1	0	1
Rituximab	**24**	3	1	3	1	4	2	4	1	0

-sums of individual diagnoses do not equal total number of cases since some cases had multiple diagnoses and others simply one for SARDs-CTD or SARDs-VD

Table 3.11 Annual Total and Mean Per-Patient-Year Prescription Quantity and Costs for the Biologic Therapies, 2005-2007

Drug	Year	Rank for Total Prescription Quantity	Prescription Quantity	Proportion of Total Prescriptions	Mean Prescriptions per-PY	Rank for Total Prescription Cost	Total Cost (2007 CDN)	Proportion of Total Prescription Costs	Mean Cost per-Prescription (2007 CDN)	Mean Cost per-PY (2007 CDN)
Etanercept	**2005**	283	127	0.04%	0.01	20	$179,580.37	0.59%	$1414.02	$17.31
	2006	280	159	0.04%	0.01	13	$258,183.34	0.72%	$1623.79	$21.43
	2007	257	214	0.05%	0.02	11	$348,392.62	0.94%	$1628.00	$25.97
Infliximab	**2005**	488	22	0.007%	0.00	48	$91,754.47	0.32%	$ 4,170.66	$8.85
	2006	471	35	0.01%	0.00	36	$138,375.57	0.38%	$ 3953.59	$11.49
	2007	386	75	0.02%	0.01	17	$276,036.63	0.74%	$3680.49	$20.57
Rituximab	**2005**	552	11	0.003%	0.00	176	$15,289.29	0.05%	$1389.94	$1.47
	2006	455	39	0.01%	0.00	173	$19,414.30	0.05%	$497.80	$1.61
	2007	428	51	0.01%	0.00	97	$54,114.94	0.15%	$1061.08	$4.03
combined	**2005**	-	160	0.05%	0.01	-	$286,624.13	1.74%	-	$27.63
	2006	-	233	0.06%	0.01	-	$415,973.21	2.13%	-	$34.53
	2007	-	340	0.07%	0.03	-	$678,544.19	3.03%	-	$50.57

Table 3.12a Drug Classes Contributing Most to the Twelve-Year Increase in Mean Per-Patient-Year Prescription Costs

Class	Proportion (%)	Twelve-Year Net Increase in Per-PY Costs (2007 CDN)
Immunosuppressants	20	$109
Lipid-Modifying Agents	13	$71
Anti-hypertensives	11	$61
Analgesics	10	$55
Anti-epileptics	9	$50
subtotal	**63%**	**$346**
Total Net Difference	**100%**	**$553**

Table 3.12b Drugs Contributing Most to the Twelve-Year Increase in Mean Per-Patient-Year Prescription Costs

Generic Drug	Proportion (%)	Twelve-Year Net Increase in Per-PY Costs (2007 CDN)
Bosentan	11	$61.31
Mycophenolate mofetil	10	$57.68
Atorvastatin	10	$54.01
Rabeprazole	9	$49.92
Gabapentin	6	$33.26
subtotal	**46%**	**$256.18**
Total Net Difference	**100%**	**$553.05**

Table 3.13a Drug Classes Contributing Most to the Twelve-Year Increase in Mean Per-Patient-Year Dispensed Prescriptions

Class	Proportion (%)	Twelve-Year Net Increase in Per-PY Prescriptions
Psychoanaleptics	12	1.30
RAAS Agents	9	0.97
Lipid-Modifying Agents	8	0.92
Anti-epileptics	8	0.91
Bisphosphonates	6	0.64
subtotal	**43%**	**4.74**
Total Net Difference	**100%**	**11.21**

Table 3.13b Drugs Contributing Most to the Twelve-Year Increase in Mean Per-Patient-Year Dispensed Prescriptions

Generic Drug	Proportion (%)	Twelve-Year Net Increase in Per-PY Prescriptions
Rabeprazole	8	0.87
Ramipril	7	0.75
Levothyroxine	5	0.54
Atorvastatin	4	0.48
Methadone	4	0.45
subtotal	**28%**	**3.09**
Total Net Difference	**100%**	**11.21**

Table 3.14 Twelve Year Changes in Prescription Quantity and Cost, Selected Drug Classes

Drug Class	% of Total Prescriptions	%-Change in Mean Price	%-Change in Total Prescriptions	%-Change in Mean Prescriptions per-PY
Analgesics	8%	55% ($26.13-$40.55)	-16% (9.88-8.27)	25% (2.27-2.83)
Psycholeptics	7%	7% ($20.69-$22.16)	-19% (8.66-7.02)	21% (1.99-2.40)
Psychoanaleptics	6%	-29% ($61.94-$44.28)	44% (4.97-7.14)	114% (1.14-2.44)
Antacids	6%	-25% ($95.04-$71.28)	-3% (6.15-5.95)	44% (1.41-2.03)
Systemic Corticosteroids	4%	-11% ($13.47-$11.99)	-43% (6.26-3.56)	-15% (1.44-1.22)
Systemic Antibiotics	4%	6.41% ($34.65-$36.87)	-41% (6.23-3.69)	-12% (1.43-1.26)
RAAS Agents	4%	-35% ($90.80-$58.64)	75% (2.65-4.62)	160% (0.61-1.58)
Diuretics	4%	-30% ($12.28-$8.63)	3% (3.77-3.89)	53% (0.87-1.33)
Anti-inflammatory Agents	3%	-25% ($54.61-$41.19)	-36% (4.12-2.64)	-5% (0.95-0.90)
Anti-malarials	3%	-33% ($70.46-$47.51)	0.35% (2.88-2.89)	49% (0.66-0.99)
Calcium Channel Blockers	3%	-34% ($112.40-$73.90)	-21% (3.11-2.46)	18% (0.71-0.84)
Drugs for Obstructive Airway Diseases	3%	7% ($70.08-75.32)	-39% (3.52-2.15)	-9% (0.81-0.73)
Beta-Blockers	2%	-53% ($47.60-$22.40)	54% (1.79-2.75)	129% (0.94-0.41)
Bisphosphonates	2%	-35% ($81.43-$53.03)	156% (0.99-2.53)	281% (0.23-0.86)
Sex Hormones and Modulators	2%	-1.25% ($41.50-40.98)	-39% (2.57-1.57)	-9% (0.59-0.54)
Lipid-Modifying Agents	2%	-43% ($155.06-$88.22)	398% (0.62-3.10)	641% (0.14-1.06)
Diabetes Therapies	2%	-3% ($40.52-$39.31)	2% (1.83-1.88)	52% (0.42-0.64)
Immunosuppressants	2%	89% ($167.48-$315.86)	-2% (1.61-1.58)	47% (0.37-0.54)
Cardiac Therapies	2%`	-38% ($41.86-$26.12)	-61% (2.83-1.11)	-42% (0.65-0.38)
Anti-neoplastics	1%	9% ($68.17-$74.24)	6% (0.94-1.00)	58% (0.22-0.34)

Table 3.15 Crude Annual Mean Net Overall Per-Patient-Year Costs – Narrow Definition (2007 Canadian dollars)

Year	SARDS	SARDs-CTD	SARDs-VD
1996	$1,982.16	$1,834.61	$3,285.35
1997	$1,986.95	$1,797.41	$3,960.67
1998	$2,140.39	$1,962.26	$3,692.23
1999	$1,933.33	$1,748.99	$4,265.96
2000	$1,978.37	$1,783.07	$4,219.59
2001	$2,020.59	$1,876.23	$3,477.23
2002	$2,037.15	$1,931.06	$3,381.31
2003	$2,122.98	$1,923.07	$5,018.92
2004	$1,993.88	$1,906.44	$3,142.83
2005	$1,937.44	$1,814.87	$3,241.42
2006	$2,022.44	$1,879.85	$3,725.51
2007	$2,004.39	$1,876.04	$3,293.68
Overall	**$2,010.78**	**$1,867.69**	**$3,645.53**
%-Change	1.12%	2.26%	0.25%

Table 3.16 Crude Annual Mean Net Overall Per-Patient-Year Costs – Broad Definition (2007 Canadian dollars)

Year	SARDs	SARDs-CTD	SARDs-VD
1996	$4,200.63	$3,610.06	$10,406.56
1997	$4,523.96	$3,933.19	$11,400.50
1998	$3,973.99	$3,505.34	$9,063.90
1999	$3,910.43	$3,363.26	$11,004.19
2000	$3,583.64	$3,189.72	$8,461.29
2001	$3,442.54	$3,088.13	$8,143.64
2002	$3,345.85	$3,014.51	$8,022.00
2003	$3,327.45	$2,932.49	$8,805.63
2004	$2,894.18	$2,671.09	$6,191.89
2005	$2,815.94	$2,566.50	$6,015.81
2006	$2,862.51	$2,537.94	$6,785.12
2007	$2,673.74	$2,471.95	$4,520.48
Overall	**$3,202.34**	**$2,866.14**	**$7,390.01**
%-Change	-36.35%	-31.53%	-56.56%

3.11 Figures

Figure 3.1a Twelve-Year Proportion of Gross Medical Costs by Component – SARDs

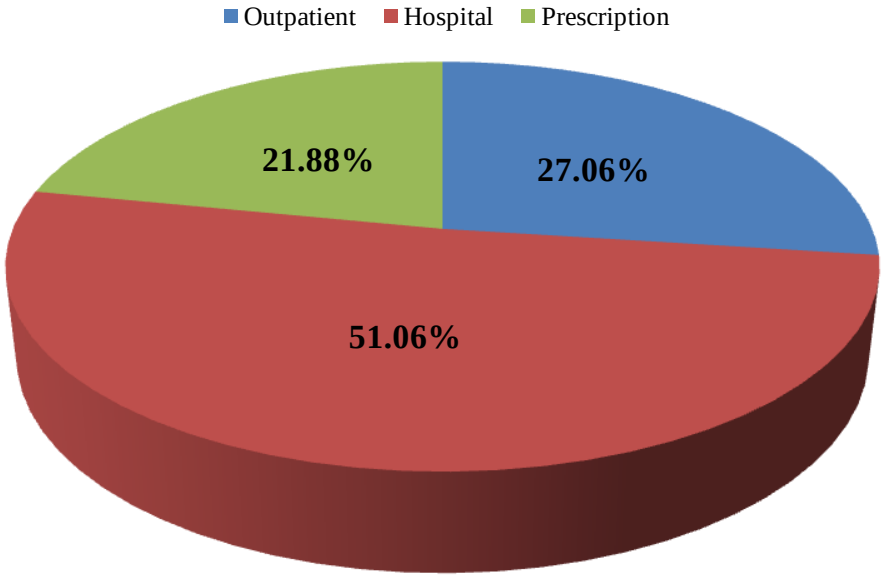


Figure 3.1b Twelve-Year Proportion of Gross Medical Costs by Component – SARDs-CTD

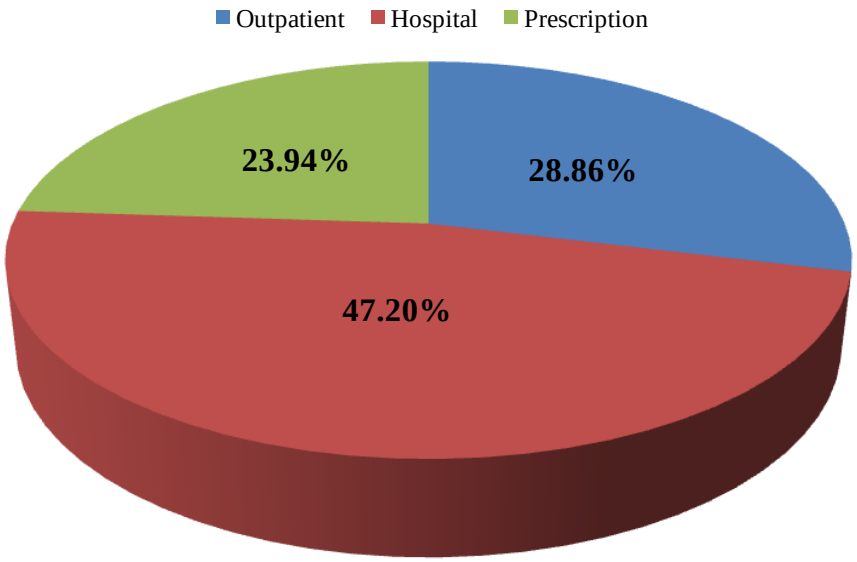


Figure 3.1c Twelve-Year Proportion of Gross Medical Costs by Component – SARDs-VD

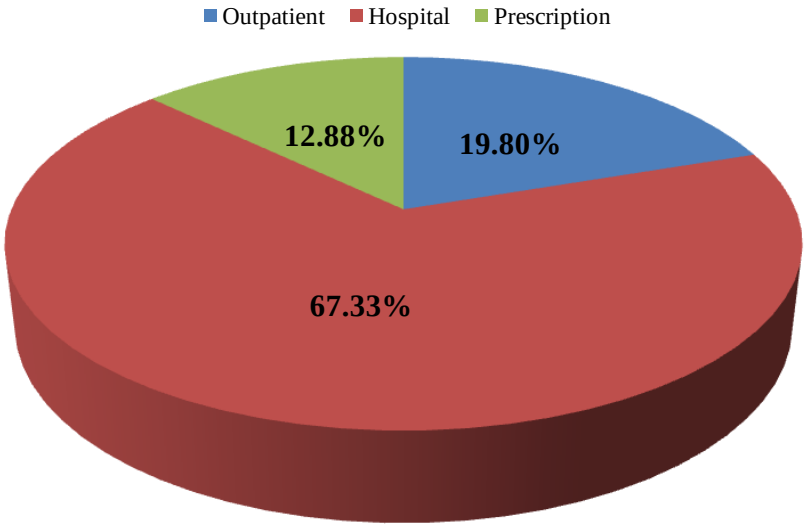


Figure 3.2a Annual Proportion of Gross Direct Medical Costs by Component – SARDs

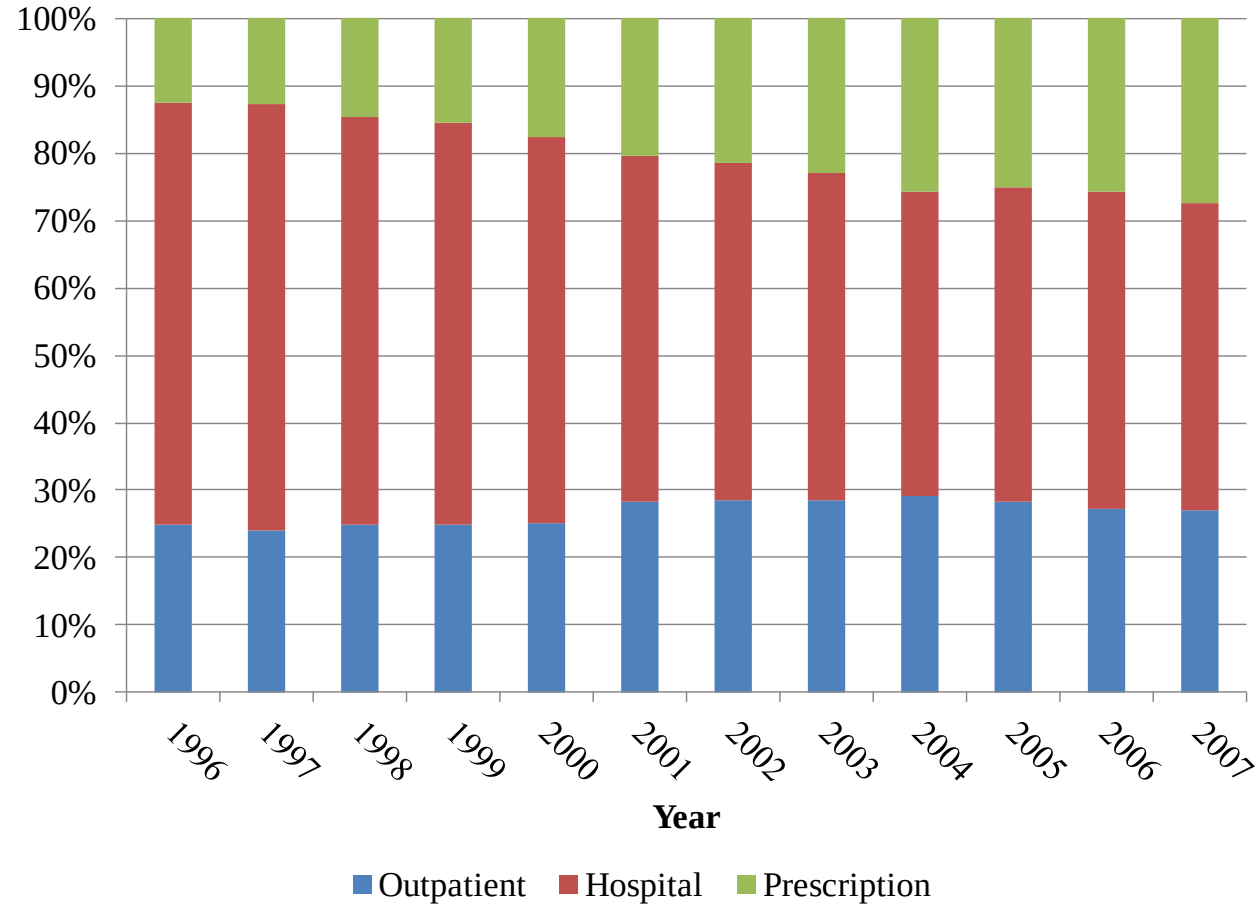


Figure 3.2b Annual Proportion of Gross Direct Medical Costs by Component – SARDs-CTD

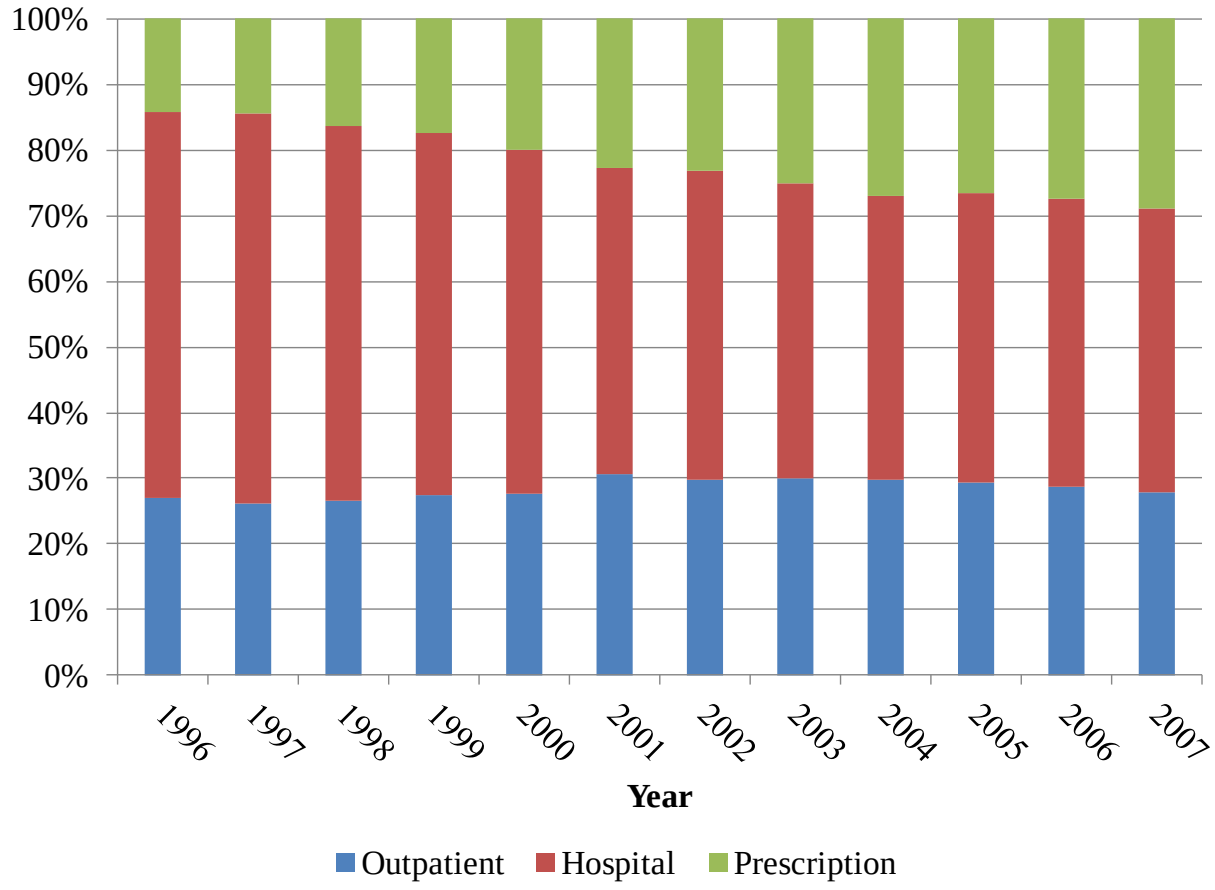


Figure 3.2c Annual Proportion of Gross Direct Medical Costs by Component – SARDs-VD

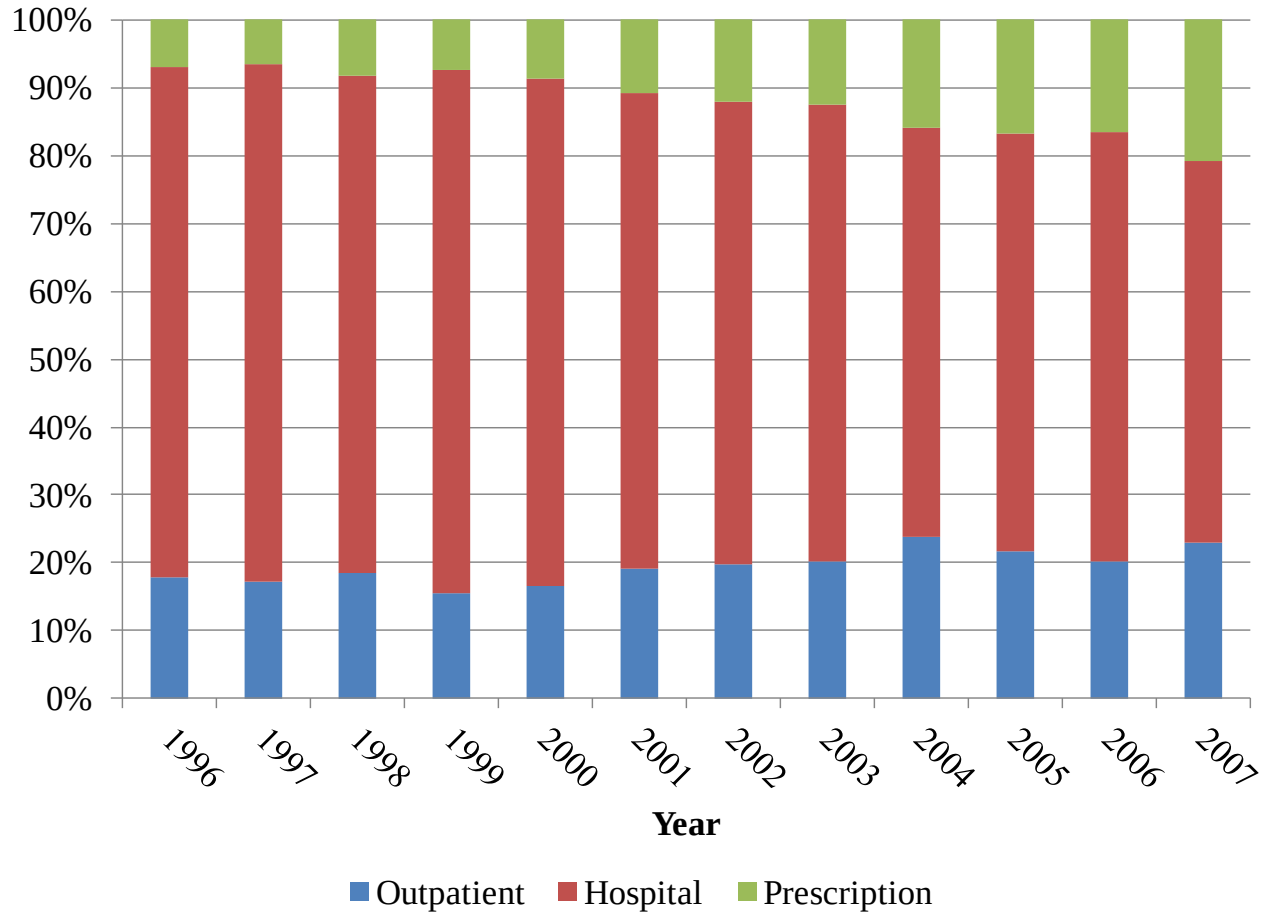


Figure 3.3a Crude Annual Mean Overall Gross Direct Medical Costs, Per-Patient-Year (2007 Canadian dollars)

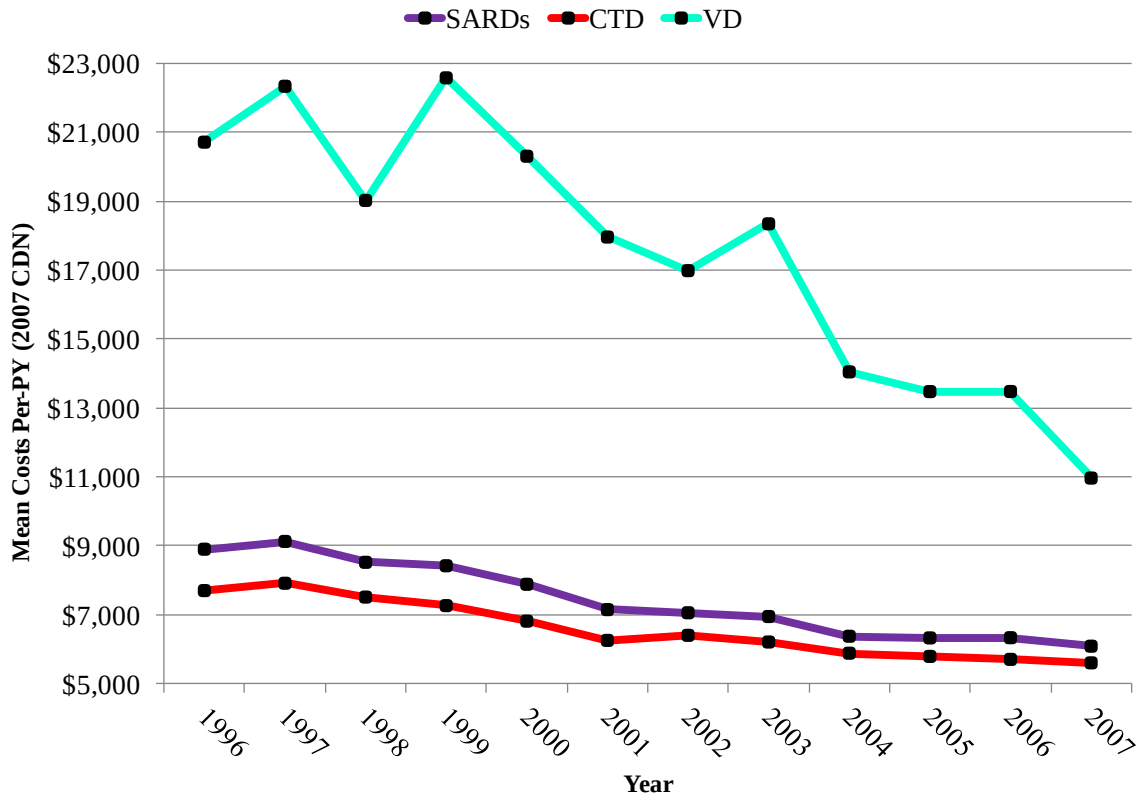


Figure 3.3b Crude Annual Mean Overall Gross Direct Medical Costs, Per-Patient-Year (2007 Canadian dollars) – SARDs and SARDs-CTD only

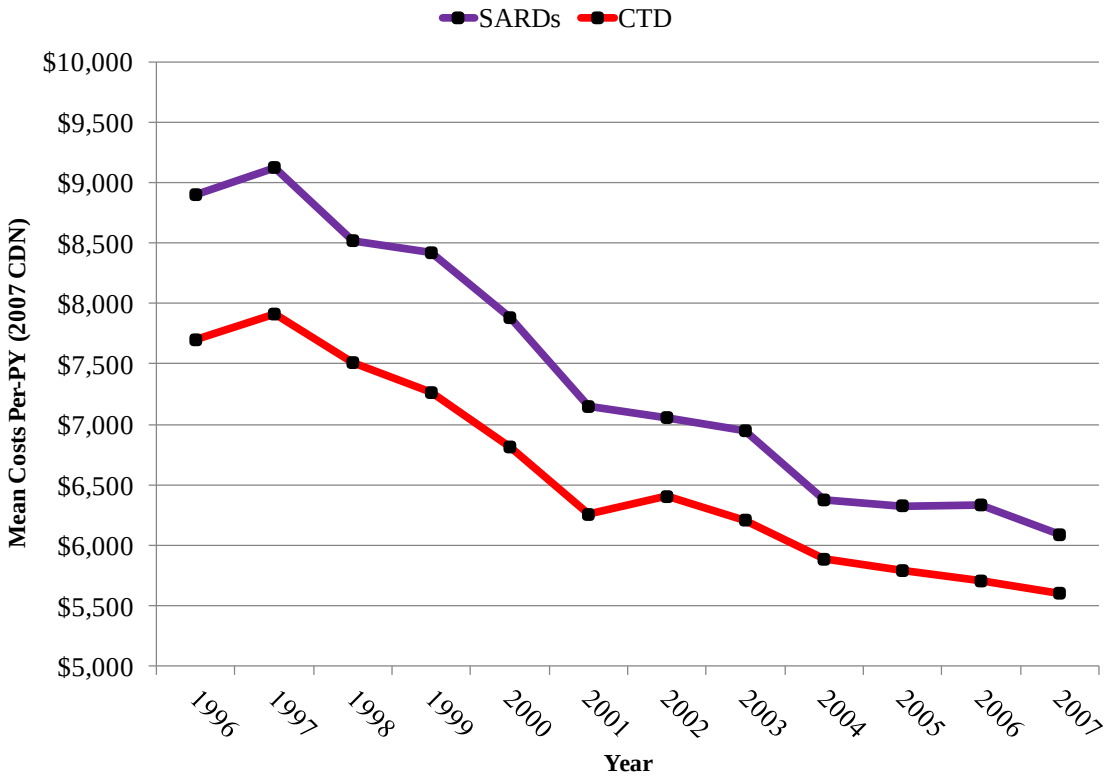


Figure 3.4 Crude Annual Mean Gross Direct Medical Costs, Per-Patient Year – Overall and By Component, all SARDs cases (2007 Canadian dollars)

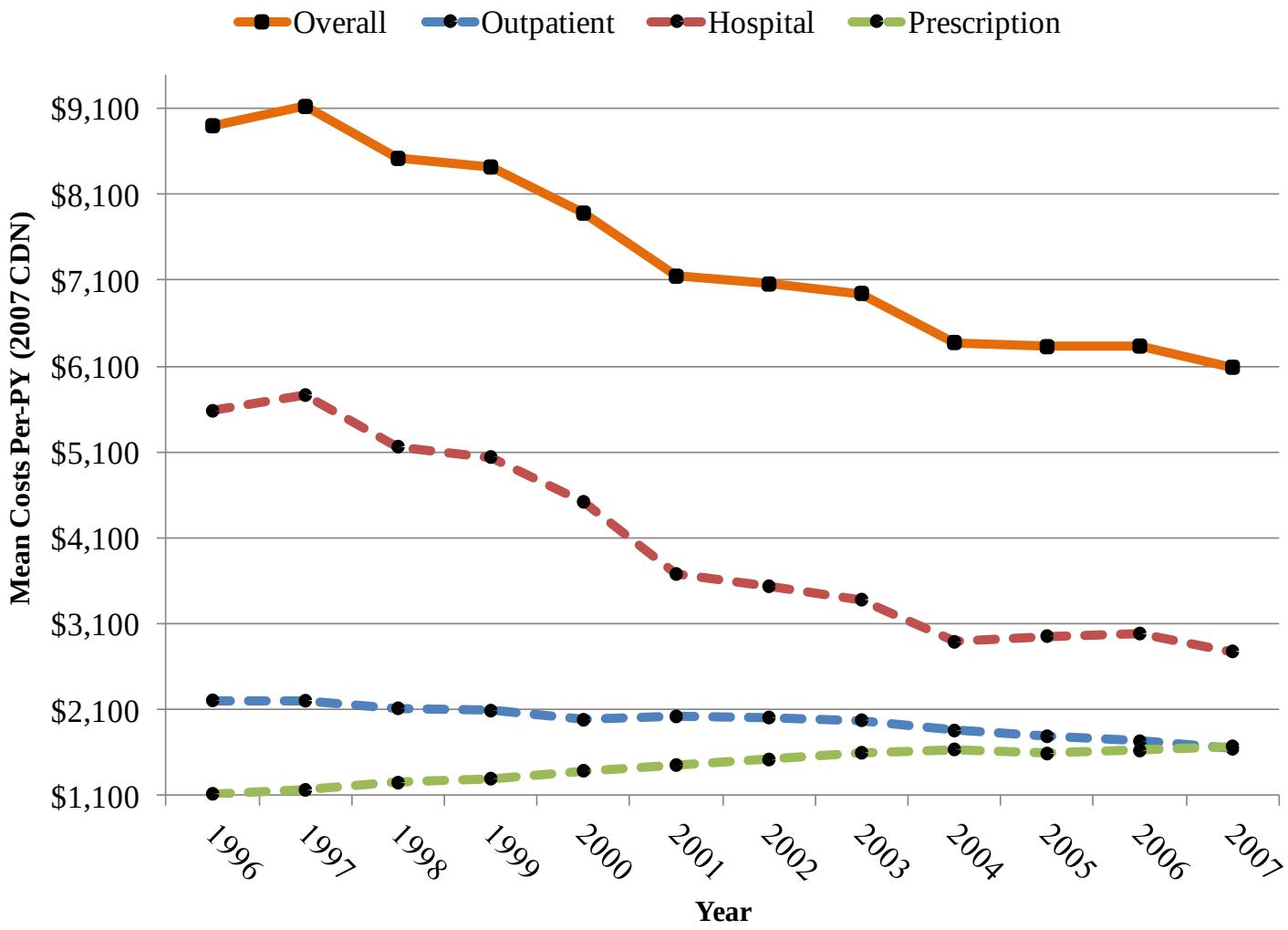


Figure 3.5 Crude Annual Mean Gross Outpatient Costs, Per-Patient-Year (2007 Canadian dollars)

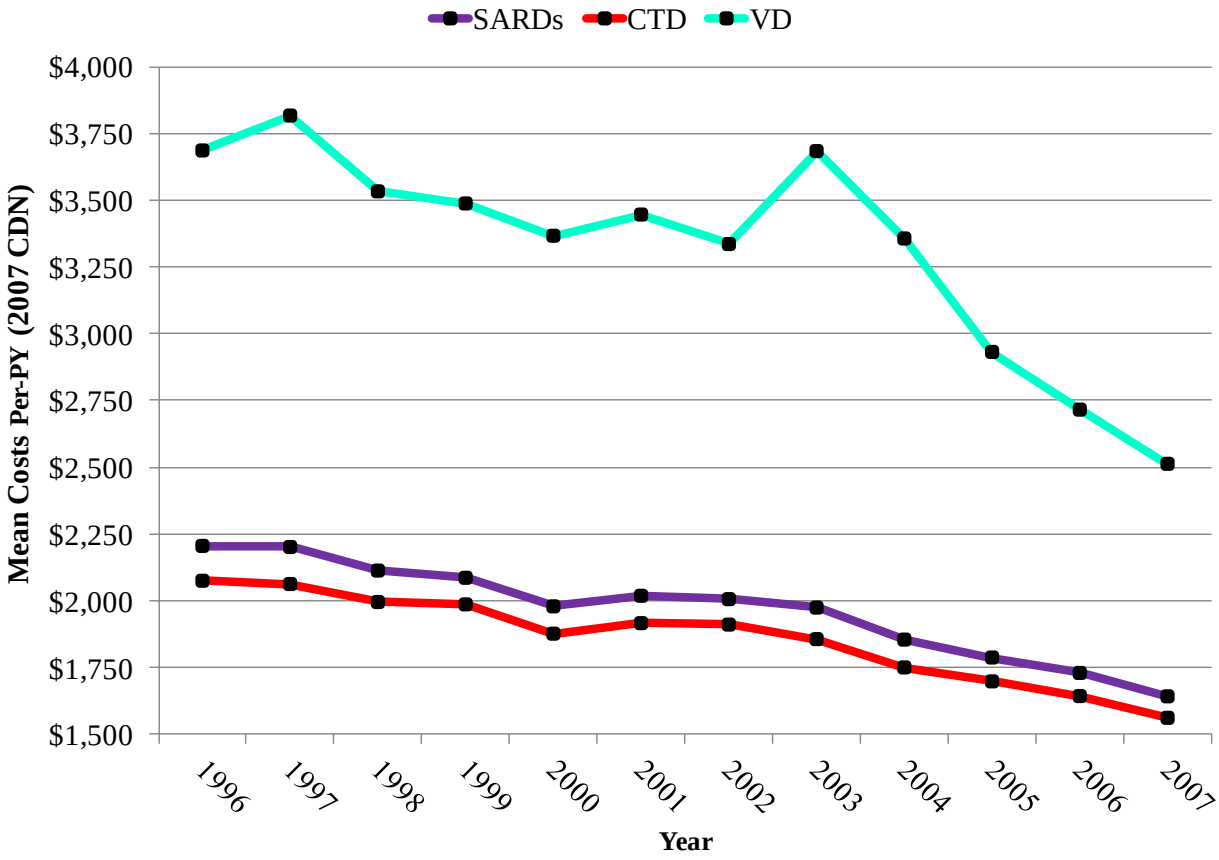


Figure 3.6 Crude Annual Mean Gross Hospital Costs, Per-Patient-Year (2007 Canadian dollars)

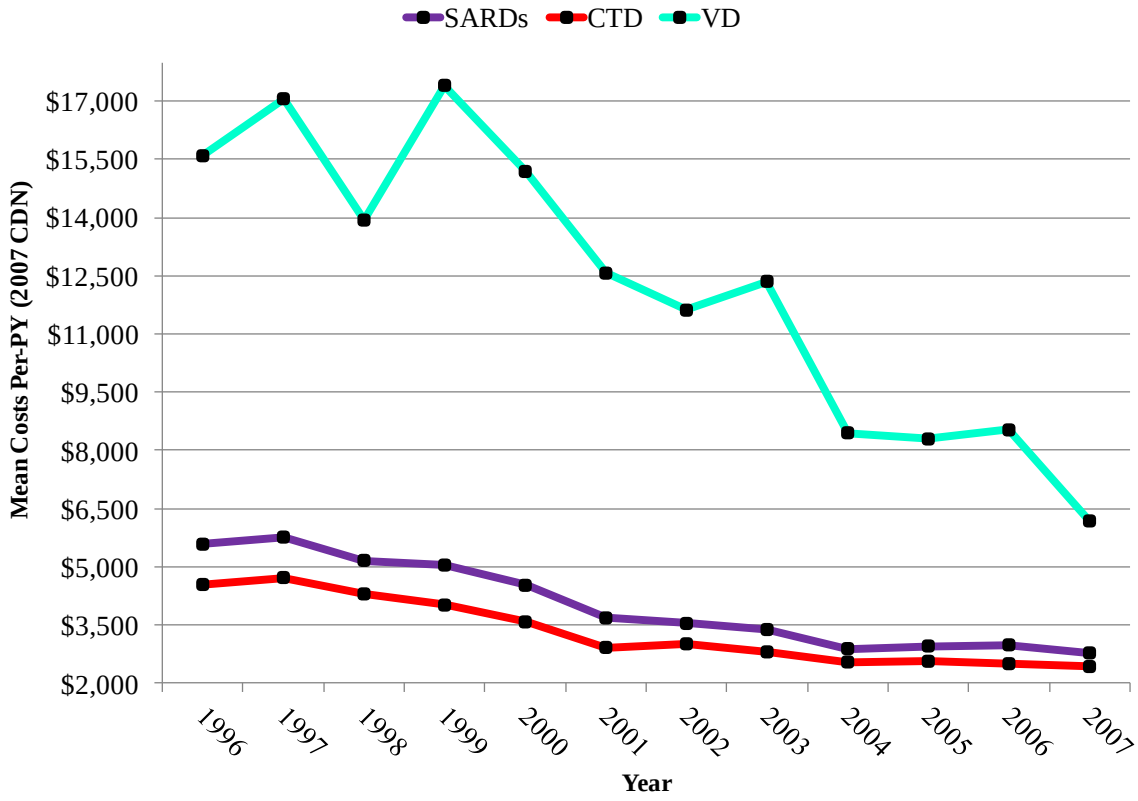


Figure 3.7 Annual Mean Length of Stay Per-Admission, Amongst Hospitalized Cases (days)

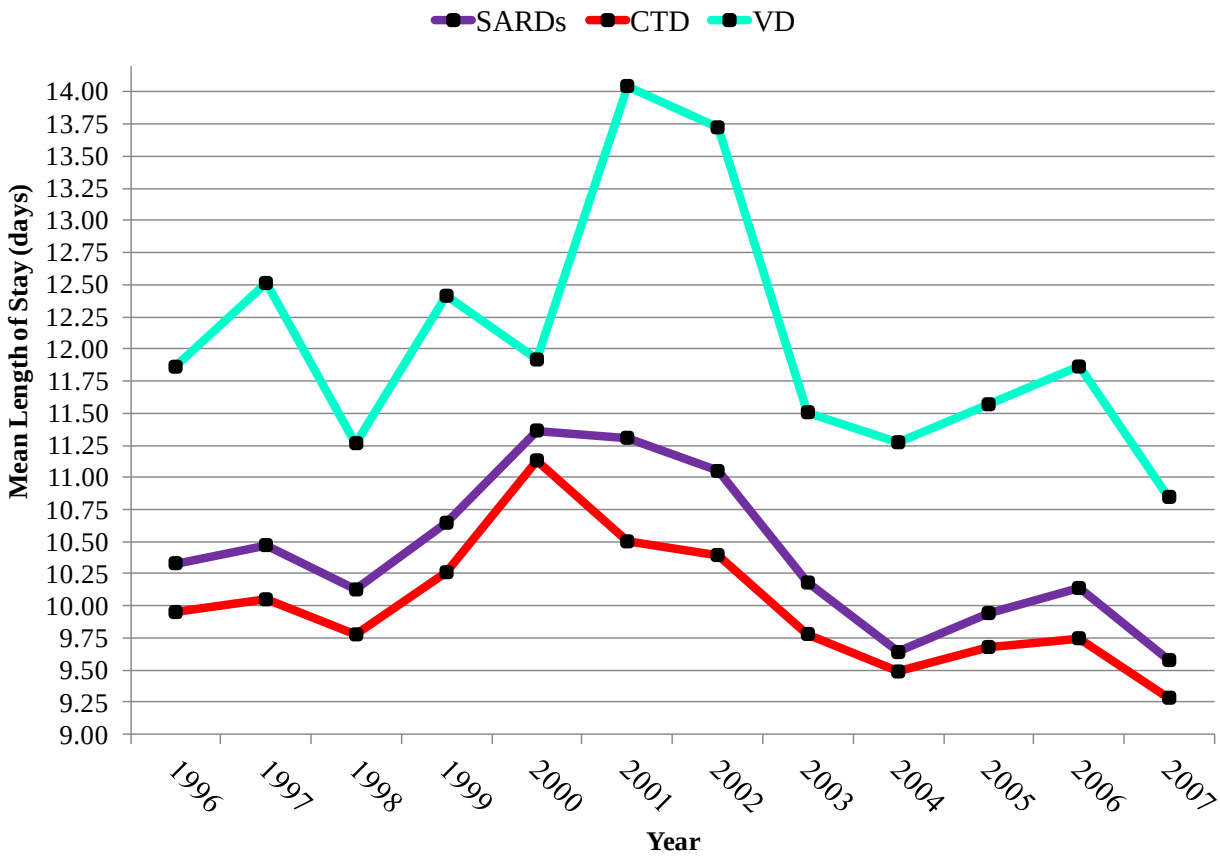


Figure 3.8 Annual Mean Length of Stay Per-Year, Amongst Hospitalized Cases (days)

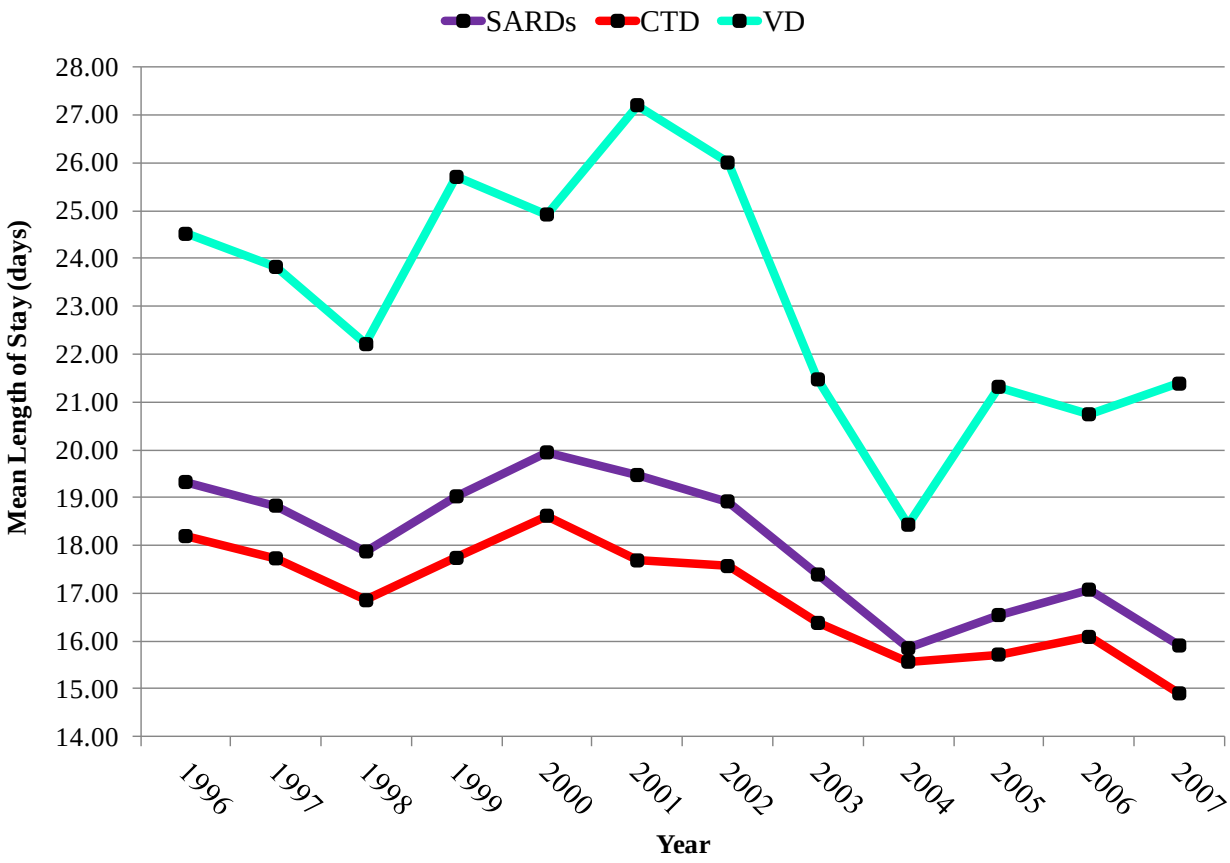


Figure 3.9 Crude Annual Mean Gross Prescription Costs, Per-Patient-Year (2007 Canadian dollars)

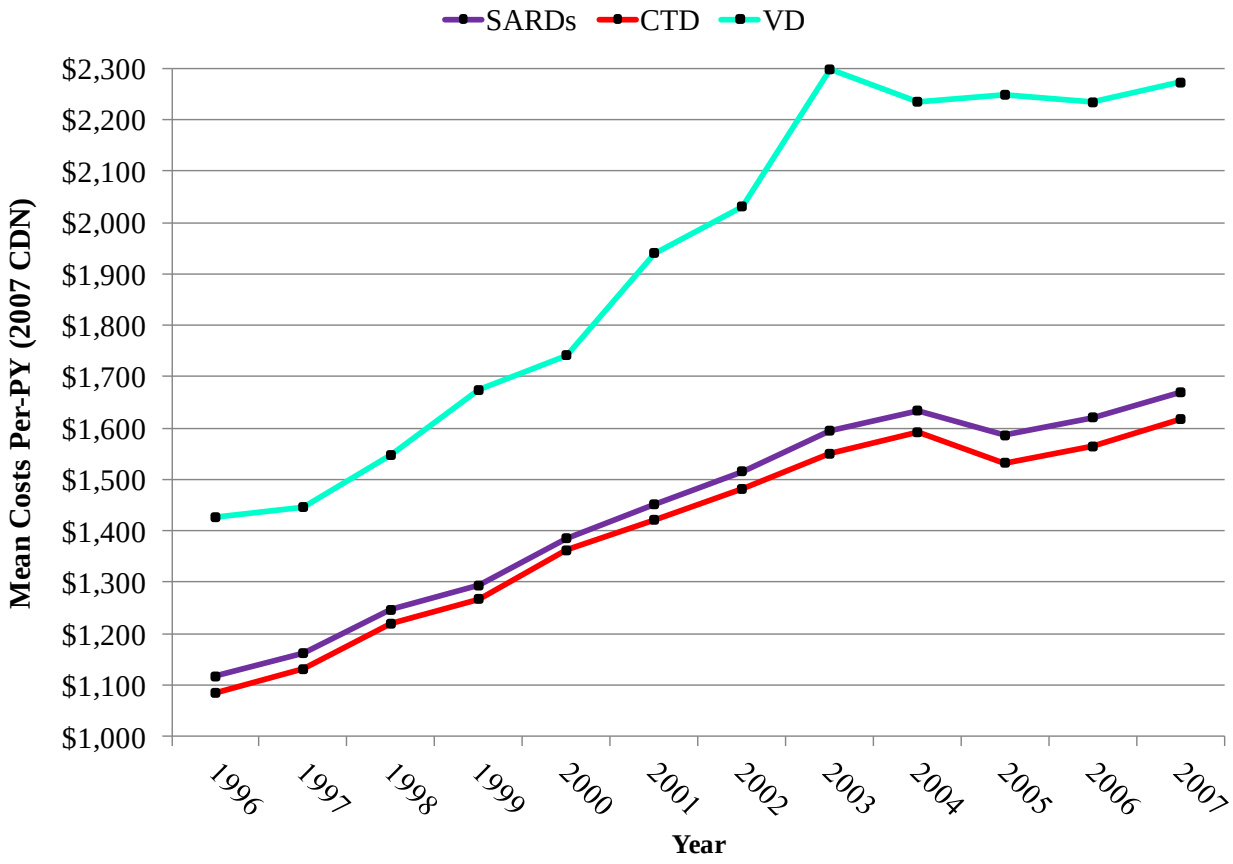


Figure 3.10 Gross Crude Annual Mean Number of Prescriptions Dispensed, Per-Patient-Year

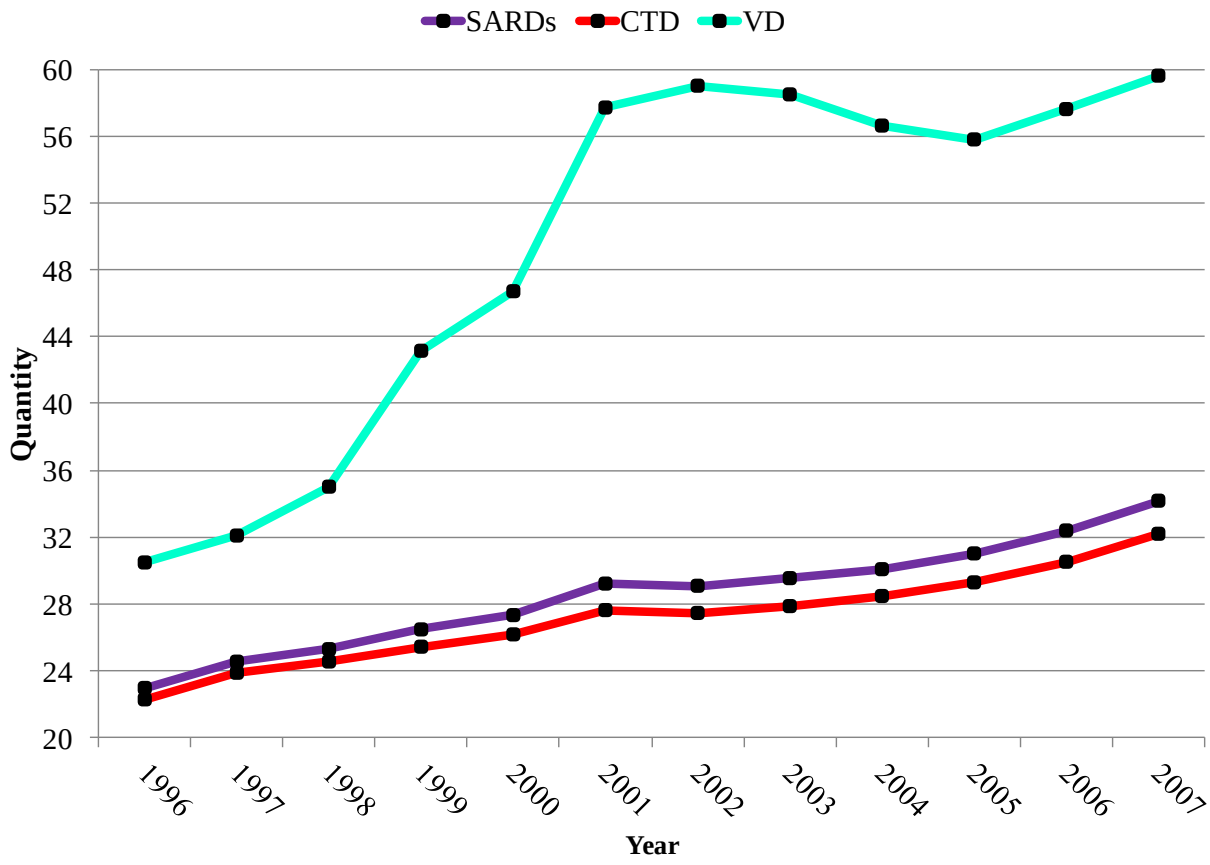


Figure 3.11a Top-Ten Most Frequently-Prescribed Drug Classes – SARDs

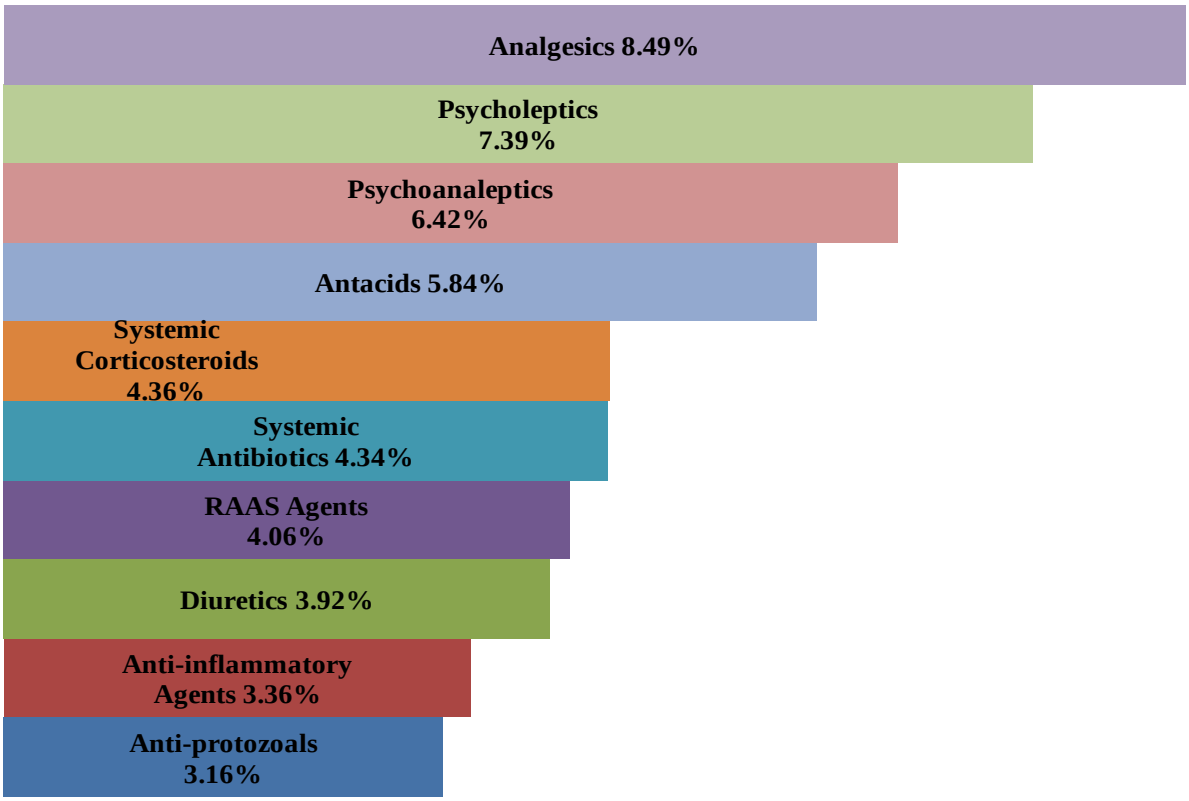


Figure 3.11b Top-Ten Most Frequently-Prescribed Drug Classes – SARDs-CTD

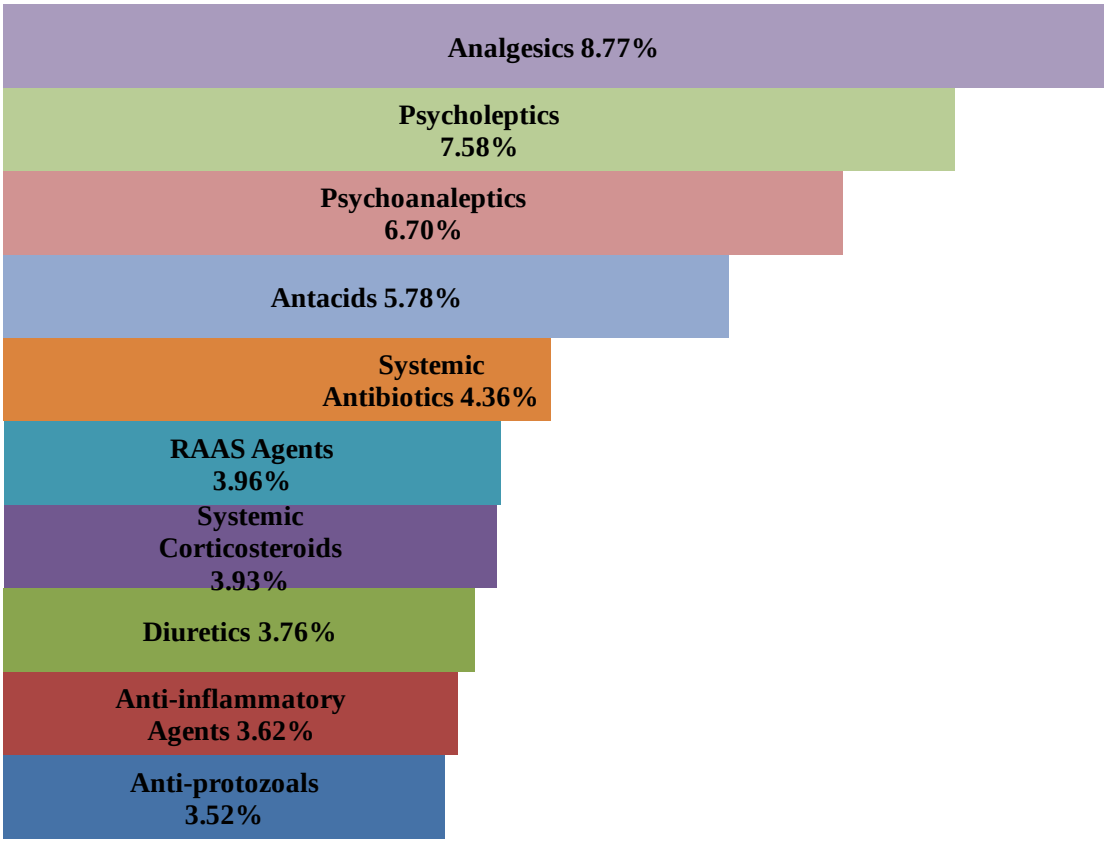


Figure 3.11c Top-Ten Most Frequently-Prescribed Drug Classes – SARDs-VD

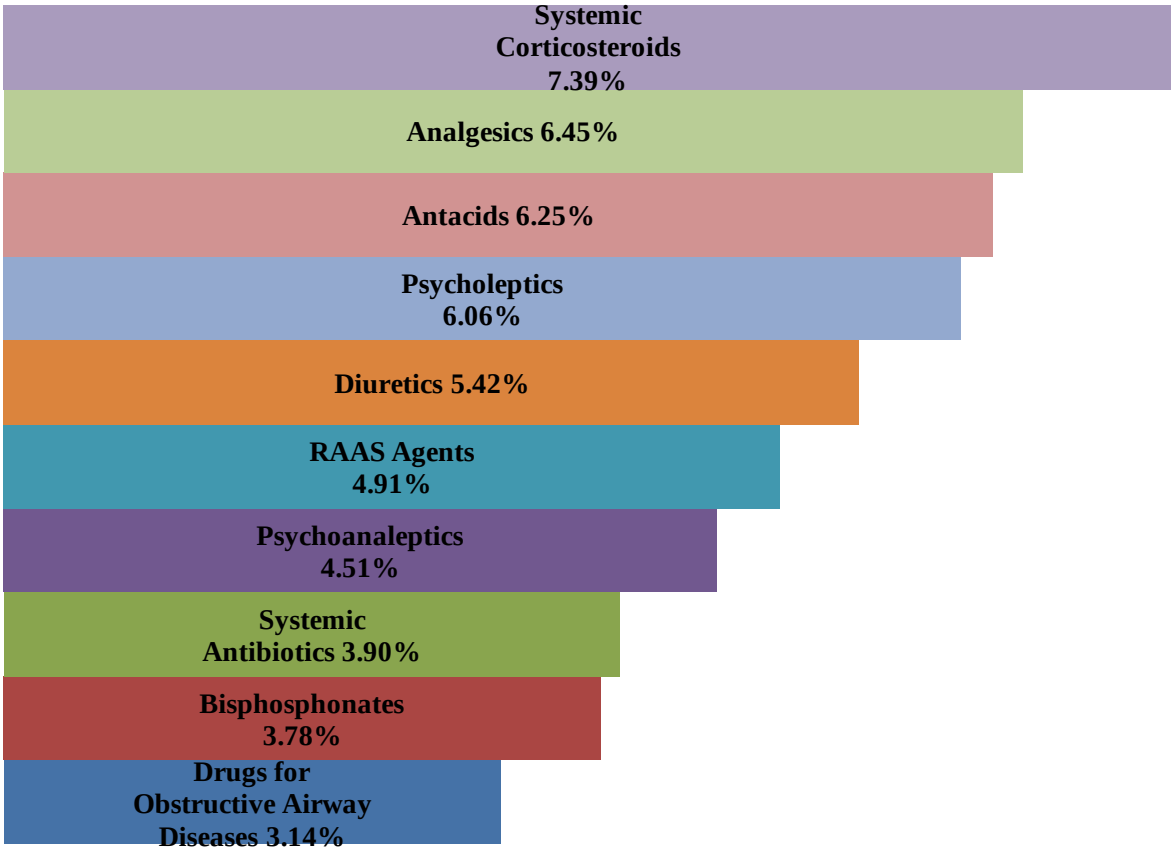


Figure 3.12a Top-Ten Most Frequently-Prescribed Drugs – SARDs

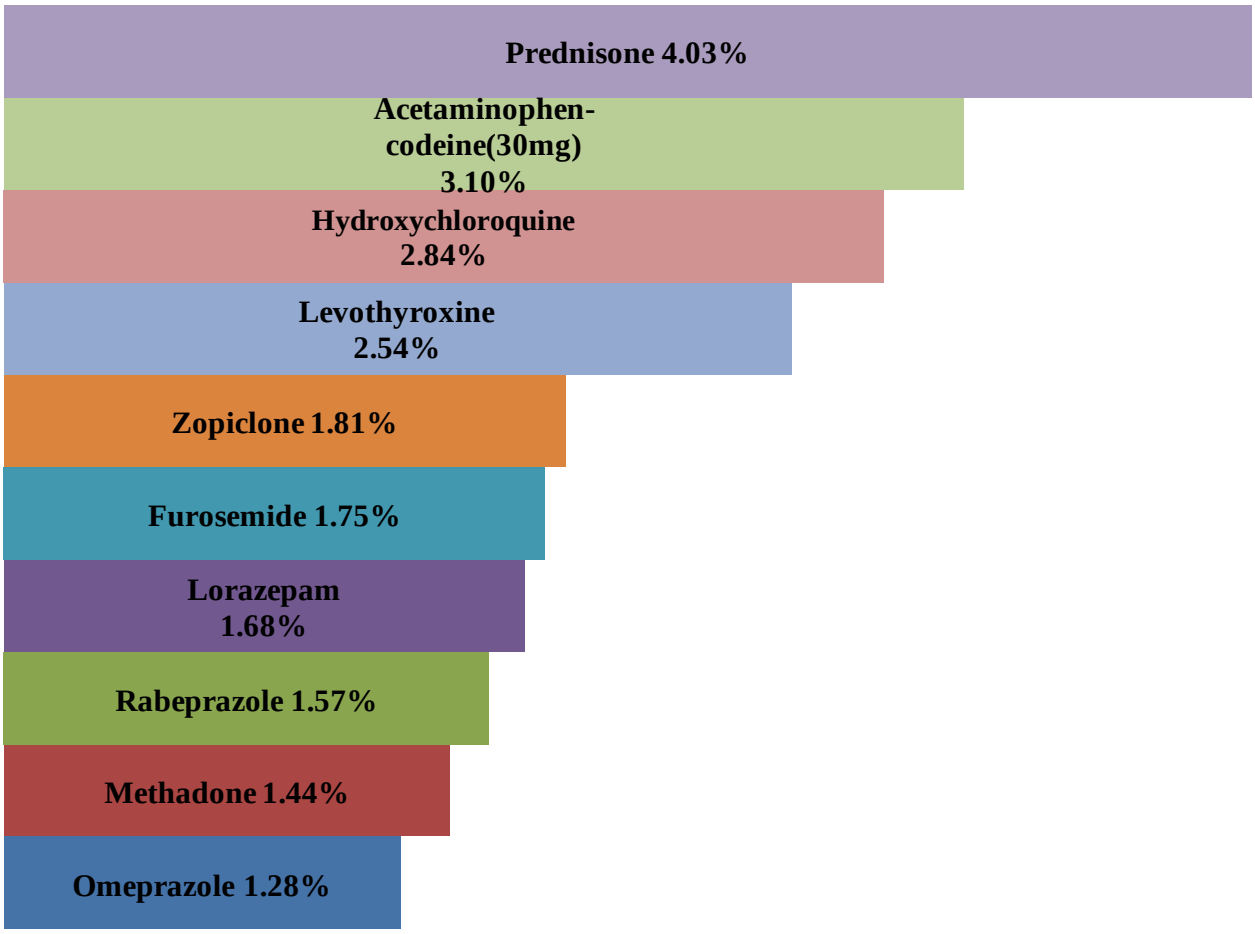


Figure 3.12b Top-Ten Most Frequently-Prescribed Drugs – SARDs-CTD

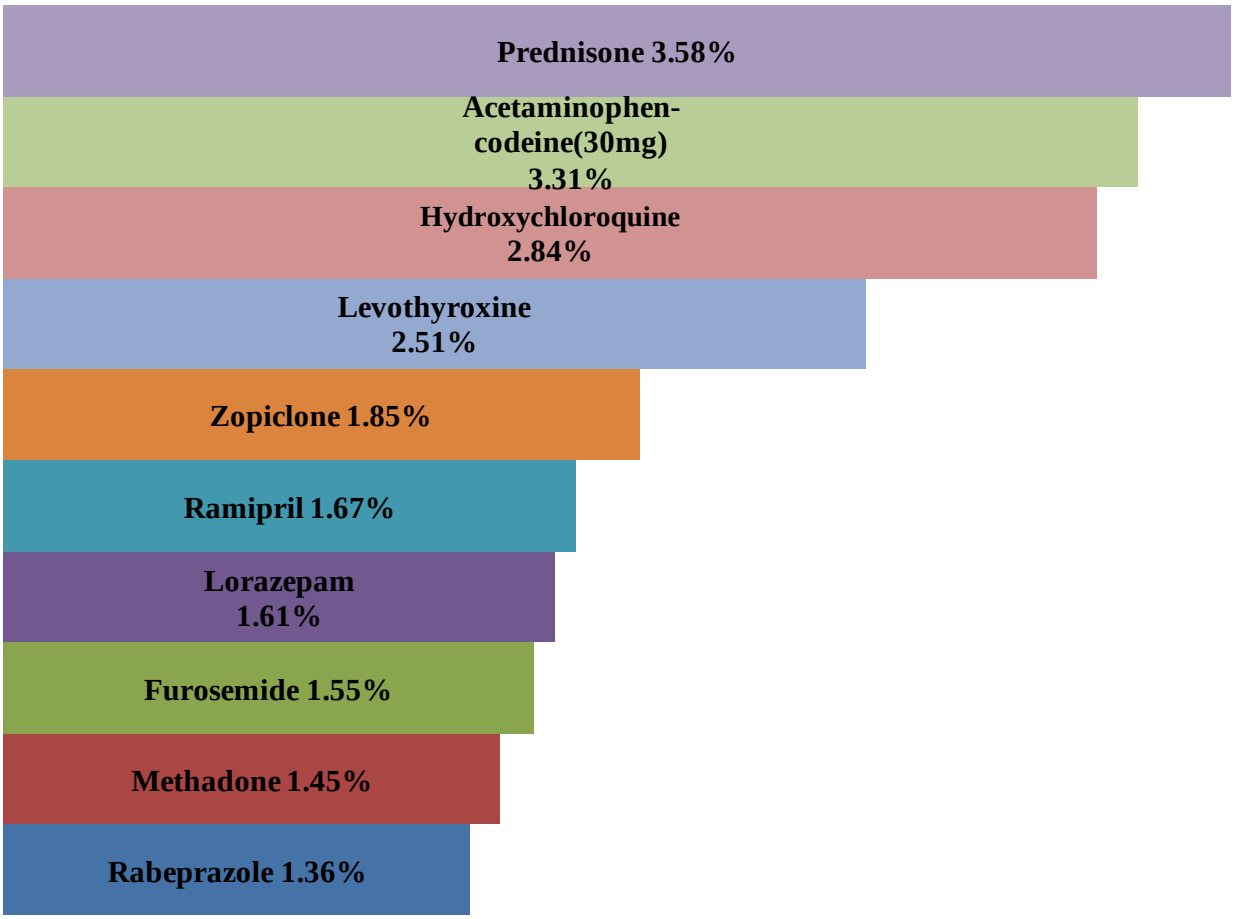


Figure 3.12c Top-Ten Most Frequently-Prescribed Drugs – SARDs-VD

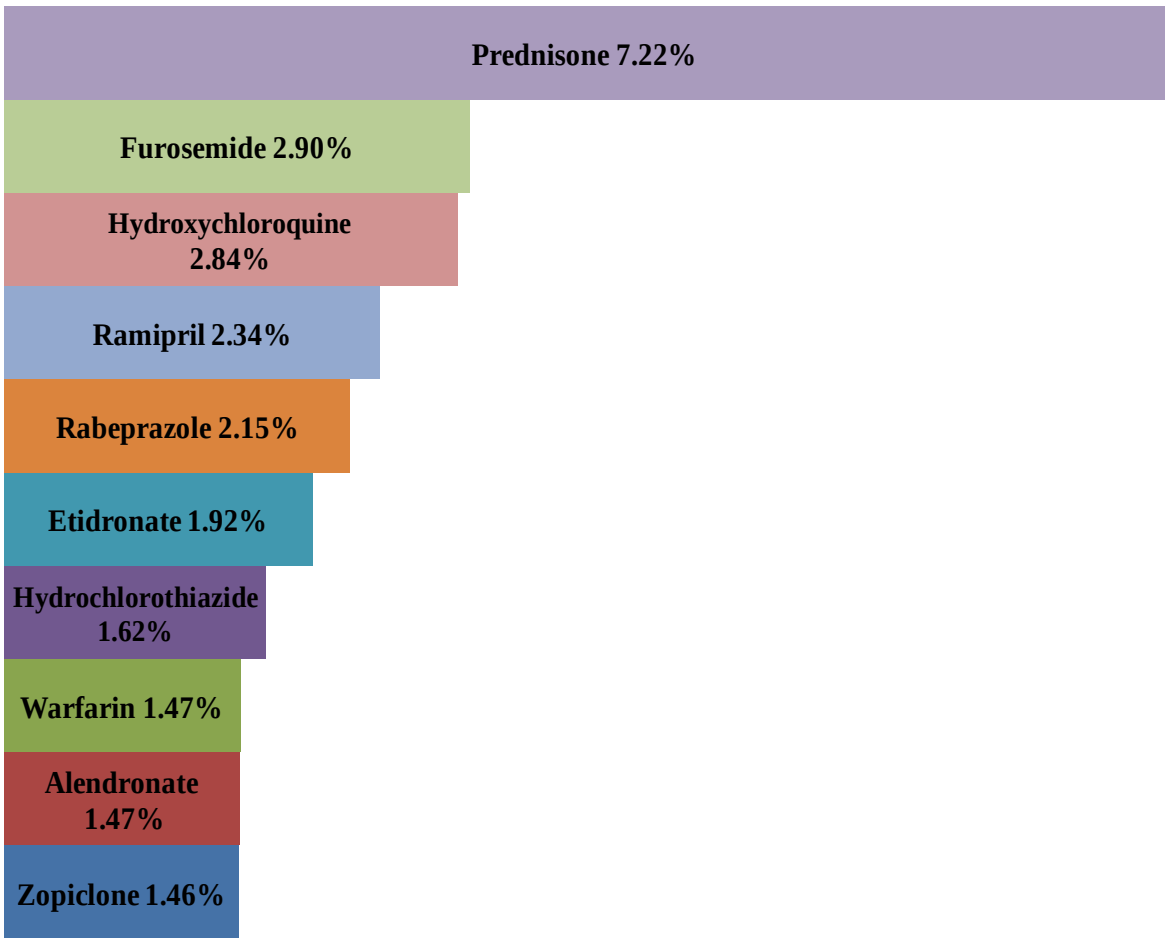


Figure 3.13a Top-Ten Most Costly Drug Classes – SARDs

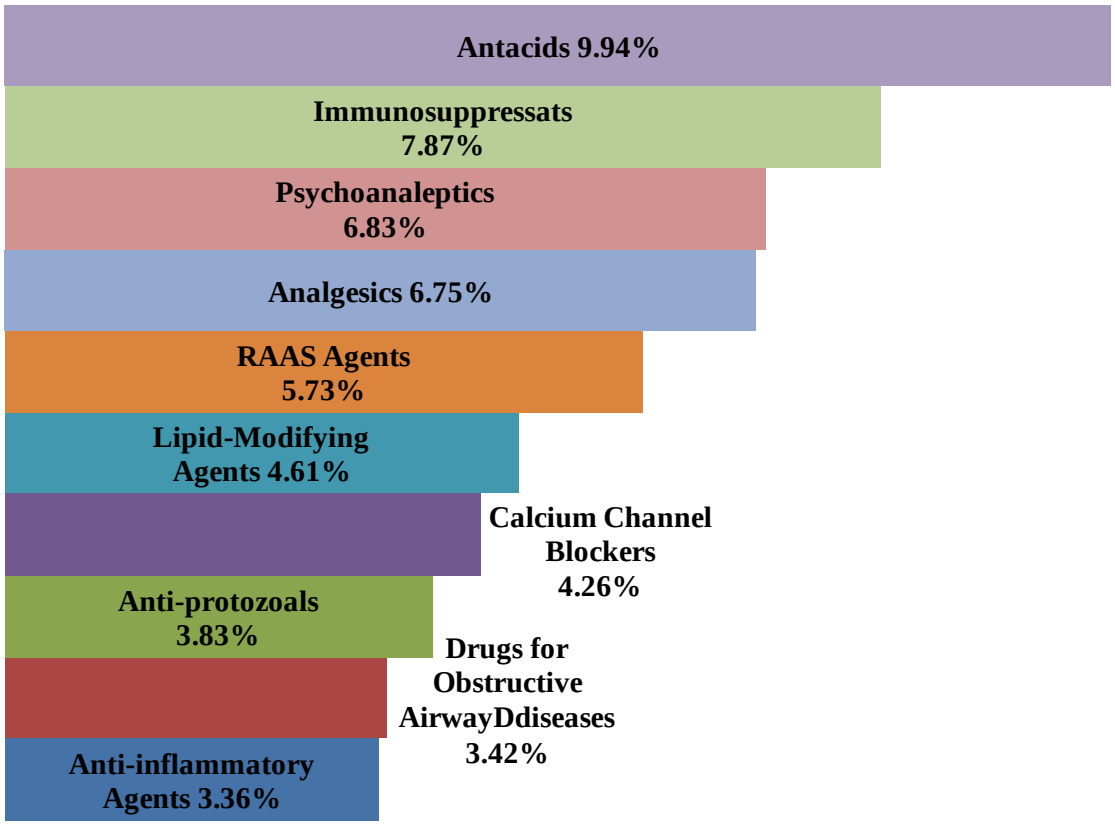


Figure 3.13b Top-Ten Most Costly Drug Classes – SARDs-CTD

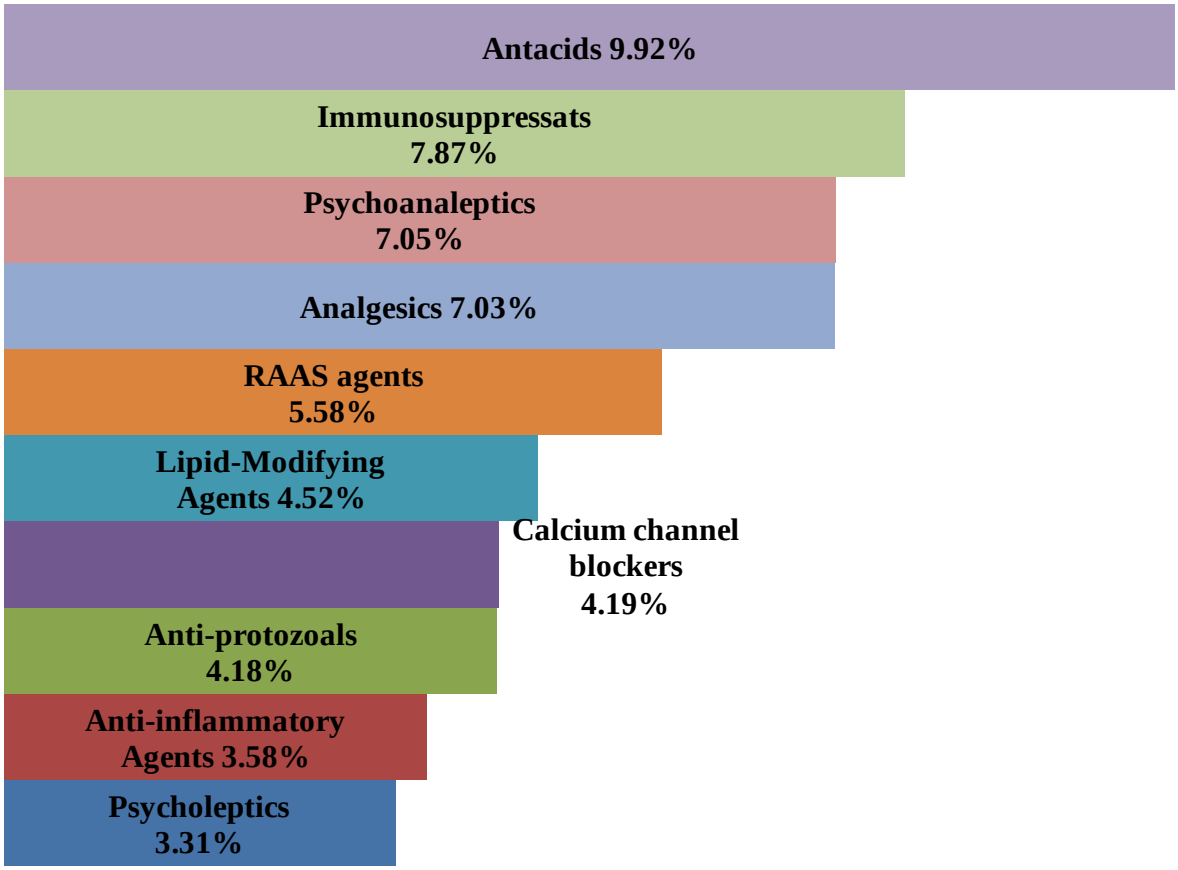


Figure 3.13c Top-Ten Most Costly Drug Classes – SARDs-VD

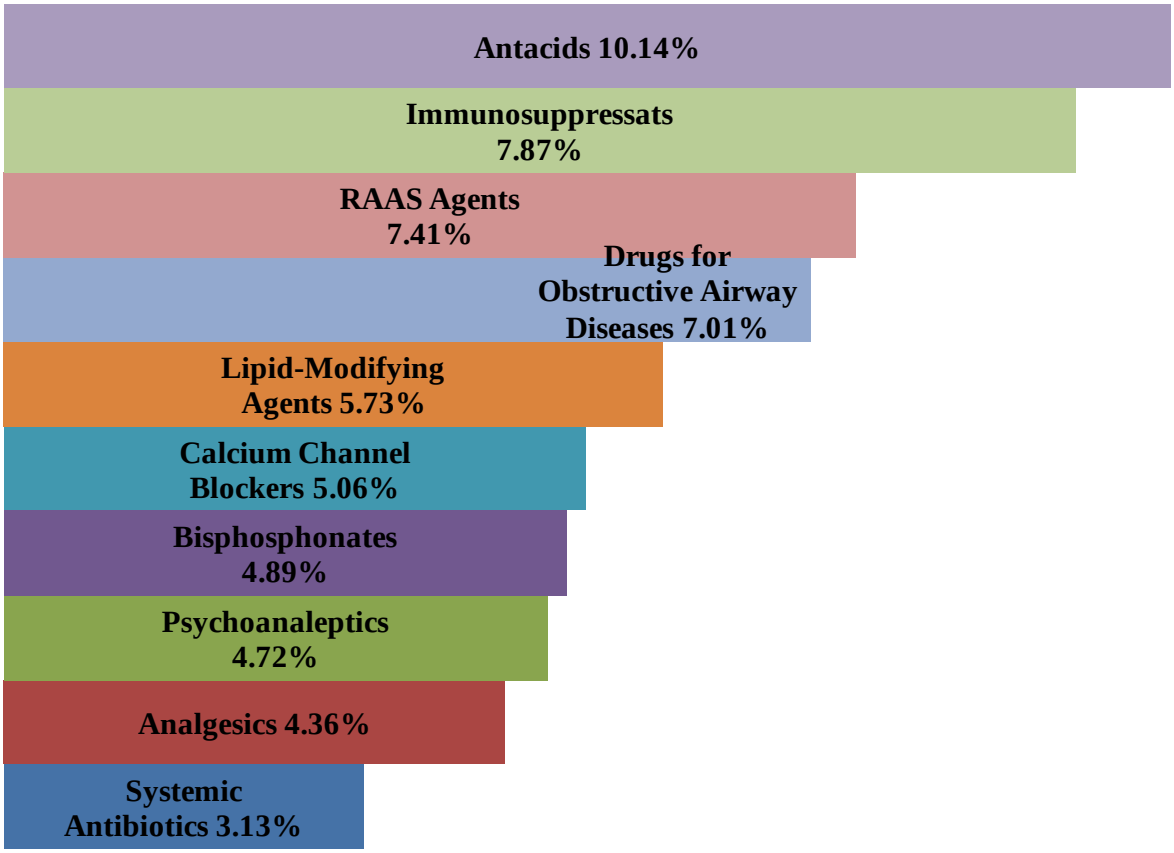


Figure 3.14a Top-Ten Most Costly Drugs – SARDs

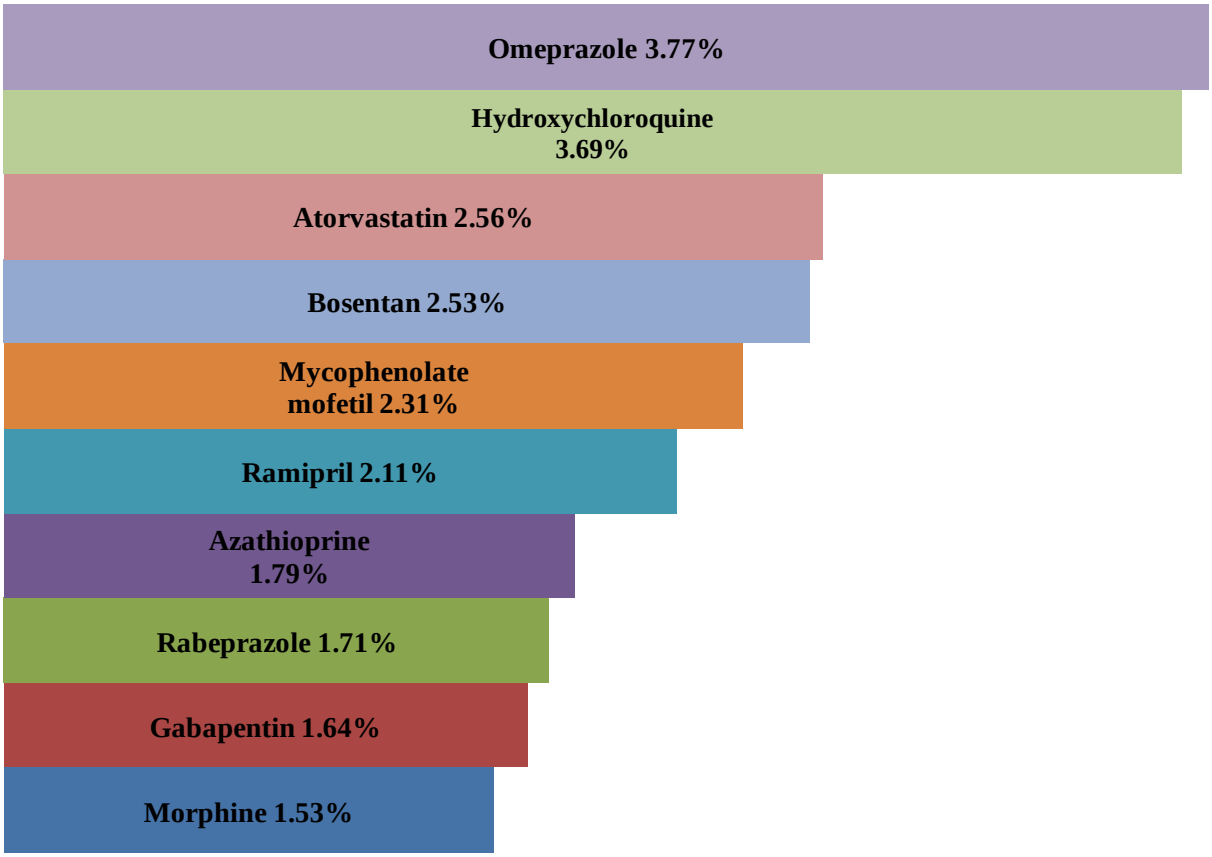


Figure 3.14b Top-Ten Most Costly Drugs – SARDs-CTD

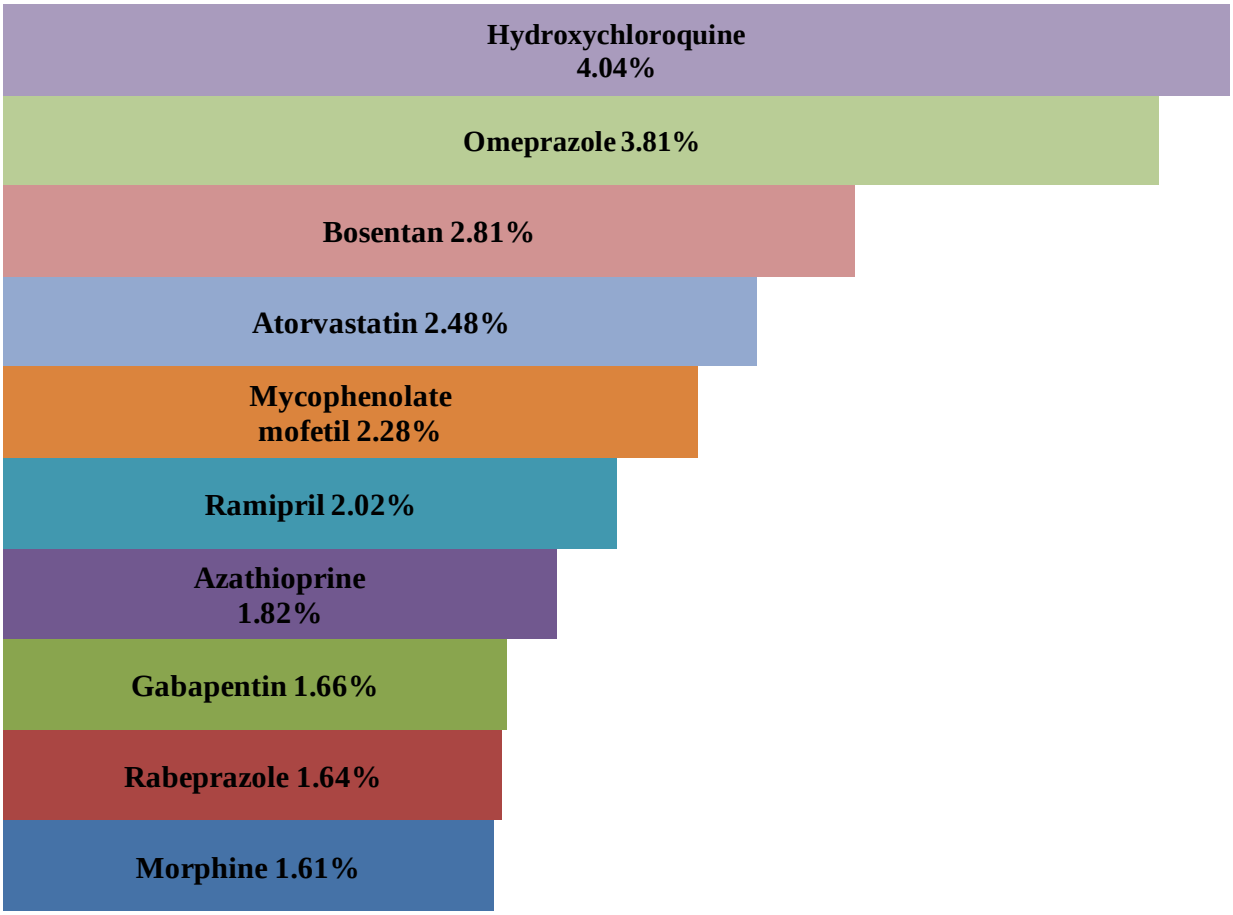


Figure 3.14c Top-Ten Most Costly Drugs – SARDs-VD

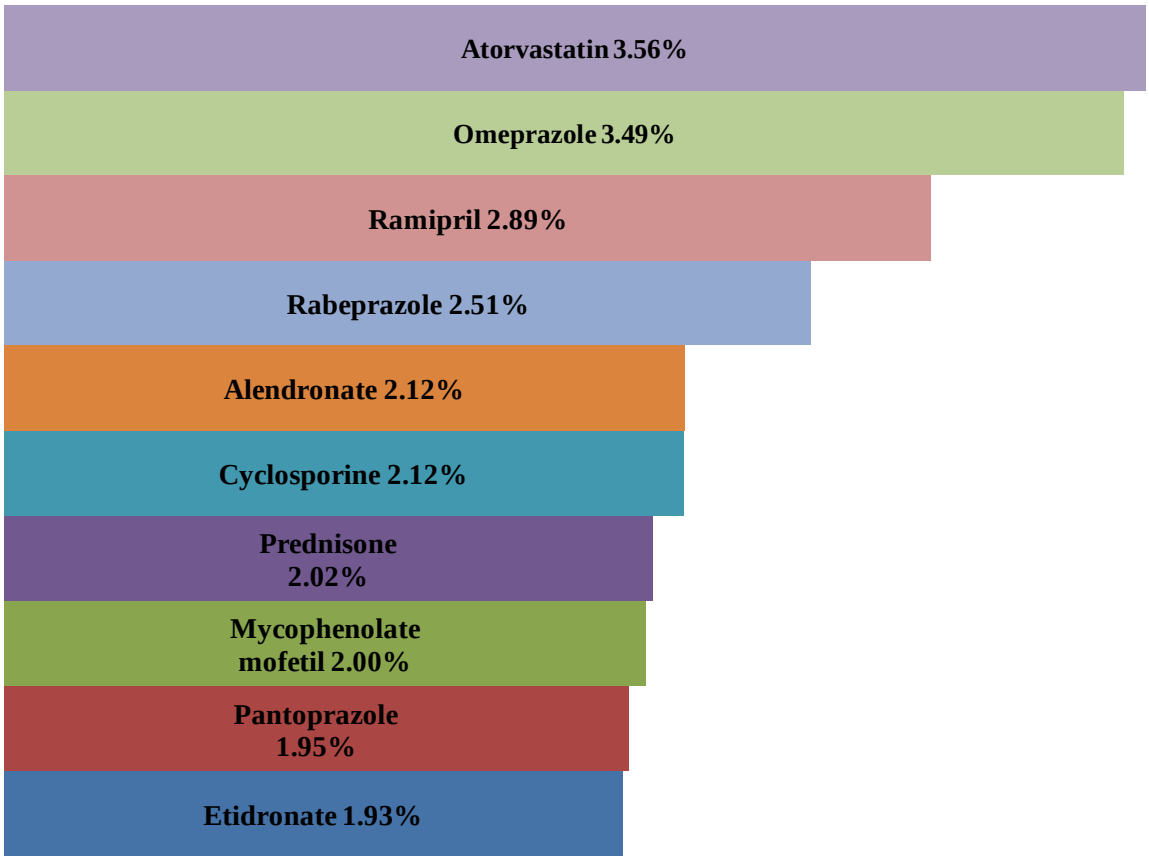


Figure 3.15a Drug Classes Contributing Most, On-Average, to the Twelve-Year Increase in Mean Per-Patient-Year Prescription Costs

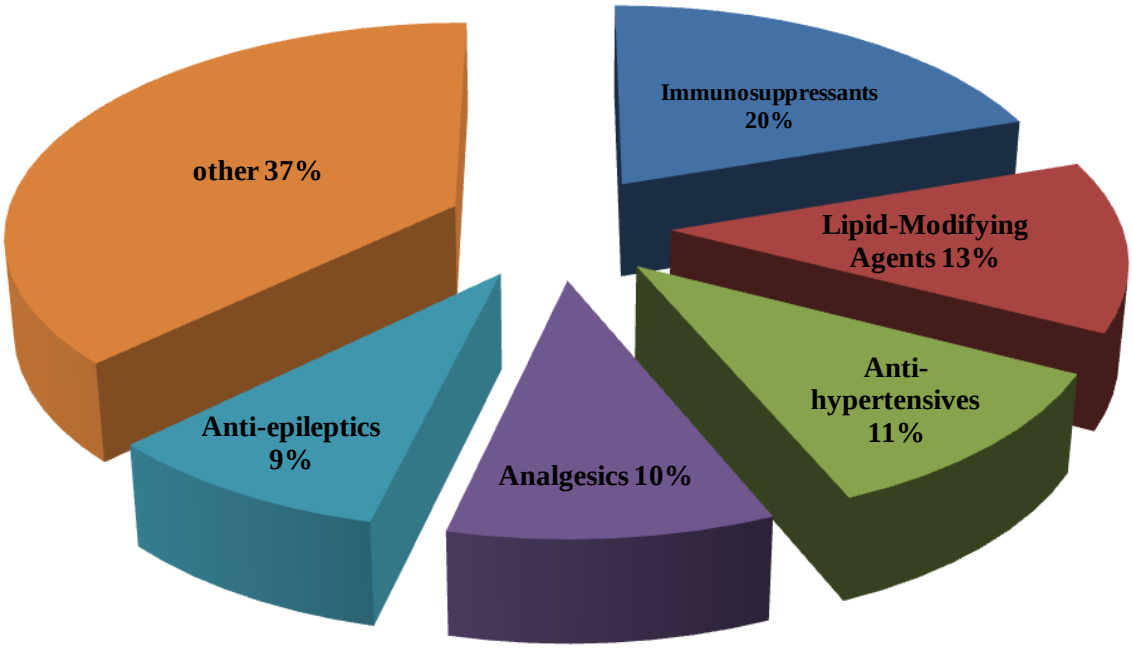


Figure 3.15b Drugs Contributing Most, On-Average, to the Twelve-Year Increase in Mean Per-Patient-Year Prescription Costs

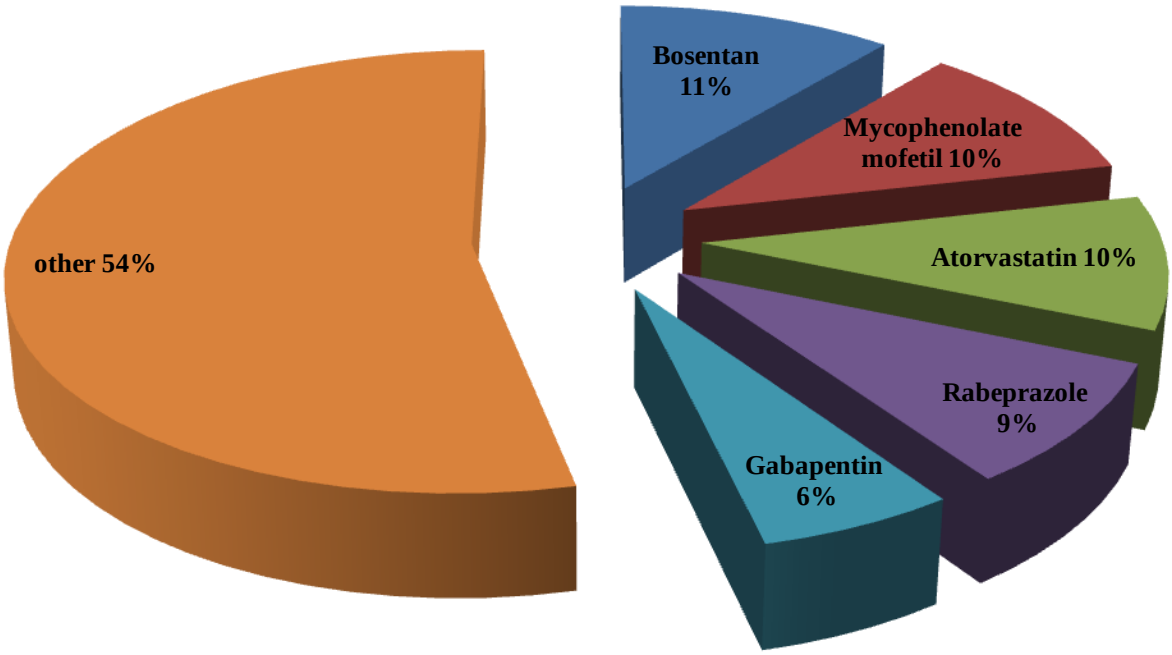


Figure 3.16a Drug Classes Contributing Most, On-Average, to the Twelve-Year Increase in Mean Per-Patient-Year Dispensed Prescriptions

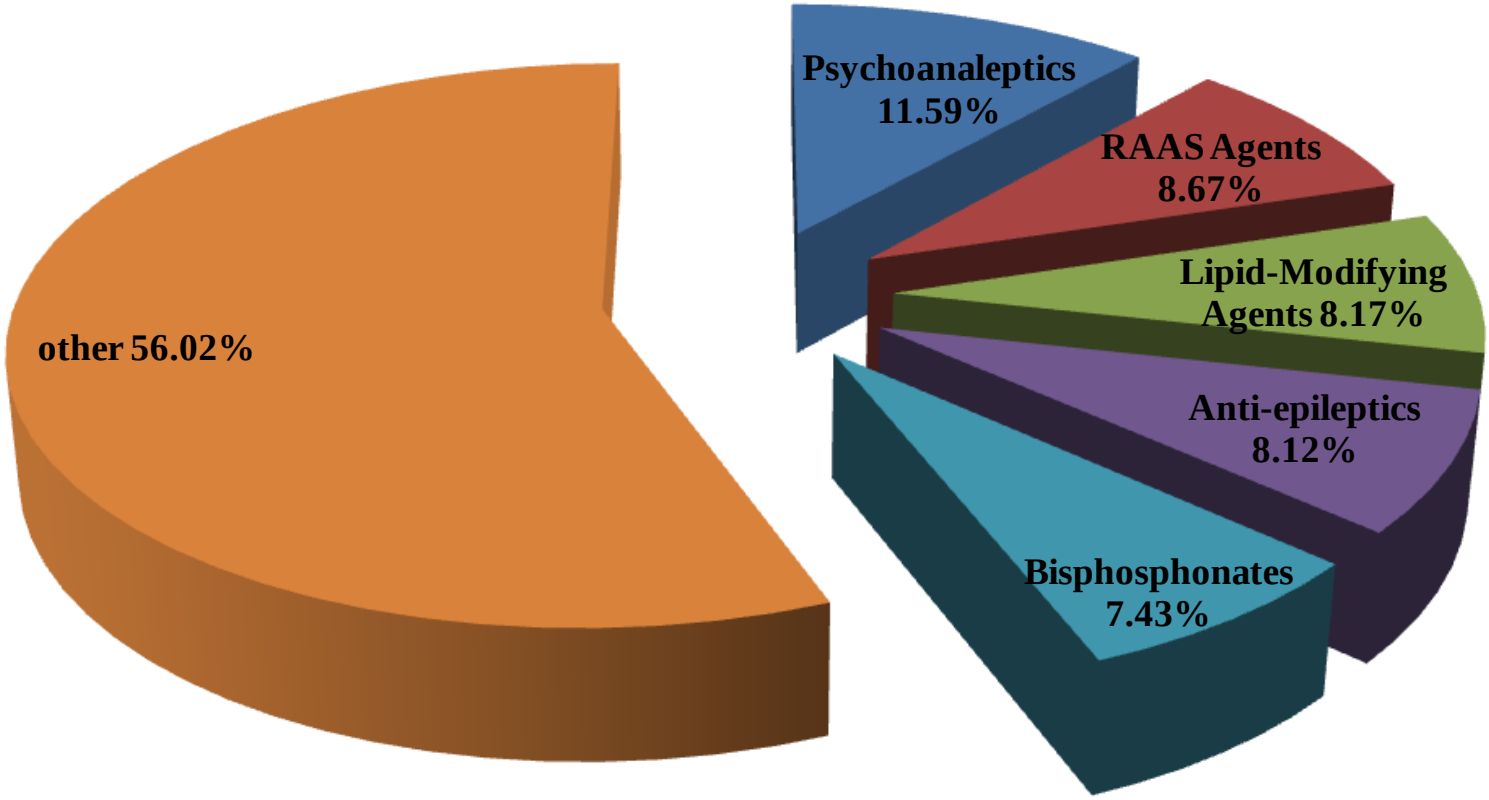


Figure 3.16b Drugs Contributing Most, On-Average, to the Twelve-Year Increase in Mean Per-Patient-Year Dispensed Prescriptions

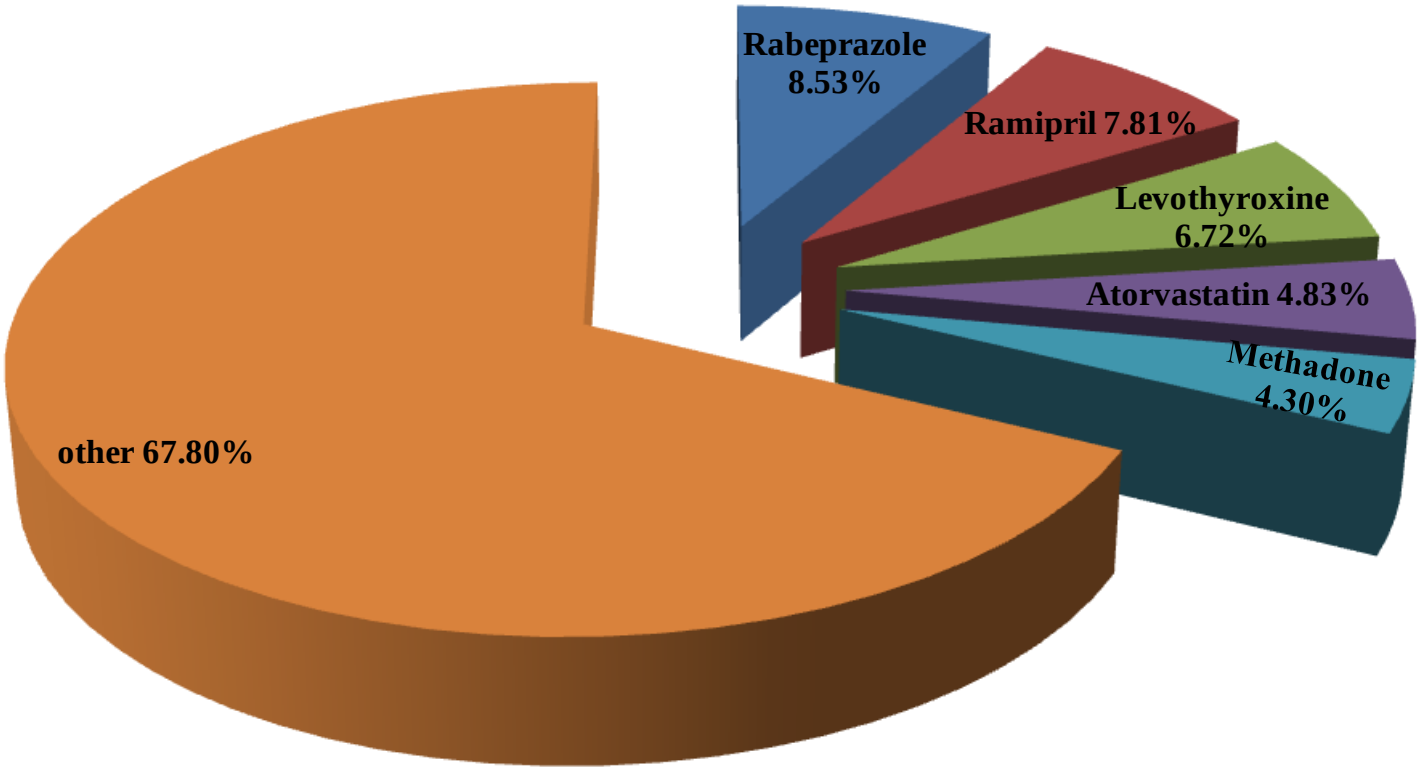


Figure 3.17a Twelve-Year Proportion of Overall Net Direct Medical Costs by Component, Narrow Definition – SARDs

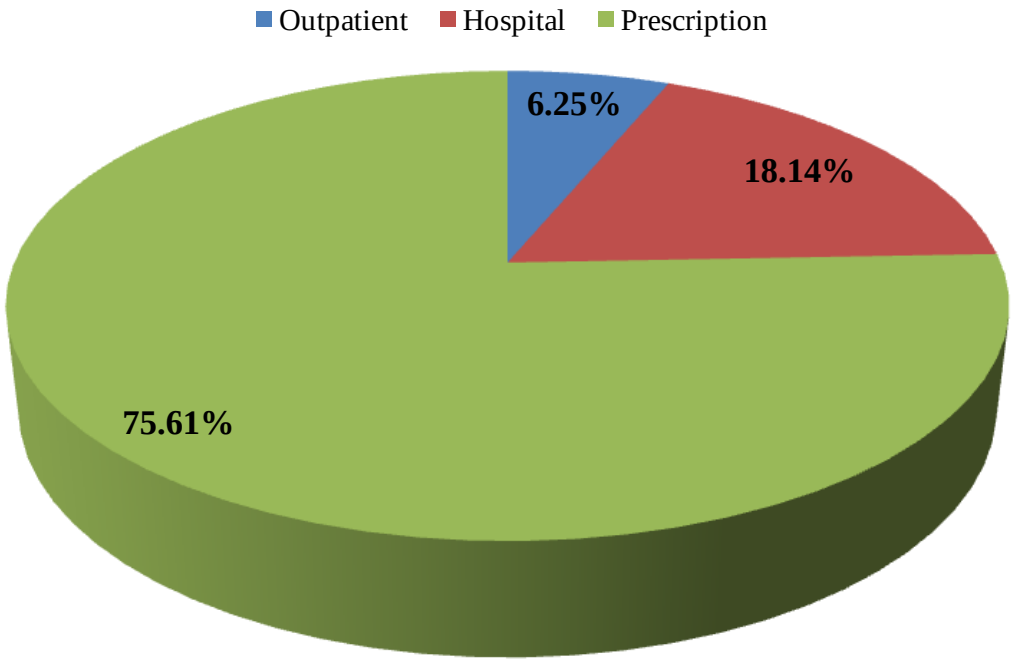


Figure 3.17b Twelve-Year Proportion of Overall Net Direct Medical Costs by Component, Narrow Definition – SARDs-CTD

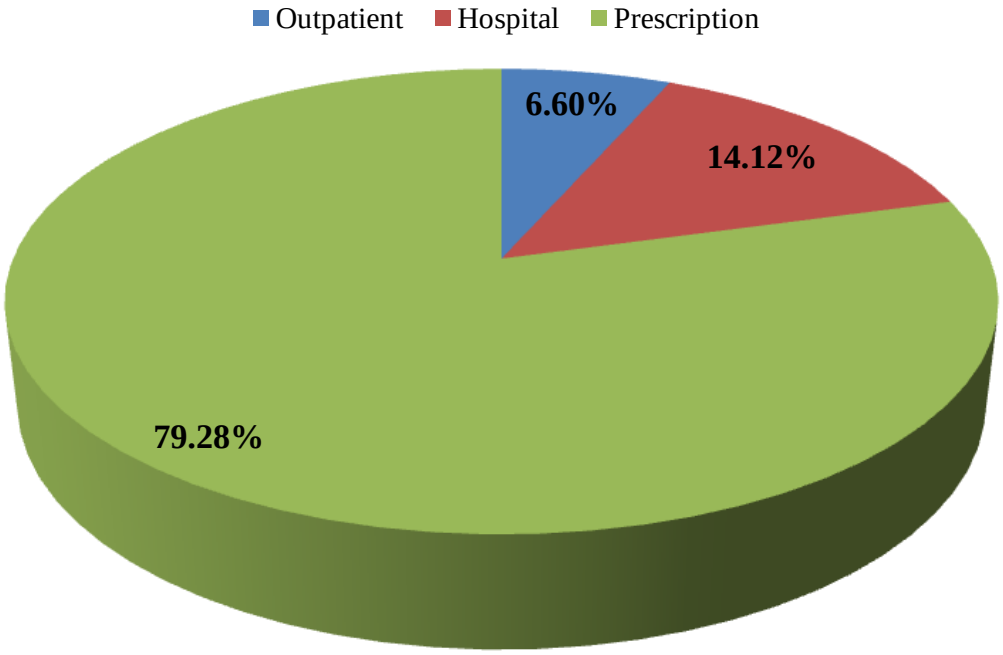


Figure 3.17c Twelve-Year Proportion of Overall Net Direct Medical Costs by Component, Narrow Definition – SARDs-VD

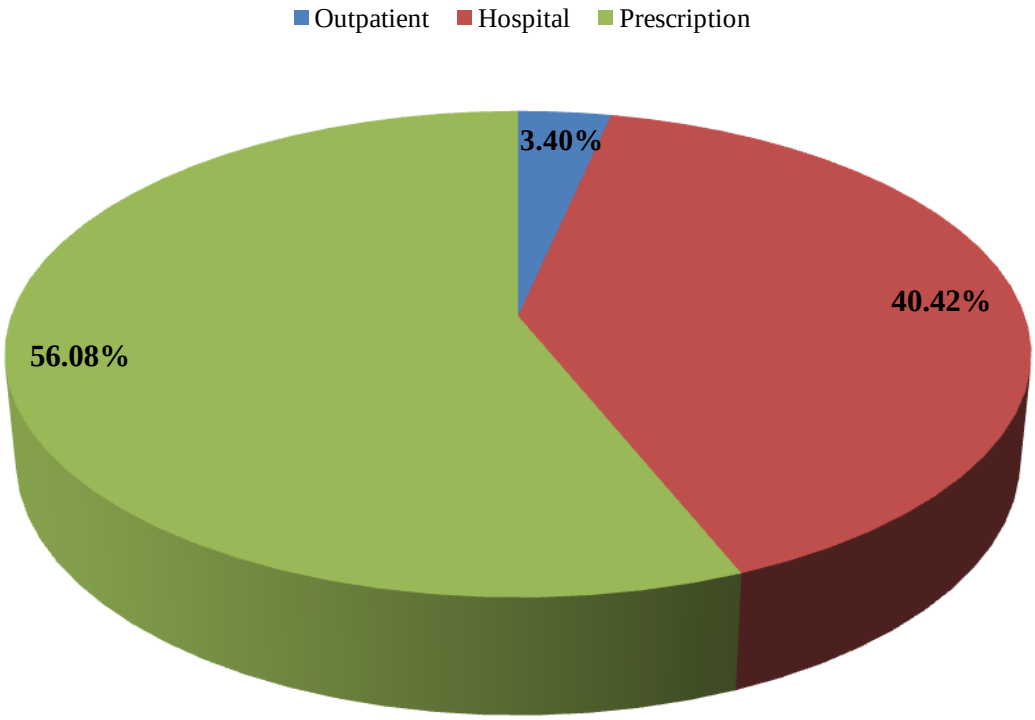


Figure 3.18a Annual Proportion of Gross Overall Direct Medical Costs Attributable to SARDs – all SARDs cases

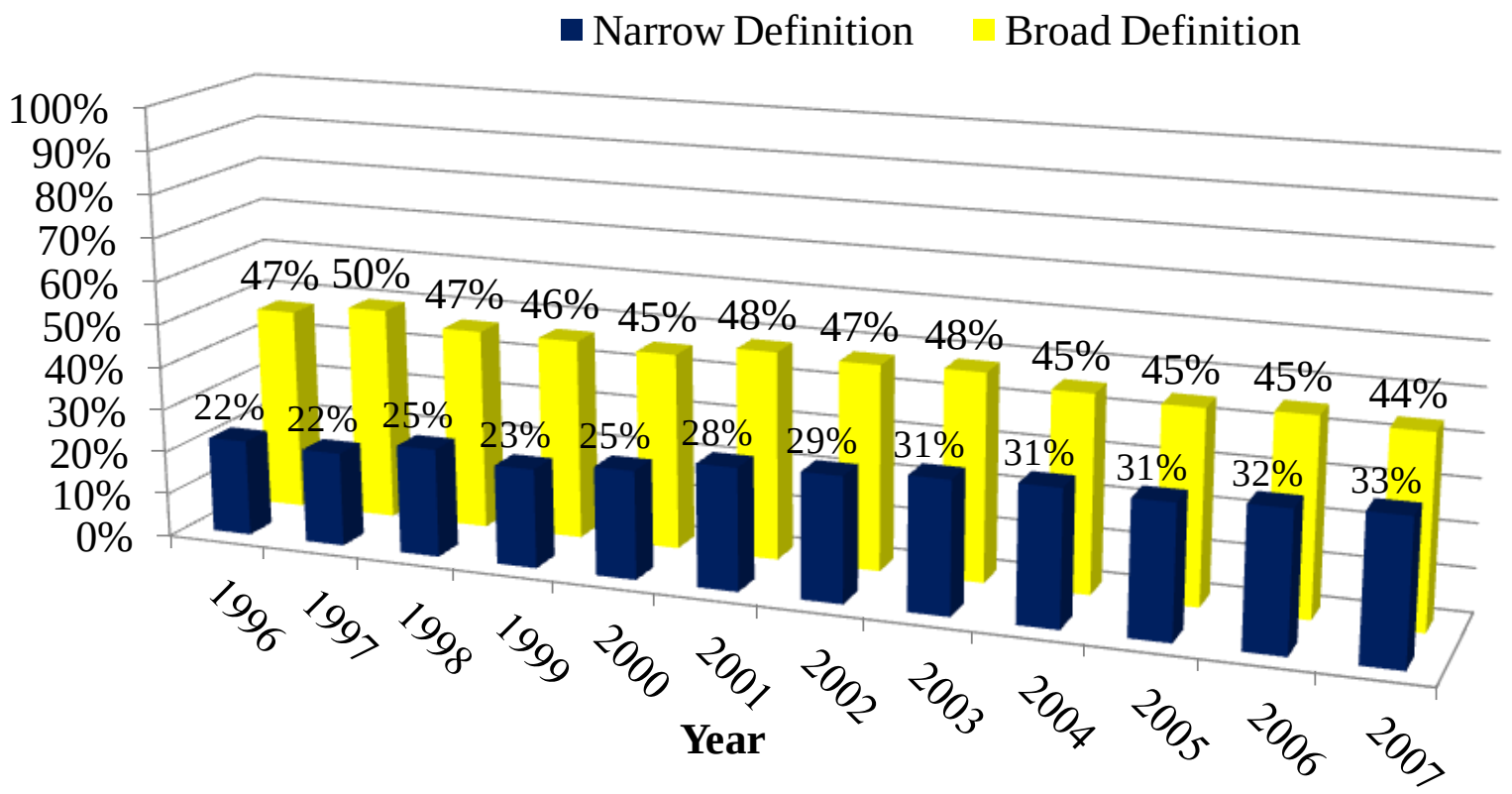


Figure 3.18b Annual Proportion of Gross Overall Direct Medical Costs Attributable to SARDs – SARDs-CTD

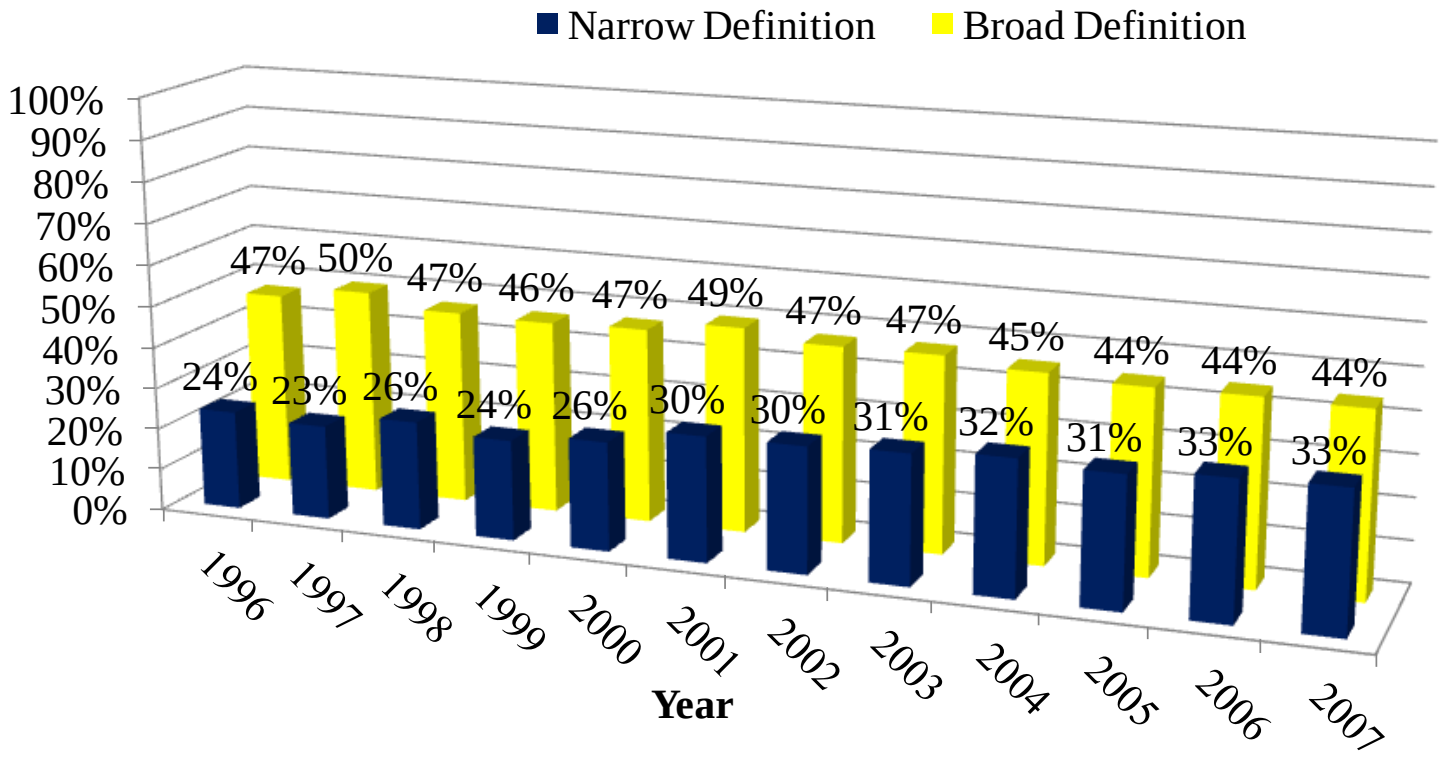


Figure 3.18c Annual Proportion of Gross Overall Direct Medical Costs Attributable to SARDs – SARDs-VD

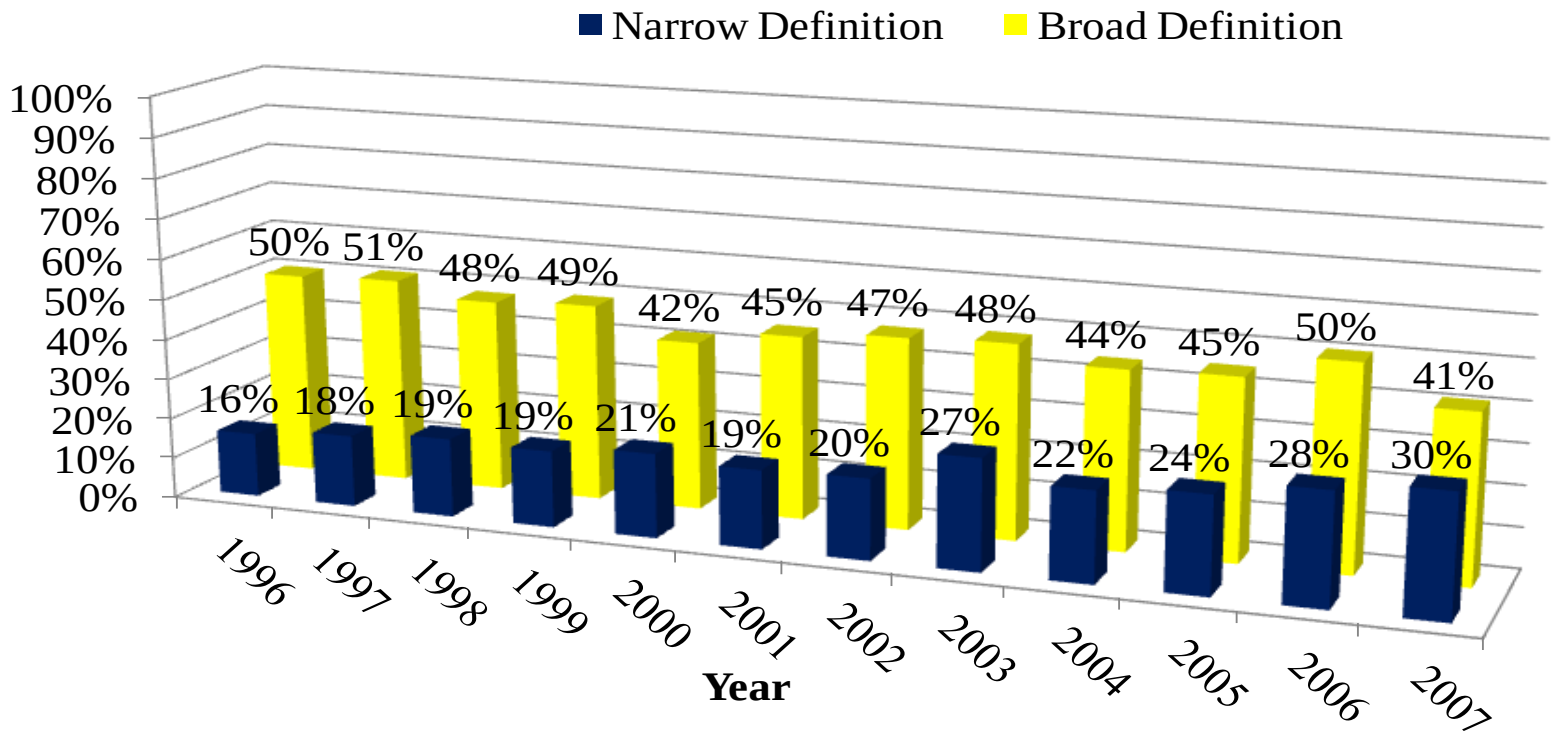


Figure 3.19a Twelve-Year Proportion of Net Direct Medical Costs by Component, Narrow Definition – SARDs

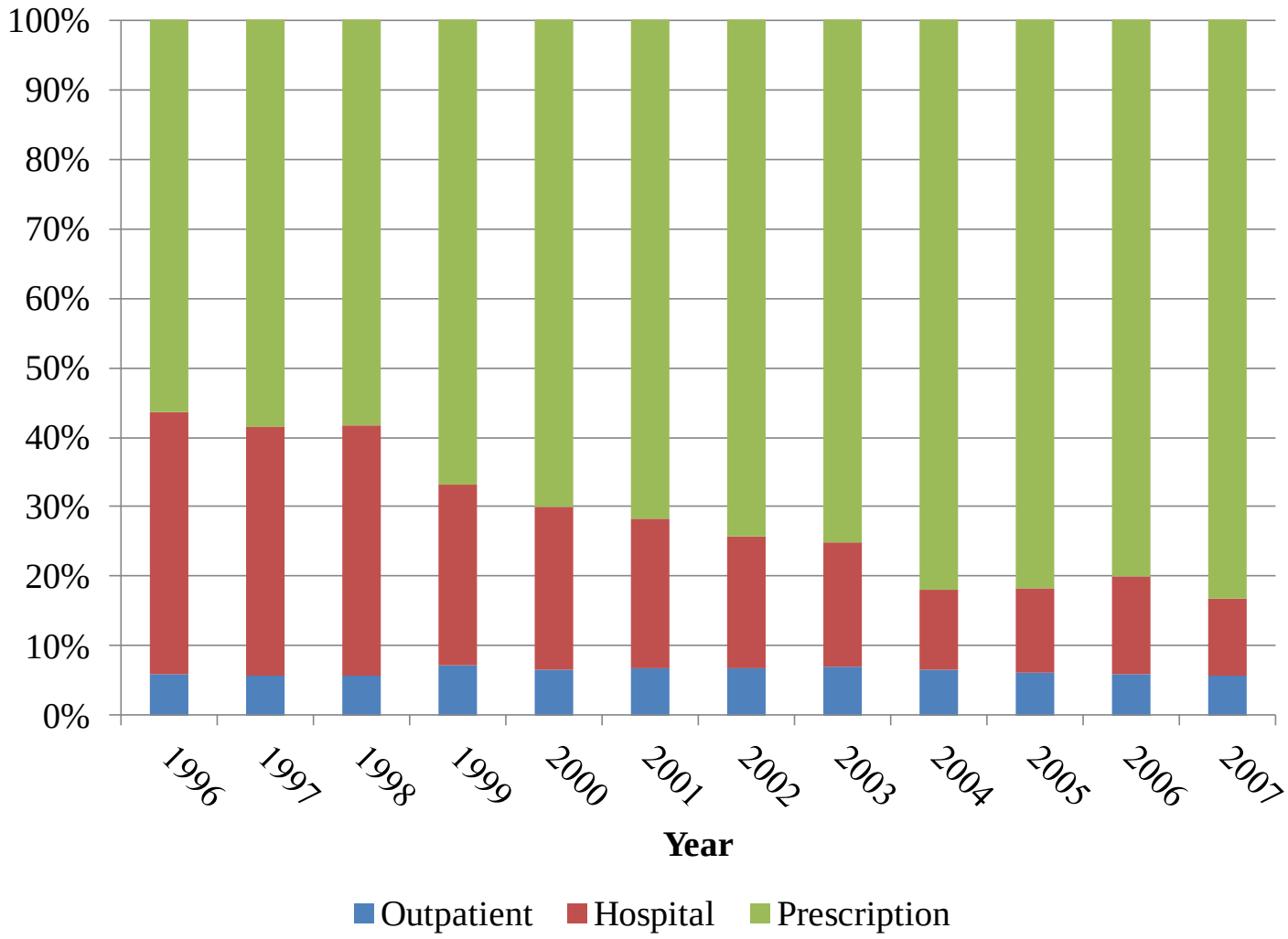


Figure 3.19b Twelve-Year Proportion of Net Direct Medical Costs by Component, Narrow Definition – SARDs-CTD

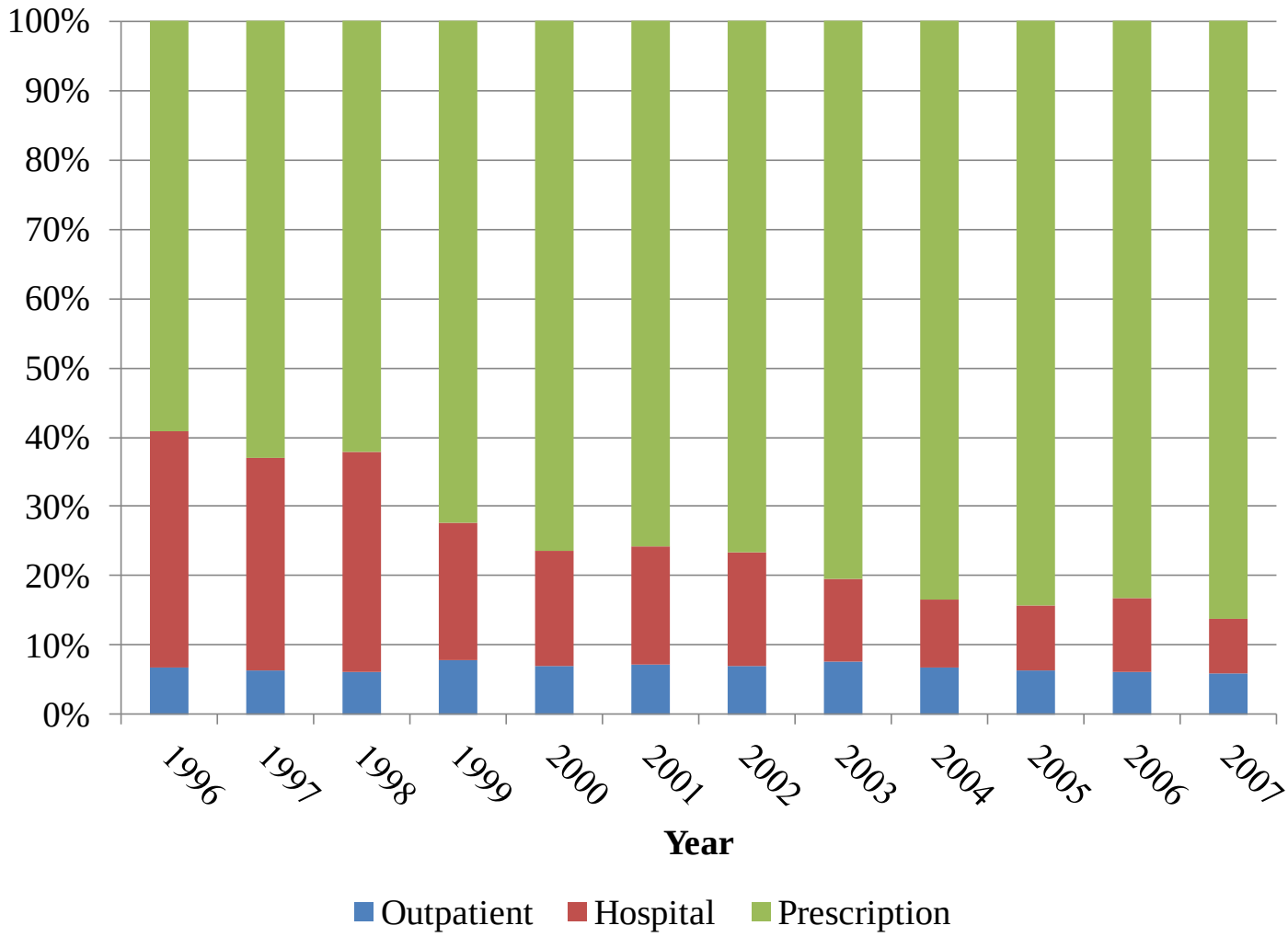


Figure 3.19c Twelve-Year Proportion of Net Direct Medical Costs by Component, Narrow Definition – SARDs-VD

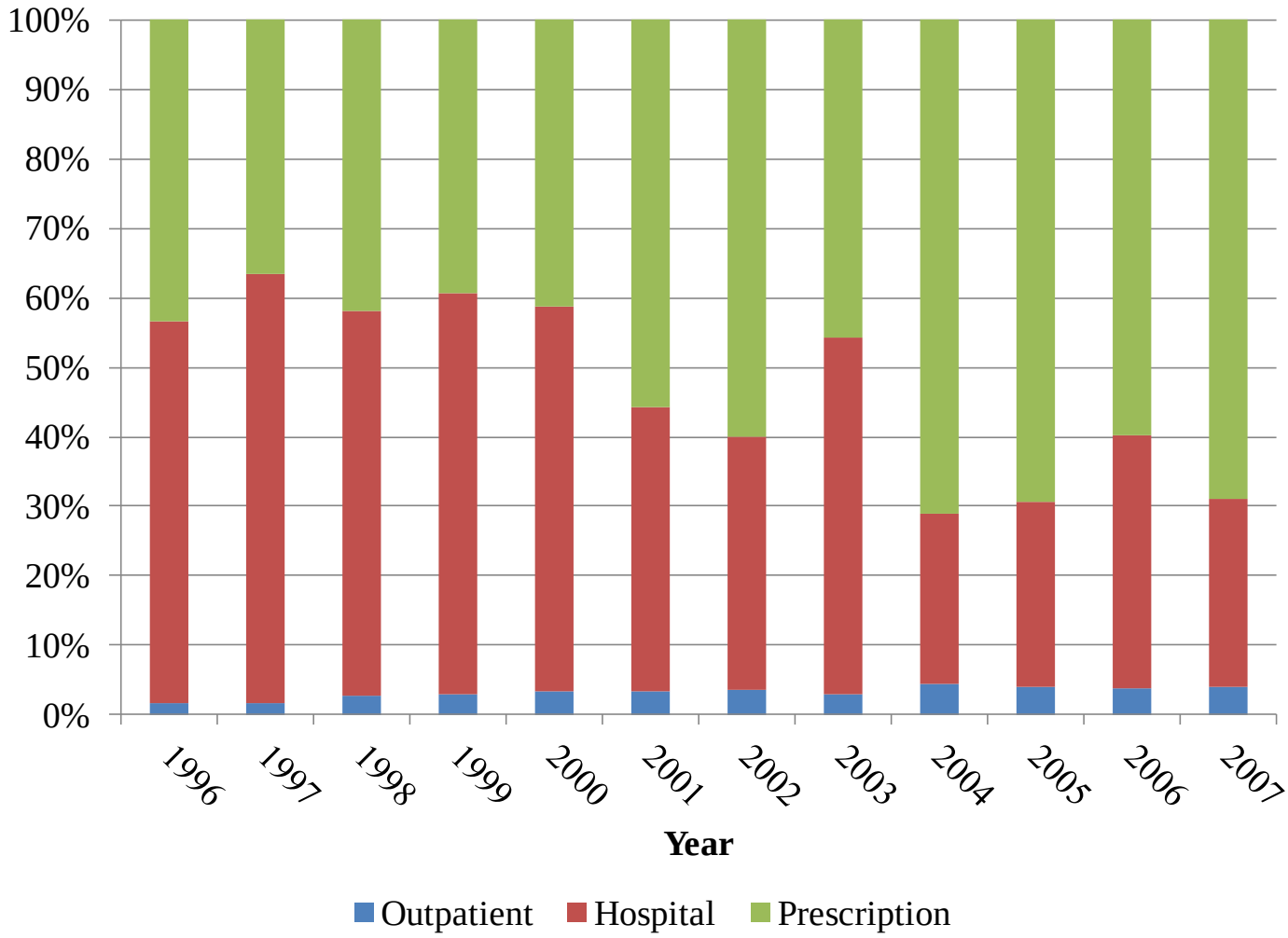


Figure 3.20 Crude Annual Mean Attributable Overall Direct Medical Costs, Per-Patient-Year – Narrow Definition (2007 Canadian dollars)

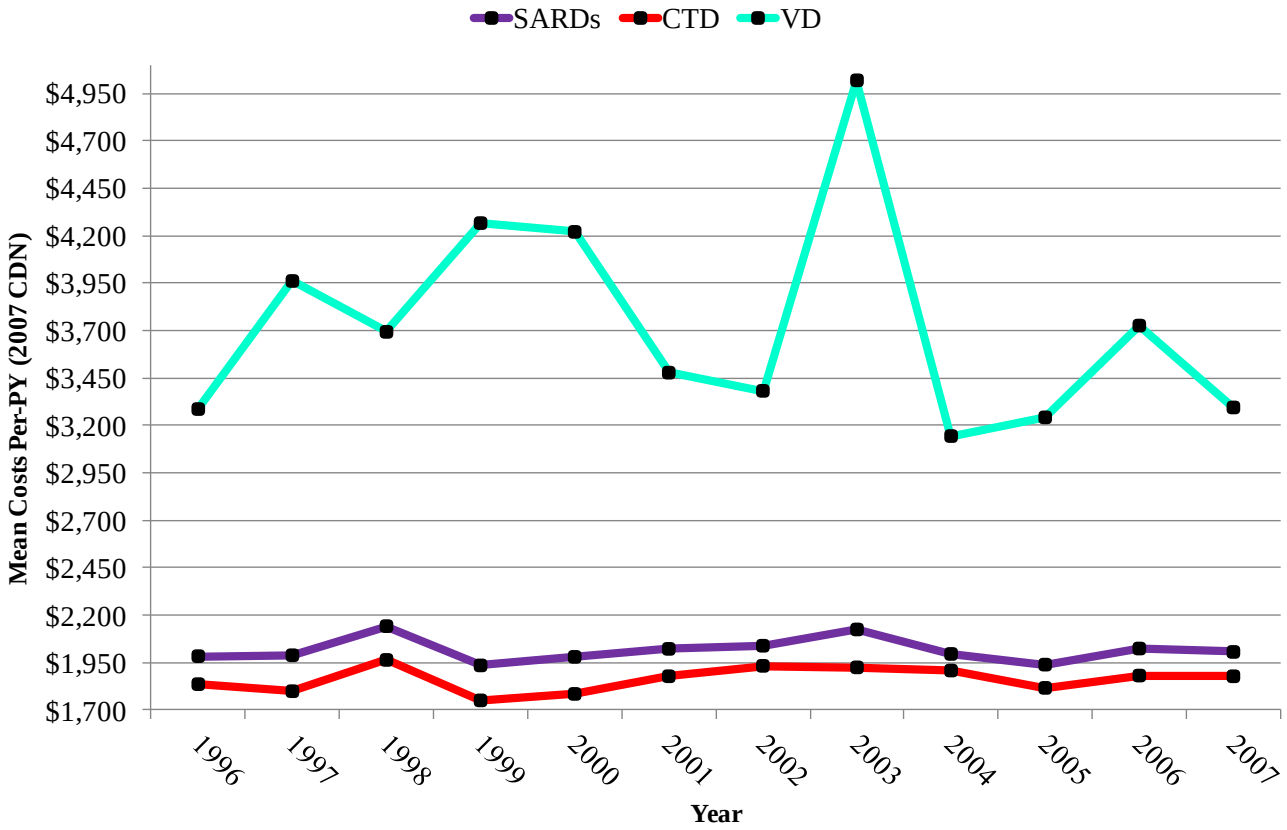


Figure 3.21a Twelve-Year Proportion of Overall Net Direct Medical Costs by Component, Broad Definition – SARDs

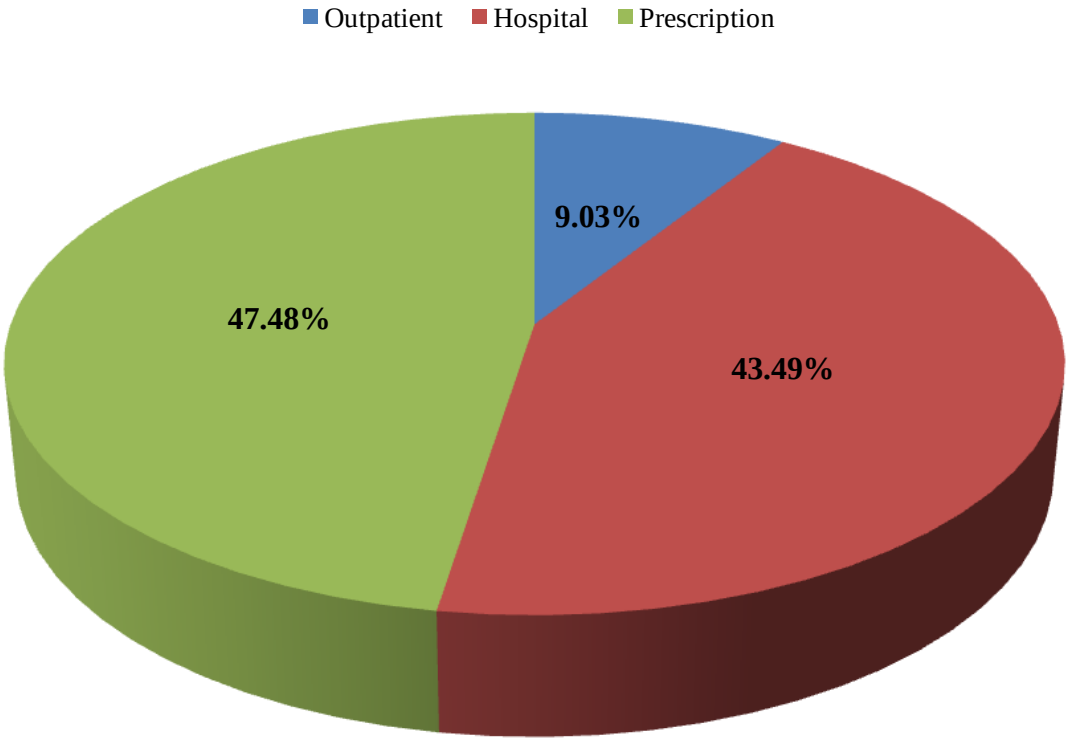


Figure 3.21b Twelve-Year Proportion of Overall Net Direct Medical Costs by Component, Broad Definition – SARDs-CTD

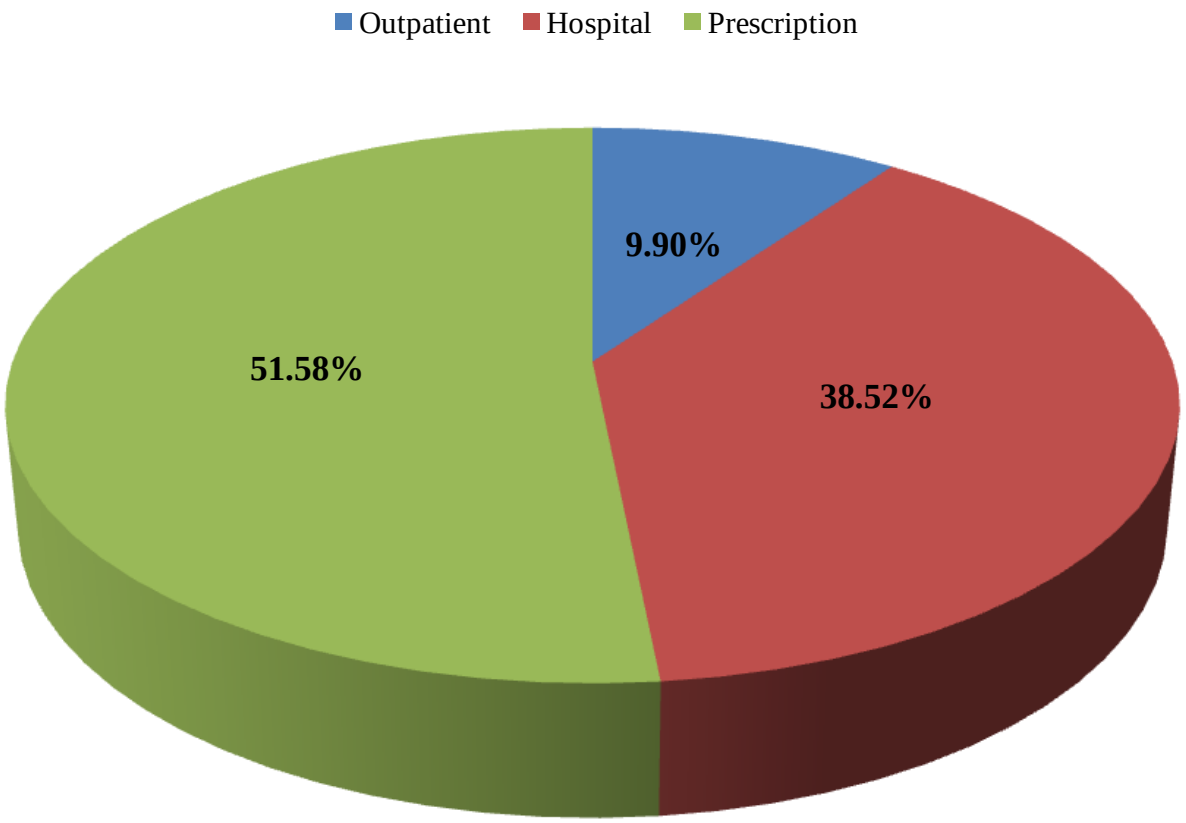


Figure 3.21c Twelve-Year Proportion of Overall Net Direct Medical Costs by Component, Broad Definition – SARDs-VD

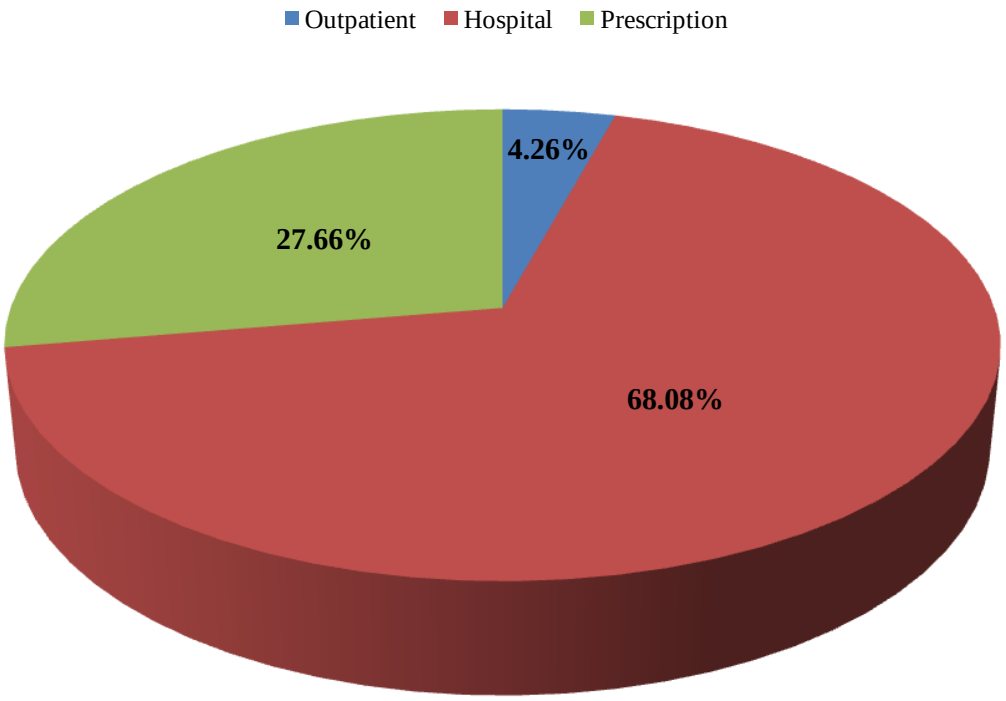


Figure 3.22a Twelve-Year Proportion of Net Direct Medical Costs by Component, Broad Definition – SARDs

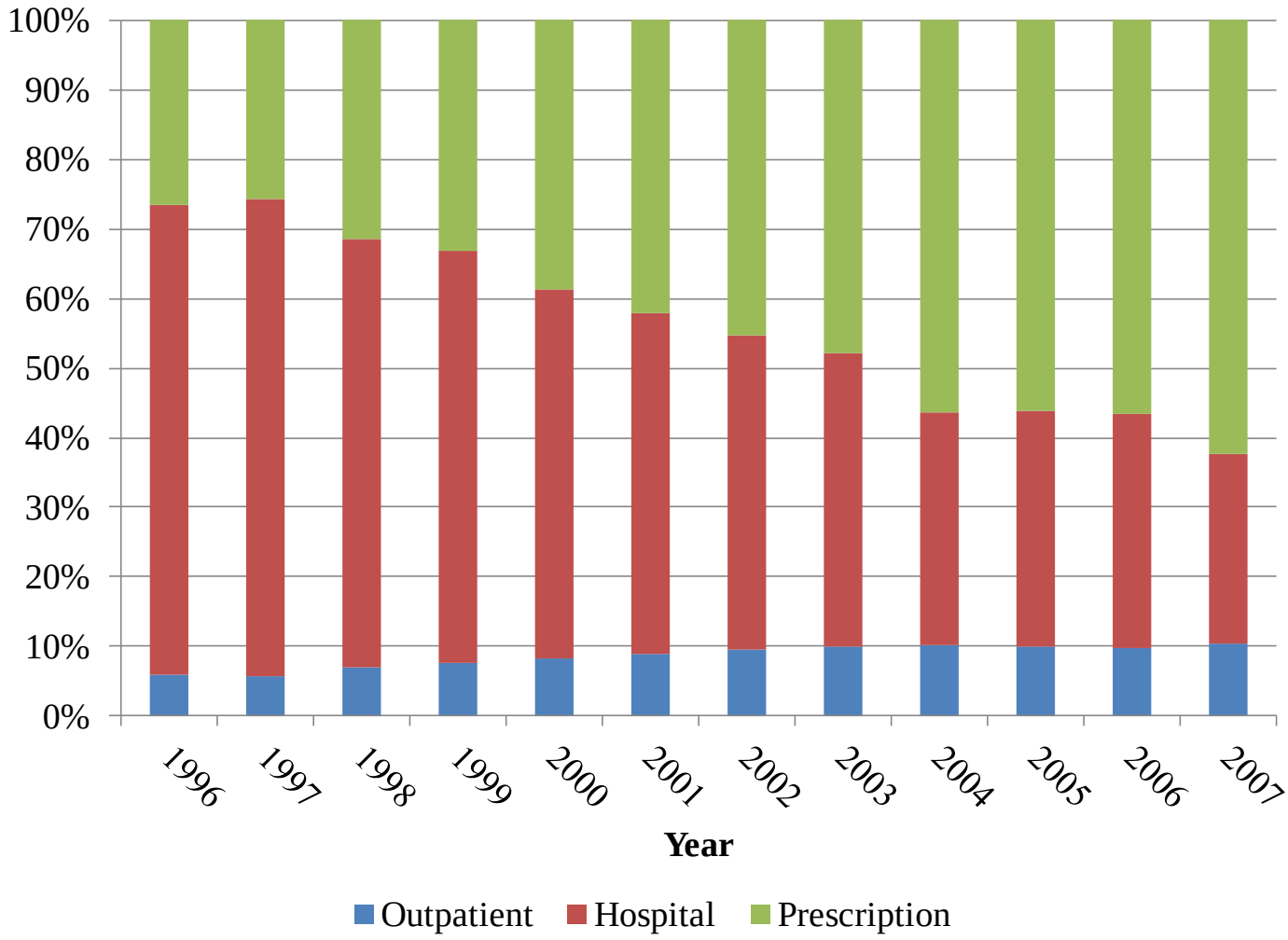


Figure 3.22b Twelve-Year Proportion of Net Direct Medical Costs by Component, Broad Definition – SARDs-CTD

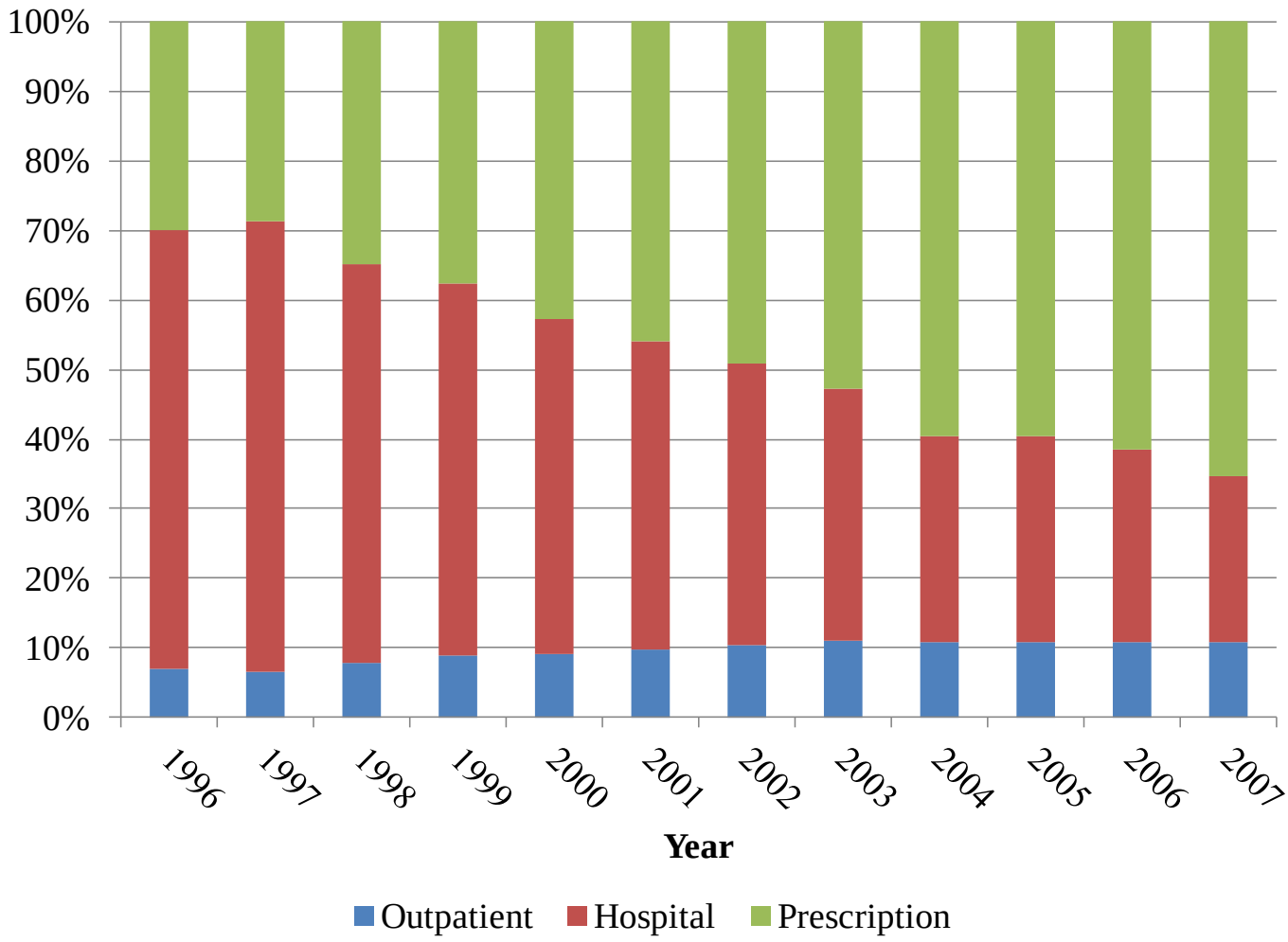


Figure 3.22c Twelve-Year Proportion of Net Direct Medical Costs by Component, Broad Definition – SARDs-VD

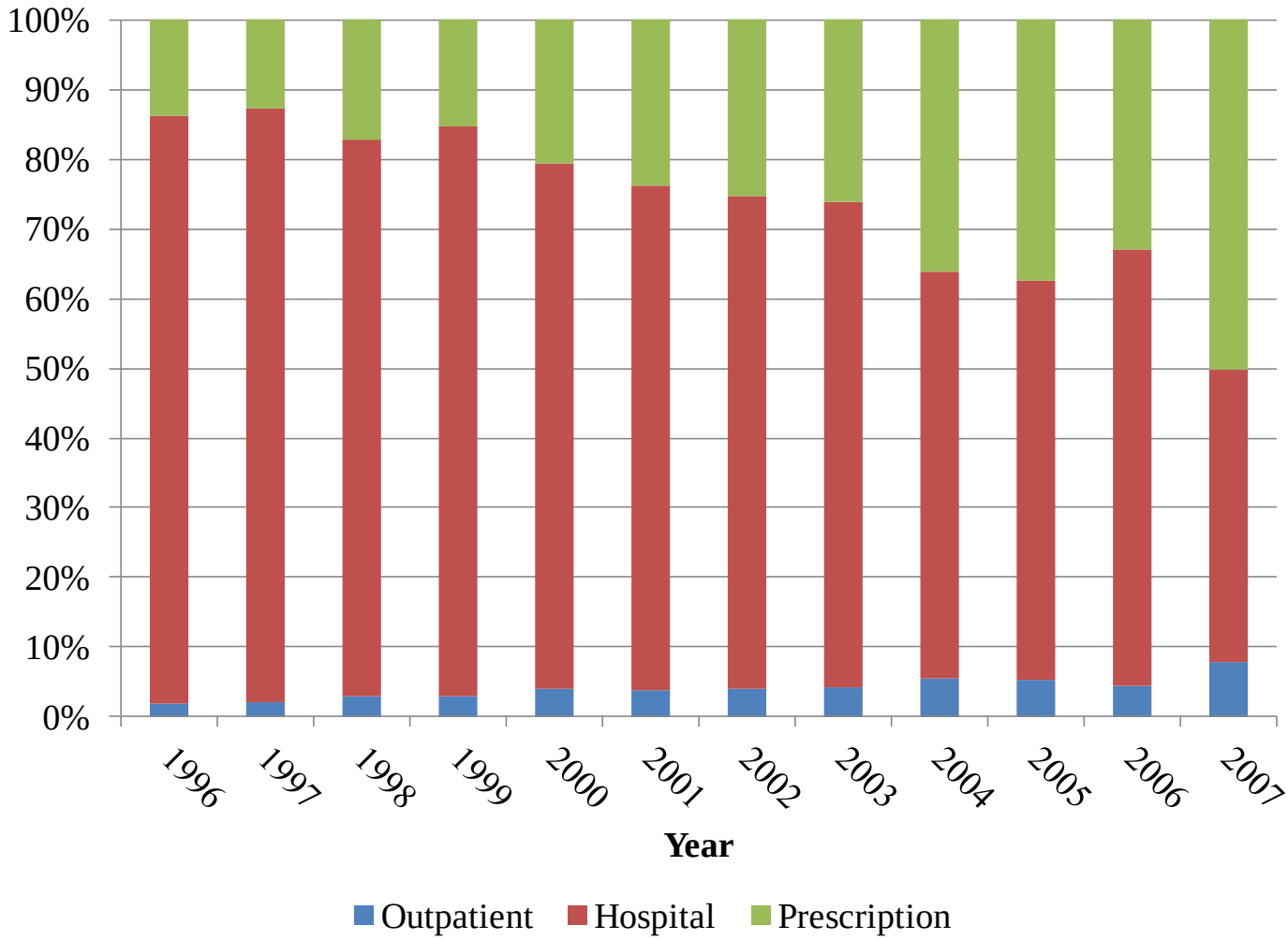
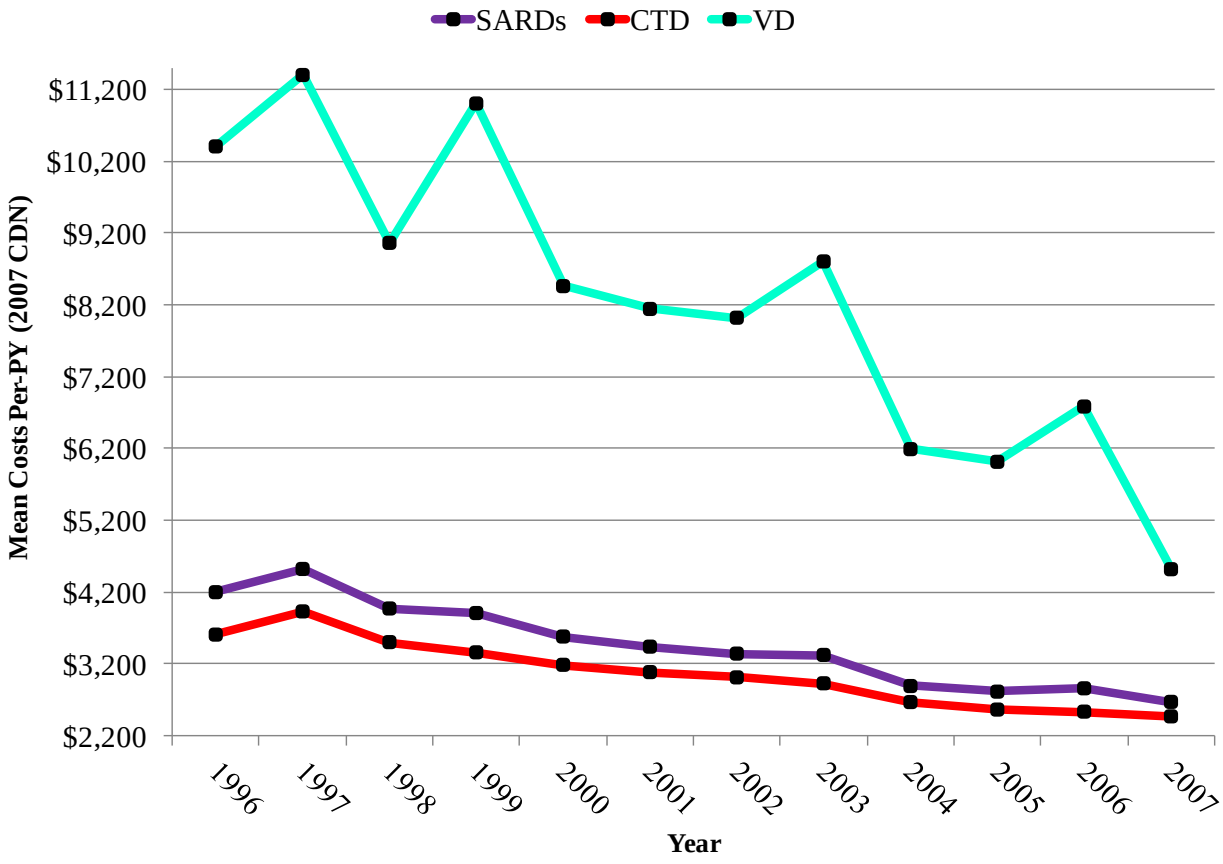


Figure 3.23 Crude Annual Mean Attributable Overall Direct Medical Costs, Per-Patient-Year – Broad Definition (2007 Canadian dollars)



4 Discussion and Conclusion

4.1 Summary of Key Findings

This research project was a longitudinal analysis of the health resource utilization and direct medical costs of SARDs at the population-level. It was one of few either longitudinal or population-based studies in Canada, or even the world, and the first to study all the SARDs together. We found the cumulative direct medical costs over a period of twelve years to be $571,216,780, $469,854,837, and $75,697,339, for SARDs, SARDs-CTD, and SARDs-VD cases, respectively. From the cumulative total for all-SARDs, $154,580,563 (27%) was for outpatient encounters, $291,664,951(51%) was from hospitalizations, and $124,971,267 (22%) was for prescription medications.

Prescription medications have been implicated in this unprecedented analysis as an important driver of the healthcare costs of SARDs at the population-level, both now and in the future. Here we have not only calculated the medical costs for all SARDs collectively, which has never been done before, but our twelve-year study period was the longest of any investigation like it. These factors, when combined with our population-based Canadian data source, made our estimates of the health resource utilization and direct medical costs of SARDs the most representative and comprehensive to-date. Our innovative efforts certainly paid off: the longitudinal trends we observed in these annual per-PY costs were most intriguing, but have some potentially alarming implications as well.

We identified 18,741 SARDs cases and found the healthcare burden of SARDs to be substantial, with annual direct medical costs averaging $6,954/PY, $6,230/PY, and $15,892/PY for all-SARDs, SARDs-CTD, and SARDs-VD, respectively. From the $6,954/PY for all-SARDs, $1,882/PY (27%) was for outpatient encounters, $3,551/PY (51%) for hospitalizations, and $1,521/PY (22%) for prescription medications. As compared to SARDs-CTD, SARDs-VD cases had a higher proportion of their costs from hospital (67% vs. 47%) and a lower proportion from medications (13% vs. 24%). Utilization of health resources is substantial too, with SARDs cases averaging 30 outpatient encounters, 0.59 hospitalizations, and 30 prescriptions per-PY. Those SARDs, SARDs-CTD, and SARDs-VD cases that had an inpatient hospitalization averaged 1.72 (STD=1.31, range=1-24), 1.68 (STD=1.27, range=1-24), and 1.90 (STD=1.47, range=1-22) annual admissions, respectively. Amazingly, although total annual

healthcare costs grew over the twelve-year period, overall mean per-PY costs decreased by 32% in this time, from $8,901/PY in 1996 to $6,087/PY in 2007 for all-SARDs. Mean per-PY outpatient costs decreased by 26%, from $2,205 to $1,641 per-PY, as did outpatient utilization, by 19% from 34 to 27 encounters per-PY. Hospitalizations showed an even larger decrease, with per-PY costs decreasing by half. Amongst the whole cohort mean annual admissions decreased by nearly as much (46%), with mean annual admissions amongst hospitalized SARDs cases decreasing too (by 11%, from 1.87-1.66). However, despite most healthcare costs decreasing over twelve years, the per-capita prescription costs for SARDs cases increased substantially in this time, by 50% from $1,117/PY to $1,670/PY. This was accompanied by an almost identical increase in prescription quantity, with the mean number dispensed annually to each case increasing by 49% in all-SARDs from 23 per-PY in 1996 to 34 per-PY in 2007.

We also compared the costs of SARDs-CTD cases with those of SARDs-VD cases, and SARDs-VD imparted a much heavier strain on the healthcare system. Their overall mean per-PY costs ($15,892/PY) were more than double those for SARDs-CTD cases ($6,230/PY), and their mean per-PY hospital costs ($10,700/PY) were more than triple those of SARDs-CTD ($2,968/PY). Correspondingly these cases had, on-average, twice as many hospital admissions (1.31/PY vs. 0.53/PY amongst all cases, 1.90 vs. 1.68 for hospitalized cases), 20 more outpatient encounters (48/PY vs. 28/PY), and 25 more prescriptions (53/PY vs. 28/PY) per-PY than did SARDs-CTD cases. However each subgroup demonstrated the same longitudinal trends, including the dramatic increase in per-PY medication costs.

Many aspects combined to make our analysis unique: it was population-based, longitudinal, used Canadian administrative data, and examined all the SARDs together. Its uniqueness, however, restricts comparisons with those studies conducted previously. The only other population-based, Canadian study (of PM/DM) reported (in 2007 Canadian dollars) similar annual per-patient outpatient ($1,042) and inpatient ($2,964) (294) costs to our per-PY estimates ($1,881/PY for outpatient and $3,146/PY for inpatient hospitalizations), thus supporting the validity of our findings. Medication costs were not included in that study. Although no investigators have calculated the healthcare costs of SARDs as a group, some clinic-based estimates do exist for some individuals SARDs. Our overall annual per-PY costs ($6,954/PY) were close to those reported (and inflated to 2007 dollars) for one Canadian SLE cohort ($6,210 per-patient) (315) but exceeded those for a Canadian SSc cohort ($5,038 per-patient).

In that study, the outpatient costs ($1,492 per-patient) were similar to ours ($1,882/PY) and mean annual medication costs ($1,575 per-patient) nearly identical to ours ($1,521/PY), but the hospital costs ($1,670 per-patient) (274) were approximately half of ours ($3,551/PY). Two additional Canadian SLE investigations produced much higher annual estimates than ours ($6,954/PY), but the first set, $8,667-$10,752 2007 CDN per-patient (276) were calculated for 1989 and 1990 so are unlikely to reflect current patterns of health resource delivery and utilization. The other investigation was more recent, but the per-patient estimates ($10,186-$12,122 2007 CDN (297)) may be less accurate since they were derived from just four weeks of utilization data. Also, the healthcare needs of clinic-based populations tend to be higher, on-average, than those in population-based cohorts like ours.

With published estimates of the direct healthcare costs of SARDs-VD severely lacking, comparisons to previous reports are difficult. The overall mean per-PY costs that we calculated for all SARDs-VD cases ($15,892/PY) were more than double those reported amongst just 67 TA cases ($6,801 2007 CDN per-patient) in Italy (318). The annual mean inpatient costs reported for TA ($3,631 2007 CDN per-patient), PAN ($4,879 per-patient) and Wegener's ($5,324 per-patient) in New York State (295) were also lower than our overall annual per-PY estimate for all SARDs-VD ($10,700/PY). However, this could be explained by US healthcare costs tending to be higher, on-average, than Canadian. We do emphasize our corresponding annual estimate for 2007 ($6,179/PY) was closer to these published estimates.

The first-ever Canadian estimates of the *net* health resource and economic burden of any SARD at the population level were also produced by us. This was done according to two definitions of SARDs-attributable healthcare consumption, though the same prescription medications were included in both definitions. The narrow definition included all outpatient claims from a rheumatologist and/or coded with a SARDs diagnosis, and all hospitalizations with a primary diagnosis of a SARD. Even under this narrow, most conservative definition of SARDs-related health services, SARDs-related annual costs accounted for 29% of gross healthcare costs and averaged $2,011 per-PY. Prescription medications were especially influential here, with 76% of net costs ($1,520/PY) from medications, and SARDs cases averaging 30 attributable prescriptions per-PY. Hospital services contributed to 18% ($365 per-PY) of costs and outpatient just 6% ($126 per-PY), with SARDs responsible for an average of 0.04 hospital admissions and two outpatient encounters per-PY in these cases. While SARDs-VD cases incurred higher gross per-PY

healthcare costs than SARDs-CTD, somewhat less (only 23%) of these were actually attributable to SARDs under this definition.

All services from the narrow were included under the broad definition too, as were other SARDs-related outpatient services and hospitalizations with a SARD as any discharge diagnosis. The immense burden of SARDs was particularly apparent under this definition, with these disorders responsible for nearly half (46%) of all the direct medical costs incurred by our cases. This was consistent for the SARDs-CTD and SARDs-VD subgroups, with the overall annual burden of SARDs averaging $3,202/PY, $2,866/PY, and $7,390/PY, respectively for each group. Attributable hospital costs were almost four-times greater under this definition at $1,393/PY (44%) for all-SARDs, though prescription costs remained the largest contributor (47% of net costs). Mean per-PY net outpatient costs and encounters doubled under this broad definition but - averaging $289 and four encounters per-PY for all-SARDs - were still relatively low. This attribution analysis suggests SARDs-VD-specific care may actually be more expensive than care specific to SARDs-CTD. Nearly the same percentage of gross healthcare costs for SARDs-VD and SARDs-CTD cases (47% and 46%, respectively) were attributable to these disorders under the broad definition, but the actual annual mean per-PY attributable cost estimate was still two-and-a-half-times greater for SARDs-VD ($7,390/PY) than SARDs-CTD ($2,866/PY).

Longitudinally, annual mean per-PY costs were relatively stable for each group under the narrow definition but decreased under the broad. The twelve-year decrease in mean per-PY net costs (36%) was slightly greater than that for gross costs (32%). Over twelve years these net mean per-PY costs decreased by twice as much in SARDs-VD cases (by 57%) than SARDs-CTD (28%).

As with gross costs, the innovative design of our study - our grouping of the SARDs, population-based analysis, twelve-year study period, and use of Canadian administrative data - also limit comparisons of our attribution estimates to previous work. This problem is compounded by the paucity of estimates available as to the incremental costs of any SARD. Table 1.9a lists the findings (all standardized to 2007 Canadian dollars) of the six previous investigations that produced estimates of incremental mean per-patient costs. Our net overall per-PY estimate under our broad definition was close to annual per-patient estimates for SjD in the UK ($3,085) (311) and SLE (in the

absence of nephritis) in the US ($2,964) (301). Although the four other per-patient cost estimates were much higher than ours (299,302,304,316), the *gross* per-patient estimates were much higher in these investigations too . We found 29-46% of gross healthcare costs could be attributed to SARDs, and this percent varied amongst the prior studies. Three reported higher percents (57% of total costs for SjD cases (311), and 63% (299), and 66% (302) of total costs for SLE cases) while the percent was similar or lower (15-42% (304), 23-31% (301)) than ours in two other SLE investigations.

4.1.1 Burden of SARDs

Even when viewed in isolation the per-capita healthcare costs of SARDs cases are clearly substantial. When compared to average per-capita provincial healthcare spending in BC, our most current annual estimate for all-SARDs cases ($6,087/PY in 2007) exceeded the BC estimate for that year ($3,231 2007 Canadian dollars (290)) nearly two-times. The magnitude of these costs is made more apparent when they are compared to the costs of other types of arthritis. The annual mean per-patient costs, in 2007 Canadian dollars, incurred by Canadians with RA, OA, juvenile idiopathic arthritis (JIA), and fibromyalgia are tabulated in Table 1.10. As described in Chapter 1 some previous cost estimates for some individual SARDs exceeded multiple estimates for RA. The estimates we calculated reinforced this, being comparable to, and actually exceeding, many of the estimates for RA and other arthritides, all of which are more prevalent than SARDs (Table 1.10). As well, these studies and others have suggested the intensity of health resource consumption, particularly with regards to hospital use, is lower in these other forms of arthritis (278,279,319). This may mean SARDs not only impart a high cost burden, but also a health services burden that is even larger than these other arthritides.

While population-based estimates for arthritis in Canada are lacking, our approach has been used to estimate the costs of other chronic conditions at the population-level in Canada. With two such investigations (for the costs of diabetes cases in Saskatchewan) producing overall per-patient estimates for 1996 ($4,296 2007 CDN)(442) and 2001 ($3,777 2007 CDN)(439) that were about half of the mean per-PY costs incurred by SARDs cases in those years ($8,901/PY and $7,148/PY, respectively) we do not believe we have overestimated the direct medical costs of SARDs with these methods.

4.1.2 Longitudinal Trends

Over our twelve-year study we observed that the overall mean per-PY direct medical costs of SARDs cases have decreased (with specific decreases for the outpatient and hospital components), while mean per-PY medication costs have increased. We described in Chapter 1 how no longitudinal Canadian studies have produced annual per-patient cost estimates. However in the approximately eight years between two cross-sectional studies on the direct medical costs of SLE cases - by the same investigators using a similar patient population - the average annual per-patient costs decreased by 44%, from $11,124 2007 CDN (for 1989-1990) (276) to $6,210 2007 CDN (for 1995-1997) (315). Between two similarly-conducted Canadian investigations of RA, a 67% decrease in the per-patient hospital costs of RA cases (from $2,767(277) to $907(278) 2007 CDN) was observed over approximately eight years. All of these decreases add to the plausibility of our findings, and as we will describe further in section 4.2 of this chapter, may stem from increased healthcare efficiencies.

Only two other longitudinal individual SARD studies exist for comparison (304,324), both of which were also population-based. The first followed a US cohort of "newly-active" SLE cases in a Medicaid database for five years: their mean annual per-patient costs decreased in the second year but increased by an average of 16% in each subsequent year (304). These authors attribute their findings to a pattern where the acute illness that first led to diagnosis or flare stabilizes in the second year, thus decreasing per-patient costs. They believe the annual costs subsequently increased from continued "disease progression" (304). But the cohort in this study was restricted to "newly-active" cases – either incident cases or prevalent cases beginning a new "episode of care" (defined as those who did not have an SLE-coded health encounter in the six-months preceding their index SLE encounter) (304). Since we did not employ the same restrictions one may expect the SLE cases in this US study to have different per-PY cost and utilization patterns, on average, than our cohort, which may explain why we instead observed a decrease in mean per-PY costs.

The second study (by Chiu and Lau) followed a cohort of SLE cases in Taiwan for up to eight years, from 2000 to 2007. The data source was the Taiwanese National Health Insurance Research Database, covering at least 96% of the population. Diagnostic accuracy was enhanced in this study since all SLE cases had their diagnosis verified in order to qualify for free medical insurance (324). Mean annual per-patient costs, which included outpatient and

hospital components, increased during this time but only by 15% (from $1,421 to $1,628), or $207 (324) 2007 CDN. Two factors could account for the disparity between these observations and ours: healthcare costs and delivery practices may differ between Canada and Taiwan, and the per-patient Taiwanese costs could have increased if Taiwan implemented more expensive SLE treatments during this time that had already been established in Canada. Second, although Chiu and Lau did not intend to exclusively tabulate the net costs of SLE, only those claims coded for SLE were included in their analysis, which limits its comparability to our gross analysis.

In addition to these disease-specific estimates, our findings are consistent with some longitudinal healthcare spending trends observed in the general Canadian population. From 1990 to 2010, mean per-capita drug costs (including non-prescription drugs) increased by 265% (from $250 to $912 1997 CDN) (444). Our observations as to the *types* of drugs consumed longitudinally also mirrored national trends. In our analysis the two classes contributing most to the growth in mean per-PY costs over twelve years were immunosuppresants (accounting for 20% of the difference in mean per-PY costs) and lipid-modifying agents (accounting for 13%). These same classes were also the top-two contributors (at 12% and 10%, respectively) towards wholesale drug spending increases from 2004/05 to 2009/10 amongst the general Canadian population (444).

4.2 Interpretation of Findings

4.2.1 Decreases in Mean Per-Patient-Year Outpatient Utilization and Costs

In longitudinal analyses it is important to be consistent regarding the types and quantities of encounters captured each year. But this was impossible for outpatient encounters since billings from supplementary benefit practitioners (including physiotherapists, chiropractors, optometrists, massage therapists, naturopaths, acupuncturists, and podiatrists) were only available through the 2001/02 fiscal year. MSP stopped covering most of their services after this point (429,431). These billings only contributed to 8% of the outpatient claims we captured through 2001, but the average annual decrease in per-PY outpatient costs was more than twice as high in the years after 2002 (3.9%), when this change took place, than the years before (1.7%). Therefore, this longitudinal inconsistency may explain some of the corresponding decrease in per-PY outpatient costs, and, to a lesser extent, per-PY overall costs. To examine this, we compared the magnitude of the five-year decreases in outpatient costs and encounters before and

after this change took place. The decreases in the five years following it (2002-2007) were more than twice as much as those in the five years previous to it (1997-2001): 16.9% vs. 8.3%, for costs, and 8.43% vs. 3.64% for encounters. The partial absence of these encounters may also explain why our twelve-year average outpatient and overall per-PY estimates ($1,882/PY and $6,954/PY, respectively) were lower than per-patient estimates from some other Canadian reports ($2,922-$3,165 2007 CDN for outpatient, $8,667-$10,752 overall) (276) ($3,390-$3,578 2007 CDN for outpatient, $10,186-$12,122 overall) (297), which did include these encounters.

4.2.2 Increases in Mean Per-Patient-Year Prescription Costs

Our most remarkable finding was the twelve-year *increase* in annual mean per-PY prescription costs, which was in contrast to the twelve-year decrease in overall annual mean per-PY direct medical costs. There are likely multiple reasons for such a large (50%) increase. But we must first emphasize this mean per-capita increase was observed after all annual costs were standardized to 2007 dollars, so inflationary increases are not the explanation.

Proportion of Cases Dispensed a Prescription

The Canadian Institute for Health Information (CIHI) has proposed many other explanations for longitudinal increases in drug costs (444). Since our annual per-PY estimates were crude (calculated amongst all cases followed each year, and not just those receiving prescriptions), total prescription costs, and therefore mean per-PY costs as well, may increase if there were annual increases in the proportion of cases dispensed a prescription. But we did not observe a large increase: this annual proportion only grew by 4% over the twelve years, from 86% of cases in 1996 to 90% in 2007. Therefore this factor would only have made a minor contribution to the nearly 600% increase in total annual drug costs we observed. As well, the annual mean per-PY estimates calculated amongst users (or only those cases dispensed a prescription) (Appendix B) were very similar to the crude annual per-PY estimates (Appendix B) and these costs demonstrated nearly the same twelve-year increase (54%) as crude mean per-PY costs. This shows, instead of being driven by the rising costs of small number of cases, the 50% increase in mean per-PY costs reflected an increase in the costs incurred by most cases.

Mean Number of Prescriptions Dispensed Per-Patient-Year

A rise in the annual number of prescriptions dispensed to each case, on-average, could also drive up both total (444), and mean per-PY drug costs. Such a rise (11 prescriptions per-PY, on-average or 49%) did occur within our cohort: cases were dispensed an average of 23 prescriptions per-PY in 1996 and 34 per-PY in 2007 (Appendix B). Of interest, the cost of each prescription over twelve years averaged $50.71 2007 CDN, which, when multiplied by 11 (the mean difference in per-PY prescriptions over twelve years), equals $557.81. As this amount is almost equal to the actual dollars by which mean per-PY drug costs increased from 1996 to 2007 ($553.05, on-average), this rise in annual mean prescriptions dispensed per-PY can be considered a major factor in the twelve-year drug cost increase.

Unit Drug Prices

CIHI cites two other potential contributors to rising drug costs, unit price increases (particularly for the same drugs), and a changing and more-expensive drug mix (444). These factors are difficult to separate because the drug mix for SARDs cases was not stagnant over the twelve years. But unit price increases are an unlikely explanation since we observed nearly-identical increases in total drug costs and prescription quantities (586% and 582%, respectively), and mean per-PY costs and prescriptions, over the twelve years. If it was just a matter of the prices increasing, prescription costs would have increased much more than the quantity did. CIHI also discounts the influence of price increases. They reported that while nationally total drug costs increased from 1998 to 2007, drug prices overall actually decreased in this time, by an average of 2.7% each year (444). Our observations were similar: the average cost of each prescription changed little from 1996 to 2007, increasing by only 0.48% over the twelve years (from $48.61 to $48.84 2007 CDN), and by 0.10% annually, on-average.

More importantly, average prices *decreased* within many drug classes. Table 3.14 shows - for the major classes of drugs dispensed to the cohort - the twelve-year change in their annual mean prices, and in thirteen of these twenty classes the average annual price decreased. Of particular note are the many classes in which the annual mean unit price *decreased* while mean per-PY consumption actually *increased*. The drugs in many of these classes - RAAS agents, calcium channel blockers, bisphosphonates, and lipid-modifying agents – are commonly used in the management of SARDs and their associated comorbidities. Therefore with the mean annual unit price decreasing in most classes where mean per-PY consumption increased, unit price increases should not account for our findings.

Emergence of Expensive Prescriptions

Although unit price increases for the same drugs would explain little of the per-PY cost increase, a more-expensive drug mix would. As illustrated in Chapter 3 and Appendix B, some of the most frequently-prescribed drugs each year were acetaminophen-codeine, prednisone, and levothyroxine. But given their low mean unit costs - $13, $12, and $12, respectively - increased dispensing of just these types of prescriptions could not lead to such a massive (50% per-PY) cost increase. In fact, over twelve years mean per-PY consumption actually decreased for two of these oft-prescribed-but-inexpensive drugs: prednisone by 16% and acetaminophen-codeine(30mg) by 38%.

Instead, some more expensive medications were prescribed to the cohort over the course of the study period, and in greater quantities. These drugs (and their average unit prices) included mycophenolate, which was only prescribed to our cohort after 1997 ($535 2007 CDN), and bosentan ($3,877), infliximab ($3,956), and etanercept ($1,609), all three of which were approved in 2001 (89). Given their high prices, the emergence of these drugs certainly had an impact, albeit moderate, on annual prescription costs. While they made no contribution to drug costs in 1996 or 1997, these five medications accounted for 10% of mean per-PY prescription costs in 2007. This occurred despite these being rarely dispensed (only accounting for 0.45% of total prescriptions in 2007). And their growing contribution to annual drug expenditures was not from their unit costs increasing, since the mean unit price for three of these drugs decreased between 2005 and 2007. Table 3.12b shows how bosentan and mycophenolate were the top contributors, on-average, to the twelve-year increase in per-PY drug costs. With so few prescriptions dispensed for these drugs, they would not have been responsible for the cost increase for most individuals. Still with these drugs costing so much and accounting for a rising share of total annual prescriptions (from 0.29% in 2003 to 0.37% in 2005 and 0.45% in 2007) the impact of this changing and more-expensive drug mix should be noted.

Higher Outpatient Drug Consumption

Rises in per-PY prescription consumption and the emergence of more expensive drugs are likely the primary explanations for the increases in prescription medication quantity and costs; however, there is an additional, methodological one. Nationally, there has been a shift in drug spending from the hospital to outpatient setting. In 1996, about 40% of drug spending occurred in an outpatient setting and 60% in hospital, but this share has steadily

increased and in 2007 actually exceeded the inpatient share(446). Since PharmaNet captures all prescriptions dispensed on an outpatient basis, but not inpatient medications, this shift would lead to more prescriptions appearing in PharmaNet over time, followed by a higher mean number of prescriptions dispensed per-PY.

4.2.3 Potential for Improved Healthcare Efficiencies

Our study has many positive findings. From the patient perspective, spending less time in hospital and making fewer physician visits may provide them with a better quality of life. From the government (payer) perspective our findings are suggestive of improvements in healthcare delivery, with care being provided more efficiently and at a lower cost. One example is the proportion of hospital admissions that were inpatient, which decreased from 75% of admissions in 1996 to 56% of admissions in 2007. In terms of spending, the crude average cost of each outpatient encounter decreased by 9% over twelve years, and the cost of each hospital admission by 8% (from $6,285-$6,069/PY). Also, the twelve-year decreases we observed in mean per-PY outpatient and hospital utilization were less (19% and 46%, respectively) than the corresponding decreases in mean per-PY costs (26% and 50%, respectively). If these decreases were equal, it would suggest the mean per-PY cost decreases resulted only from decreases in consumption.

These longitudinal decreases in spending and resource consumption may be concerning to some but simply spending more money on healthcare and/or providing more services does not always lead to better outcomes. SARDs are no exception and this point was emphasized by Clarke *et al* while reporting on the healthcare costs and outcomes for Canadian, American, and British SLE cases in two studies. In their first study, the overall direct per-patient costs of the three cohorts did not differ significantly, but the Canadian cohort experienced significantly better outcomes (315). When this analysis was expanded, the Canadian and British cohorts incurred lower (20% and 13%, respectively) average per-patient costs but had similar outcomes to the American (314). The scope of our analysis prevented us from examining which outpatient encounters or types of admissions showed the largest decreases. With this information of particular value to healthcare administrators, we may detail this in the future.

4.2.4 Potential for Lower Costs and Better Outcomes from Greater Prescription Use

The increases that occurred in per-PY drug use and costs can be interpreted positively or negatively. The positive interpretation is the increased drug use per-PY (and subsequent drug costs) has contributed to the decrease in overall per-PY costs by helping to improve the health status of these cases and thus reduce the need to consume many health services. This would be in addition to the system-wide improvements in health care delivery that have certainly reduced many costs. We could not study clinical outcomes directly, and as described above, the quantity of health resources consumed does not always correlate with disease state or outcomes. However, one indicator of SARDs outcomes may be the mean number of all hospital admissions combined (inpatient and day case) per-PY. Even if healthcare efficiencies shifted certain inpatient procedures to the day care setting, the total number of admissions should not be affected by this. Since we observed a 46% decrease in total admissions per-PY over twelve years, outcomes may actually be improving for the average SARD case.

The emerging SARDs therapies are themselves expensive, but concerns have been raised about the additional healthcare costs associated with their use. For instance, rituximab needs to be given by IV infusion (90) and monthly lab tests are required during the first year of mycophenolate treatment (63). But much of this additional consumption (including any additional laboratory tests and physician visits) would have been billed to MSP and therefore captured in our data. This means per-PY overall and outpatient costs still decreased, on-average, in spite of any additional outpatient services that were required. In fact, in actual dollars the twelve-year ($564/PY for all-SARDs) *decrease* in mean annual per-PY outpatient costs actually exceeded the same mean per-PY *increase* in prescription costs ($553/PY for all-SARDs). With the mean per-PY increases in drug spending offset by decreases in outpatient and hospital spending, prescription drugs could be a good healthcare investment. From this perspective access to new drug therapies, even the more expensive ones, should be expanded if outcomes could continue to improve without an increase in overall average per-capita healthcare costs. Greater drug consumption may be the trade-off to reduce hospitalization and improve the management of these chronic disorders, Given that many of the drugs of interest were only available during the last half of our study period (or less), further investigation of their impact on long-term outcomes is required.

4.2.5 Potential for Rising Comorbidity Burdens and Complication Rates

Unfortunately a much more alarming explanation exists for the increasing mean per-PY drug costs. In it, more efficient health care delivery is the primary reason for the decreases in overall per-PY costs. This means - instead of greater medication consumption contributing to better outcomes in SARDs – it may be an indication of patients requiring additional drug therapies after developing more comorbidities and/or complications.

This possibility is supported by many of our findings. Although new and expensive drugs contributed somewhat to the longitudinal increase, the five main emerging drugs still only combined for 10% of drug costs in 2007. This means the majority of costs were from 'ordinary', less-expensive drugs. And while two of these expensive drugs - bosentan and mycophenolate - combined to account for 21% of the twelve-year increase in mean per-PY drug costs (Table 3.12b), this contribution was averaged amongst the whole cohort. Although the increase was experienced by most cases - with at least 86% of cases dispensed a prescription each year, and the twelve-year increase in mean prescriptions dispensed to users per-PY (55%) almost matching the number dispensed to all cases (49%) - most cases were not dispensed these therapies so they would not have affected their annual drug costs. Finally, unlike for the per-PY outpatient and hospital decreases, the twelve-year increases we observed in per-capita costs (50%) and prescriptions (49%) were nearly identical. If the increase in drug costs resulted mainly from funding these expensive but infrequently-used drugs, the number of prescriptions dispensed per-PY would not have increased so much alongside it.

We were not able to investigate which secondary conditions developed in SARDs cases, and at what rates, in this analysis but as described in section 4.7, we intend to explore this in our future work. We suspect, however, they may include diabetes, nephritis, and cardiovascular disease. Risk for cardiovascular disease is elevated in many SARDs including SLE (447,448) and Wegener's (449), and this may stem from the inflammatory nature of these diseases and exposure to GC (28,450,451). GC exposure may also increase the risk of diabetes (17,26), and other chronic kidney diseases may result from SARDs-VD, SSc, and SjD (17,452,453), in addition to lupus nephritis. With diabetes managed primarily medically and on an outpatient basis, an increase in mean per-PY admissions from these conditions would not be expected, and hospital admissions for our cohort actually decreased by 44%.

However with multiple medications required to manage these conditions (4,27,454,455), a rise in mean per-PY prescriptions would be expected.

The longitudinal per-PY increases we observed for specific drugs and drug classes support these possibilities even more. Along with GC and immunosuppressants, ACE-II inhibitors and/or ACE-II receptor antagonists are often prescribed for lupus nephritis (27,455) and other chronic kidney diseases (17,453), and in our cohort, mean annual per-PY prescriptions for this class (RAAS Agents) rose by 160%. In addition to RAAS Agents, mean per-PY prescriptions increased for other anti-hypertensive classes including calcium channel blockers (by 18%), diuretics (by 53%), and beta-blockers (by 129%) (Table 3.14). This suggests the prevalence of hypertension (one cardiovascular morbidity that is particularly common in TA (29) and may be present in half of lupus cases (28)) may have increased amongst our cohort. Similarly an increase in the development of atherosclerosis (which may be accelerated in Wegener's (456), and is the "most common manifestation of cardiovascular disease" in lupus cases, according to the Johns Hopkins Lupus Centre (28)) could explain the 641% increase in mean per-PY prescriptions for lipid-modifying agents we observed. The annual mean number of prescriptions for diabetes medications also increased, by 52% per-PY (Table 3.14), with mean per-PY costs for these drugs rising almost equally (by 48%).

If comorbidity burdens are increasing, new SARDs therapies like belimumab may be useful (particularly for lupus nephritis (4,27)), and could actually reduce the long-term risk of comorbidities. Their potential long-term benefits warrant further investigation, and as detailed more in section 4.7, such an investigation is in our plans.

4.2.6 Implications for Patients

The decreases in mean per-PY health resource utilization that we observed, such as less-frequent hospitalization, are a positive development for patients. But mean per-PY medication consumption is rising, and the implications of this for patients could be quite negative. The side effects of these drugs may reduce quality-of-life, while the possible development of secondary illnesses could further decrease physical health and well-being. The serious financial implications of these medication increases should not be ignored either. In BC, all residents pay an annual premium for medical insurance, which entitles them to receive all medically-necessary hospital and outpatient services (431) without additional charge or co-payment. However they are personally responsible for most prescription costs, with

partial subsidy available from the province under the income-tested PharmaCare program (431). Although our main prescription medication estimates were based on the full cost of each prescription, we also explored those prescription costs paid by PharmaCare (using data available on each PharmaNet record), and our findings were disturbing. As total mean per-PY prescription costs increased (by 50%), those costs that PharmaCare covered *decreased* by almost the same magnitude, 46% on-average, over twelve years. In 2007, the mean per-PY prescription costs for all-SARDs were $1,670/PY, but on average, only $509 was subsidized by the province, leaving patients responsible for an average of $1,161.

When costs increase for other healthcare components, on an individual-level responsibility for these extra costs is shared amongst all taxpayers. Instead as prescription costs rise SARDs cases will face additional personal costs. Many BC residents have employer-sponsored insurance to reduce prescription costs but, as noted by Aghdassi *et al* with regards to SLE, complications can limit patients' ability to work and thus their access to prescriptions. This manifests in two ways: their income may be insufficient to pay for their prescriptions, and their access to this employer-sponsored insurance is reduced (297). Therefore in addition to research aimed at reducing comorbidity risks, these increasing drug costs call for a re-examination of public drug policies and programs. For instance, Health Canada's approval of rituximab for Wegener's granulomatosus in late 2011 has increased the likelihood that, for Wegener's cases, its cost will be covered. But CanVasc, a Canadian SARDs-VD advisory group, has noted such funding and approval decisions are made by each province separately (116). With these decisions tending to be inconsistent amongst provinces, some patients may still be forced to pay these extremely high costs themselves or go without. Further research is needed to determine the effectiveness of these high-cost medications in the long-term. If they could actually improve health status and decrease health resource utilization, they would become cost-effective and this would be of great interest to policy makers and patients. However if per-capita drug costs continue to rise but public drug policies remain stagnant, adherence to many medications (and not just the most expensive) could very well decrease, potentially leading to further health problems and higher healthcare costs for patients and government in the long term.

4.3 Limitations

The array of data available for each claim, and systematic way in which it is collected and recorded, are but some advantages of administrative data. However we still faced some limitations using this data source with regards to the exclusion of some health encounters, costing precision, and the accuracy of our cases' SARDs diagnoses. These must be kept in mind when interpreting our estimates.

4.3.1 Omitted Health Care Costs

Our tabulation of healthcare costs was restricted to provincially-funded health services. This meant services funded by other public agencies and levels of government (federal and municipal) were not included in our estimates. However with 93% of public healthcare spending in BC funded by the province in each of 1996 and 2007 (290), we still captured most costs incurred by the public payer. With the 2007 estimate of average per-capita public sector healthcare spending in BC ($3,458 2007 Canadian dollars (290)) differing little from the baseline (non-SARDs) mean per-PY overall healthcare costs we calculated for the same year ($3,414/PY), we have further assurance of the completeness of our cost capture.

Within the scope of provincially-paid health resources, we attempted to include all funded health care services in our cost estimates. But since we could only include consumption captured by MSP and the hospital dataset (Discharge Abstract Database, or DAD), some costs were omitted. The provincial government pays a large portion of ambulance costs (431), approximately $450 per-trip in 2007 (457), but data on the use of ambulance services are not available from PopData BC. The MSP database includes amounts paid to all fee-for-service (FFS) practitioners but not to those compensated under different schemes like contracts or salaries. With these arrangements employed more and more in rural areas of the province (429), we may have omitted many services provided there.

Many ER physicians are compensated under a non-FFS arrangement, and at the same time, outpatient ER visits (those not resulting in an inpatient admission) are not included in the DAD either (429). A portion of physician costs from these visits were captured, as some ER physicians (91% in 1998/99 (458)) do bill MSP for each encounter. But most other associated costs, including staff, equipment, supplies, and medications (which are not recorded in PharmaNet either) were not included. To give an idea of these costs, a recent Canadian SLE study

estimated the average cost per ER visit at $173 (297), but without ER utilization data we could not reliably approximate these costs for our cohort. Since a BC report found ER users were more likely to be female (458) – and the majority of SARDs cases are female – and had poorer health and greater health resource utilization than the general population (458), a not-insignificant, and likely growing quantity (as nationally, the cost of an average ER visit increased by 47% from 2003-2008 (446)) portion of health care costs may have been missed. This omission must be considered when interpreting our annual cost estimates.

Since the consumption of other health care components is not recorded by the province, we were unable to tabulate their costs. These items include non-prescription medications, vitamins, natural health products, assistive devices (including eyeglasses and hearing aids), and most dental services (431). But with the provincial government not funding these items – patients do – their omission is justified. Still, caution must be taken when comparing our estimates to others, particularly clinic-based ones, which did include these additional items.

In the end, the vast quantity of health care expenses that we did include is a reliable proxy of provincial healthcare spending. In fact while keeping in mind SARDs cases consume more health resources than the average individual, our overall mean per-PY cost estimate for 2007 ($6,087 2007 Canadian dollars per-PY) far exceeded average provincial per-capita healthcare spending in BC ($3,231 2007 Canadian dollars (290)) that same year. With the exception of non-physician outpatient encounters (whose contribution should not be great), any omissions were consistent amongst study years and disease groups so would not impact our subgroup comparisons or longitudinal analyses. If anything, we are presenting a conservative, not an exaggerated, estimate of the net burden economic healthcare burden of SARDs, and this more ideal.

4.3.2 Underestimated Day Surgery Costs

Day surgeries performed from 2001 and onwards comprised about 27% of all our cohort's admissions but we very likely underestimated the costs of these procedures. Instead of using case-mix methodology, these costs were calculated by adjusting the year-2000 sum by the subsequent annual increases in inflation. But with care continuously shifting from the inpatient to the day-case setting, the average annual increase in inflation (2.42%) was actually much less than the average annual increase in day surgery costs from 1996 to 2000 (20%) and the annual

increase in number of day-case hospitalizations (21%, on-average, from 2001 to 2007). We had little choice in this matter though. PopDataBC did not provide the Resource Intensity Weight (RIW) for each day surgery so we could not use case-mix methodology. As detailed in Chapter 2, several approaches for estimating these costs were explored, and we selected the most conservative one. This may explain why we calculated lower per-capita day surgery costs than some Canadian investigations did (274,315). It may also explain why our overall per-PY costs were similar to those reported for SLE in 1989 and 1990 (276), when day surgeries were less frequent. Still with day surgeries making up a relatively small proportion of overall costs in our analysis (at most, just 3.7% of annual hospital costs from 1996-2000), any underestimation should have minimal effect on our overall per-PY estimates or longitudinal observations.

4.3.3 Minor Costing Uncertainties

Other uncertainties exist in our hospital cost estimates. Since case-mix methodology could not be used for extended or Alternate Level of Care (ALC) separations either, their costs were determined by multiplying a widely-used BC government per-diem rate by the LOS. But any imprecision here would only have a minor impact on our annual costs with ALC separations accounting for just 0.6% of all separations, and 11.6% of all hospital days. The annual number of ALC separations also decreased greatly over the period, from a total of 53 in 1996 to just two in 2007.

We also faced some uncertainties even when calculating the cost of each inpatient hospitalization with case-mix methodology. This involves multiplying the annual average cost for a hospitalization in BC (called the Cost-Per-Weighted-Case, or CPWC) by the Resource Intensity Weight (RIW) of each separation, a measure of the resource consumption required for the specific stay. Since CIHI did not provide annual cost-per-weighted-case (CPWC) values previous to 2004/05, these were estimated from the later years' values. But each year's value reflects specific year-to-year changes in health service delivery, including expensive technological innovations and increasingly-complex caseloads (438). This means, even with our conservative approach (as detailed in the Methods, Chapter 2), the older CPWC values, and the corresponding-years' hospital costs, may have been slightly overestimated.

Our study period spanned several editions of the RIW, and the one we had to use for the year-2007 separations was derived differently than the others. The magnitude and direction of any impact from these different derivations is

currently unknown. In theory it reduces the comparability of our 2007 costs to previous years', but the real impact is likely minimal. For both hospital and overall costs, the decrease in per-PY costs from 2006 to 2007 (7% and 4%, respectively) differed little from the average annual cost decreases observed over twelve years (6% and 3%, respectively).

4.3.4 Capture of Attributable Outpatient Encounters

The limitations of administrative pertaining to the coding of diagnoses and specialist codes may have affected our attribution analysis. While we tried to capture SARDs-related encounters by including all (non-rheumatologist) billings coded for SARDs, many would have been coded for the morbidity necessitating that encounter, such as nephritis or pneumonia. Since MSP only allows one diagnosis per claim, these diagnoses would have taken the place of the underlying SARD, thus reducing the number of SARDs-related encounters captured under the narrow definition. Given the high consumption of health resources mandated by SARDs treatment and follow-up, it is difficult to believe only seven percent of all outpatient encounters by SARDs cases, or, on-average, only two per-PY (as were attributable under our narrow definition), were related to SARDs. By failing to capture all attributable visits under this definition, we may have underestimated our annual per-PY incremental cost estimates. With this method of cost attribution dependant on the logistics of diagnostic coding, it may lack precision and estimates as to the burden of disease should be interpreted with caution.

Some logistics with coding also limited the capture of rheumatologist billings. Although these were identified by the specialty code on the claim, Rheumatology was not coded as a separate specialty by MSP until January 1, 1998. In theory this would also have underestimated our SARDs-attributable cost estimates. However the actual implications of this appear mixed. For instance, the percent of the total gross costs that were attributable to SARDs under the narrow definition was lower in 1996 and 1997 (22%) when compared to other years (Appendix B). But the proportion of attributable outpatient costs for all-SARDs changed minimally (from 5.1% to 5.7%) from 1997 (when Rheumatology was not coded) to 1998 (the first year that it was). The proportion of outpatient encounters that were deemed attributable in 1996 and 1997 (6%) was also not much different in later years. The effect may have been greater for SARDs-VD cases than SARDs-CTD, with percent of attributable costs and encounters rising more from 1997 to 1998 in these cases (SARDs-VD costs and encounters each by about 1% vs. about 0.5% for costs

and 0.15% for encounters in SARDs-CTD). We attempted to make up for these potential omissions by including additional encounters in our broad definition. But while the sensitivity for attributable encounters increased in this definition, we may also have included encounters not actually related to SARDs and thus decreased the specificity of the attribution estimate.

4.3.5 Accuracy of SARDs Diagnoses

An odd pattern became apparent while examining the number of SARD cases we captured each year. As shown in Table 3.1, we had 3,305 cases in 1996 and 14,372 in 2007, making for an enormous twelve-year increase of about 335%. In comparison, the general population of BC only increased by 11% in this period (273). Avina-Zubieta *et al* calculated the annual prevalence and incidence of SARDS in BC residents aged 20 years and older with the same data, and some of their findings are listed in Table 4.1. According to their estimates (which accounted for growth in the general population), the prevalence of SARDs-CTD increased by 302% over twelve years and SARDs-VD by 252%, while the incidence of each increased by 172% and 125%, respectively (1). We described in Chapter 1 how the incidence of many SARDs appears to be increasing, and given the chronic nature of these disorders, this would also contribute to an increase in prevalence. The increased incidence may stem from increased clinical recognition, the aging population, or a true rise in their development, but for such massive increases to occur over just twelve years is not clinically-plausible.

We examined the external validity of these case numbers by comparing the annual prevalence rates for SARDs-CTD in BC (237 per-100,000 in 2003 and 389 per-100,000 in 2007 (1)) as calculated from our data, to those also calculated with administrative data by Bernatsky *et al* from three other Canadian provinces. Since these prevalence estimates were similar - ranging from 260 to 410 per-100,000 in 2003 (5)) (Table 1.2) – they support the validity of our data and prevalence estimates, at least for the later years of our study. Many other explanations are possible for these apparent increases. The introduction of a new or more sensitive diagnostic test could have suddenly driven up case numbers by identifying cases that would otherwise have done undetected. It is suspected the incidence of some SARDs-VD in the UK increased in the 1980s after the introduction of the ANCA test (7,459), but no major diagnostic test for any SARD was introduced during this period. A large rise in the number of practicing rheumatologists in BC could have led to more SARDs diagnoses, but between the 2001/02 and 2007/08 fiscal years

the number of rheumatologists only increased by 10 (from 43 to 53) (460). Since the BC population also increased in this time (by 6% (273)), it meant the average number of patients per rheumatologist only increased by 5% (from 954 to 1005 (460)). With access to rheumatology services (and potentially, in turn, SARDs diagnoses) increasing very little in this period, this is unlikely to have accounted for the 137% increase we observed from 2001 to 2007. Finally the BC population on the whole is growing older and with some SARDs, particularly SARDs-VD, mainly affecting those 50 years of age and older, somewhat of an increase in case numbers would be expected. Still the proportion of the BC population that was aged 50 years and older only increased by 28% (from 27% of the population in 1996 to 34% in 2007) in this period (273), meaning this age shift should only have contributed to one-twelfth of the twelve-year (335%) increase.

Instead we believe the primary explanation lies with the exclusion criteria applied to potential cases after initial screening. Potential cases with eligible SARD-coded encounters from 1990 onwards were identified, but to optimize diagnostic accuracy these individuals continued to be screened for exclusionary encounters through either 2007 or end-of-follow-up (from either death or de-registration from MSP). These encounters are detailed in Chapter 2 but included (for cases first diagnosed by a non-rheumatologist) a rheumatologist visit where the SARD diagnosis was not confirmed or, for any case, a subsequent diagnosis of a different type of inflammatory arthritis, such as RA or psoriatic arthritis. Each additional year of follow-up that was available for a potential case equated to another year in which that case could be excluded. The unbalanced case numbers arose from those identified late in the study period having fewer years in which to be excluded. There was no minimum follow-up required of any case, or maximum timeframe for the exclusionary encounter to occur. This meant, when compared with those identified in the 1990's, many more of the potentially ineligible cases identified in later years remained in the final cohort. In fact, when our colleagues went back and did not apply these exclusion criteria to any potential cases, the annual case numbers balanced out.

Instead of eliminating our exclusion criteria, diagnostic accuracy could be increased by implementing a minimum follow-up period. This would allow all potential cases to be thoroughly screened for exclusionary encounters, but there is a trade-off. Requiring cases to have, for instance, five years of follow-up - as in Li *et al* (304) - may introduce a survival bias since only cases that could be followed for that length of time would be eligible. If the

mean annual healthcare costs of these cases were systematically different from those with less follow-up time (which is possible if more complex cases tended to incur high annual costs for 1-2 years but then died from these complications), biased estimates would be produced.

With eighteen years of potential follow-up time (1990-2007), some potential cases may have had an exclusionary encounter many years after the index visit. However we suspect most exclusionary encounters occurred within five years of the initial SARD diagnosis, and in our cohort the highest annual increases in the prevalence of SARDs-CTD did occur between approximately 2002 and 2005 (two-to-five years before our follow-up period ended) (Table 3.1). A similar pattern was with the annual prevalence of SARDs-VD.

While this injects some uncertainty into the SARDs-status of our cohort, we at least have assurance our case definitions were quite sensitive. Still, the effect it had on our annual and longitudinal cost estimates is unclear. In later years the inclusion of milder cases with less-certain diagnoses may have brought down our annual per-PY cost estimates and partially accounted for the 32% decrease in overall per-PY costs. Looking at Figures 3.3 and 3.4, overall mean per-PY costs decreased the most from 1997 until 2001, and it is after this point the 'excess' cases really became apparent. In fact, the annual average decrease in mean per-PY costs from 1997 to 2001 was 4.2%, but dropped to 2.6% from 2002 to 2007. Using consistent methods of case ascertainment throughout a longitudinal analysis is vital for making valid comparisons of annual estimates. However it may be more correct to include these uncertain cases in our cohort. While still maintaining some diagnostic specificity (which we did with our rigorous inclusion criteria), capturing the costs of all potential SARDs cases (even questionable ones) may actually produce a more accurate estimate of the total healthcare burden of these diseases. Further research on the internal validity of this diagnostic algorithm is required, and we intend to undertake this.

4.4 Strengths

Despite these limitations, our study has several strengths. By using population-based data our analysis incorporated a large patient sample, multiple years of health claims, and precise unit costs. Given this country's single-payer healthcare system, using *Canadian* administrative data allowed for a comprehensive tabulation of health resource consumption and increased the generalizability of our findings by minimizing selection bias. Not only is ours the

first analysis of the SARDs together, but these factors also make ours the largest and longest study of the healthcare costs of SARDs to date.

4.4.1 Maximum Case Ascertainment and Sample Size

By grouping SARDs diagnoses and identifying potential cases over eighteen years (1990-2007) we obtained 18,741 cases - the second-largest sample known for any SARDs costing study. This maximized statistical power and the external validity of our findings. Bernatsky *et al* have proposed that administrative data may fail to capture cases with milder disease who don't seek care during the study period (5,381,434), but it is unlikely a true case would go for a period as long as ours without needing SARDs-related care. SLE, like many individual SARDs, often relapses and remits but the period of disease quiescence (during which cases often don't need treatment specific to SLE (340)) tends to span only a few years. In a study of the Hopkins Lupus Cohort, this phase accounted for the smallest proportion of follow-up time, with an average of only 2.3 years and a maximum of 5.7 (461). With the exception of new arrivals to BC, most potential cases would have had at least this much screening time. Finally, Bernatsky *et al* have also reported high sensitivities for the ICD-9 codes pertaining to SARDs (exceeding 88% for all but SLE) (434) that we used to identify cases, meaning we should have captured most cases with these codes. It must be emphasized that clinic-based data holds no advantage over population-based in this respect, with such mild or early-onset cases unlikely to attend at a tertiary rheumatology clinic.

4.4.2 Minimally-Biased and Comprehensive Estimates

Even population-based cohorts may over-represent one socioeconomic class or health state, but our study population was minimally biased in these respects. Most adult SARD cases in the province could have been included, regardless of care provider or area of residence, two factors identified in Chapter 1 as potentially influencing health resource utilization. Our estimates therefore incorporated the health resource consumption of a wide spectrum of SARDs cases, and should accurately reflect the per-PY costs of the average case. Enhancing this further was the systematic and detailed records held by PopDataBC and single-payer nature of BC's health system. This allowed us to capture nearly every publically-funded health service consumed, including every community-dispensed prescription, records unavailable in most other Canadian databases. Since the exact cost of each outpatient and

prescription claim was available, these estimates should highly reflect the amounts paid by the provincial government, maximizing the accuracy of our cost estimates.

4.4.3 Longitudinal Design

We not only estimated the annual healthcare consumption of SARDs cases, but produced these estimates for each of twelve years. When a cross-sectional investigation produces a solitary cost estimate, there is no context available for interpretation, and without knowing if healthcare costs are rising or falling, it is difficult to predict future research and health care needs. Since multiple cross-sectional estimates may not be comparable if determined with different methods and study populations, any longitudinal inferences made from these must be taken with caution. We know of only two other individual SARDs studies producing such longitudinal estimates (304,324), and these had much shorter follow-up periods. Our longitudinal data also let us evaluate the potential impact of new therapies and changes in funding and service delivery on annual mean per-PY costs. For instance, our average annual decreases in per-PY outpatient costs were greater after paramedical services (including physiotherapists, chiropractors, optometrists, massage therapists, naturopaths, acupuncturists, and podiatrists) ceased to be reimbursed. Of particular interest to health policymakers is how the approval of bosentan, infliximab, and etanercept in 2001 may have driven up per-PY medication costs in subsequent years.

4.5 Contribution

4.5.1 Knowledge Gaps

In quantifying the previously-unknown burden of SARDs on the Canadian health care system at the population-level, we filled many gaps in this research that were identified in Chapter 1. Despite their shared pathogenesis, manifestations, and treatments, this is, to our knowledge, the first time health resource utilization and direct medical costs have been quantified for the SARDs collectively. Grouping the SARDs made great biological sense and greatly increased the size of our cohort: at 18,741 cases, it was nearly unmatched and dwarfed those seen in clinic-based studies. In quantifying the healthcare burden of these rare and relatively-unknown diseases, we made clear their public health impact. This should make research to improve outcomes and care for SARDs (and in doing so,

reduce this health resource burden) a priority in Canada, and inspire more groups to conduct clinical and health services research relating to SARDs.

Prior to our work Canadian estimates existed for some individual SARDs, but most were determined with a tertiary clinic population. The small samples and short follow-up periods inherent with these studies, and greater severity of disease within their cohorts, limited the external validity of these estimates. Our estimates were instead produced using population-based data. This was only the second Canadian study to do so, and the first to encompass all three healthcare components, making ours the most generalizable Canadian estimates to-date. Little was unknown about the trajectory of these costs over time, with few longitudinal estimates produced from any country (and none from Canada), so we have made a significant contribution in studying these costs over twelve years (the longest of any SARDs study). This information could be valuable when planning for future needs: the positive effects of any past efficiencies implemented in the delivery of outpatient and hospital services are supported by the decreases in mean per-PY outpatient and hospital costs we observed. At the same time the contribution to overall costs from prescriptions came to equal the outpatient contribution in the last year of our study, and in subsequent years will likely exceed it. The large increases we observed in per-PY medication consumption and costs should make it clear this healthcare component will be a main driver of future healthcare costs in SARDs, and we would not have been able to determine this in a cross-sectional analysis.

On top of this work, we also estimated the incremental costs of SARDs, which though minimally studied and not ever reported for Canada, are especially important for health policy and justifying increased research support. When previously faced with estimates of the healthcare costs of individuals SARDs, it was difficult for Canadian decision-makers to know how much of these costs were actually due to the SARD, but this information is now available. These factors combine to make our analysis truly unique and capable of producing the most reliable and comprehensive estimates to date.

4.5.2 Future Cost-Effectiveness Analysis

This study was not a formal cost-effectiveness analysis but the estimates we produced could make a valuable contribution towards one in the future, particularly for the new-but-costly drugs for SARDs. Similar breakdowns of

healthcare costs were useful in earlier discussions of care for RA. It was reported that much of medical costs in RA stemmed from hospitalizations, particularly operations to correct joint destruction and deformity caused by this disease. Having this information supported the widespread use of the some of the same biologic therapies now being introduced for SARDs (namely infliximab and etanercept), if they could reduce this joint damage and subsequent need for costly surgery in RA (462).

4.6 Applications and Knowledge Translation

With our work spanning the clinical pharmacy, rheumatology, and population health and economics disciplines, these findings will be of interest to many audiences. Estimates of the current costs of SARDs could be used by patients to lobby for better treatments to improve their health and quality of life. Our detailed breakdowns by component, year, and disease subgroup will be especially useful to health care administrators, policy makers, and health economics researchers to help further improve health care efficiencies and allocate future resources. It is imperative clinicians are made aware of the rises we observed in drug use and costs, particularly as they may be tied to rising comorbidity burdens. By working with patients to reduce their occurrence, and detect and treat these conditions earlier, clinicians could put a significant dent in these burdens.

With this in mind, and the innovative nature of our assembled cohort and study design, we will be proactive in disseminating our findings. Preliminary results were presented in poster format to the North American arthritis community at the Canadian Arthritis Network (CAN), and Canadian Network for Improved Outcomes in Systemic Lupus Erythematosus (CaNIOS) annual meetings in 2011. With these organizations valuing consumer partnerships, we were able to educate patients at these venues too. We presented a poster at the American Association for the Advancement of Science (AAAS) annual meeting in February 2012, which allowed us to reach a broader audience interested in scientific and public policy, and did so too at the meeting of the Canadian Rheumatology Association (CRA) in March 2012. Since our CRA abstract will be published in the international, peer-reviewed *Journal of Rheumatology*, our findings will reach beyond the physical conference. Estimates pertaining to the net burden of SARDs will be communicated to those who regularly measure the value and impact of drugs and technologies in a poster at the Canadian Agency for Drug and Technologies in Health (CADTH) Symposium in April 2012. We will

also present a poster at the 2012 conference of the Canadian Association for Population Therapeutics (CAPT), with the abstract appearing later in the *Journal of Population Therapeutics and Clinical Pharmacology*. CAPT focuses on pharmacoepidemiology, so there we will emphasize this possibility that rising comorbidity burdens are driving drug costs in SARDs. We also intend to publish this work, with a focus on the attributable costs of SARDs, in a relevant, peer-reviewed rheumatology journal. Aside from these formal settings, our findings and their implications will be discussed with colleagues associated with the Arthritis Research Centre of Canada (ARC), and other institutions across the country.

4.7 Future Work

Our findings here were very exciting, but only preliminary. With this vast quantity of health utilization data we look forward to investigating these findings more deeply and gaining a more comprehensive understanding of the health resource burden of SARDs.

4.7.1 Discrete Longitudinal Analysis

Although our analysis was longitudinal, the entire cohort was not followed from a single point in time. Cases could enter at any time during the period, with no minimum follow-up period. This served to minimize survival bias but also restricted our ability to interpret the longitudinal trends. For instance the 32% decrease in overall mean per-PY costs could be from our longstanding (1996-entry) cases requiring fewer health services as their disease stabilizes. In an alternative scenario the healthcare needs of such cases do not decrease over time, but annual mean per-PY costs decreased on the whole because many of these costly cases died and thus ceased to incur these high costs. Stratifying our cohort by year of entry would let us compare the consumption patterns of cases followed for different periods, including the types and intensities of inpatient hospitalizations. We performed a trial analysis with only those SLE cases followed from 1996, and the decreases in annual mean per-PY outpatient and overall costs were half those observed for the whole SLE cohort. At the same time their mean per-PY prescription increases were more than double. With this further indication of disease progression and complications necessitating greater prescription use, a complete stratified analysis of the whole cohort would help us understand the role of comorbidities in the long-term healthcare costs of SARDs.

4.7.2 Updated Health Utilization Data

Our dataset was large in terms of the size of the cohort (over 18,000 cases), number of encounters captured (over six million outpatient claims), and study period (twelve years). However this will be surpassed when PopDataBC updates our data through December 31, 2011. Our request for this has already been approved. Not only will our sample size increase but we will be able to see if the same cost and utilization trends continued. The contribution made by some expensive drugs – including the biologics, mycophenolate, and atorvastatin – was growing in our final years of study, and we are interested as to how much they are impacting drug costs now. What was most intriguing though, was in 2007 – the final year of study - mean per-PY outpatient and prescription costs were nearly the same, especially after differing by over $1000 per-PY, on-average, in 1996. With prescription costs increasing so much over twelve years and actually exceeding the outpatient (by an average of $29 per-PY) in the last year, we anticipate the annual per-PY prescription costs of the average SARDs case to now exceed the outpatient. This could have huge implications on health policy, further justifying a re-examination of prescription drug subsidies.

The precision of our hospital cost estimates will also be enhanced. Not only will the RIWs for all ALC and day separations be included, but we will have at least ten years with which to calculate costs using most current, ICD-10-derived, RIW values. This will provide insight into how this missing hospital data impacted our current estimates, particularly the extent to which our day surgery costs were underestimated.

4.7.3 Control Data

One of our objectives was to quantify the net health resource and economic burden that SARDs impart on the provincial healthcare system. We did so here by tabulating separately the costs for healthcare services deemed attributable to SARDs, but this approach may have lacked precision. Instead several studies on individual SARDs (299,304,311) have used the costs incurred by a matched control group to calculate this burden. Unforeseen delays in obtaining PharmaNet data for a control group prevented us from doing so here, but our request has now been approved. By comparing the costs of SARDs cases to those of an age- and sex-matched random sample of BC residents who do not have a SARD diagnosis, we will soon produce an even more reliable estimate of the incremental costs of SARDs.

4.7.4 Impact of Complications and Comorbidities

These preliminary findings suggest comorbidity burdens and complication rates may be growing amongst SARDs cases, which may explain the growing drug costs. This possibility needs to be investigated in more detail, and with these conditions arising after many years, our updated dataset will make us even better equipped to do so. We would identify these secondary conditions through the appearance of their corresponding diagnostic codes on the outpatient claims and hospital discharges of SARDs cases. With our patient-level data, we could then access the prescription records of these cases to see how many prescriptions they were dispensed, and which ones, and evaluate any association between these conditions and per-PY prescriptions quantities and costs. Stratifying cases by year of cohort entry would be involved here too, since we would expect the incidence of these comorbidities to be greater in the more longstanding cases. Finally our analysis was motivated, in-part, by the expense of some emerging SARDs therapies. To assess their impact on long-term complication risk and thus their cost-effectiveness, we may also perform a pharmacoepidemiologic analysis where the complication rates of cases exposed to these new drugs would be compared to those not exposed.

4.7.5 Significant Cost Predictors

Identifying any clinical or demographic predictors of costs in SARDs - which may include female sex, age, and disease severity - could also help reduce complications and healthcare costs. With our updated dataset, we plan to do this using multivariate linear regression. If high-risk patients could be better-identified and treated aggressively, long-term outcomes may be improved.

4.8 Conclusion

This population-based study of the collective healthcare burden of SARDs over twelve years was the first of its kind in the world. We have shown the direct medical costs of SARDs cases at the population-level are substantial (totalling $571,216,780 2007 CDN over twelve years) - with mean per-PY costs averaging $6,087/PY CDN in 2007. With the net healthcare costs of SARDs averaging $2,674/PY in 2007 (and accounting for 44% of total healthcare costs for these cases), and total net costs exceeding $38 million in BC that year, SARDs themselves are clearly responsible for much of this burden.

The long-term reductions in health care costs we observed are encouraging and suggestive of more efficient health service delivery. But in contrast to the overall cost decreases, per-PY prescription quantities and costs are increasing greatly, with many patients personally financing a growing proportion of these costs. The use of immunosuppressants and bisphosphonates, and some specific ACE inhibitors, PPIs, thyroid therapies, and statins accounted for much of these increases. In addition, the contribution from some very expensive vasodilators and biologic therapies toward these drug costs is small but growing. The proportion of overall costs from prescriptions has more than doubled over twelve years and came to exceed the outpatient proportion in 2007. If this trend continues for SARDs cases, medication costs will become more important than the costs of outpatient care.

With per-PY prescription numbers increasing nearly as much as costs, comorbidity burdens and complication rates may be rising amongst longstanding cases, and this warrants further investigation. The connection between SARDs and these secondary conditions (such as cardiovascular disease) is currently underappreciated, but must be communicated, since preventive therapies and other measures could slow their development and reduce healthcare costs. Some expensive ($20,000 per-patient annually), but potentially-better, SARDs therapies are emerging, and further research to assess their impact on long-term comorbidity risk, and not just short-term outcomes, will be needed.

4.9 Tables

Table 4.1 Changes in the Incidence and Prevalence Rates for SARDs in BC, 1996-2007 (1)

	SARDs-CTD		SARDs-VD	
	Incidence (per-100,000)	**Prevalence (per-100,000)**	**Incidence (per-100,000)**	**Prevalence (per-100,000)**
1996	16.25	44.26	2.37	5.34
2007	96.62	388.55	9.06	31.91
12-year increase	**172%**	**302%**	**125%**	**252%**

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Appendices

Appendix A: Diagnostic Codes, Fee Items, and Drug Classes

International Classification of Diseases (ICD) Codes for SARDs, 9th and 10th Revisions

Diagnosis	ICD-9	ICD-10
All connective tissue disorders (SARDs-CTD)	710, 710.X	M32.1, M32.8, M32.9 M34.X M35.0 , M35.1 M33.0, M33.1, M33.9 M33.2
Vasculitic disorders (SARDs-VD)	446.0 446.4 446.5 446.7	M30.0 M31.3 M31.5 M31.4

Additional SARDs-Attributable MSP Claims Included in the Broad Definition, by Specialty, Diagnosis, and/or Drug Therapy

Physician Specialty	Included Claims
Ophthalmology *-specialty code '06'*	-all encounters for all cases with a SjD diagnosis at an index visit -all encounters for all cases with an SLE diagnosis at an index visit -all encounters for all cases prescribed an anti-malarial at any time
Respiratory Medicine *-specialty code '49'* *-beginning January 1, 2006*	-all encounters for all cases with a SSc diagnosis at an index visit

Additional SARDs-Attributable MSP Claims Included in the Broad Definition, by Fee Item

Test/ Procedure		**Fee Item**
X-ray	chest	08551-08557
	hand	08525
	foot	08535
	hip	08530
	spine	08540-08543 08549
CT scan		08690-08696
Bone scan		09834
Sialogram		00723 008510
Ultrasounds		08638 08644 08648-08650 08658 08662 08670
Pulmonary function tests		00928-00946
Endoscopy		00907-00909 07780-07783 10740-10744 02357 10735
Renal biopsy		00742 08112 10912
Muscle biopsy		03211
Skin biopsy		13600
Lung biopsy		00739
Nerve biopsy		07028
Electromyography		00900-00902 00923
Dialysis		10903 33708 33723 33750-33759 33761 77380

Test/ Procedure		**Fee Item**
Laboratory investigations	haematology	90020 90140 90325 90465 90025 90145 90330 90475 90027 90150 90335 90480 90029 90155 90340 90485 90030 90160 90345 90490 90035 90165 90350 90495 90039 90170 90355 90500 90040 90175 90357 90505 90046 90180 90360 90510 90047 90185 90365 90512 90050 90190 90370 90515 90055 90200 90375 90520 90060 90205 90377 90525 90063 90210 90380 90530 90065 90215 90385 90535 90068 90220 90390 90540 90070 90225 90400 90545 90072 90235 90405 90550 90073 90240 90410 90555 90080 90245 90415 90560 90085 90265 90420 90565 90090 90280 90425 90095 90285 90427 90100 90290 90430 90105 90295 90435 90110 90300 90440 90115 90305 90445 90120 90310 90450 90130 90315 90455 90135 90320 90460 90038-90040 90045-90047
	immunology	91840 91811 91830 91845 91812 91831 91800 91813 91835 91801 91814 91850 91802 91815 91855 91803 91821 91856 91805 91822 91857 91810 91825 91858
	virology	90675 90831 90825 90833 90690 00030 90830 90700 90815 90831 91765 90820 90832

Test/ Procedure		**Fee Item**			
	urinalysis, urine microscopy, urine culture	92367 92369 92375 92378 92382 92385 92390 92391 92395 92396 92400 92405 92406			
	general chemistry	91000 91005 91005 91010 91020 91021 91023 91025 91027 91030 91031 91035 91036 91037 91040 91042 91050 91055 91060 91061 91065 91070 91075 91130 91145 91146 91160 91170 91175 91180 91185 91190 91191 91195 91196 91200 91201 91205	91206 91210 91215 91216 91220 91221 91225 91226 91227 91228 91230 91231 91232 91235 91236 91240 91245 91246 91250 91260 91260 91265 91265 91270 91270 91275 91275 91280 91295 91300 91305 91310 91315 91320 91325 91326 91327 91328	91330 91335 91340 91345 91350 91351 91352 91353 91355 91356 91360 91365 91366 91367 91368 91369 91370 91375 91386 91387 91388 91400 91401 91402 91405 91406 91410 91415 91420 91421 91422 91425 91430 91434 91435 91440 91445 91450	91455 91460 91465 91470 91475 91482 91484 91486 91488 91490 91492 91494 91496 91498 91500 91502 91504 91506 91508 91510 91512 91514 91516 91518 91520 91522 91523 91524 91526 91528 91529 91530 91532 91536

Test/ Procedure		Fee Item			
		91538	91560	91599	91640
		91540	91561	91600	91645
		91542	91562	91601	91650
		91544	91564	91602	91660
		91546	91565	91603	91665
		91548	91566	91605	91666
		91550	91568	91610	91670
		91551	91570	91615	91675
		91552	91572	91620	91680
		91554	91573	91630	91681
		91556	91574	91631	91682
		91558	91575	91635	91685
		91559	91576	91636	91690
		91695	91730	91790	91900
		91705	91735	91795	91901
		91706	91740	91796	91902
		91707	91745	91860	91905
		91708	91750	91865	91910
		91709	91760	91870	91911
		91710	91761	91880	91912
		91715	91762	91881	91915
		91715	91770	91882	91920
		91716	91775	91885	91925
		91717	91777	91890	91930
		91720	91780	91895	91935
		91725	91785	91896	
		91936	91956	91975	
		91940	91957	91985	
		91941	91958	91990	
		91945	91959	91992	
		91946	91960	91995	
		91950	91965	91997	
		91955	91970	92000	

Test/ Procedure		**Fee Item**
		92015 92100 92170 92251 92016 92101 92180 92255 92020 92102 92185 92260 92025 92103 92190 92263 92026 92105 92195 92266 92030 92108 92197 92267 92031 92110 92200 92270 92035 92115 92201 92275 92040 92120 92202 92280 92045 92125 92203 92280 92050 92130 92204 92285 92055 92131 92205 92290 92056 92135 92210 92305 92060 92145 92215 92311 92065 92146 92220 92315 92070 92147 92225 92320 92071 92148 92227 92325 92072 92149 92230 92330 92075 92150 92231 92332 92080 92152 92232 92335 92085 92155 92233 92340 92090 92156 92235 92345 92091 92157 92236 92346 92092 92160 92240 92350 92095 92165 92250 92351 92500-92515 92520-92531 92535-92550
	serum proteins	91285 91290 91390 91395
	thrombophilia investigations	90123 90125 90127
	muscle enzymes	93115
	synovial fluid analysis	92377 93010

Classes of Medications Attributable to SARDs

Alpha-adrenergic blocking agents	Diuretics
Alpha-glucosidase inhibitors	Estrogens
Angiotensin II receptor antagonists	Fibric acid derivatives
Angiotensin-II converting enzyme (ACE-II) inhibitors	Gold compounds
Anti-arrhythmic agents	Heavy metal antagonists
Anti-coagulants	HMG-CoA reductase inhibitors
Anti-depressants	Insulins
Anti-inflammatory agents	Meglitinides
Anti-malarials	Nitrates and nitrites
Anti-neoplastic agents	Non-steroidal anti-inflammatory agents
Beta-adrenergic blocking agents	Pilocarpine tablets and drops
Biguanides	Progestins
Calcium-channel blocking agents	Sulfonamides (systemic)
Cardiotonic agents	Sulfonylureas
Central alpha-agonists	Tetracyclines
Contraceptives	Thiazolidinediones
Corticosteroids (excluding intra-articular injections)	Vasodilating agents, miscellaneous

Most Prescribed Drug Categories and Generic Drugs within each Anatomical Therapeutic Chemical (ATC) Class (Second Level)

Drug Class	**Drug**
RAAS Agents	ACE-II inhibitors; angiotension-II receptor antagonists
Analgesics	Morphine; ASA; paracetamol; hydromorphone; oxycodone; fentanyl; pethidine; sumatriptan; clonidine; codeine; butorphanol; tramadol; zolmitriptan
Psycholeptics	Zopiclone; lorazepam; oxazepam; temazepam; quetiapine; diazepam; risperdone; alprazolam; olanzapine
Psychoanaleptics	Amitriptyline; citalopram; venlafaxine; paroxetine; trazadone; sertraline; fluoxetine
Antacids	Proton pump inhibitors (PPIs); histamine-II receptor antagonists; prostaglandins; calcium carbonate
Diuretics	Furosemide; hydrochlorothiazide; spironolactone
Anti-malarials	Hydrocychloroquine; chloroquine; quinine
Anti-epileptics	Clonazepam; gabapentin; valproic acid; carbamazepine; phenytoin; topiramate
Drugs for Obstructive Airway Diseases	Beta-blockers, anticholinergics, inhaled corticosteroids, leukotriene receptor antagoinists; xanthines
Lipid-Modifying Agents	Statins, fibrates, ezetimbe, colestyramine, nicotinic acid
Immunosuppressants	Azathioprine; ciclosporin; mycophenolate; tacrolimus; leflunomide; etanercept; anakinra; infliximab; sirolimus; adalimumab
Cardiac Therapies	Digoxin, nitroglycerin, nitrates, anti-arrhythmics
Anti-neoplastics	Methotrexate, cyclophosphamide, chlorambucil
Anti-hypertensives	Clonidine; hydralazine; bosentan; prazosin; methyldopa
Diabetes Therapies	Insulin, metformin, sulphonamides, thiazolidinediones

Appendix B: Additional Results

Total Direct Medical Costs (2007 Canadian dollars)

Year	SARDs	SARDs-CTD	SARDs-VD
1996	$26,040,962.03	$20,469,549.41	$4,588,941.75
1997	$29,541,868.27	$23,285,820.58	$5,422,988.34
1998	$30,781,014.36	$24,826,817.95	$4,738,950.32
1999	$35,510,696.81	$28,273,242.91	$5,758,660.04
2000	$38,103,648.72	$30,528,055.05	$5,501,672.33
2001	$38,510,053.79	$31,370,786.30	$4,974,130.71
2002	$42,712,647.25	$36,201,500.95	$4,955,860.13
2003	$50,635,782.60	$42,139,060.40	$6,749,584.07
2004	$55,786,478.03	$47,923,607.97	$6,446,657.22
2005	$65,629,712.25	$55,758,978.35	$7,803,246.05
2006	$76,293,422.85	$63,642,323.57	$9,542,004.26
2007	$81,670,492.92	$69,399,798.03	$9,214,644.21
Overall	**$571,216,779.87**	**$469,854,837.66**	**$75,697,339.44**
%-Change	213.62%	239.04%	100.80%

Total Direct Medical Costs, by Component (2007 Canadian dollars)

	Outpatient			Hospital			Prescription		
Year	**SARDs**	**SARDs-CTD**	**SARDs-VD**	**SARDs**	**SARDs-CTD**	**SARDs-VD**	**SARDs**	**SARDs-CTD**	**SARDs-VD**
1996	$6,451,603.32	$5,515,450.59	$817,031.51	$16,322,932.25	$12,070,511.68	$3,455,823.63	$3,266,426.46	$2,883,587.15	$316,086.61
1997	$7,125,132.47	$6,068,940.07	$927,131.14	$18,655,277.38	$13,889,644.66	$4,144,643.48	$3,761,458.42	$3,327,235.85	$351,213.72
1998	$7,632,512.63	$6,593,233.24	$880,521.36	$18,647,434.71	$14,203,903.42	$3,472,855.04	$4,501,067.01	$4,029,681.29	$385,573.92
1999	$8,795,961.10	$7,731,162.72	$889,860.74	$21,259,913.60	$15,607,894.68	$4,441,836.79	$5,454,822.12	$4,934,185.51	$426,962.51
2000	$9,564,219.98	$8,407,042.29	$912,609.82	$21,842,019.69	$16,019,030.79	$4,116,983.60	$6,697,409.04	$6,101,981.98	$472,078.91
2001	$10,873,871.75	$9,608,873.33	$954,813.12	$19,815,170.08	$14,632,480.16	$3,481,723.26	$7,821,011.96	$7,129,432.81	$537,594.32
2002	$12,139,328.11	$10,802,112.48	$973,693.41	$21,397,645.29	$17,022,732.76	$3,389,377.59	$9,175,673.85	$8,376,655.71	$592,789.13
2003	$14,387,060.94	$12,597,665.04	$1,355,988.28	$24,625,160.84	$19,021,409.37	$4,547,957.59	$11,623,560.81	$10,519,985.99	$845,638.20
2004	$16,223,482.58	$14,252,443.27	$1,540,976.48	$25,264,012.18	$20,706,851.57	$3,879,815.58	$14,298,983.28	$12,964,313.14	$1,025,865.17
2005	$18,536,401.66	$16,346,434.18	$1,698,140.71	$30,646,005.72	$24,656,138.26	$4,802,828.01	$16,447,304.87	$14,756,405.91	$1,302,277.34
2006	$20,827,482.73	$18,325,103.99	$1,923,135.96	$35,942,543.40	$27,868,079.25	$6,037,175.22	$19,523,396.72	$17,449,140.33	$1,581,693.08
2007	$22,023,505.40	$19,333,832.18	$2,111,833.94	$37,246,835.43	$30,033,005.68	$5,193,208.71	$22,400,152.09	$20,032,960.17	$1,909,601.56
Overall	**$154,580,562.68**	**$135,582,293.36**	**$14,985,736.47**	**$291,664,950.57**	**$221,766,978.46**	**$50,964,228.50**	**$124,971,266.62**	**$112,505,565.84**	**$9,747,374.47**
%-Change	241.36%	250.54%	158.48%	128.19%	148.81%	50.27%	585.77%	594.72%	504.14%

Crude Annual Mean Per-Patient-Year Outpatient Costs (2007 Canadian dollars)

Year	SARDs	SARDs-CTD	SARDs-VD
1996	$2,205.24	$2,074.71	$3,687.24
1997	$2,201.10	$2,062.39	$3,817.97
1998	$2,112.81	$1,994.88	$3,533.86
1999	$2,085.75	$1,986.08	$3,488.51
2000	$1,978.74	$1,876.33	$3,367.56
2001	$2,018.29	$1,915.81	$3,446.98
2002	$2,005.59	$1,910.38	$3,336.47
2003	$1,974.05	$1,855.96	$3,684.75
2004	$1,854.01	$1,749.89	$3,357.25
2005	$1,786.99	$1,697.63	$2,932.04
2006	$1,729.09	$1,642.57	$2,715.97
2007	$1,641.48	$1,561.04	$2,512.84
Overall	**$1,881.92**	**$1,782.75**	**$3,146.17**
%-Change	-25.56%	-24.76%	-31.85%

Total Outpatient Encounters

Year	SARDs	SARDs-CTD	SARDs-VD
1996	98,319	84,789	11,721
1997	109,690	94,467	13,152
1998	121,668	106,339	13,079
1999	143,031	126,631	13,625
2000	160,944	142,916	14,357
2001	175,926	157,478	14,118
2002	178,918	160,210	14,117
2003	217,620	192,473	19,207
2004	249,884	220,632	23,049
2005	290,978	256,349	27,429
2006	331,931	292,333	31,343
2007	366,839	323,214	35,089
Overall	**2,445,748**	**2,157,831**	**230,286**
%-Change	273.11%	281.20%	199.37%

Crude Annual Mean Number of Outpatient Encounters, Per Patient-Year

Year	SARDs	SARDs-CTD	SARDs-VD
1996	33.61	31.89	52.90
1997	33.89	32.10	54.16
1998	33.68	32.17	52.49
1999	33.92	32.53	53.41
2000	33.30	31.90	52.98
2001	32.65	31.40	50.97
2002	29.56	28.33	48.37
2003	29.86	28.36	52.19
2004	28.56	27.09	50.22
2005	28.05	26.62	47.36
2006	27.56	26.20	44.26
2007	27.34	26.10	41.75
Overall	**29.78**	**28.37**	**48.35**
%-Change	-18.64%	-18.18%	-21.07%

Total Hospital Admissions

Year	SARDs	SARDs-CTD	SARDs-VD
1996	2,597	2,133	409
1997	2,705	2,193	458
1998	2,916	2,420	434
1999	3,240	2,694	476
2000	3,273	2,727	442
2001	3,273	2,764	416
2002	3,448	3,001	350
2003	4,196	3,473	595
2004	4,670	3,957	567
2005	5,312	4,496	645
2006	5,975	5,050	733
2007	6,450	5,533	719
Overall	**48,055**	**40,441**	**6,244**
%-Change	148.36%	159.40%	75.79%

Total Hospital Admissions by Type

	SARDs			SARDs-CTD			SARDs-VD		
Year	**Inpatient**	**Day Case**	**ALC**	**Inpatient**	**Day Case**	**ALC**	**Inpatient**	**Day Case**	**ALC**
1996	1,947	597	53	1,563	537	33	341	50	18
1997	1,974	655	76	1,575	567	51	356	79	23
1998	2,070	772	74	1,682	683	55	341	74	19
1999	2,280	903	57	1,839	815	40	381	79	16
2000	2,211	1,032	30	1,766	942	19	368	66	8
2001	2,209	1,059	5	1,805	954	5	337	79	0
2002	2,207	1,241	0	1,857	1,144	0	288	62	0
2003	2,654	1,541	1	2,123	1,349	1	459	136	0
2004	2,854	1,816	0	2,367	1,590	0	394	173	0
2005	3,169	2,142	1	2,609	1,886	1	444	201	0
2006	3,558	2,417	0	2,899	2,151	0	521	212	0
2007	3,630	2,818	2	3,024	2,507	2	475	244	0
Overall	**30,763**	**16,993**	**299**	**25,109**	**15,125**	**207**	**4,705**	**1,455**	**84**
%-Change	86.44%	372.03%	-96.23%	93.47%	366.85%	-93.94%	39.30%	388.00%	-100.00%

Crude Annual Mean Number of Hospital Admissions, Per-Patient-Year

Year	SARDs	SARDs-CTD	SARDs-VD
1996	0.89	0.80	1.85
1997	0.84	0.75	1.89
1998	0.81	0.73	1.74
1999	0.77	0.69	1.87
2000	0.68	0.61	1.63
2001	0.61	0.55	1.50
2002	0.57	0.53	1.20
2003	0.58	0.51	1.62
2004	0.53	0.49	1.24
2005	0.51	0.47	1.11
2006	0.50	0.45	1.04
2007	0.48	0.45	0.86
Overall	**0.59**	**0.53**	**1.31**
%-Change	-45.84%	-44.32%	-53.65%

Crude Annual Mean Number of Inpatient Admissions, Per-Patient-Year

Year	SARDs	SARDs-CTD	SARDs-VD
1996	0.67	0.59	1.54
1997	0.61	0.54	1.47
1998	0.57	0.51	1.37
1999	0.54	0.47	1.49
2000	0.46	0.39	1.36
2001	0.41	0.36	1.22
2002	0.36	0.33	0.99
2003	0.36	0.31	1.25
2004	0.33	0.29	0.86
2005	0.31	0.27	0.77
2006	0.30	0.26	0.74
2007	0.27	0.24	0.57
Overall	**0.37**	**0.33**	**0.99**
%-Change	-59.35%	-58.47%	-63.27%

Crude Annual Mean Number of Day Admissions, Per-Patient-Year

Year	SARDs	SARDs-CTD	SARDs-VD
1996	0.20	0.20	0.23
1997	0.20	0.19	0.33
1998	0.21	0.21	0.30
1999	0.21	0.21	0.31
2000	0.21	0.21	0.24
2001	0.20	0.19	0.29
2002	0.21	0.20	0.21
2003	0.21	0.20	0.37
2004	0.21	0.20	0.38
2005	0.21	0.20	0.35
2006	0.20	0.19	0.30
2007	0.21	0.20	0.29
Overall	**0.21**	**0.20**	**0.31**
%-Change	2.93%	0.21%	24.44%

Crude Annual Mean Per-Patient-Year Hospital Costs (2007 Canadian dollars)

Year	SARDS	SARDs-CTD	SARDs-VD
1996	$5,579.38	$4,540.48	$15,596.04
1997	$5,763.00	$4,720.08	$17,067.85
1998	$5,161.92	$4,297.60	$13,937.88
1999	$5,041.27	$4,009.56	$17,413.28
2000	$4,518.88	$3,575.21	$15,191.82
2001	$3,677.87	$2,917.41	$12,569.40
2002	$3,535.19	$3,010.52	$11,614.09
2003	$3,378.83	$2,802.35	$12,358.58
2004	$2,887.15	$2,542.36	$8,452.76
2005	$2,954.40	$2,560.61	$8,292.65
2006	$2,983.94	$2,497.96	$8,526.08
2007	$2,776.13	$2,424.90	$6,179.33
Overall	**$3,550.83**	**$2,968.11**	**$10,699.65**
%-Change	-50.24%	-46.59%	-60.38%

Annual Proportion of Admissions as Inpatient and Day-Case

	SARDs		SARDs-CTD		SARDs-VD	
Year	**Inpatient**	**Day-Case**	**Inpatient**	**Day-Case**	**Inpatient**	**Day-Case**
1996	74.97%	22.99%	73.28%	25.18%	83.37%	12.22%
1997	72.98%	24.21%	71.82%	25.85%	77.73%	17.25%
1998	70.99%	26.47%	69.50%	28.22%	78.57%	17.05%
1999	70.37%	27.87%	68.26%	30.25%	80.04%	16.60%
2000	67.55%	31.53%	64.76%	34.54%	83.26%	14.93%
2001	67.49%	32.36%	65.30%	34.52%	81.01%	18.99%
2002	64.01%	35.99%	61.88%	38.12%	82.29%	17.71%
2003	63.25%	36.73%	61.13%	38.84%	77.14%	22.86%
2004	61.11%	38.89%	59.82%	40.18%	69.49%	30.51%
2005	59.66%	40.32%	58.03%	41.95%	68.84%	31.16%
2006	59.55%	40.45%	57.41%	42.59%	71.08%	28.92%
2007	56.28%	43.69%	54.65%	45.31%	66.06%	33.94%
Overall	**64.02%**	**35.36%**	**62.09%**	**37.40%**	**75.35%**	**23.30%**
%-Change	-24.93%	90.05%	-25.41%	79.97%	-20.76%	177.60%

-these proportions may not sum to 100% because a third type of admission (ALC) made a minor contribution to the total

Total Number of Prescriptions

Year	SARDs	SARDs-CTD	SARDs-VD
1996	67,202	59,250	6,755
1997	79,455	70,276	7,794
1998	91,371	81,156	8,727
1999	111,652	99,038	11,010
2000	132,112	117,298	12,663
2001	157,427	138,596	15,990
2002	176,069	155,282	17,228
2003	215,341	189,188	21,533
2004	263,245	231,934	26,000
2005	321,856	282,068	32,327
2006	390,293	340,592	40,808
2007	458,636	398,854	50,119
Overall	**2,464,659**	**2,163,532**	**250,954**
%-Change	**582.47%**	**573.17%**	**641.95%**

Crude Annual Mean Number of Prescriptions, Per-Patient-Year

Year	SARDs	SARDs-CTD	SARDs-VD
1996	22.97	22.29	30.49
1997	24.55	23.88	32.10
1998	25.29	24.55	35.02
1999	26.48	25.44	43.16
2000	27.33	26.18	46.73
2001	29.22	27.63	57.73
2002	29.09	27.46	59.03
2003	29.55	27.87	58.51
2004	30.08	28.48	56.64
2005	31.03	29.29	55.82
2006	32.40	30.53	57.63
2007	34.18	32.20	59.64
Overall	**30.01**	**28.45**	**52.69**
%-Change	48.82%	44.49%	95.62%

Annual Mean Number of Prescriptions, Per-Patient-Year (amongst users)

Year	SARDs		SARDs-CTD		SARDs-VD	
	Mean	**STD**	**Mean**	**STD**	**Mean**	**STD**
1996	22.38	29.67	22.14	30.09	24.52	26.33
1997	23.79	34.08	23.41	34.60	27.61	29.57
1998	23.32	34.74	22.78	34.76	30.26	35.45
1999	24.39	36.01	23.76	35.65	33.73	41.93
2000	26.14	41.46	25.34	40.46	39.02	56.27
2001	27.82	48.57	26.56	44.64	48.51	91.61
2002	28.11	52.95	26.73	49.52	54.11	96.88
2003	27.66	54.08	26.51	50.41	43.92	94.35
2004	28.76	57.19	27.63	54.68	44.10	85.02
2005	30.20	65.62	28.81	63.94	48.27	87.05
2006	31.89	74.62	30.40	72.55	48.93	92.37
2007	34.61	78.73	32.78	75.27	56.34	109.23
Overall	**29.06**	**60.24**	**27.85**	**57.91**	**44.84**	**84.75**
%-Change	**54.70%**		48.03%		129.80%	

Crude Annual Mean Per-Patient-Year Prescription Costs (2007 Canadian dollars)

Year	SARDs	SARDs-CTD	SARDs-VD
1996	$1,116.51	$1,084.70	$1,426.49
1997	$1,161.99	$1,130.69	$1,446.32
1998	$1,245.97	$1,219.24	$1,547.45
1999	$1,293.48	$1,267.56	$1,673.82
2000	$1,385.62	$1,361.87	$1,741.99
2001	$1,451.65	$1,421.46	$1,940.77
2002	$1,515.95	$1,481.44	$2,031.26
2003	$1,594.87	$1,549.87	$2,297.93
2004	$1,634.08	$1,591.74	$2,235.00
2005	$1,585.59	$1,532.50	$2,248.54
2006	$1,620.83	$1,564.06	$2,233.77
2007	$1,669.56	$1,617.49	$2,272.21
Overall	**$1,521.44**	**$1,479.32**	**$2,046.41**
%-Change	49.53%	49.12%	59.29%

Annual Mean Per-Patient-Year Prescription Costs (amongst users) (2007 Canadian dollars)

Year	SARDs		SARDs-CTD		SARDs-VD	
	Mean	**STD**	**Mean**	**STD**	**Mean**	**STD**
1996	$1,097.49	1,538.50	$ 1,084.87	1,542.42	$1,179.65	1,466.15
1997	$1,130.65	1,486.48	$ 1,112.85	1,487.11	$1,249.32	1,453.90
1998	$1,151.32	1,655.07	$ 1,132.91	1,671.07	$1,343.32	1,457.38
1999	$1,200.02	1,793.27	$ 1,190.41	1,819.90	$1,316.20	1,467.37
2000	$1,333.52	1,895.72	$ 1,322.80	1,921.55	$1,493.53	1,608.28
2001	$1,398.23	1,969.33	$ 1,381.74	1,978.57	$1,633.28	1,871.81
2002	$1,474.37	2,215.64	$ 1,451.57	2,236.46	$1,847.23	1,914.96
2003	$1,506.73	2,674.41	$ 1,485.36	2,681.69	$1,740.47	2,755.12
2004	$1,576.35	3,017.10	$ 1,554.30	3,053.26	$1,787.82	2,545.91
2005	$1,549.70	2,689.77	$ 1,511.13	2,685.12	$1,950.07	2,795.29
2006	$1,606.94	2,991.50	$ 1,565.64	2,944.59	$1,938.84	3,336.52
2007	$1,694.23	3,334.38	$ 1,649.17	3,329.24	$2,157.78	3,478.33
Overall	**$1482.62**	**2632.61**	**$1455.16**	**2633.49**	**$1759.80**	**2643.31**
%-Change	54.37%		52.02%		82.92%	

Top-Five Most Frequently-Prescribed Drugs, by Year

	SARDs		SARDs-CTD		SARDs-VD	
Year	**Drug**	**Quantity**	**Drug**	**Quantity**	**Drug**	**Quantity**
1996	Prednisone	3916	Acetaminophen-codeine(30mg)	3284	Prednisone	677
	Acetaminophen-codeine(30mg)	3599	Prednisone	3111	Acetaminophen-codeine(30mg)	287
	Hydroxychloroquine	1703	Hydroxychloroquine	1667	Furosemide	222
	Omeprazole	1579	Omeprazole	1423	Digoxin	159
	Lorazepam	1396	Lorazepam	1296	Warfarin	144
1997	Prednisone	4268	Acetaminophen-codeine(30mg)	3737	Prednisone	700
	Acetaminophen-codeine(30mg)	3988	Prednisone	3433	Furosemide	288
	Hydroxychloroquine	2175	Hydroxychloroquine	2135	Acetaminophen-codeine(30mg)	218
	Omeprazole	1865	Omeprazole	1650	Digoxin	192
	Lorazepam	1717	Lorazepam	1581	Omeprazole	180
1998	Prednisone	4626	Acetaminophen-codeine(30mg)	3925	Prednisone	791
	Acetaminophen-codeine(30mg)	4187	Prednisone	3716	Furosemide	363
	Hydroxychloroquine	2766	Hydroxychloroquine	2731	Digoxin	212
	Omeprazole	2093	Omeprazole	1865	Salbutamol	199
	Levothyroxine	1891	Lorazepam	1725	Acetaminophen-codeine(30mg)	198
1999	Prednisone	5604	Acetaminophen-codeine(30mg)	4605	Prednisone	973
	Acetaminophen-codeine(30mg)	4840	Prednisone	4505	Furosemide	447
	Hydroxychloroquine	3527	Hydroxychloroquine	3471	Omeprazole	273
	Omeprazole	2626	Omeprazole	2313	Etidronate	269
	Levothyroxine	2404	Levothyroxine	2169	Digoxin	249
2000	Prednisone	6213	Prednisone	5038	Prednisone	1015
	Acetaminophen-codeine(30mg)	5199	Acetaminophen-codeine(30mg)	4902	Furosemide	457
	Hydroxychloroquine	4351	Hydroxychloroquine	4272	Omeprazole	314
	Omeprazole	3000	Omeprazole	2646	Ramipril	308
	Levothyroxine	2892	Levothyroxine	2610	Hydrochlorothiazide	294
2001	Prednisone	6916	Prednisone	5525	Prednisone	1184
	Acetaminophen-codeine(30mg)	5532	Acetaminophen-codeine(30mg)	5203	Furosemide	505
	Hydroxychloroquine	5007	Hydroxychloroquine	4925	Ramipril	441
	Levothyroxine	3770	Levothyroxine	3358	Etidronate	367
	Omeprazole	3495	Omeprazole	3105	Levothyroxine	349
2002	Prednisone	7553	Prednisone	6138	Prednisone	1148
	Acetaminophen-codeine(30mg)	5990	Acetaminophen-codeine(30mg)	5699	Furosemide	518
	Hydroxychloroquine	5495	Hydroxychloroquine	5416	Levothyroxine	505
	Levothyroxine	4345	Levothyroxine	3775	Ramipril	421
	Omeprazole	3359	Methadone	3025	Etidronate	416
2003	Prednisone	9208	Prednisone	7177	Prednisone	1608

	SARDs		SARDs-CTD		SARDs-VD	
	Year	**Drug**	**Quantity**	**Drug**	**Quantity**	**Drug**
2003	Acetaminophen-codeine(30mg)	6720	Hydroxychloroquine	6629	Furosemide	736
	Hydroxychloroquine	6714	Acetaminophen-codeine(30mg)	6312	Levothyroxine	584
	Levothyroxine	5415	Levothyroxine	4763	Ramipril	518
	Ramipril	4010	Ramipril	3417	Etidronate	422
2004	Prednisone	10,476	Prednisone	8056	Prednisone	2004
	Acetaminophen-codeine(30mg)	7828	Hydroxychloroquine	7433	Rabeprazole	938
	Hydroxychloroquine	7549	Acetaminophen-codeine(30mg)	7392	Levothyroxine	876
	Levothyroxine	6956	Levothyroxine	5993	Furosemide	588
	Rabeprazole	5602	Rabeprazole	4540	Etidronate	506
2005	Prednisone	12041	Prednisone	9247	Prednisone	2220
	Acetaminophen-codeine(30mg)	9004	Hydroxychloroquine	8646	Rabeprazole	1172
	Hydroxychloroquine	8790	Acetaminophen-codeine(30mg)	8459	Levothyroxine	1088
	Levothyroxine	8550	Levothyroxine	7258	Ramipril	771
	Rabeprazole	6959	Rabeprazole	5646	Furosemide	759
2006	Prednisone	13,432	Prednisone	10,102	Prednisone	2723
	Levothyroxine	10,711	Hydroxychloroquine	10,046	Levothyroxine	1309
	Hydroxychloroquine	10,217	Levothyroxine	9148	Rabeprazole	1250
	Acetaminophen-codeine(30mg)	9397	Acetaminophen-codeine(30mg)	8674	Ramipril	1127
	Rabeprazole	9156	Rabeprazole	7763	Furosemide	1107
2007	Prednisone	15,049	Hydroxychloroquine	11,592	Prednisone	3079
	Levothyroxine	12,971	Prednisone	11,367	Rabeprazole	1749
	Hydroxychloroquine	11,801	Levothyroxine	11,185	Levothyroxine	1514
	Rabeprazole	11,739	Rabeprazole	9797	Ramipril	1496
	Ramipril	10,535	Acetaminophen-codeine(30mg)	9402	Furosemide	1284

Top-Ten Most Costly Drugs, by Year (2007 Canadian Dollars)

	SARDs			SARDs-CTD			SARDs-VD		
Year	**Drug**	**Total Annual Cost**	**Total Annual Quantity**	**Drug**	**Total Annual Cost**	**Total Annual Quantity**	**Drug**	**Total Annual Cost**	**Total Annual Quantity**
1996	Omeprazole	$266,829.51	1579	Omeprazole	$ 239,729.02	1423	Omeprazole	$ 23,062.27	143
	Azathioprine	$ 142,453.56	1027	Azathioprine	$ 132,167.03	945	Enalapril	$ 10,651.83	111
	Hydroxychloroquine	$ 131,872.84	1703	Hydroxychloroquine	$ 128,755.45	1667	Diltiazem	$ 9,495.63	62
	Enalapril	$ 87,412.46	868	Nifedipine	$ 79,113.47	759	Cyclosporine	$ 9,418.54	7
	Nifedipine	$ 86,304.60	842	Enalapril	$ 76,504.65	753	Cyclophosphamide	$ 8,942.85	119
	Cisapride	$ 78,083.97	662	Cisapride	$ 70,895.80	593	Calcitonin	$ 7,992.55	30
	Diltiazem	$ 74,087.17	485	Diltiazem	$ 63,197.52	417	Prednisone	$ 7,469.05	677
	Ranitidine	$ 53,493.69	956	Ipratropium	$ 45,372.21	380	Ranitidine	$ 7,235.77	124
	Ipratropium	$ 50,801.18	455	Ranitidine	$ 45,227.55	818	Nitroglycerine	$ 6,647.90	118
	Prednisone	$ 46,861.19	3916	Morphine	$ 40,356.68	419	Warfarin	$ 6,608.12	144
1997	Omeprazole	$ 315,730.99	1865	Omeprazole	$ 280,270.93	1650	Omeprazole	$ 27,926.50	180
	Hydroxychloroquine	$ 167,077.95	2175	Hydroxychloroquine	$ 163,694.16	2135	Enalapril	$ 14,528.97	158
	Azathioprine	$ 153,395.47	1190	Azathioprine	$ 141,575.28	1097	Cyclosporine	$ 10,668.68	11
	Enalapril	$ 86,725.80	884	Cisapride	$ 72,388.34	672	Budesonide	$ 9,087.80	55
	Cisapride	$ 82,480.26	781	Nifedipine	$ 71,798.26	732	Ranitidine	$ 8,956.23	147
	Nifedipine	$ 78,542.37	804	Enalapril	$ 71,523.21	717	Cyclophosphamide	$ 7,971.11	103
	Cyclosporine	$ 78,305.95	182	Cyclosporine	$ 67,637.27	171	Cisapride	$ 7,950.80	94
	Diltiazem	$ 65,242.59	571	Paroxetine	$ 58,655.66	573	Prednisone	$ 7,448.55	700
	Ranitidine	$ 63,008.40	1111	Diltiazem	$ 57,632.98	508	Hematopoietic agents	$ 6,670.08	7
	Paroxetine	$ 61,285.76	600	Ranitidine	$ 51,934.81	938	Nitroglycerine	$ 6,665.60	130
1998	Omeprazole	$ 377,606.98	2093	Omeprazole	$ 337,425.03	1865	Omeprazole	$ 32,388.14	187

	SARDs			SARDs-CTD			SARDs-VD		
Year	**Drug**	**Total Annual Cost**	**Total Annual Quantity**	**Drug**	**Total Annual Cost**	**Total Annual Quantity**	**Drug**	**Total Annual Cost**	**Total Annual Quantity**
1998	Hydroxychloroquine	$ 221,072.62	2766	Hydroxychloroquine	$ 218,476.02	2731	Enalapril	$ 15,133.81	160
	Azathioprine	$ 151,717.12	1446	Azathioprine	$ 143,432.36	1356	Cisapride	$ 10,341.80	116
	Morphine	$ 124,320.62	974	Morphine	$ 117,386.62	873	Budesonide	$ 8,972.45	38
	Cisapride	$ 100,493.02	908	Cisapride	$ 87,671.96	776	Etidronate	$ 8,913.37	165
	Nifedipine	$ 83,543.38	847	Nifedipine	$ 78,789.41	798	Alendronate	$ 8,581.19	67
	Paroxetine	$ 82,309.71	733	Paroxetine	$ 75,636.48	667	Amlodipine	$ 8,288.34	55
	Enalapril	$ 81,635.51	788	Cyclosporine	$ 72,521.02	257	Prednisone	$ 7,776.48	791
	Cyclosporine	$ 79,456.25	276	Sertraline	$ 66,831.27	553	Nitroglycerine	$ 7,757.49	162
	Sertraline	$ 74,761.39	630	Enalapril	$ 65,839.13	622	Ranitidine	$ 7,529.79	143
1999	Omeprazole	$ 447,576.00	2626	Omeprazole	$ 404,180.78	2313	Omeprazole	$ 36,640.78	273
	Hydroxychloroquine	$ 296,164.91	3527	Hydroxychloroquine	$ 292,300.54	3471	Etidronate	$ 13,820.19	269
	Azathioprine	$ 139,631.48	1489	Azathioprine	$ 131,736.00	1382	Budesonide	$ 9,939.63	52
	Morphine	$ 111,080.26	1212	Morphine	$ 105,581.40	1133	Amlodipine	$ 9,841.43	78
	Paroxetine	$ 104,056.83	991	Paroxetine	$ 95,695.71	889	Cyclophosphamide	$ 9,678.68	156
	Cisapride	$ 97,929.67	875	Cisapride	$ 86,105.32	750	Enalapril	$ 9,516.23	167
	Etidronate	$ 91,814.27	1603	Sertraline	$ 79,032.96	813	Cisapride	$ 9,463.86	110
	Sertraline	$ 85,737.65	883	Cyclosporine	$ 78,999.55	359	Prednisone	$ 8,406.98	973
	Cyclosporine	$ 83,255.51	429	Nifedipine	$ 78,345.80	849	Salbutamol	$ 8,133.40	233
	Nifedipine	$ 83,138.72	908	Etidronate	$ 75,124.18	1286	Ipratropium	$ 7,944.25	148
2000	Omeprazole	$ 505,440.69	3000	Omeprazole	$ 459,896.81	2646	Omeprazole	$ 37,053.78	314
	Hydroxychloroquine	$ 347,812.00	4351	Hydroxychloroquine	$ 342,483.56	4272	Ramipril	$ 15,247.14	308
	Azathioprine	$ 140,281.15	1571	Morphine	$ 132,454.88	1324	Etidronate	$ 14,359.60	275
	Morphine	$ 137,256.36	1388	Azathioprine	$ 132,079.57	1463	Enalapril	$ 12,225.11	194
	Paroxetine	$ 128,974.63	1238	Paroxetine	$ 117,396.43	1059	Paroxetine	$ 11,236.07	176
	Cyclosporine	$ 114,232.91	460	Cyclosporine	$ 104,929.82	398	Budesonide	$ 9,964.50	93
	Ramipril	$ 111,751.18	1465	Celecoxib	$ 98,837.10	1218	Prednisone	$ 9,596.49	1015
	Etidronate	$ 111,385.65	2019	Ramipril	$ 94,100.11	1128	Alendronate	$ 9,101.81	99
	Celecoxib	$ 103,776.72	1334	Pantoprazole	$ 93,131.90	718	Nitroglycerine	$ 8,969.89	228
	Pantoprazole	$ 103,352.07	803	Nifedipine	$ 92,938.22	984	Atorvastatin	$ 8,220.34	64
2001	Omeprazole	$ 550,499.83	3495	Omeprazole	$ 508,064.80	3105	Omeprazole	$ 34,321.05	339
	Hydroxychloroquine	$ 397,116.88	5007	Hydroxychloroquine	$ 391,547.89	4925	Ramipril	$ 19,947.59	441
	Ramipril	$ 164,936.96	2492	Morphine	$ 156,587.54	1968	Etidronate	$ 15,684.08	367
	Morphine	$ 164,187.63	2110	Azathioprine	$ 141,246.73	1656	Atorvastatin	$ 14,158.25	108
	Atorvastatin	$ 159,575.06	1042	Ramipril	$ 140,603.91	2003	Paroxetine	$ 12,373.19	221
	Pantoprazole	$ 151,288.65	1269	Atorvastatin	$ 140,393.85	906	Alendronate	$ 12,117.64	171
	Azathioprine	$ 151,213.28	1821	Pantoprazole	$ 136,636.37	1135	Prednisone	$ 11,693.90	1184
	Paroxetine	$ 145,809.27	1420	Paroxetine	$ 131,777.00	1189	Budesonide	$ 10,971.61	81
	Cyclosporine	$ 125,127.89	381	Cyclosporine	$ 115,385.58	314	Pantoprazole	$ 10,828.58	108

	SARDs			SARDs-CTD			SARDs-VD		
Year	**Drug**	**Total Annual Cost**	**Total Annual Quantity**	**Drug**	**Total Annual Cost**	**Total Annual Quantity**	**Drug**	**Total Annual Cost**	**Total Annual Quantity**
2001	Etidronate	$ 121,699.02	2448	Nifedipine	$ 108,525.69	1179	Enalapril	$ 9,899.31	127
2002	Omeprazole	$ 532,836.19	3359	Omeprazole	$ 485,826.31	2897	Omeprazole	$ 37,234.57	402
	Hydroxychloroquine	$ 450,626.47	5495	Hydroxychloroquine	$ 444,914.54	5416	Ramipril	$ 22,806.10	421
	Atorvastatin	$ 216,920.89	1536	Atorvastatin	$ 192,001.71	1338	Atorvastatin	$ 18,891.68	170
	Ramipril	$ 209,119.46	3085	Ramipril	$ 179,556.71	2564	Etidronate	$ 16,424.41	416
	Pantoprazole	$ 196,514.17	1758	Pantoprazole	$ 177,455.22	1525	Pantoprazole	$ 15,571.74	189
	Morphine	$ 169,792.63	2185	Morphine	$ 159,873.22	1977	Prednisone	$ 13,480.24	1148
	Azathioprine	$ 164,975.79	1972	Azathioprine	$ 153,999.02	1821	Alendronate	$ 13,198.81	233
	Mycophenolate mofetil	$ 154,702.14	313	Mycophenolate mofetil	$ 144,125.74	281	Cyclosporine	$ 10,636.49	70
	Paroxetine	$ 152,834.39	1570	Paroxetine	$ 140,235.29	1311	Paroxetine	$ 10,133.11	239
	Cyclosporine	$ 150,552.39	489	Bosentan	$ 131,983.51	29	Nifedipine	$ 9,411.06	96
2003	Omeprazole	$ 487,453.57	3154	Hydroxychloroquine	$ 476,852.67	6629	Omeprazole	$ 37,120.24	377
	Hydroxychloroquine	$ 483,046.66	6714	Omeprazole	$ 438,845.17	2696	Cyclosporine	$ 35,425.20	111
	Bosentan	$ 379,886.39	89	Bosentan	$ 379,886.39	89	Ramipril	$ 28,281.56	518
	Atorvastatin	$ 301,951.54	2253	Atorvastatin	$ 267,584.75	1979	Atorvastatin	$ 26,626.81	228
	Mycophenolate mofetil	$ 275,160.41	493	Mycophenolate mofetil	$ 248,754.93	452	Fentanyl	$ 21,628.27	76
	Ramipril	$ 275,082.54	4010	Ramipril	$ 237,860.23	3417	Prednisone	$ 19,269.61	1608
	Pantoprazole	$ 234,116.59	2049	Pantoprazole	$ 212,391.48	1794	Pantoprazole	$ 18,860.94	228
	Cyclosporine	$ 222,405.01	749	Cyclosporine	$ 179,902.70	618	Infliximab	$ 18,677.81	4
	Alendronate	$ 199,865.87	2290	Alendronate	$ 177,566.27	1908	Anakinra	$ 18,037.31	11
	Azathioprine	$ 185,354.25	2203	Azathioprine	$ 173,454.45	2038	Etidronate	$ 17,494.14	422
2004	Bosentan	$ 590,581.21	138	Bosentan	$ 590,581.21	138	Cyclosporine	$ 43,247.80	107
	Hydroxychloroquine	$ 486,998.12	7549	Hydroxychloroquine	$ 480,489.67	7433	Atorvastatin	$ 42,293.67	325
	Atorvastatin	$ 427,752.93	3046	Atorvastatin	$ 377,895.59	2689	Rabeprazole	$ 41,257.87	938
	Mycophenolate mofetil	$ 404,825.50	671	Mycophenolate mofetil	$ 354,178.99	580	Mycophenolate mofetil	$ 35,720.54	65
	Rabeprazole	$ 349,077.79	5602	Omeprazole	$ 314,541.12	2224	Ramipril	$ 29,528.79	486
	Ramipril	$ 343,939.52	4814	Ramipril	$ 301,513.43	4173	Alendronate	$ 26,013.90	437
	Omeprazole	$ 343,412.02	2461	Rabeprazole	$ 298,486.33	4540	Prednisone	$ 23,675.09	2004
	Cyclosporine	$ 284,878.52	854	Gabapentin	$ 232,293.86	2317	Pantoprazole	$ 23,300.47	243
	Gabapentin	$ 256,176.09	2655	Cyclosporine	$ 228,747.47	692	Omeprazole	$ 22,575.38	184
	Alendronate	$ 248,588.38	2886	Venlafaxine	$ 223,917.72	2103	Interferon beta	$ 22,342.09	4
2005	Atorvastatin	$ 538,375.38	4263	Bosentan	$ 497,718.91	125	Atorvastatin	$ 61,412.79	599
	Mycophenolate mofetil	$ 499,804.68	898	Hydroxychloroquine	$ 481,828.33	8646	Rabeprazole	$ 52,356.58	1172

	SARDs			SARDs-CTD			SARDs-VD		
Year	**Drug**	**Total Annual Cost**	**Total Annual Quantity**	**Drug**	**Total Annual Cost**	**Total Annual Quantity**	**Drug**	**Total Annual Cost**	**Total Annual Quantity**
2005	Bosentan	$ 497,718.91	125	Atorvastatin	$ 468,517.57	3606	Etanercept	$ 47,809.42	31
	Hydroxychloroquine	$ 488,313.95	8790	Mycophenolate mofetil	$ 451,109.02	789	Ramipril	$ 40,320.10	771
	Rabeprazole	$ 440,418.57	6959	Rabeprazole	$ 378,967.35	5646	Mycophenolate mofetil	$ 37,264.17	78
	Ramipril	$ 425,639.47	6386	Ramipril	$ 370,468.35	5389	Alendronate	$ 33,788.82	552
	Gabapentin	$ 329,759.15	3657	Gabapentin	$ 298,262.69	3201	Cyclosporine	$ 31,461.79	71
	Omeprazole	$ 311,260.59	2664	Omeprazole	$ 284,350.37	2392	Pantoprazole	$ 31,045.56	306
	Venlafaxine	$ 293,681.86	3016	Venlafaxine	$ 277,153.00	2831	Omalizumab	$ 26,327.39	11
	Alendronate	$ 279,380.51	3584	Oxycodone	$ 246,119.77	3534	Prednisone	$ 26,203.86	2220
2006	Bosentan	$ 733,224.07	183	Bosentan	$ 733,224.07	183	Atorvastatin	$ 78,756.03	804
	Mycophenolate mofetil	$ 657,059.20	1189	Mycophenolate mofetil	$ 584,665.64	1023	Rabeprazole	$ 59,977.64	1250
	Atorvastatin	$ 643,066.91	5266	Atorvastatin	$ 552,205.19	4382	Ramipril	$ 55,361.79	1127
	Rabeprazole	$ 546,776.07	9156	Hydroxychloroquine	$ 534,805.32	10046	Omalizumab	$ 51,367.87	26
	Hydroxychloroquine	$ 541,807.54	10217	Rabeprazole	$ 477,548.57	7763	Mycophenolate mofetil	$ 42,822.78	88
	Ramipril	$ 520,176.79	8776	Ramipril	$ 448,527.10	7374	Etanercept	$ 38,469.55	21
	Gabapentin	$ 397,213.55	4848	Venlafaxine	$ 373,244.27	4028	Pantoprazole	$ 37,332.30	421
	Venlafaxine	$ 393,588.50	4317	Gabapentin	$ 359,847.07	4201	Alendronate	$ 33,755.66	655
	Pantoprazole	$ 324,815.64	2989	Oxycodone	$ 285,927.65	4121	Prednisone	$ 30,339.74	2723
	Omeprazole	$ 300,061.87	2656	Pantoprazole	$ 278,808.78	2421	Amlodipine	$ 29,103.73	416
2007	Bosentan	$ 822,591.17	250	Bosentan	$ 822,591.17	250	Atorvastatin	$ 89,179.82	1032
	Mycophenolate mofetil	$ 773,937.04	1475	Mycophenolate mofetil	$ 667,532.84	1199	Rabeprazole	$ 77,963.92	1749
	Atorvastatin	$ 724,704.13	6473	Atorvastatin	$ 625,553.36	5324	Hydromorphone	$ 57,747.91	323
	Rabeprazole	$ 669,745.82	11739	Hydroxychloroquine	$ 588,134.32	11592	Mycophenolate mofetil	$ 57,245.95	132
	Hydroxychloroquine	$ 595,597.51	11801	Rabeprazole	$ 580,439.23	9797	Ramipril	$ 53,984.19	1496
	Gabapentin	$ 483,041.48	6135	Gabapentin	$ 433,902.66	5174	Omalizumab	$ 43,575.60	21
	Ramipril	$ 462,368.63	10535	Ramipril	$ 396,990.53	8761	Alendronate	$ 37,174.12	964
	Oxycodone	$ 373,931.39	5690	Oxycodone	$ 364,154.37	5456	Clopidogrel	$ 36,179.45	521
	Pantoprazole	$ 350,602.06	3380	Venlafaxine	$ 327,751.28	4741	Amlodipine	$ 36,159.89	547
	Venlafaxine	$ 349,246.53	5266	Etanercept	$ 314,540.58	197	Pantoprazole	$ 35,807.57	442

Total Attributable Overall Direct Medical Costs - Narrow Definition (2007 Canadian dollars)

Year	SARDs	SARDs-CTD	SARDs-VD
1996	$5,798,955.67	$4,877,152.89	$727,978.01
1997	$6,431,909.74	$5,289,189.37	$961,781.57
1998	$7,732,149.20	$6,485,422.41	$919,981.38
1999	$8,153,189.54	$6,808,247.61	$1,088,175.80
2000	$9,562,438.79	$7,989,187.31	$1,143,509.55
2001	$10,886,271.22	$9,410,376.92	$963,193.82
2002	$12,330,359.85	$10,919,025.07	$986,779.62
2003	$15,472,428.75	$13,053,182.51	$1,846,963.47
2004	$17,447,450.21	$15,527,454.49	$1,442,560.52
2005	$20,097,048.53	$17,475,367.92	$1,877,319.93
2006	$24,360,944.79	$20,972,226.81	$2,637,971.01
2007	$26,892,535.98	$23,235,260.82	$2,768,065.17
Overall	**$165,165,682.27**	**$141,817,033.17**	**$17,364,279.84**
%-Change	363.75%	376.41%	280.24%

Total Attributable Overall Direct Medical Costs - Broad Definition (2007 Canadian dollars)

Year	SARDs	SARDs-CTD	SARDs-VD
1996	$12,289,281.93	$9,597,051.39	$2,305,919.75
1997	$14,644,404.25	$11,574,082.60	$2,768,422.44
1998	$14,356,046.43	$11,585,414.07	$2,258,421.75
1999	$16,490,927.41	$13,092,065.99	$2,806,986.45
2000	$17,321,546.90	$14,291,784.87	$2,293,009.04
2001	$18,547,268.34	$15,488,738.44	$2,255,787.72
2002	$20,251,613.93	$17,045,289.67	$2,341,088.43
2003	$24,250,718.08	$19,904,779.52	$3,240,471.85
2004	$25,325,486.47	$21,755,374.54	$2,842,079.53
2005	$29,209,786.96	$24,712,844.19	$3,484,157.40
2006	$34,479,836.71	$28,314,073.58	$4,804,427.39
2007	$35,873,108.94	$30,615,699.00	$3,799,084.30
Overall	**$263,040,026.37**	**$217,977,197.84**	**$35,199,856.04**
%-Change	191.91%	219.01%	64.75%

Total Attributable Dispensed Prescriptions

Year	SARDs	SARDs-CTD	SARDs-VD
1996	67,182	59,238	6,747
1997	79,434	70,263	7,786
1998	91,311	81,111	8,712
1999	111,512	98,927	10,981
2000	131,918	117,135	12,633
2001	157,013	138,259	15,918
2002	175,380	154,711	17,117
2003	214,301	188,505	21,209
2004	261,288	230,577	25,478
2005	318,951	279,960	31,620
2006	386,231	337,501	39,897
2007	454,041	395,524	48,897
Overall	**2,448,562**	**2,151,711**	**246,995**
%-Change	575.84%	567.69%	624.72%

Total Attributable Prescription Costs (2007 Canadian dollars)

Year	SARDs	SARDs-CTD	SARDs-VD
1996	$3,266,189.05	$2,883,381.14	$316,055.22
1997	$3,761,281.34	$3,327,086.58	$351,185.92
1998	$4,500,362.10	$4,029,046.42	$385,503.89
1999	$5,453,068.30	$4,932,494.79	$426,899.42
2000	$6,693,042.01	$6,097,891.67	$471,910.08
2001	$7,815,860.31	$7,124,775.55	$537,135.36
2002	$9,167,617.09	$8,369,378.83	$592,283.16
2003	$11,613,748.48	$10,511,419.38	$844,432.39
2004	$14,287,537.20	$12,954,657.15	$1,024,329.88
2005	$16,432,327.70	$14,743,558.74	$1,300,504.78
2006	$19,507,039.41	$17,435,050.03	$1,579,580.27
2007	$22,382,072.98	$20,017,273.67	$1,907,545.24
Overall	**$124,880,145.99**	**$112,426,013.93**	**$9,737,365.60**
%-Change	585.27%	594.23%	503.55%

Crude Annual Mean Per-Patient-Year Attributable Prescriptions

Year	SARDs	SARDs-CTD	SARDs-VD
1996	22.96	22.28	30.45
1997	24.54	23.88	32.06
1998	25.28	24.54	34.96
1999	26.44	25.41	43.05
2000	27.29	26.14	46.62
2001	29.14	27.57	57.47
2002	28.98	27.36	58.65
2003	29.40	27.77	57.63
2004	29.86	28.31	55.51
2005	30.75	29.07	54.60
2006	32.06	30.25	56.35
2007	33.84	31.94	58.18
Overall	**29.81**	**28.29**	**51.86**
%-Change	47.37%	43.31%	91.08%

Crude Annual Mean Per-Patient-Year Attributable Prescription Costs (2007 Canadian dollars)

Year	SARDs	SARDs-CTD	SARDs-VD
1996	$1,116.42	$1,084.62	$1,426.35
1997	$1,161.94	$1,130.64	$1,446.20
1998	$1,245.77	$1,219.05	$1,547.17
1999	$1,293.06	$1,267.12	$1,673.57
2000	$1,384.72	$1,360.96	$1,741.37
2001	$1,450.69	$1,420.53	$1,939.12
2002	$1,514.62	$1,480.15	$2,029.53
2003	$1,593.53	$1,548.60	$2,294.65
2004	$1,632.77	$1,590.55	$2,231.66
2005	$1,584.14	$1,531.16	$2,245.48
2006	$1,619.47	$1,562.79	$2,230.78
2007	$1,668.21	$1,616.22	$2,269.76
Overall	**$1,520.33**	**$1,478.27**	**$2,044.31**
%-Change	49.42%	49.01%	$1,426.35

Total Attributable Outpatient Encounters - Narrow Definition

Year	SARDs	SARDs-CTD	SARDs-VD
1996	6,250	5,907	194
1997	6,469	6,042	264
1998	7,697	7,071	380
1999	10,138	9,309	507
2000	10,828	9,870	616
2001	11,592	10,690	455
2002	12,991	11,994	544
2003	16,934	15,328	864
2004	18,393	16,629	1,066
2005	19,623	17,811	1,156
2006	21,426	19,158	1,467
2007	22,075	19,688	1,628
Overall	**164,416**	**149,497**	**9,141**
%-Change	253.20%	233.30%	739.18%

Total Attributable Outpatient Encounters - Broad Definition

Year	SARDs	SARDs-CTD	SARDs-VD
1996	11,065	10,185	625
1997	13,240	12,026	914
1998	15,997	14,567	1,029
1999	20,103	18,397	1,198
2000	22,579	20,649	1,332
2001	24,901	22,938	1,208
2002	28,299	26,058	1,381
2003	35,445	32,116	2,060
2004	38,822	35,206	2,395
2005	43,546	39,617	2,707
2006	48,923	44,386	3,163
2007	56,806	50,387	4,754
Overall	**359,726**	**326,532**	**22,766**
%-Change	413.38%	394.72%	660.64%

Total Attributable Outpatient Costs - Narrow Definition (2007 Canadian dollars)

Year	SARDs	SARDs-CTD	SARDs-VD
1996	$343,184.52	$324,657.28	$11,424.98
1997	$361,451.70	$336,609.99	$16,009.68
1998	$434,286.58	$395,698.20	$24,646.63
1999	$584,602.10	$533,359.00	$32,619.64
2000	$619,502.20	$559,560.37	$39,074.01
2001	$727,971.60	$668,203.17	$32,333.87
2002	$834,513.59	$770,306.79	$34,539.50
2003	$1,092,989.26	$990,986.95	$55,797.74
2004	$1,144,774.30	$1,039,521.79	$63,465.46
2005	$1,228,712.73	$1,114,624.60	$73,188.94
2006	$1,430,693.98	$1,280,776.42	$97,445.03
2007	$1,513,630.92	$1,350,415.71	$110,584.18
Overall	**$10,316,313.48**	**$9,364,720.27**	**$591,129.66**
%-Change	341.05%	315.95%	867.92%

Total Attributable Outpatient Costs- Broad Definition (2007 Canadian dollars)

Year	SARDs	SARDs-CTD	SARDs-VD
1996	$716,436.33	$662,028.79	$40,699.29
1997	$833,568.84	$755,284.60	$58,865.36
1998	$997,639.47	$902,402.83	$68,222.93
1999	$1,265,175.78	$1,153,398.95	$80,473.06
2000	$1,419,331.88	$1,291,248.41	$90,073.28
2001	$1,654,128.56	$1,519,431.81	$85,342.87
2002	$1,923,188.28	$1,768,972.22	$91,274.35
2003	$2,411,392.71	$2,192,173.02	$137,046.00
2004	$2,583,884.72	$2,350,157.00	$156,122.54
2005	$2,912,543.95	$2,649,349.87	$182,028.50
2006	$3,356,567.23	$3,052,051.39	$210,881.98
2007	$3,690,474.48	$3,284,301.15	$297,208.57
Overall	**$23,764,332.23**	**$21,580,800.04**	**$1,498,238.73**
%-Change	415.12%	396.10%	630.25%

Crude Annual Mean Per-Patient-Year Attributable Outpatient Encounters – Narrow Definition

Year	SARDs	SARDs-CTD	SARDs-VD
1996	2.14	2.22	0.88
1997	2.00	2.01	1.09
1998	2.13	1.83	1.53
1999	2.40	1.82	1.99
2000	2.24	2.08	2.27
2001	2.15	1.97	1.64
2002	2.15	1.89	1.86
2003	2.32	1.77	2.35
2004	2.10	1.88	2.32
2005	1.89	1.73	2.00
2006	1.78	1.60	2.07
2007	1.65	1.55	1.94
Overall	**2.00**	**1.86**	**1.72**
%-Change	-22.98%	-30.39%	121.26%

Crude Annual Mean Per-Patient-Year Attributable Outpatient Costs – Narrow Definition (2007 Canadian dollars)

Year	SARDs	SARDs-CTD	SARDs-VD
1996	$117.30	$122.12	$51.56
1997	$111.66	$114.39	$65.93
1998	$120.22	$119.72	$98.92
1999	$138.62	$137.02	$127.88
2000	$128.17	$124.89	$144.18
2001	$135.12	$133.23	$116.73
2002	$137.87	$136.23	$118.35
2003	$149.97	$146.00	$151.62
2004	$130.82	$127.63	$138.27
2005	$118.45	$115.76	$126.37
2006	$118.78	$114.80	$137.62
2007	$112.82	$109.03	$131.58
Overall	**$125.59**	**$123.14**	**$124.10**
%-Change	-3.83%	-10.72%	155.20%

Crude Annual Mean Per-Patient-Year Attributable Outpatient Encounters – Broad Definition

Year	SARDs	SARDs-CTD	SARDs-VD
1996	3.78	3.83	2.82
1997	4.09	4.09	3.76
1998	4.43	4.41	4.13
1999	4.77	4.73	4.70
2000	4.67	4.61	4.92
2001	4.62	4.57	4.36
2002	4.68	4.61	4.73
2003	4.86	4.73	5.60
2004	4.44	4.32	5.22
2005	4.20	4.11	4.67
2006	4.06	3.98	4.47
2007	4.23	4.07	5.66
Overall	**4.38**	**4.29**	**4.78**
%-Change	11.95%	6.19%	100.55%

Crude Annual Mean Per-Patient-Year Attributable Outpatient Costs – Broad Definition (2007 Canadian dollars)

Year	SARDs	SARDs-CTD	SARDs-VD
1996	$244.89	$249.03	$183.67
1997	$257.51	$256.67	$242.41
1998	$276.16	$273.04	$273.80
1999	$300.01	$296.30	$315.48
2000	$293.64	$288.19	$332.37
2001	$307.02	$302.94	$308.10
2002	$317.74	$312.85	$312.76
2003	$330.87	$322.96	$372.41
2004	$295.28	$288.55	$340.14
2005	$280.78	$275.14	$314.29
2006	$278.66	$273.57	$297.82
2007	$275.06	$265.18	$353.64
Overall	**$289.32**	**$283.76**	**$314.55**
%-Change	12.32%	6.48%	92.54%

Total Attributable Hospital Admissions - Narrow Definition

Year	SARDs	SARDs-CTD	SARDs-VD
1996	300	224	59
1997	267	209	44
1998	290	230	52
1999	263	197	50
2000	262	205	44
2001	230	170	48
2002	252	192	48
2003	354	217	109
2004	256	162	73
2005	297	190	87
2006	359	245	91
2007	219	151	48
Overall	**3,349**	**2,392**	**753**
%-Change	-27.00%	-32.59%	-18.64%

Total Attributable Hospital Admissions - Broad Definition

Year	SARDs	SARDs-CTD	SARDs-VD
1996	1,083	882	168
1997	1,111	895	178
1998	1,107	922	157
1999	1,122	911	167
2000	1,008	812	155
2001	968	787	139
2002	937	763	137
2003	1,105	801	250
2004	978	744	180
2005	955	715	194
2006	1,088	796	237
2007	958	773	139
Overall	**12,162**	**9,801**	**2,101**
%-Change	-11.54%	-12.36%	-17.26%

Total Attributable Hospital Costs - Narrow Definition (2007 Canadian dollars)

Year	SARDs	SARDs-CTD	SARDs-VD
1996	$2,189,582.10	$1,669,114.47	$400,497.81
1997	$2,309,176.70	$1,625,492.80	$594,585.97
1998	$2,797,500.52	$2,060,677.79	$509,830.86
1999	$2,115,519.14	$1,342,393.82	$628,656.74
2000	$2,249,894.58	$1,331,735.27	$632,525.46
2001	$2,342,439.31	$1,617,398.20	$393,724.59
2002	$2,328,229.17	$1,779,339.45	$359,956.96
2003	$2,765,691.01	$1,550,776.18	$946,733.34
2004	$2,015,138.71	$1,533,275.55	$354,765.18
2005	$2,436,008.10	$1,617,184.58	$503,626.21
2006	$3,423,211.40	$2,256,400.36	$960,945.71
2007	$2,996,832.08	$1,867,571.44	$749,935.75
Overall	**$29,969,222.82**	**$20,026,298.97**	**$7,035,784.58**
%-Change	36.87%	11.89%	87.25%

Total Attributable Hospital Costs- Broad Definition (2007 Canadian dollars)

Year	SARDs	SARDs-CTD	SARDs-VD
1996	$8,306,656.55	$6,051,641.46	$1,949,165.24
1997	$10,049,554.07	$7,491,711.42	$2,358,371.16
1998	$8,858,044.86	$6,653,964.82	$1,804,694.93
1999	$9,772,683.33	$7,006,172.25	$2,299,613.97
2000	$9,209,173.01	$6,902,644.79	$1,731,025.68
2001	$9,077,279.47	$6,844,531.08	$1,633,309.49
2002	$9,160,808.56	$6,906,938.62	$1,657,530.92
2003	$10,225,576.89	$7,201,187.12	$2,258,993.46
2004	$8,454,064.55	$6,450,560.39	$1,661,627.11
2005	$9,864,915.31	$7,319,935.58	$2,001,624.12
2006	$11,616,230.07	$7,826,972.16	$3,013,965.14
2007	$9,800,561.48	$7,314,124.18	$1,594,330.49
Overall	**$114,395,548.15**	**$83,970,383.87**	**$23,964,251.71**
%-Change	17.98%	20.86%	-18.20%

Crude Annual Mean Per-Patient-Year Attributable Hospital Admissions – Narrow Definition

Year	SARDs	SARDs-CTD	SARDs-VD
1996	0.10	0.08	0.06
1997	0.08	0.07	0.18
1998	0.08	0.07	0.21
1999	0.06	0.05	0.20
2000	0.05	0.05	0.16
2001	0.04	0.03	0.17
2002	0.04	0.03	0.16
2003	0.05	0.03	0.30
2004	0.03	0.02	0.16
2005	0.03	0.02	0.15
2006	0.03	0.02	0.13
2007	0.02	0.01	0.06
Overall	**0.04**	**0.03**	**0.15**
%-Change	-84.08%	0.08	2.13%

Crude Annual Mean Per-Patient-Year Attributable Hospital Costs – Narrow Definition (2007 Canadian dollars)

Year	SARDs	SARDs-CTD	SARDs-VD
1996	$748.43	$627.86	$1,807.44
1997	$713.35	$552.39	$2,448.54
1998	$774.39	$623.49	$2,046.14
1999	$501.64	$344.85	$2,464.52
2000	$465.48	$297.22	$2,334.04
2001	$434.78	$322.47	$1,421.39
2002	$384.66	$314.68	$1,233.43
2003	$379.48	$228.47	$2,572.64
2004	$230.29	$188.25	$772.91
2005	$234.84	$167.95	$869.57
2006	$284.19	$202.25	$1,357.11
2007	$223.36	$150.79	$892.34
Overall	**$364.86**	**$266.28**	**$1,477.12**
%-Change	-70.16%	-75.98%	-50.63%

Crude Annual Mean Per-Patient-Year Attributable Hospital Admissions – Broad Definition

Year	SARDs	SARDs-CTD	SARDs-VD
1996	0.37	0.33	0.76
1997	0.34	0.30	0.73
1998	0.31	0.28	0.63
1999	0.27	0.23	0.65
2000	0.21	0.18	0.57
2001	0.18	0.16	0.50
2002	0.15	0.13	0.47
2003	0.15	0.12	0.68
2004	0.11	0.09	0.39
2005	0.09	0.07	0.33
2006	0.09	0.07	0.33
2007	0.07	0.06	0.17
Overall	**0.15**	**0.13**	**0.44**
%-Change	-80.71%	0.33	-78.19%

Crude Annual Mean Per-Patient-Year Attributable Hospital Costs – Broad Definition (2007 Canadian dollars)

Year	SARDs	SARDs-CTD	SARDs-VD
1996	$2,839.32	$2,276.41	$8,796.53
1997	$3,104.51	$2,545.89	$9,711.89
1998	$2,452.05	$2,013.25	$7,242.92
1999	$2,317.36	$1,799.84	$9,015.15
2000	$1,905.28	$1,540.57	$6,387.55
2001	$1,684.82	$1,364.65	$5,896.42
2002	$1,513.50	$1,221.51	$5,679.72
2003	$1,403.05	$1,060.92	$6,138.57
2004	$966.12	$791.99	$3,620.10
2005	$951.02	$760.20	$3,456.04
2006	$964.38	$701.57	$4,256.51
2007	$730.47	$590.55	$1,897.07
Overall	**$1,392.69**	**$1,104.11**	**$5,031.16**
%-Change	-74.27%	-74.06%	-78.43%