The Burden of Herpes Zoster and Postherpetic Neuralgia in Manitoba

A 15 YEAR POPULATION BASED COHORT STUDY USING ADMINISTRATIVE HEALTHCARE DATA

BY KEVIN FRIESEN

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

Master of Science

College of Pharmacy
Rady Faculty of Health Sciences
University of Manitoba
Winnipeg, Manitoba, Canada

ABSTRACT

Herpes zoster (HZ) is a common disease, having a lifetime prevalence of 20%-30%, with 10% of cases converting to postherpetic neuralgia (PHN). Treating these conditions results in a significant burden to the healthcare system. We hypothesized that the growth and aging of our population is causing this burden to rise.

Administrative healthcare data from April 1997 to April 2014 were used to conduct a burden of disease study of HZ and PHN in Manitoba, Canada. Expenditures were grouped into three domains: pharmacotherapy, medical care, and hospitalization. Episode and total provincial costs were determined within each domain by year. HZ epidemiology, conversion to PHN, and drug utilization were examined. Trend analysis was performed for all results.

Changes were found within each domain. Key medications became generic and the resulting reduction in price offset increased drug utilization leaving drug-episode costs unchanged. Mean per-episode medical costs increased moderately. However, increases in HZ cases drove total annual expenditures within these domains up. A dramatic reduction in HZ-related hospitalizations counteracted these trends, resulting in no change in overall burden of disease. The total healthcare cost of treating HZ and PHN in Manitoba in 2011/12 was $1,997,183, only slightly less than the $2,095,633 burden determined for 1997/98, the first study year.

It is unclear if hospitalization rates can continue to offset these other trends, as there may be a floor to how low these rates can drop. In this case, the long-term trends in

drug and medical costs, amplified by changes in population demographics and the recent jump in incidence rates, may lead the burden of HZ to rise in the future.

ACKNOWLEDGEMENTS

I would like to acknowledge the patience, guidance, encouragement, and deep support provided to me by my advisor, Dr Shawn Bugden.

I want to express my deepest appreciation for the members of my advisory committee, Dr. Jamie Falk, Dr. Silvia Alessi-Severini, and Dr. Dan Chateau. Their experience, guidance, insight, and feedback was invaluable.

I want to acknowledge my family for all they have done for me, thanks Mom, Ken, Byron, and Sylvester. Additionally, I want to acknowledge the role played by my fellow students. I would especially like to thank Kevin Hamilton and Juliano Amador da Silva for their friendship, encouragement, and humour.

A special thanks goes to those at the Manitoba Centre for Health Policy, in particular, Heather Prior and Charles Burchill, for the answering my many SAS and analysis related questions.

Finally, I would like to acknowledge the financial support of Merck Canada who provided the funding for my research

DEDICATION

This thesis is dedicated to my Dad.

THESIS PREFACE

This thesis has been written in a grouped manuscript style, sometimes referred to as a sandwich thesis. This style of thesis is comprised of several research papers intended for publication in peer reviewed journals.

This thesis is comprised of three papers looking at the burden of herpes zoster and postherpetic neuralgia in Manitoba. They are preceded by two chapters of background information, and a third chapter which provides a more detailed explanation on the foundational methods used to construct the cohort and define episodes and costs. Following this are the three aforementioned papers presenting the primary results. The final chapter summarizes the findings of the thesis and discusses their implications.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ATC – Anatomical therapeutic chemical classification system

BOD – Burden of disease

CI – Confidence interval

DALY – Disability adjusted life years

DPIN – Drug program information network

HALY – Health adjusted life years

HIPC – Health information privacy committee

HZ – Herpes zoster

ICD-9-CM – International classification of diseases, 9th revision, clinical modification

ICD-10-CA - – International classification of diseases, 9th revision, Canadian enhancement

ICER – Incremental cost-effectiveness ratio

LTPT – Long-term persistence substudy

MCHP – Manitoba centre for health policy

NSAID – Nonsteroidal anti-inflammatory drug

PHN – Postherpetic neuralgia

PY – Person years

QALY – Quality adjusted life years

SPS – Shingles prevention study

STPS – Short-term persistence substudy

RCT – Randomized controlled trial

VZ – Varicella zoster

VZV – Varicella zoster virus

ZAP – Zoster associated pain

Chapter 1. Herpes Zoster and Postherpetic Neuralgia

1.1. Thesis Introduction

HZ is an acute condition characterized by raised red rash, typically localized to band or stripe like patterns, and significant amounts of pain. The lifetime prevalence at 60 years of age is between 20% and 30% percent.[1–4] Between 10 and 30 percent of zoster cases will develop a chronic pain syndrome that persists despite resolution of viral infection and dermatological symptoms.[5,6] This syndrome is called post-herpetic neuralgia (PHN), and can be a very difficult condition to treat, and can last from several months to over 2 years.[7–10]

While we have a good understanding of how HZ and PHN affects the lives of individuals with the illness, when it comes to the burden at the healthcare system level we lack reliable estimates of the current cost in the Canadian context. The high lifetime prevalence of HZ, a high rate of medical consultation, the costs of pharmacological treatment, occasional need for hospitalization, and the long duration of PHN coalesce to produce a significant disease burden. Although a significant number of studies have looked at the cost of HZ, the majority of these studies have been outside of a Canadian context. The most recent Canadian studies use decade old data and are incomplete in spectrum of costs considered.

In 2009, a vaccine for herpes zoster was introduced to the Canadian market. Due to its relatively high costs and moderate efficacy it remains uncertain whether it should be recommended for all adults at risk, if so who should receive it, and finally, who should pay for it.

It is the objective of this thesis project to enumerate the number of HZ cases in the province, measure the mean and total costs, determine prescribing practices related to its treatment, and examine trends in these parameters over an extended period of time. This baseline data on the burden of HZ is an important and necessary background to inform future public health decisions related to this disease, including the assessment of the role and impact of the HZ vaccine introduced in 2009.

1.2. Herpes Zoster Pathogenesis

Herpes zoster is caused by reactivation of the varicella zoster virus (VZV). The initial (primary) infection with VZV most commonly occurs in childhood and results in varicella zoster (VZ), also known as chickenpox. In children, VZ is a relatively mild condition resulting in widespread dermatological symptoms including fever, maculopapular sores, itching, and malaise, and typically resolves within seven to fourteen days.[11] While less frequently seen, adult cases of VZ do occur and generally result in more severe symptoms and complications.[11] As the infection resolves the virus is cleared from the skin and systemic circulation. However, viral infection of sensory neurons innervating the affecting regions of the skin is not cleared. In these neurons the virus stops replicating and enters a state of dormancy in dorsal root ganglia. Hidden from the immune system in neuronal cell bodies, it persists for the lifetime of its host.[12–15]

VZV is one of the most highly infectious and readily transmissible common infectious diseases. Prior to the introduction of a vaccine VZ was a near universal part of childhood. In this pre-vaccine era over half of children 3 years of age and under would test positive for VZV antibodies. This rate of infection rises to over 90% by age 15,

exceeding 97% by age 40.[16] Thus the pool of at-risk persons is virtually the entire general population, excluding those vaccinated before becoming infected.

The immune system continuously works to supress the virus with the cell mediated arm being key to continued suppression. Cell mediated immunity declines with age, and can be suppressed by stress, diseases such as AIDs and immunological disorders, and drugs such as chemotherapy or treatment with anti-TNF biological therapy.[1,14,17]

Reactivation of reservoirs of latent virus, typically occurring within a singular ganglia, causes viral replication to restart. The virus then travels down the nerve tract causing a fresh infection of the skin region (dermatome) innervated by that specific ganglia, resulting in HZ.[1,11,18] It is for this reason that HZ symptoms tend to be localized to distinctive bands or stripes across the body

Postherpetic neuralgia (PHN) is a common complication of HZ, and is defined as pain that persists for a prolonged period of time after rash healing. Different diagnostic criteria specify various durations of pain, with a duration greater than 90 days post-onset being one of the most common criteria used in epidemiological and burden of disease studies. The pathogenesis of PHN is thought to be distinct and possibly related to permanent pathophysiological changes in the sympathetic dorsal root ganglia themselves.[19,20] This is supported by post-mortem studies which have found atrophy and other pathological changes in affected ganglia, but not in the contralateral ganglia.[8,19]

1.3. Symptoms of Herpes Zoster

The appearance of dermatological symptoms are frequently preceded by a prodromal phase lasting several days, characterized by tingling, itching, paresthesia, pain, and increased sensitivity to touch. At this early stage in illness, making a diagnosis can be difficult as these symptoms are not unique to HZ, but are shared by a variety of conditions.[21]

The prodromal phase ends with the appearance of a maculopapular rash, generally within one, occasionally two, or rarely more, dermatomes. The left and right sides of the body are separately innervated by sensory ganglia located on each side of the spinal cord. Sensory neurons exit the spinal cord at each level meeting peripheral neurons in the dorsal root ganglia. Bundles of these peripheral neurons then exit from the ganglia and enervate distinct bands of skin, called dermatomes. It is this bilateral innervation to specific dermatomes that leads to the localization of the rash. This distinct distribution is the key symptom in the differential diagnosis of herpes zoster.[9,22] The rash most commonly affects the trunk, face, or scalp, but can occur anywhere on the surface of the body. Itching and hypersensitivity to touch commonly affect these areas. The rash usually crusts over in 7 to 10 days.

Pain is generally the most troubling symptom and the reason that HZ patients seek medical care. This pain can be split into two basic types: zoster associated pain (ZAP), and postherpetic neuralgia (PHN).

The term ZAP refers to the pain which occurs during an acute HZ episode, sometimes beginning in the prodromal period before the appearance of visible dermatological

symptoms, and is often the symptom that drives patients to seek medical care. Pain can range in intensity from mild to severe; it is often described as burning, throbbing, or lancinating; and can be continuous, intermittent, or evoked by touch.[23] Skin becomes sensitized to the point that even the feeling of clothing against skin can be unbearable. It is important to aggressively manage ZAP, as increasing symptom severity has been linked to increased risk of developing PHN.[9,24] Complete resolution of rash and ZAP is typically achieved within 4 to 6 weeks of onset.[9,22]

PHN is a neuropathic syndrome defined as HZ-related pain that continues despite resolution of the acute HZ episode. It persists despite cessation of active viral infection, potentially a result of sensory sensitization causing allodynia or damage to neuronal bodies in the dorsal root ganglia.[8] No standard diagnostic criteria exists for PHN, specifically in regards to the duration of pain required with criteria ranging from 30 days to 6 months appearing in the literature.[7,825] Many of the recent epidemiological and burden of disease studies have used pain at 90 days post-HZ onset as the diagnostic criterion, a definition adopted for the purposes of this thesis.

Symptoms of PHN follow the same dermatomal distribution as the acute episode, a key consideration for differential diagnosis. The duration of PHN is highly variable, lasting from several months to years, with a typical episode lasting around one year. This pain is often resistant to treatment with analgesic medications and may require the use of antidepressant, anticonvulsant, or local anaesthetic drugs.[7,8] A number of risk factors for the development of PHN have been identified. These include female sex, increasing age, severe pain at onset of zoster, prodromal symptoms, and increasing severity of rash.[7,8,19,20]

1.4. Treatment

1.4.1. Antiviral Treatment of Herpes Zoster

The early use of antiviral drugs is the most important component to the management of a HZ episode. Current recommendations are for treatment to begin within 72 hours of the onset of rash, as treatment effectiveness rapidly declines when delayed beyond this point. Treatment should also be initiated in patients continuing to experience new lesion formation.[23,26,27]

In Canada, three oral antiviral drugs are currently approved by Health Canada for the treatment of HZ. These are famciclovir and valacyclovir, both dosed three times a day, and acyclovir which is taken five times a day.[23,26,27] The high frequency of acyclovir dosing makes treatment adherence difficult, which may impact its effectiveness. The introduction of valacyclovir and famciclovir, with their easier dosage regimen, has led to their preferential usage and a decline in the popularity of acyclovir.[23] .

ACYCLOVIR	
Normal Dose	
	800 mg 5 times per day
Reduced Renal Function	
CrCl 10-25 mL/min	800 mg every 8 hours
CrCl 0-10 mL/min	800 mg every 12 hours
Hemodialysis	250 mg after each session
FAMCICLOVIR	
Normal dose	
	500 mg every 8 hours
Reduced Renal Function	
CrCl 40-59 mL/min	500 mg every 12 hours
CrCl 20-39 mL/min	500 mg once daily
CrCl <20 mL/min	250 mg once daily
Hemodialysis	250 mg after each session
VALACYCLOVIR	
Normal dose	
	1000 mg every 8 hours
Reduced Renal Function	
CrCl 30-49 mL/min	1000 mg twice daily
CrCl 10-29 mL/min	1000 mg once daily
CrCl <10 mL/min	500 mg once daily
Hemodialysis	250 mg after each session

Table 1.4-1: Antiviral treatment of herpes zoster. Treatment should be initiated within 72 hours of symptoms and continue for 7 days. Abbreviations: CrCl, creatinine clearance.[26,27,29]

As these drugs are renally excreted, dosage adjustment is required in patients with renal impairment and are based on creatinine clearance (table 1.4-1). Immuno-suppressed patients and those ill enough to require hospitalization may benefit from the use of intravenous acyclovir. Parenteral formulations of valacyclovir and famciclovir are not currently available.

Patients with acyclovir-resistant HZ should be treated with intravenous foscarnet.[23] Cross-resistance has been shown to both valacyclovir, which is a pro-drug to acyclovir, and famciclovir, which has the same mechanism of action.[28]

Prompt antiviral treatment can substantially decrease the duration and intensity of pain and shorten the time to healing.[7,8,26,29] While it has been suggested that antiviral treatment decreases the likelihood of developing PHN, the evidence for this is equivocal.[25,29] Antiviral medication is ineffective in the treatment of established PHN as no active viral infection process is present.[30]

1.4.2. Treatment of Zoster Associated Pain and Postherpetic Neuralgia.

It is important to aggressively manage ZAP not only to provide relief to the patient, but also to decrease the risk of PHN as a correlation between early symptom severity and an increased risk of PHN has been noted.[9,23,24] The most important means to reduce pain is through the early use of antiviral drugs. However, analgesic treatment is frequently also required.

There are few good, randomized controlled trials for the treatment of ZAP. One randomized controlled trial (RCT) of 87 subjects comparing oxycodone, gabapentin, and placebo found that oxycodone, but not gabapentin, provide significant pain relief as

compared to placebo treatment.[20] Current recommendations are to treat ZAP symptomatically with analgesics such as acetaminophen, ASA, non-steroidal anti-inflammatory drugs (NSAIDs), local anaesthetics such as topical lidocaine. For severe pain opioid analgesics may be use.[9,22,23] In cases of pain not responsive to these agents the use of anticonvulsants and antidepressants, agents typically used to treat PHN, are commonly recommended despite a lack of good evidence.[9,22]

The use of corticosteroids in combination with antiviral drugs has been shown to be effective in reducing ZAP.[31] However, it should only be used concomitantly with antiviral treatment, or after cessation of viral replication. It is frequently reported that the use of steroids can reduce the conversion of ZAP to PHN. [21,26,31] However, the two placebo controlled studies upon which this recommendation is based actually reported that the combination of acyclovir and prednisone or prednisolone failed to show any benefit beyond that conferred by treatment with acyclovir alone.[32,33]

PHN is a challenging condition to treat, and the effectiveness of pharmacological therapy is limited. The Canadian Pain Society consensus statement on the treatment of neuropathic pain recommends as first line therapy for PHN one of tricyclic antidepressants (TCAs), gabapentin, or pregabalin.[34] Opioids and topical lidocaine are listed as second line alternatives. The European Federation of Neurological Societies 2010 treatment guidelines for neuropathic pain makes similar recommendations. Opioids, while effective, are not recommended as first line therapy due to side effects, the development of tolerance, and the risk of dependency.[35] A variety of other drugs are also discussed in the literature, including a number used for other forms of neuropathy,

although their efficacy for PHN is disputed. These include duloxetine, carbamazepine, venlafaxine valproic acid/divalproex sodium, tramadol, NSAIDs, and SSRIs.[7,8,23,34–36]

1.5. Varicella Zoster Virus Vaccines

1.5.1. Varicella Zoster Vaccine (Varivax®)

The VZV vaccine was first introduced to the Canadian market in 1998 and is indicated for the prevention of VZ in individuals aged 12 months and older (Varivax™, Merck Canada).[37,38] The first universal, publically funded vaccination program in Canada was implemented in Prince Edward Island in the year 2000, partly in response to a province-wide varicella outbreak the year before.[39] Similar programs were soon implemented across Canada, with Manitoba adding the vaccine to the schedule of routine childhood immunizations in 2004.[40] The effect of the vaccination program on the incidence of VZ has been substantial. Between 1994 and 2000 there were, on average, 1550 hospitalizations due to VZ each year in Canada. Following the introduction of publically funded, vaccination programs the annual rate of hospitalization dropped to 114 per year.[41] Universal VZ vaccination programs have also been implemented in the USA, Australia, Germany, Japan, Taiwan, and Greece.[42]

While the vaccine has been effective in reducing the incidence of VZ, it is not clear what impact these programs will have on the future incidence and burden of herpes zoster in vaccinated individuals. The varicella vaccine contains a live, attenuated version of VZV. While this virus is less virulent than the wild type virus, it is infectious and can produce VZV-type latent infections. These latent infections are generally localized to the dorsal root ganglia innervating the injection site, although about 5% of vaccinated children have detectable levels of virus in their blood stream.[15] Rare cases of vaccine-virus

related HZ have been reported, typically appearing in the same dermatome as the injection site. [15] However, the neurovirulance of this attenuated strain appears to be a much lower wild-type VZV. Thus, for the vaccinee, the risk of VZ and HZ are both expected to be reduced by vaccination, although not enough time has passed for us to be sure about what effect this will have on their lifetime risk of HZ.

1.5.2. Herpes Zoster Vaccine

In 2009 a VZV vaccine (Zostavax, Merck Canada) indicated for the prevention of HZ in those 50 years of age and older was introduced to the Canadian market.[38,43] The vaccine is comprised of the same components used in Merck's VZ vaccine, but at a 14-fold higher antigen concentration.

The Shingles Prevention Study (SPS), a three year randomized, placebo-controlled trial (RCT) of 38,546 patients, looked at the efficacy of the HZ vaccine in patients 60 years of age and older. [44,45] Subjects were followed for a mean of 3.1 years. A 61% reduction in the primary endpoint of burden of illness, as defined by a symptom severity-by-duration measure, was seen. The incidence of HZ was reduced by 51%, with 5.4 cases/1000 person-years (PY) in the vaccinated arm compared to 11.1 cases/1000 PY in the placebo treated group. This reduction in zoster incidence varied by age, with the highest degree of reduction seen in those aged 60-69 (64% reduction), with significantly lower efficacy in those ≥ 70 years of age (38%). There was also a 67% decrease in the incidence of PHN.[44,45]

The Short-Term Persistence Substudy (STPS) was a follow up RCT using a subset of 14,720 SPS study participants.[46] This extension was designed to measure the

persistence of protection of the HZ vaccine by extending the observation period of this sub-cohort to seven years in total. The vaccine effectiveness against the primary endpoint of burden of illness declined from 61% in SPS to 50% in the STPS cohort. The reduction in the secondary endpoints of HZ incidence declined from 51% to 40%, and for PHN incidence to from 67% to 60%. Statistical significance for both the secondary endpoints of HZ and PHN incidence was lost by the sixth year. Overall, there was a clear trend towards decreasing efficacy with time as measured from the beginning of the SPS trial to the end of the STPS trial.[46]

The final extension of SPS, the Long-Term Persistence Substudy (LTPS), further extended the period of observation to up to 11 years, enrolling for 6867 individuals from the vaccine arms of SPS and STPS.[47] As the placebo arms of the earlier trials had been offered immunizations following their conclusion, no control group was available for LTPS. Instead, comparisons were made using observations from the placebo controlled arms of SPS and STPS. An increase in HZ incidence by calendar time had been observed in the earlier trials. For this reason, the primary analysis used a theoretical comparison group that modelled the effect of this calendar time effect. A sensitivity analysis that did not include this effect was also reported. Efficacy on the primary endpoint of burden of illness decreased with time in all comparisons. In the primary analysis, compared to the modelled comparison group, vaccine efficacy for burden of illness was statistically significant until year eleven, the final study year. In contrast, the sensitivity analysis using actual data from SPS/STPS (without this modelled calendar effect), was statistically significant from placebo until year nine.[47]

Thus it appears that the HZ vaccine is effective, although to a lesser degree than we have come to expect based on our experience with childhood vaccines against diphtheria, polio, measles, mumps, rubella, and VZ. Research into alternative vaccine formulations is ongoing. Positive results have been reported for a non-living, glycoprotein-based HZ vaccine using a novel adjuvant to increase efficacy.[48] A number of questions remain regarding the currently available HZ vaccine (Zostavax™). For example, at what age should persons be vaccinated to achieve optimal benefit? Are booster doses necessary, and if so, when? Numerous pharmacoeconomic studies have been published looking into the cost utility of HZ vaccination programs, with sometimes divergent results. It is clear that a vaccination program would not be cost neutral,[49–51] and reported incremental cost-effectiveness ratios (ICER) range from $633 to $200,000 CDN per quality adjusted life year (QALY) and higher, depending on the parameterization.[49,51–53] A consistent finding is that the major determinant of whether the vaccine is cost-effective is the price of the vaccine itself, which is currently listed at $190.63 (McKesson Canada, PharmaClik online catalog, accessed May 16, 2016). Many studies reporting ICERs at the low end of the range have used unrealistic values for parameterization, with durations of effective protection ranging from 15 years up to lifelong, and only using the short term outcome (around 3 years) of the SPS trial, rather than using the results of the STPS and LTPS trials.[49,51]

Studies of cost-effectiveness in the context of the Canadian healthcare systems have been published. A 2009 study reported that vaccination of 60 to 75 year olds was cost-effective with an ICER of $41,709/QALY. However, the parameters used in their discrete-event simulation unduly favoured this conclusion, using a half-life of vaccine

effectiveness of 15 years, high rates of hospitalization for both HZ and PHN cases, and high drug costs.[50] A 2014 review of 11 previously published pharmacoeconomic analyses in the setting of foreign healthcare systems concluded that vaccination would be cost-effective at a willingness to pay threshold of $100,000/QALY. However, they also noticed substantial variability in the reported ICERs.[51]

1.5.3. Long Term Effects of Varicella and Herpes Zoster Vaccines on HZ Rates

The hypothesis that exposure to persons with active VZ infections confers protection against HZ was first suggested in the pioneering work of Dr. Hope-Simpson.[54] His research, published in 1965, presented evidence that VZ and HZ were caused by the same virus, and that HZ was caused by reactivation of a previously acquired VZV infection. Hope-Simpson also observed that rates of HZ were significantly lower during years of VZ outbreaks.

If exposure to VZ decreases the risk of HZ, an obvious implication is that eliminating this protective pool of virus would increase HZ rates in latently infected individuals, an idea widely reported in the medical literature.[42,55–57] Bennett and Watson expressed this best when they wrote "…increasing childhood varicella vaccination may have the paradoxical effect of increasing the rate of HZ infection because adults from the pre-vaccine era will be exposed to less exogenous virus and thus will not receive the periodic boosting of immunosurveillance that keeps the disease in check".[30]

More recently, Brisson et al showed that adults living with children had a reduced propensity to develop HZ, and that this protective effect was independent of the age of the parents.[55] A short report of a study using physician survey data found that

pediatricians had significantly lower rates of HZ than psychiatrists, which correlated to the reported differences in exposure to patients with VZ.[58] A case control study also found that adults with HZ were significantly less likely to have been exposed to VZ than age and sex matched controls, again suggesting that exposure to VZ had a protective effect against developing HZ.[59]

Numerous epidemiological studies have attempted to examine this issue using real world data, with not entirely consistent results.[42] While the majority of these observational studies have shown increases in rates of HZ in the period following widespread use of the VZ vaccine, a number of these trends began prior to their introduction. In addition, methodological issues in a number of the positive studies call their conclusions into question. A good example of the issues are found in the results of two recent Canadian studies, one conducted in Alberta, the other in Ontario. The Alberta study found rates of HZ increased after the province added VZ to their childhood immunization schedul. However, only crude incidences were reported, and the trend had beginnings in the pre-vaccine period.[60] The Ontario study reported no trend toward an increase in the incidence of HZ in the five years following the provinces introduction of their vaccine program. However, there was an increase observed in their final year of observation. Mathematical models have been constructed that take into account the exogenous boosting hypothesis and the effect of childhood VZ vaccination in both the near and long term time frame. These models suggest that the peak effect of decreased exposure to VZ on HZ rates lages after implementation of universal vaccination by between 5 to 20 years, dependent on the duration of the boosting effect. [42,55,57,61] Clearly additional research, and possibly the passage of time, is needed before we can fully determine the long-term impact of childhood VZ vaccination.

Chapter 2. Burden of Disease Analysis

2.1. Introduction to Burden of Disease Analysis

The term “burden of disease” (BOD) encompasses a *“wide range of different approaches that aim at assessing the impact of disease events on various dimensions of human life including health”.*[62] In general, this form of analysis seeks to quantify the burden caused by disease, illness, disability, injury, or other health related conditions to those afflicted, to healthcare systems, or society as a whole.[62–67]

There are a number of reasons for measuring the burden of disease. Knowledge of the impact and cost of sickness and disease enables governments and healthcare providers to set priorities for spending of healthcare dollars. It can highlight areas where more research effort is needed, to identify unmet healthcare needs, and can provide means to compare and contrast the impacts of various and dissimilar diseases and conditions. These studies can be used to guide healthcare policy decisions, are used by pharmaceutical companies to argue for drug approval and drug coverage, are used as stepping stones in subsequent research on the disease, and have even been used in court cases to recover tobacco-related health care costs from tobacco companies[65,66].

There are two primary components that need to be specified in any BOD study beyond simply the disease of interest. These are:

- Perspective: the person, group, or system impacted by the disease of interest
- Burden to be measured: for example, costs, losses, and the effects of the diseases of interest

2.2. Perspectives

The perspective used to analyze burden determines how we define and measure the burden, the types of impacts we are interested in, and the data needed to conduct the analysis. Common perspectives taken in a BOD study include 1) that of the healthcare systems, health management organizations (HMOs) or health insurers; 2) a societal perspective, and 3) that of individuals with the disease or illness of interest.

2.2.1. Health System Perspectives

The healthcare system perspective looks primary at direct medical costs incurred during the provision of care. This perspective is used when looking at economic costs to universal public healthcare systems such as what exists in Canada and most industrialized nations, private health management organizations (HMOs) and health insurance providers, Medicare and Medicaid in the USA, and other types of social welfare programs that provide healthcare support.

2.2.2. Societal Perspectives

At the largest scale, disease burden can be measured from a societal perspective. Societal costs include the direct medical costs measured in the health system perspective, as well as additional indirect economic and non-economic costs. These indirect costs include such things as lost productivity, unemployment insurance, and disability payments. More abstract impacts such as opportunity costs are also sometimes considered. [65,66]

2.2.3. Individual Perspective

When analyzing burden from the perspective of individuals we are most concerned with the impacts directly borne by the patient. These impacts can be either economic or non-

economic. The economic costs considered are those out-of-pocket expenses paid directly by individuals related to the treatment of the disease, and/or those costs related to living with the disease.

2.3. Types of Burden

The type of burden being considered is intimately connected to the perspective taken, as the measures quantified will be those that fall within the scope of this perspective, whether it be health system, societal, or individual.

2.3.1. Direct Medical Costs

Direct medical costs are the primary consideration when measuring burden using a healthcare system perspective, as well as being incorporated into societal burden studies. These are costs that are directly related to the treatment or management of a disease. Examples of direct medical costs include those due to prescription drug therapy, physician visits, services provided by allied healthcare professionals, diagnostic and imaging tests, and the cost of hospitalization.

2.3.2. Indirect Economic Costs

Indirect costs are those related to living with the ongoing effects of an illness, and typically are non-medical expenses. These costs are generally not considered from the healthcare system perspective, but are commonly incorporated into societal studies and when burden is assessed from an individual perspective, although the specific items incorporated will depend on who is bearing the burden. Examples of indirect costs include lost or reduced revenue from missing work or loss of employment; disability and social assistance payments; increased childcare costs in order to attend medical

appointments, receive treatment, while being hospitalized, or if unable to provide care personally; the employment of in-home care-providers, aides, and housekeeping assistance when an individual is no longer able to do this herself; home remodelling and vehicle renovation when mobility is impaired; and other costs related to disease-specific effects borne by individuals.

2.3.3. Non-Economic Costs

It is also possible to quantify the impact of disease on life expectancy and quality of life. The simplest measure to explain, although not always easy to determine, is lost life years (LLY), the decrease in years of life expectancy due to disease. Frequently, the impact on longevity and the change in the quality of life are expressed together using a measure called quality of life adjusted years (QALYs) which multiplies the number of years of life by a utility factor ranging between 1 for perfect health, and 0 for death. Numbers between these extremes represent varying degrees of loss of quality of life. Related measures include health adjusted life years (HALYs), and disability adjusted life years (DALYs). [62–65]

2.4. Sources of Epidemiological and Healthcare Utilization Data

Many epidemiological and burden of disease studies utilize retrospective chart reviews, survey data collected from the general population or physicians, or gather data prospectively from sentinel physicians and clinics. Statistical techniques are then used to make inferences about the larger population or healthcare system. In the cases of prospective studies, physicians are typically trained to collect clinical data using a specified set of diagnostic criteria, recording data collected during the course of providing medical care in a standardized format. Advantages of this method include the

amount of clinical detail and the ability to prospectively collect the data necessary to answer new questions that existing data may not be able to address.

Another method of epidemiological research are database studies, often using administrative health care data generated during the normal operations of the healthcare system. Cases are frequently identified using diagnostic codes, the utilization of specific medical services, and drug use. Diagnoses are commonly recorded using International Classification of Diseases (ICD) diagnostic codes. ICD codes are an extensively utilized systematic means of classifying diseases and procedures for administrative and billing purposes, making it a valuable research tool. Advantages of using administrative data include much larger sample sizes, up to the size of entire populations, the greatly reduced cost and time needed to carry out a study, and the availability of extant data over extended periods of time. However, administrative data are not collected for research purposes but rather to manage resources within the healthcare system, thus the depth of clinical detail is also generally limited

A hybrid of clinical data and large database research is the use of clinical databases, such as the general practice research database (GPRD) and its successor the clinical practice research datalink (CPRD), both run by the United Kingdom's Deparment of Health.[68] These databases consist of electronic medical records system, with data entry done by physicians at the point of care. All records are anonamized, but contain record identifiers allowing for linkages to other NHS databases, such as those containing clinical laboratory results and disease registries. These combine the power of detailed clinical information via electronic medical records, with the power of large databases, and can be linked to administrative databases. This combination of detailed individual

level data across a broad range of medical services multiplied by the huge numbers of patients makes these databases invaluable for research.

2.5. Review of the Zoster Burden of Disease Literature

2.5.1. Epidemiology of Herpes Zoster and Postherpetic Neuralgia

There is a substantive extant body of research examining the epidemiology of HZ and PHN in a variety of geographical locations, various periods of time, and using an array of methodological techniques.

The lifetime prevalence of HZ was reported at 28% in Canada, and 30% in the UK in a single, well executed database study.[2] A second report using the Weekly Returns Service dataset, gathered by a network of sentinel physicians, found similar results with a lifetime prevalence of 22% for males, and 32% for females.[3] Another UK based study using general practitioner survey results from a 1% sample reported lifetime HZ rates of 28%.[4] There rates are relatively consistent across methodologies, and have been repeatedly reproduced.

There is more variance in studies reporting incidence rather than lifetime prevalence rates, although clearly these are two related concepts. Among studies that have used data derived from general practice based studies, the observed incidence rate of HZ varies, with rates varying from 1.4 to 5.23/1000 PY.[3,6,69–71] The incidence of HZ goes up with age, rising to 10 to 12 cases/1000 PY by age 85.[4] These rates, as a whole, are generally lower than those rates derived from database studies.

Among database studies, reported rates of HZ range from 3.46 cases/1000 PY up to 9.6 cases/1000 PY.[5,10,72,73] Age specific incidence rates of 6.21 cases/1000 PY at 50-54 years of age, and 13.19 cases/1000 PY at age ≥ 85 have also been reported.[72]

We also have zoster incidence rates from RCT trials, including the SPS and STPS HZ vaccine efficacy study. These trials reported rates of HZ in the placebo arm of 11.1 and 14.0 cases/1000 PY.[44,46] It is important to note that the RCT trials enrolled only patients ≥ 60 years of age, and are best compared to age-specific HZ rates rather than population-wide incidence.

The robust relationship between increasing age and increasing incidence of HZ, with the rate increasing rapidly after the age of 45, is important to note when considering changes in the burden of HZ. . Between 1997 and 2013, the number of persons registered with Mantioba Health 60 years of age or older has increased by over 32,000, and an overall all shift in the age structure to more aged persons (Appendix A). This trend is expected to continue. It has been projected that by the year 2042, the size of the senior population is expected to at least double, and the contribution to the total population will increase from 14% in 2012, to between 19% and 23%.[74]

Examining the incidence of PHN or the rate of conversion from HZ to PHN is complicated by the lack of a standardized definition of PHN. The primary criterion needed to define and diagnose PHN for the purposes of an epidemiological study is the duration of the post-HZ pain. As mentioned previously, the duration used ranges from 30 days to up 6 months, and measured from either onset or resolution of HZ symptoms.

Additionally, the severity of pain required for the determination of a case is typically not explicitly mentioned.

Administrative data research is restricted to symptoms that require medical treatment, as episodes not requiring a physician's care or drug treatment are essentially invisible. For these types of studies, only "clinically relevant" PHN, meaning PHN cases where persons seek treatment, can be detected and reported. This approach would miss the burden of disease associated with cases of PHN not requiring medical care. In contrast, prospective studies can actively search for PHN cases by requesting patients return for follow up observation at a specified time. This observation may explain the higher PHN conversion rates reported in these studies, with estimates that up to 50% of HZ episodes convert to PHN.[6]

Rates of conversion from HZ to PHN using the 90 day cut-off range from 5% to 14.5%.[4–6,10,69,73] When studies using this definition are compared, the calculated rates found using physician collected data, administrative databases, and data from RCT are similar, although outliers can be found. A small number of studies report PHN incidence rates rather than conversion rates. One database study reported an estimate of 0.13 to 1.33 cases of PHN/1000 PY.[72] The SPS and STPT RCTs also calculated incidence rates, reporting values of 1.38 and 1.76 cases/1000 PY, respectively.[44,46]

Rates of HZ-related hospitalizations are infrequently included in purely epidemiological reports, but are part of the majority of BOD as they are a major driver of the HZ burden. There is a high degree of variation in reported rates of hospitalization. Reported estimates range from 1.3% to 10% of HZ cases hospitalized, and that in the general

population there are between 1.2 and 4.5 HZ hospitalizations/10,000 PY.[2,10,71–73] Death is an uncommon outcome of HZ and is commonly not reported. A 2011 German study reported a HZ mortality rate in those over age 50 of 2.1 deaths per 1,000,000 PY. The mortality rate was strongly influenced by age, with rates in the 50 to 64 year age group being 0.2 deaths/1,000,000 PY. [72] A UK study using data from 1994 to 1999 reported a mortality rate of 0.4 deaths/10,000 HZ cases in the under 60 cohort, and 20-40 deaths/ 10,000 HZ cases in the 60 year and older cohort.[4]

2.5.2. Economic Burden

Numerous BOD studies examining the economic burden of HZ and PHN have been published. These studies have been conducted from a number of perspectives, in numerous healthcare settings, and in various periods of history. Despite this, questions still remain surrounding a number of issues, and this is especially true in the Canadian context where a full assessment of HZ burden is lacking.

Estimates of the economic burden of zoster and PHN have also had a large variance in their estimates, more so than that of epidemiological studies. Estimates of the mean cost of HZ range from under $100 to over $6000 per episode.[4,6,10,69,71,73,75] Prescription drug expenditures account for a large portion of the burden. In some studies drugs are the leading driver of cost.[6]

Per episode costs are substantially higher for persons that develop PHN, due in large part to the extended duration of illness as compared to HZ, with treatment continuing for three months to two years, with an average length of one year. The estimated cost to

treat an episode of PHN, using the 90 day definition, range from $270 up to $1593.[4,6,10,69,71,73,75]

Hospitalization, although uncommon, has a huge impact on the burden calculation. For an otherwise uncomplicated (i.e. no PHN) case of HZ, being hospitalized multiplies the cost of an episode by 7 to 77 times. For persons with PHN, hospitalization multiplies cost by 3 to 26 times.[10,71]

A robust finding from the prior work on economic burden of zoster is that prescription medications, in particular antiviral agents including acyclovir, famciclovir, and valacyclovir, account for the largest single direct medical cost in the outpatient treatment of HZ.[10,69,71] For episodes of PHN, analgesics and adjuvant agents used for the pain account for the largest portion of medication cost for the treatment of post-herpetic neuralgia. Drug treatment can account for anywhere from 30% to over 80% of outpatient costs.[10,69,73]

After drug costs, outpatient medical visits are typically the next largest component of economic burden, and can account for up to 35 to 45 percent of total outpatient costs.[73] Some studies have reported that medical care costs exceed medication costs for episodes of HZ[73] or PHN.[69]

Consultation rates for zoster are extremely high, and the assumption that all zoster patients seek medical care is built into the methodology of most database studies. Consultation rates may vary by country, depending on access to the healthcare system, expectations of patients regarding the utility of medical care, and population demographics. This may partly account for the variance in burden between different

countries, and also limits the generalizability of results, as do differences in drug coverage, and structural differences in health care systems.

Chapter 3. Project Outline – Methods and Objectives

3.1. Study Objectives

The primary objective of this thesis was to determine, and report, the overall burden of HZ and PHN in Manitoba using the perspective of the provincial healthcare system. Due to this choice of perspective, only direct medical costs are included in this analysis. These costs are grouped into three primary domains: pharmacological treatment using prescription drug costs, medical service utilization, and HZ-related hospitalizations.

Secondary objectives were to examine how HZ infection, ZAP, and PHN are treated pharmacologically, and how treatment patterns have evolved over time. Changes in the choice of drugs used, and changes in the price of different drugs, particularly the introduction of generic formulations of these drugs, would be expected to have impacts on the cost of pharmacotherapy.

An additional secondary objective was to examine the epidemiology of HZ, and whether it changed over the study period. A number of previous studies have reported an increase in the incidence of HZ in various countries around the world, but this is far from a universal observation. The extended duration of our observation period enabled us to determine if an increase had occurred in Manitoba.

The final objective was to conduct an exploratory analysis of HZ vaccine uptake in Manitoba.

3.2. Methodology Overview

The purpose of providing a methodology section outside of that already incorporated into each research paper (Chapter 4-6) is to allow space to provide additional detail on the core methods common to all, and diagrams to clarify some of the definitions used. These core methods include identification of distinct episodes of HZ, diagnosing PHN in the absence of a specific ICD-9 CM code, method of differentiating incident from prevalent use of a drug class. An explanation for why two separate reporting time frames are used dependent upon the analysis has also been presented.

Methods distinct to each paper are described only within their respective chapter.

3.3. Study Methodology

A retrospective observational population-based study using administrative healthcare data was conducting to determine the burden of HZ and PHN in Manitoba. In this study, a cohort comprised of all individuals registered with Manitoba Health, Seniors and Active Livingwas used. This cohort is virtually equivalent to the entire population of Manitoba, Canada. The timeframe of data collection used was from April 1st 1995 to March 31st 2014, with results reported for episodes diagnosed after April 1st 1997.

Administrative healthcare data are created during the normal, day to day operations of the healthcare system. It is not produced for the purposes of research and lacks most of the detail that would be present in a medical chart or electronic medical record database. Instead, it is primarily transactional in nature, and is necessary to allow for the healthcare system to operate. Administrative data are a commonly used data source in burden of disease studies as it allows researchers to determine the real world cost of

healthcare by using actual costs gathered from the treatment of real people, frequently across large groups of patients.

In Manitoba, these data are collected by the different sectors of the healthcare system and sent to the Manitoba Centre for Health Policy (MCHP) for inclusion in the Population Health Research Data Repository. The MCHP maintains this large collection of data, use it for the research they do on behalf of the provincial government, and make it available to outside researchers on a cost-recovery basis. This repository also contains some non-healthcare governmental data such as educational records, census data, family services records, and income assistance records. All records in the Repository's databases are de-identified to protect patient privacy, but contain a pseudorandomized identification number to allow for the cross-linking of an individual's records across separate databases.

3.3.1. Data Sources

For this study four data sources from the Repository were used. These include the Drug Program Information Network (DPIN), medical services records, hospital discharge abstracts, the Manitoba Immunization Monitoring System (MIMS), and the Manitoba Health insurance registry.

The DPIN system is a real-time, electronic, point-of-sale system used by community pharmacists to process all prescription claims. It is used to process prescription claims to the Pharmacare program, the province's deductible-based universal drug insurance program, as well as to third party payers. In addition it is used to conduct drug utilization reviews as pharmacists are able to view all prescriptions filled by that patient regardless

of which pharmacy it was filled at. It provides information on all prescription dispensations by patient, including the date, drug identification number, anatomical therapeutic chemical (ATC) classification designation, prescriber code and specialty, amount of drug dispensed, strength, the duration of the prescription as determined by the pharmacist based on the prescription instructions, and a breakdown of costing data.

The medical services database contains records of fee-for-service medical claims generated by physicians, biomedical laboratories, and x-ray providers. Each record contains information on who received and who provided the service, service data, a tariff code designating the service received, and the first 3-digits of the International Classification of Disease version 9 - clinical modification (ICD-9 CM) diagnostic code of the condition for which the service is provided, and cost information.

Hospital discharge abstracts data provides a summary of each hospitalization in the province. These records contain admission and discharge dates, patient information, up to 16 complete ICD-9 CM or 25 ICD-10 CA (Canadian edition) diagnostics and procedure codes, hospital information, and a weighting factor that reflects the intensity of resource utilization for each hospitalization.

The MIMS database is used to track immunization histories of persons registered with Manitoba Health. Records within MIMS contain data on the types of vaccines administered, date of administration, and provider information. Starting in 2001, MIMS began to include immunization data on persons 18 years of age and older. This database was used to assess the uptake of the HZ vaccine.

The final database used was the Manitoba Health insurance registry, which contains basic demographic information on all persons registered with Manitoba Health. Registration with Manitoba Health is automatic for persons born within the province, and is required of residents in order to access the universal public healthcare system. The registry thus contains information on virtually all residents of the province, allowing full enumeration of the population from which HZ arise from and is updated semi-annually.

3.3.2. Approvals

Approvals for this study were obtained from the Manitoba Centre for Health Policy (MCHP), the University of Manitoba Health Research Ethics Board (HREB), and the provincial Health Information Privacy Committee (HIPC). Copies of these approvals may be found in the Appendix A to this document. Individual patient consent forms are not required for retrospective database studies as per the regulations of these regulatory bodies and provincial law.

3.4. Analytical Methods

The basic methodology used in this study involved the identification of all cases of HZ and PHN in the province and the episode start date. The unit of analysis for this project are these individual episodes.

We used medical services and hospital discharge abstract data to identify individuals with ICD codes for HZ. A series of criteria were developed to enable us to distinguish multiple diagnostic codes for a single individual as either being for a single episode of HZ or for multiple episodes of HZ, using the temporal relationship between ICD codes. After identifying episodes of HZ, medical services, hospitalizations, and prescriptions were assigned to the episode they arose from. Prescription drug and medical service

utilization and expenditures, and hospitalizations could then be determined on a per episode basis. All episode data were reported within the Pharmacare fiscal year, beginning on April 1st, in which diagnosis was made.

3.4.1. Episode Definition

From the combined hospital discharge abstracts and medical records databases we identified all records with a diagnostic code for HZ; ICD-9 CM code starting with “053”, or ICD-10 CA code starting with “B02”. The date of the first HZ diagnostic code in an episode was defined as the episode start date.

To be considered a new episode, as opposed to the continuation of a previous episode, two criteria must be both met:

- At least two years with no diagnostic codes, or two years from the start date of a previous episode must have elapsed, and
- Where a previous episode exists, a minimum of 180 days must have passed since that the last ICD code associated with it. .

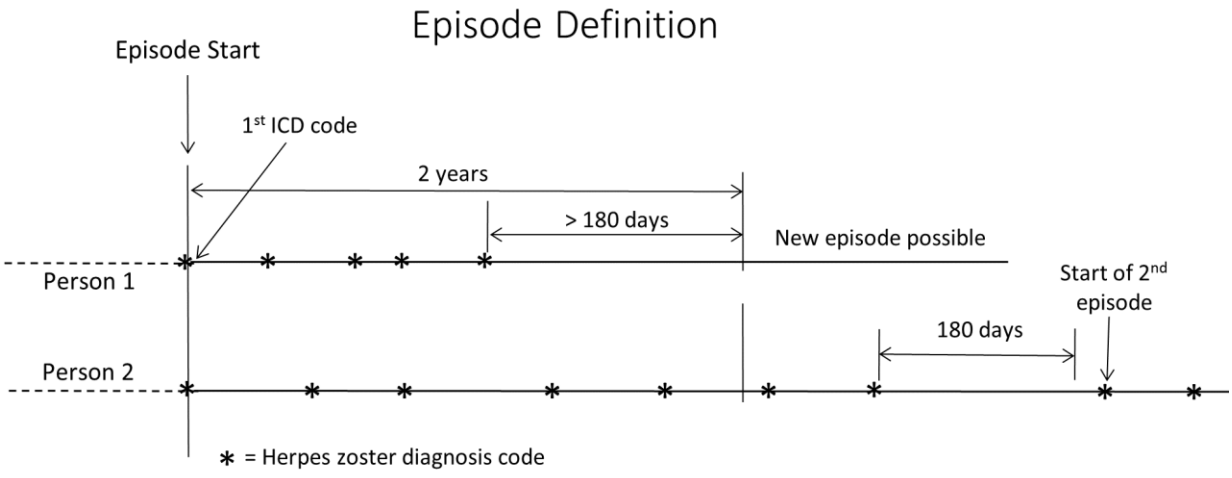


Figure 3.4-1 Episode definition

Using ICD-9 codes has been used in numerous prior HZ studies and has been shown to be both highly selective (positive predictive value 93%) and sensitive (97.5%).[76] In addition, it is estimated that between 95% and 99% of all individuals who develop HZ will seek medical attention.[73,77] Thus, the number of HZ episodes identified within our data using these steps is expected to be an unbiased estimator of the number of HZ episodes in our population.

3.4.2. Exclusion Criteria

Since the units of analysis are HZ episodes it was necessary to ensure that complete data for each individual episode was assigned to that episode. The episode criteria described above were developed with this in mind. At least 2 years of pre-episode observation time with no HZ diagnostic are required to ensure that a new diagnostic code signals the start of a new episode rather than the continuation of a previous episode. For this reason all episode with a start date on or before March 31 1997 were excluded from the cohort. However, these individuals were allowed to enter the cohort at a later time, if they later met the episode definition.

To avoid potential misdiagnosis or misclassification of VZ as HZ, all episodes of patients under 20 years of age at diagnosis were also excluded. HZ rates in this age group are very low, and it is possible that they represent a distinct group of patients that should be analyzed separately. The addition of the VZ vaccine to the routine schedule of childhood vaccinations would also complicate analysis of this cohort as it would likely contain a changing mix of wild VZV-caused HZ and cases of vaccine-related HZ.

3.4.3. Analysis Time Frame

For the determination of HZ incidence rates, and to analyze costs and utilization of antiviral treatment, collection of complete episode data (including PHN period) was not necessary. A single data point, an ICD diagnostic code with a minimum of a two year gap from a previous code, identified the episode start date, and only 30 days post diagnosis were needed to analyze antiviral drug utilization and its associated costs as per study protocol. Thus, for analysis of incidence and AV use, all episodes diagnosed after April 1, 1997 were utilized. This is the primary time frame used in chapter four, and is used in parts of chapter six.

To determine total cost per episode we needed to allow for full equal follow up time for all episodes. This is especially important as previous studies have shown that PHN is a significant contributor to total cost, and this cost is accrued slowly over the duration of an episode which can last for years. Thus episodes starting after April 1, 2012 are excluded as less than two years of data were available for these cases. This is the primary time frame reported upon in chapter five and six.

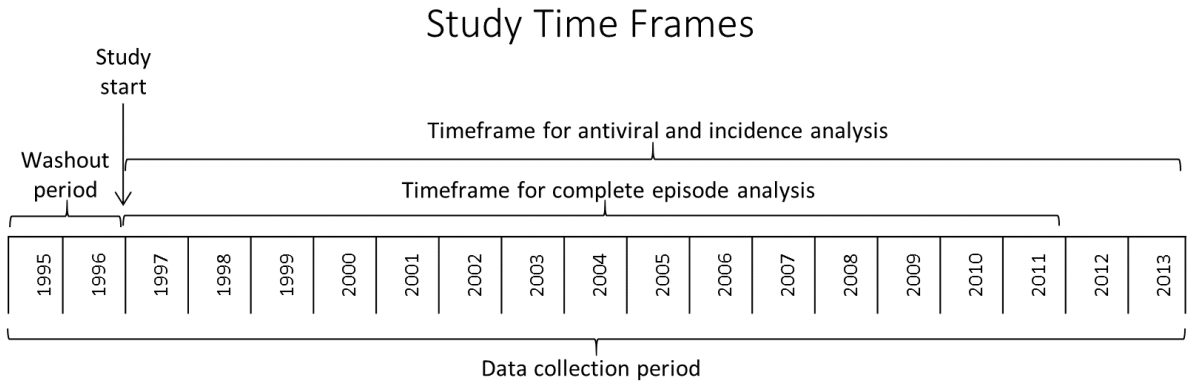


Figure 3.4-2 Study Time Frames

3.4.4. Determining Incident Drug Class Use

Aside from vaccinations, all drugs used to treat HZ and PHN are also used for a variety of other common illnesses. For example, the antiviral drugs used to treat an acute HZ episode are also used for the treatment and prevention of other herpes virus infections, in particular herpes simplex 1 and 2. Drugs used to treat ZAP and PHN are more commonly used for other painful conditions, and this use increases with patient's age, mirroring the trend seen with HZ.

In order to differentiate between the continuing use of these drugs for other conditions, and incident use associated with a new episode of HZ, a 120 day look-back period was used. Drug treatment was categorized using Anatomical Therapeutic Chemical (ATC) classes. Prescriptions for opioids (ATC codes starting with N02A), NSAIDS (M01), anticonvulsants (N03A), antidepressants (N06A), nabilone (A04AD), local anesthetics (D04A), glucocorticoids (H02AB), and ASA and acetaminophen (N02B) were considered as potential treatment of ZAP and PHN pain. The antivirals acyclovir, valacyclovir, and famciclovir were also examined and considered as a class.

All prescriptions within each drug class in this look-back period were considered separately, with total class use determined by summing the days supply of all prescriptions. Any drug class with a total of 30 days or more within the 90 days immediately preceding the episode start date were defined as prevalent drug use, and excluded from all further analysis for that episode.

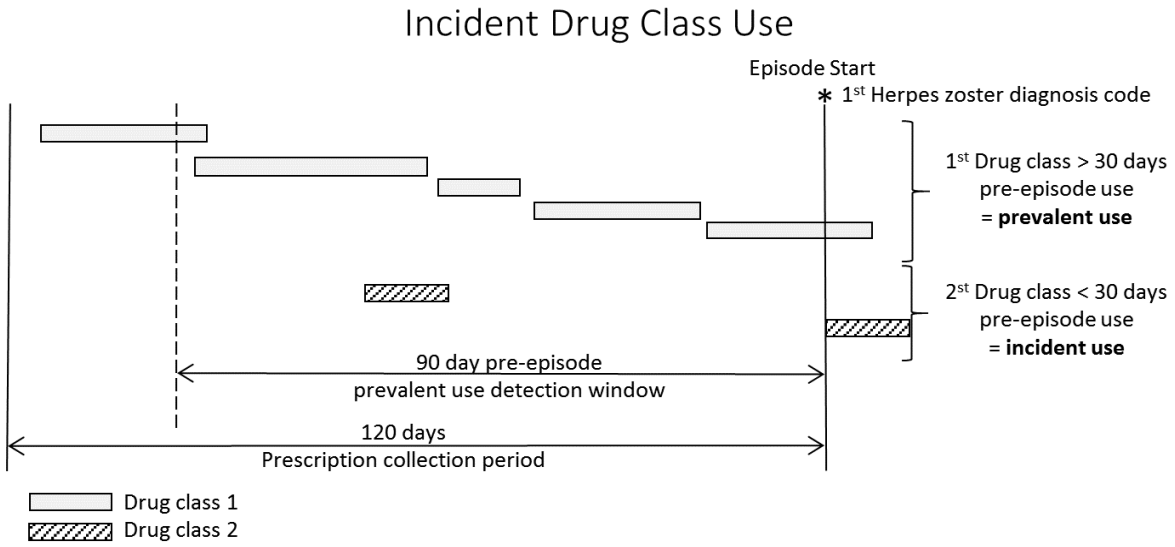


Figure 3.4-3 Incident vs prevalent drug class use

3.4.5. Diagnosis of Post-Herpetic Neuralgia

Postherpetic neuralgia does not have a specific ICD-9 CM code, but is included within the code 053.19, herpes zoster with other nervous system complications. An ICD-10 code, G53.0, does exist. However, the vast majority of diagnostic code data available for this study comes from medical services billings, which only list the first three digits of ICD-9 CM codes, and ICD-10 codes are only used for the later portions of our hospitalization data. Thus diagnostic codes are not a suitable means to identify episodes of PHN. Therefore, we infer a diagnosis of PHN using medical claims listing a ICD-9 CM diagnostic code of 053 (herpes zoster) and prescription treatment with drug classes defined above as potential PHN therapies that are dated 90 days or more post episode start date.

An additional consideration is that, in the absence of ongoing ICD codes, we cannot reliably claim that a new potential PHN prescription dispensed at a later date is for PHN, or for an alternative condition. Therefore, prescriptions dispensed in the period after the last medical billing code were required to meet criteria for continuous treatment, with the first discontinuity defining the end of drug treatment and of that episode.

As drugs used to treat pain are often prescribed or used on a *prn*, or as needed basis, we allowed for a grace period between prescriptions. Each prescription record contains the dispensation date for that prescription and a days supply variable entered by the pharmacist which approximates the duration of the prescription based on the physician's instructions. The end date of a prescription is the dispensation date plus the days supplied plus a grace period of 100% of the days supply. The presence of a discontinuity defines the end of treatment, and all prescriptions after this date were excluded from the analysis.

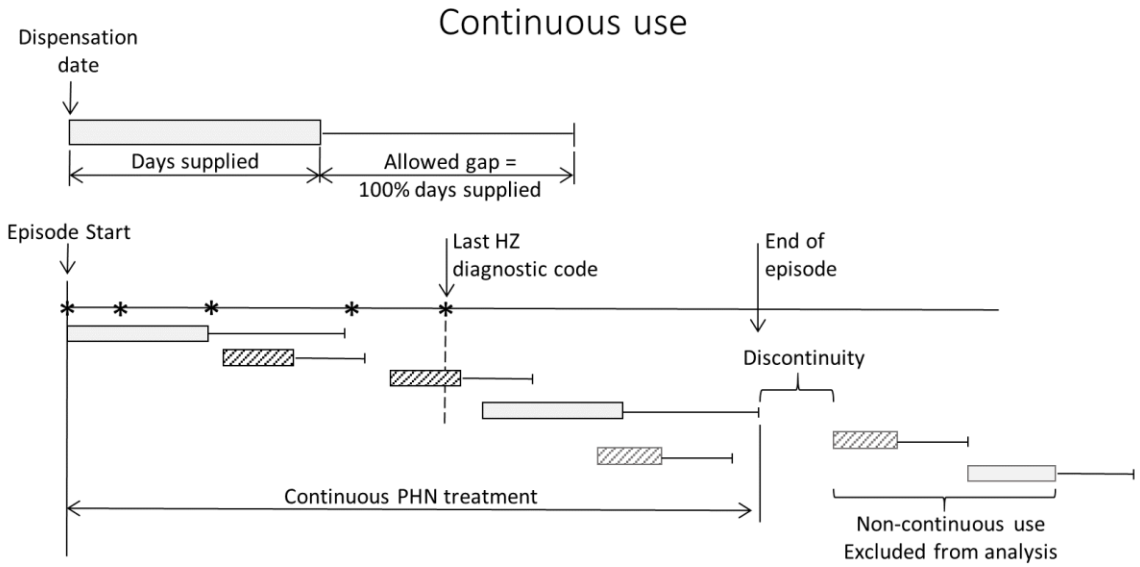


Figure 3.4-4: Defining Continuous Drug-Class Use

3.4.6. Cost Determination

Medical costs were taken directly from the medical services database, which lists the fee-for-service cost paid by Manitoba Health, Healthy Living, and Seniors to service providers. These costs are adjusted using the general Statistics Canada Consumer Price Index (CPI) for Manitoba.

Prescription drug costs, including dispensing fees, were taken directly from the DPIN database. These costs are adjusted using the CPI index for prescription drugs for Manitoba.

Hospitalization costs were determined using the resource intensity weight (RIW) given to each hospital stay by the Canadian Institutes for Health Information (CIHI), and multiplied by mean hospitalization cost in Manitoba for 2013.

All costs are adjusted for inflation and expressed in the equivalent of 2013 Canadian dollars.

3.4.7. Additional Methods

The methods specific to each of the three papers included in this thesis are described the individual papers “Methods” section.

Chapter 4. The Changing Landscape of the Antiviral Treatment of Herpes Zoster: A 17-Year Population-Based Cohort Study

Chapter Introduction

The next chapters are comprised of three full research papers, each of which has been, or is intended to be, published in a scientific journal. Each of these papers is intended to highlight specific portions of the treatment of HZ and PHN in order to develop a clear picture of the burden of disease of this relatively common disease.

The first two papers look at the pharmacological treatment of herpes zoster and postherpetic neuralgia in detail, while the third examines the healthcare system burden of disease at a more macro level.

This first paper examines the use of antiviral drugs to treat acute HZ infections in Manitoba over the period of 1997/98 to 2013/14, with a primary objective of determining changes over time in how HZ is treated in Manitoba. The use of antiviral drugs in general, as well as that of acyclovir, valacyclovir, and famciclovir specifically, is reported. Also reported are the number of episodes and the age-adjusted incidence of HZ over this time interval. Rates of antiviral treatment, as well as total annual and mean treatment costs are also reported.

4.1. Manuscript Cover Page

The Changing Landscape of the Antiviral Treatment of Herpes Zoster: A 17-Year Population-Based Cohort Study

Kevin J Friesen BSc (Pharm)[1], Silvia Alessi-Severini BSc (Pharm) PhD[1], Jamie Falk BSc (Pharm) PharmD [1], Dan Chateau PhD[2], Shawn Bugden MSc. Pharm.D[1]

[1]College of Pharmacy, Rady Faculty of Health Sciences, University of Manitoba, 750 Bannatyne Ave, Winnipeg, MB, R3E 0T5. [2]Assistant Professor, Department of Community Health Sciences, College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Mb, R3E 3P5

This work was published in ClinicoEconomics and Outcomes Research on May 20th 2016, volume 2016(8): 207-214 https://dx.doi.org/10.2147/CEOR.S102243

Running Header: Trends in Herpes Zoster Incidence, Treatment, and Cost

Keywords: Herpes zoster, burden, economics, valacyclovir, famciclovir, acyclovir

Contributions: Kevin Friesen designed the study, analysed the data, and wrote the manuscript. Shawn Bugden assisted in study design, provided guidance during the analytical phase of the study, and critically reviewed the study. Silvia Alessi-Severini was involved in the initiation of this research program and critically reviewed the manuscript. Dan Chateau and Jamie Falk both provided guidance and extensively reviewed and commented on this manuscript throughout the editing process.

The Changing Landscape of the Antiviral Treatment of Herpes Zoster: A 17-Year Population-Based Cohort Study

4.2. Abstract

Background:

Herpes zoster (HZ) is a common viral disease that produces a painful vesicular rash. Early use of antiviral medications is recommended, as it reduces pain and speeds healing. A population-based observational study was conducted to evaluate the changing burden of HZ in the province of Manitoba (Canada) over a period of 17 years.

Methods:

Administrative health care data including medical and hospital records were examined, and International Classification of Diseases, Ninth Revision, Clinical Modification and International Classification of Diseases, Tenth Revision, Clinical Modification codes were used to identify episodes of HZ between April 1, 1997 and March 31, 2014 in persons aged 20 or over. Annual age-adjusted incidence and hospitalization rates were calculated. Prescription records of HZ-diagnosed persons for acyclovir, valacyclovir, and famciclovir were used to calculate the rates and costs of antiviral treatment.

Results:

There were 73,886 identified cases of HZ between 1997/98 and 2013/14. Of these episodes, 42,187 (57.1%) were treated with antiviral medications at a total cost of $4,696,611 (CAD). The age-adjusted incidence of HZ rose from 4.70/1,000 person years in 1997/98 to 5.70/1,000 person years in 2013/14, a 21.2% increase. Antiviral

treatment rates increased from 41.7% to 66.0% of all diagnosed episodes. Mean costs per treated episode dropped from $139.61 in 1997/98 to $60.52 in 2013/14, primarily due to the introduction of generic antiviral medications. The total cost of antiviral treatment peaked in 2005/06 at $328,760 and dropped steadily thereafter to $229,366 in 2013/14. There were 1,138 HZ-related hospitalizations between 1997/98 and 2011/12, with rates decreasing from 3.1% in 1997/98 to 1.4% of all episodes in 2011/12.

Conclusions:

While both incidence of HZ and rates of antiviral treatment have risen substantially, the economic burden from antiviral treatment has been decreasing since a peak in 2005/06 and was only 2.6% higher in 2013/14 than in 1997/98. This drop in cost is attributed to the introduction of generic antiviral drugs.

.

The Changing Landscape of the Antiviral Treatment of Herpes Zoster: A 17-Year Population-Based Cohort Study

4.3. Introduction

Herpes zoster (HZ), or shingles, is a viral disease characterized by a painful, vesicular rash. It is caused by reactivation of latent varicella zoster virus (VZV), the virus responsible for varicella zoster (chicken pox) upon initial infection.[1–3] VZV infection is ubiquitous in the current adult population with 95-97% of adults over the age of 40 infected and at risk of developing HZ.[4,5] It is estimated that 20 to 30% of these persons will develop HZ at some time in their life.[1,6] The annual incidence of HZ in the general population is estimated to be between 1.2 and 6.3 cases per 1000 person years (PY). The incidence increases with age to 7.2 - 11.8 cases per 1000 PY in persons older than 60 years. [1,7,8] HZ is thus a common disease with the vast majority of adults at risk.

Anti-herpetic antiviral drugs such as acyclovir, valacyclovir, and famciclovir are the cornerstone of the acute treatment of HZ. Antiviral treatment reduces the duration and severity of symptoms and may decrease the risk of possible complications such as post-herpetic neuralgia.[9] The current recommended treatment for HZ is to begin antiviral therapy within 72 hours of the onset of symptoms and continue for 7 days.[1,10,11] Antiviral drugs have been reported to account for 50% - 70% of the drug cost for treated cases of HZ and can account for a significant portion of total treatment cost.[7,12,13]

There have been two major changes that may impact the epidemiology of HZ. The first of these was the introduction of the varicella zoster vaccines (Varivax™, Merck Canada, Kirkland, Quebec, Canada), which became available in Canada in January 1999 and were incorporated into Manitoba's publically funded childhood vaccination program in

2004. Although HZ is still possible in vaccinated persons, the virulence of the vaccine strain is attenuated and this may lead to eventual decreases in rates of HZ as these persons age into adulthood.[14] The second change was the introduction of the herpes zoster vaccine (Zostavax®, Merck) in September 2009,[15] which has been shown to be safe and effective at decreasing the incidence and burden of HZ.[16–18] However, the impact of the HZ vaccine will be highly dependent on its uptake.

The population of Canada, including the population of Manitoba (est. 1.3 million in 2015), is aging.[19] Due to the association of increasing age with a higher incidence of HZ we would expect to see increasing numbers of HZ cases and an increase in the burden of disease. However, new vaccines and varying vaccine uptake coupled with other changes in the health care system make it difficult to predict the changing burden of disease for HZ. As part of a research program to determine the burden of HZ, this study examined the epidemiology of HZ and the utilization of antiviral medications in the province of Manitoba with the objectives of determining the incidence of HZ and the cost burden of acute antiviral treatments.

4.4. Methods

A retrospective, population-based cohort study of HZ was conducted using administrative data. The eligible population included all adults over the age of 20 in Manitoba (Canada) between April 1, 1997 and March 31, 2014. Data were obtained through the Manitoba Centre for Health Policy, which maintains the provincial Population Health Research Data Repository. The repository contains copies of administrative health care data of Manitoba Health. The databases used included the Drug Program Information Network (DPIN), the Medical Services database, provincial

Hospital Discharge Abstracts, and the Manitoba Health Registry. These databases contain de-identified health-related information on all persons registered with Manitoba Health, virtually the entire population of Manitoba.[20] Scrambled patient identifiers are shared between these databases, enabling linkage of records and allowing for the longitudinal analysis of individual patients across the entire health care system.

The DPIN system is used to administer the Manitoba Pharmacare Program, a universal prescription drug care plan available to all residents of Manitoba. DPIN is used to submit claims to Pharmacare and other third-party prescription drug programs, and captures community prescription drug use by persons registered with Manitoba Health. The Medical Services database captures fee-for-service medical claims from physicians and other health providers, and includes diagnostic codes and reimbursement costs. The Hospital Discharge Abstracts database contains information on all hospitalizations for persons registered with Manitoba Health, including both admissions in Manitoba and those of Manitoba residents hospitalized in other Canadian provinces. The Manitoba Health registry contains demographic information on all persons registered with the agency and is used to provide population counts and age.

Episodes of HZ were identified using hospital discharge abstracts and medical claim records for the period between April 1, 1995 and March 31, 2014, which included a 2-year pre-study data collection period to differentiate between incident and prevalent cases. Persons with diagnostic codes for HZ (International Classification of Diseases [ICD], Ninth Revision, Clinical Modification codes starting with 053 and ICD, Tenth Revision, Clinical Modification codes starting with B02) that were not related to HZ vaccinations were categorized as cases with episode start dates based on the earliest

recorded diagnosis. Multiple episodes were allowed in cases of multiple diagnostic codes, provided that at least 2 years had elapsed from the beginning of the previous episode and there were no other diagnostic codes in the previous 180 days. Episodes with a start date prior to April 1, 1997 were excluded to ensure only incident cases were analyzed. Persons under the age of 20 years at the time of diagnosis were excluded to avoid miscoded cases of varicella zoster or varicella zoster vaccination. Hospitalizations were attributed to HZ in cases where an HZ diagnostic code appeared as either the admitting diagnosis or the diagnosis most responsible for continuing hospitalization.

Prescription records for antiviral drugs (acyclovir, valacyclovir, and famciclovir) dispensed in the period of 5 days before and up to 30 days after the appearance of the first diagnostic code for HZ were considered to be for the treatment of HZ. Prescriptions outside of this window were excluded to avoid misclassifying antiviral treatment of herpes simplex 1 or 2. Drug costs were calculated directly from the prescription records and included both cost of the drug and the dispensing fee.

The Manitoba Pharmacare fiscal year (April 1–March 31) was used in the analysis for reporting periods. Episodes, prescription rates, costs, and hospitalizations were all considered to have been incurred in the fiscal year in which the episode was first diagnosed. Mean treatment costs were calculated for antiviral-treated episodes by the drugs used within each year. The absolute number of HZ episodes and the incidence rates were calculated within each year. The age distribution of the 1997 Manitoba population was used to age-adjust incidence rates in subsequent years. Antiviral treatment rates were calculated as the percent of episodes associated with one or more anti-herpetic prescriptions. Hospitalization rates were calculated as the percent of all

episodes that resulted in HZ hospitalizations. To ensure capture of all episode-related hospitalizations, particularly those due to postherpetic neuralgia, we allowed for up to 2 years of follow-up time. Thus hospitalizations are reported only for episodes diagnosed between 1997/98 and 2011/12.

All costs have been adjusted to 2013 Canadian dollars (CAD) using Statistics Canada's consumer price index for prescription drug costs in Manitoba.

SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all data analyses. Approvals were granted by the University of Manitoba Health Research Ethics Board and the Manitoba Health Information Privacy Committee. These committees do not require individual consent for research conducted using de-identified administrative data when reasonable safeguards to protect confidentiality and security of personal health information are in place.

4.5. Results

Between April 1, 1997 and March 31, 2014, we identified 73,886 diagnosed episodes of HZ in Manitoba in those aged 20 years and older, with a crude unadjusted incidence rate of 4.99 episodes/1,000 PY. Within our observation period, 5.6% of persons experienced more than one HZ episode.

A total of 45,442 prescriptions were dispensed to treat 42,187 episodes at a total cost of $4,696,111 (CAD). Overall, 57.1% of diagnosed cases were treated with antiviral medications with a mean cost per treated episode of $111.38 (95% CI: $98.59, $124.16). From 1997/98 to 2011/12 there were 1,138 hospitalizations (1.8% of all

episodes), where HZ was either the admitting diagnosis or the diagnosis most responsible for continuing hospitalization, an overall incidence of 0.088/1,000 PY.

From 1997/98 to 2008/09, the number of HZ diagnoses climbed slowly from 3,844 to 4,295 episodes per year. However, the age-adjusted incidence of HZ diagnoses remained relatively constant at a mean of 4.70/1,000 PY (95% CI: 4.65, 4.75). The incidence rose steadily from 2009 until the end of the study period, reaching 5.70/1,000 PY in 2013/14, an increase in incidence of 21.3% from the 1997–2008 plateau (Figure 1).

The use of antiviral drugs to treat HZ increased with the increased incidence of HZ, but to a greater degree as more of these episodes were treated with antivirals. Treatment rates increased from 41.7% of HZ diagnoses being prescribed antiviral drugs in 1997/98 to 66.0% of cases in 2013/14. Over this same interval mean costs per antiviral-treated episode dropped from $139.61 to $60.52.

Of the 45,442 antiviral prescriptions identified, 4,263 (9.3%) were for acyclovir, 27,752 (60.8%) for valacyclovir, and 13,601 (29.8%) for famciclovir. Substantial changes in prescribing patterns of these drugs were observed over the study period. While acyclovir was the most commonly used antiviral to treat HZ at the start of the study period, its use dropped rapidly and by 2013/14, it was used in less than 5% of treated cases. Acyclovir was replaced by famciclovir and valacyclovir, with the use of famciclovir peaking in 2002/03 when it accounted for 49% of all HZ-related antiviral prescriptions. Since 2003/04, valacyclovir has been the dominant antiviral treatment. By the end of the study period, valacyclovir was used to treat 50.0% of all HZ diagnoses and it accounted for 80.6% of the antiviral HZ prescriptions (Figure 2).

Generic acyclovir came to the Canadian market in August 1997, the first study year, generic famciclovir in August 2006, and generic valacyclovir in May 2008. Comparing the mean costs in 1997/98 and 2013/14, the mean cost per treated episode decreased by $18.50 (15.1%) from $122.19 to $103.69/episode for acyclovir, by $46.96 (32.0%) from $146.57 to $99.61/episode for famciclovir, and by $72.11 (61.4%) from $117.50 to $45.39 for valacyclovir (Figure 3).

The total cost of treatment changed substantially over the study period, with the total cost for each drug dropping concurrent with the introduction of generic forms of each drug (Figure 4). Antiviral cost peaked in 2005/06 at $328,760, which is a 47.0% increase from 1997/98 when the total cost was $223,647. The total cost then began a decline that continued until the end of the study period. The total cost in 2013/14 was $229,366, only a 2.6% increase from 1997 and a 30.2% decrease from 2005.

There was a dramatic decrease in the rate and number of HZ-related hospitalizations concurrently with the increased rates of antiviral treatment. The number of hospitalizations dropped by 42.9% between 1997/98 and 2011/12, from 119 to 68 hospital stays per year. At the same time, there was a 36% decrease in untreated (with antiviral drugs) episodes of HZ.

4.6. Discussion

This study found that despite an increasing incidence of diagnosed HZ cases and higher rates of treatment, the aggregate population costs of HZ antiviral treatment declined in recent years. The increase in HZ incidence was an expected effect of the aging population. However, the age-adjusted incidence rate revealed an increase in HZ

incidence independent of aging, which was unexpected. While more HZ episodes and more treatments seemed to drive an initial increase in population costs, generic pricing for antiviral medications has more than compensated for these increases and has resulted in the recent reduction in overall antiviral costs.

HZ consultation rates are frequently claimed to be an accurate estimator of the actual incidence of this disease in the population. Symptom severity is thought to drive most persons to seek medical attention and it has been estimated that up to 99% of persons with HZ do so.[13,21] As such, the Manitoba-linked administrative records should provide a reliable measure of HZ incidence. The study found a relatively stable age-standardized incidence of HZ over the first two-thirds of the study period. However, starting in 2009/10, there was a sharp and continuing increase in the incidence of HZ. A similar increase in incidence was also seen in a study conducted in Ontario (Canada) in 2009: the authors were unable to determine a cause for such an increase.[22] As 2009 was also the last year of the dataset used in the study, the authors were unable to determine if it was the beginning of a trend and suggested it would be important to determine if the increase persisted. While we are no closer to determining the cause of the increase in Manitoba, it is apparent that it continued for 5 years till the end of our study period in March 2014.

One possible explanation is that the increase in incidence is an artifact of increased publicity and attention to HZ in recent years coinciding with the introduction of HZ vaccine to the Canadian marketplace in 2009. The marketing of the vaccine has raised public awareness of the signs and symptoms of HZ, possibly influencing people to seek care. Alternatively, it has been speculated that widespread varicella zoster vaccination

decreases the levels of wild-type VZV in the environment, thus eliminating the natural boosting effect of exposure in a latently infected individual.[23] Theoretical modelling of universal VZ vaccination programs suggests we can expect an initial increase in HZ rates eventually followed by sustained long term declines.[6,24,256] However, while some epidemiological studies have found such an effect, this conclusion is not universally supported.[22,25–27] Any such increases in HZ incidence, if it occurs, would obviously be mitigated to some extent by HZ vaccination programs. While the observed increases are important and warrant continued monitoring, the cause remains speculative at this point and will be difficult to be definitively ascertained.

The study showed an increased incidence of disease and a greater likelihood of treatment with antiviral therapy, but a decrease in the economic burden of disease due to treatment. While the increases in diagnosed cases of HZ and the proportion of cases treated with antivirals drive the treatment levels up, the effects on cost are overwhelmed by the drop in the price of treatment. Both acyclovir and famciclovir dropped from a stable price point associated with the brand name product to a lower stable cost associated with the generic product. It is important to recognize that in Manitoba's single payer system, generic substitution is mandatory and the vast majority of prescriptions are automatically switched to the generic product when it is available. As valacyclovir became the treatment of choice in Manitoba, the generic market was very competitive and there was a sustained downward trend in treatment cost with this drug. This was the major contributor to the overall drop in the cost of treatment.

The rate of HZ-related hospitalizations dropped throughout the study period. This downward trend in HZ-related hospitalization was also reported in the Ontario study

where the incidence dropped by approximately half between 1992 and 2009.[22] Antiviral treatment has steadily increased throughout our entire study from less than 42% in 1997/98 to over 66% in 2013/14. Antiviral treatment has been shown to decrease both the severity and duration of symptoms.[1,10] It is possible that the increasing antiviral treatment of HZ has contributed to the decreasing rates of hospitalization, but other explanations cannot be ruled out. Limitations in hospital bed availability may make it more likely that HZ is managed on an outpatient basis.

The ability to capture the entire population of the province over a time span of 17 years is a major strength of this research. The linked nature of the data allows individuals to be followed across the entire health care system. However, using administrative data also has the limitations common to all research of this type, namely that it was created not for the purpose of research but for managing the health care system, and cases are identified using ICD codes that are meant for billing purposes. Nevertheless, the reliability of HZ diagnoses is known to be very high due to the distinctive nature of the disease. In fact the use of ICD codes to diagnose zoster in administrative data is both highly selective (positive predictive value 93%) and sensitive (97.5%).[28]

4.7. Conclusion

The aggregate cost of antiviral treatment of HZ is the product of a number of factors: the numbers of episodes, treatment rates, medication choice, and treatment cost. All these factors change with time and can alternately increase or decrease costs, making predicting the net effect very difficult. Only by directly measuring the real-world burden of a disease can the overall disease resource impacts be assessed. The results of this analysis illustrate the significant impact that generic drug pricing and mandatory

substitution can have on disease management costs at the population level. Further research looking at other economic facets of HZ is needed to complete our understanding of the total burden of this disease.

4.8. Acknowledgments

The authors acknowledge the Manitoba Centre for Health Policy for use of data contained in the Population Health Research Data Repository under project #H2014:411 (HIPC# 2014/2015-35). The results and conclusions are those of the authors and no official endorsement by the Manitoba Centre for Health Policy, Manitoba Health, Seniors and Active Living or other data providers is intended or should be inferred. Data used in this study are from the Population Health Research Data Repository housed at the Manitoba Centre for Health Policy, University of Manitoba and were derived from data provided by Manitoba Health, Seniors and Active Living.

We thank Heather Prior from the Manitoba Centre for Health Policy for her assistance in preliminary data extraction.

This work was supported by a grant from Merck Canada.

4.9. Figures and Tables

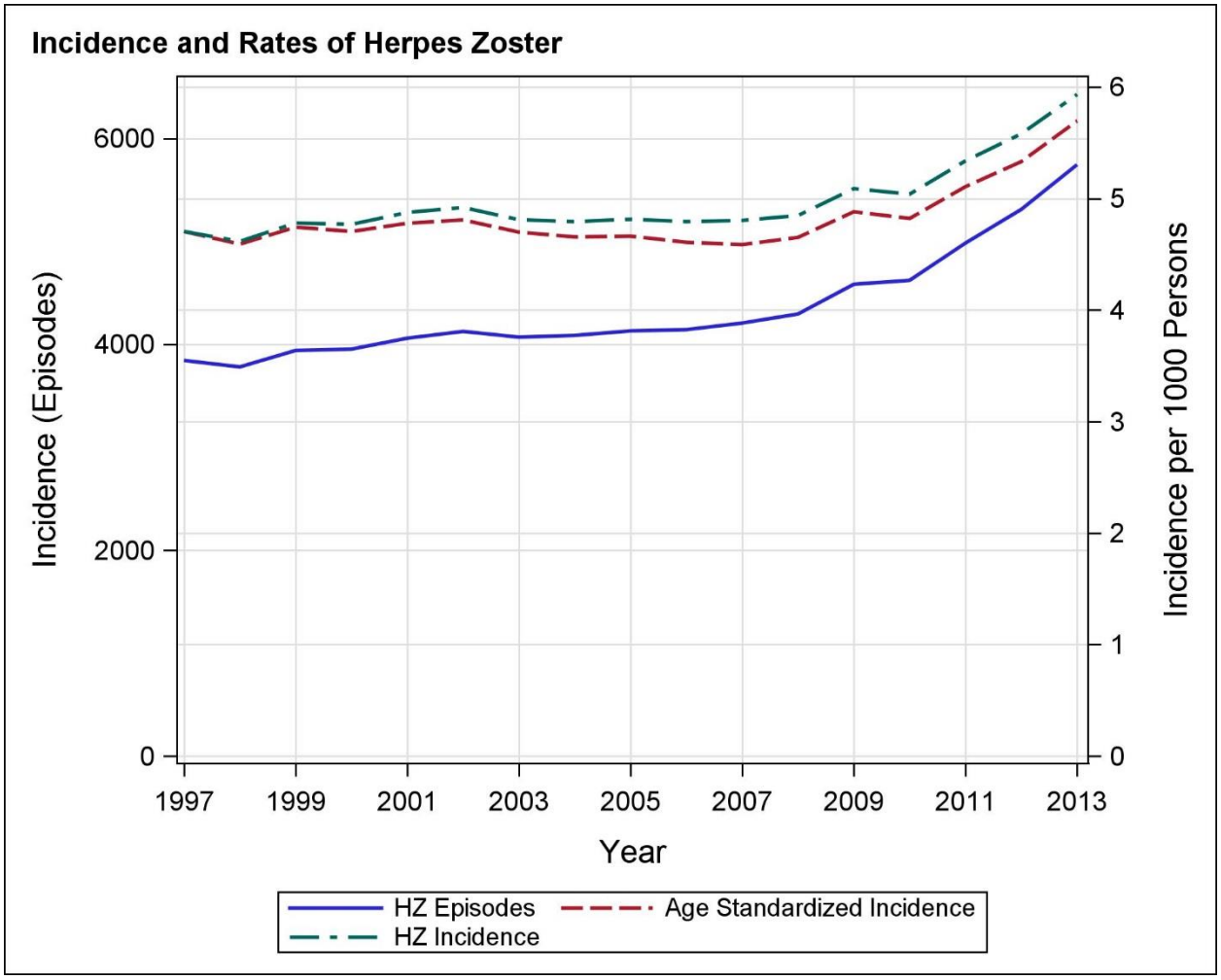


Figure 4.8-1 Episodes and incidence of herpes zoster

Herpes zoster episodes numbers with crude and age standardized incidence rates.

Population age distribution standardized to the population of Manitoba in 1997

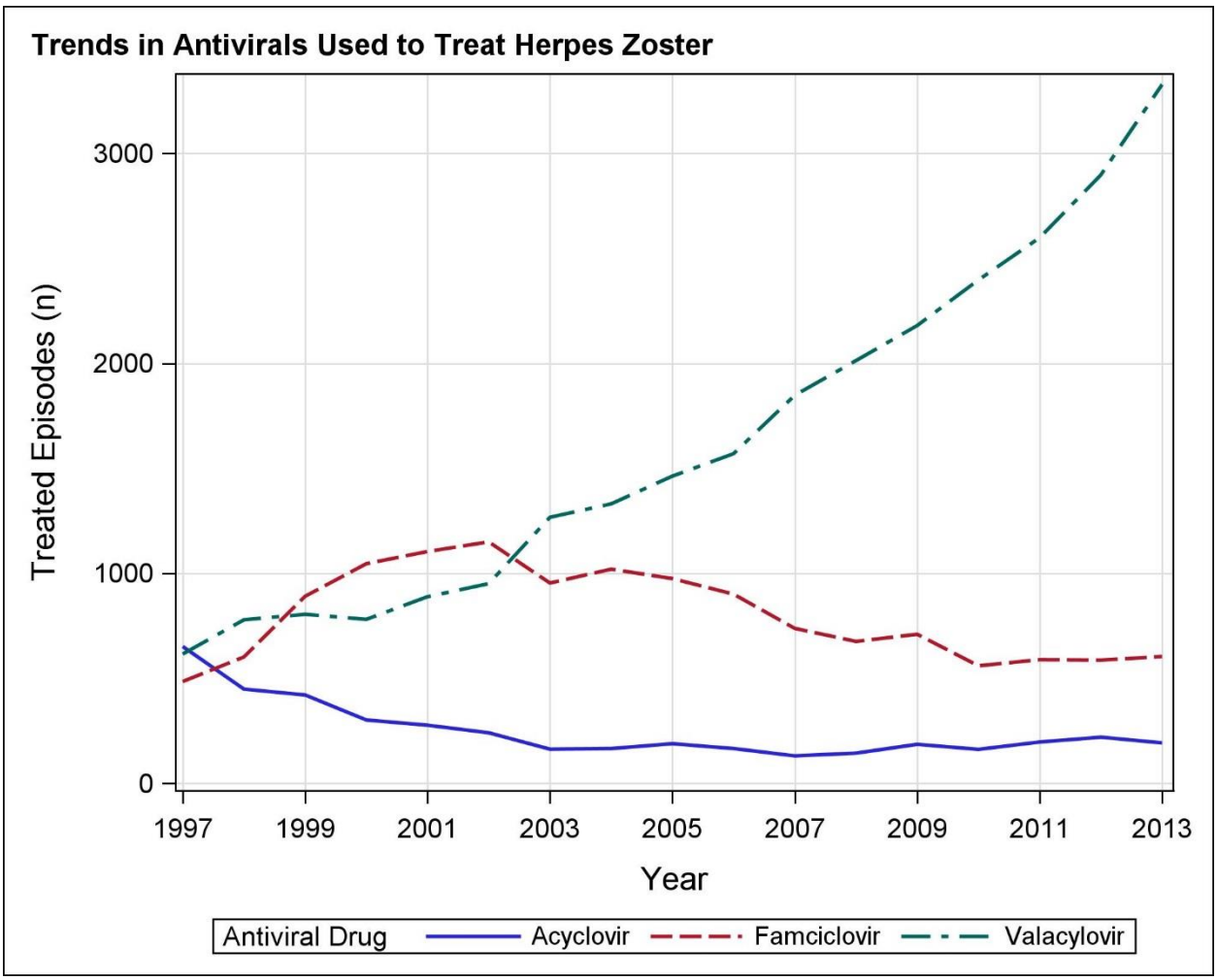


Figure 4.9-2 Antiviral treatment of herpes zoster over time

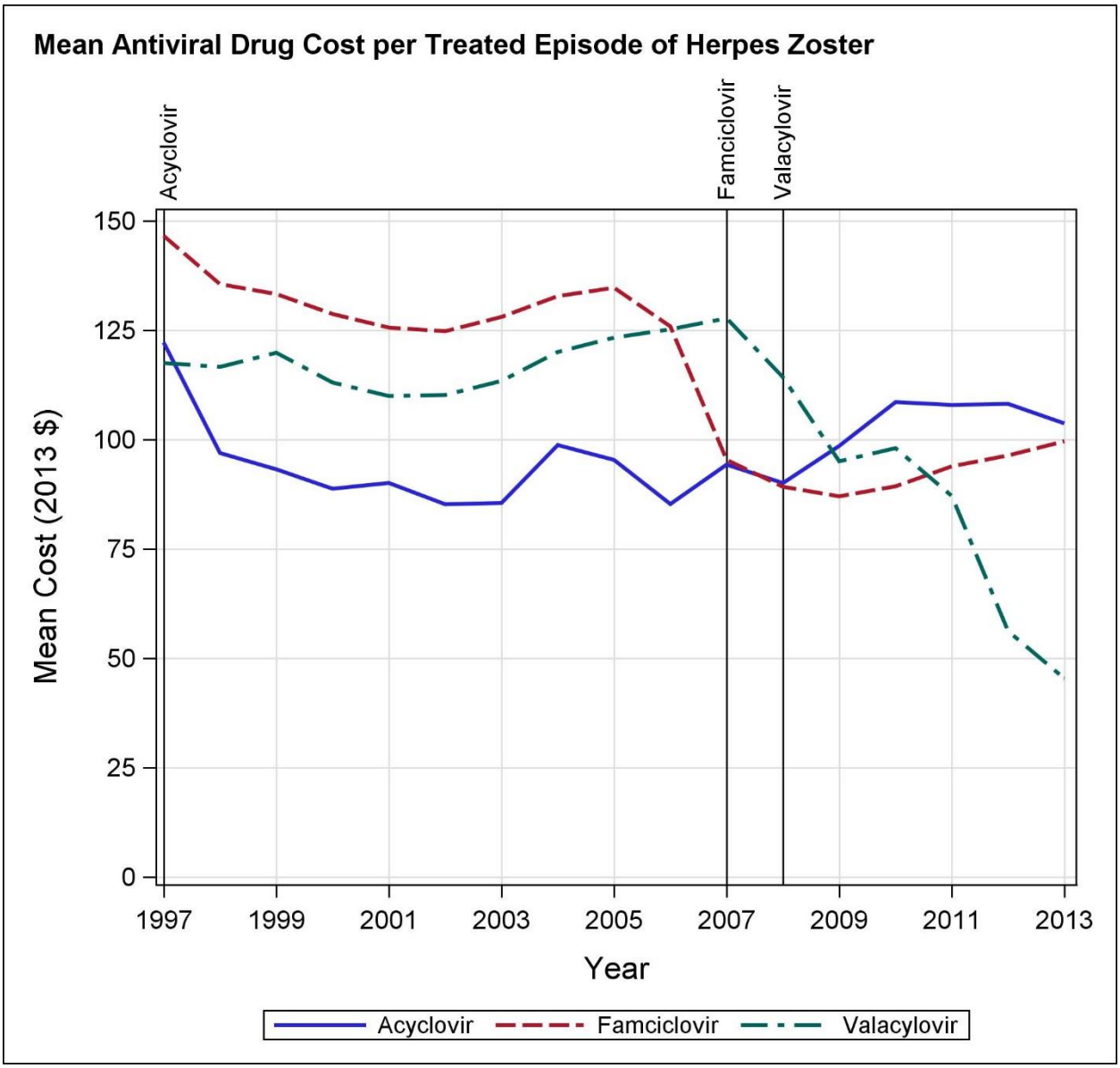


Figure 4.9-3 Mean drug treatment cost per antiviral treated herpes zoster episodes

Vertical lines indicate date generic versions of labelled drug introduced.

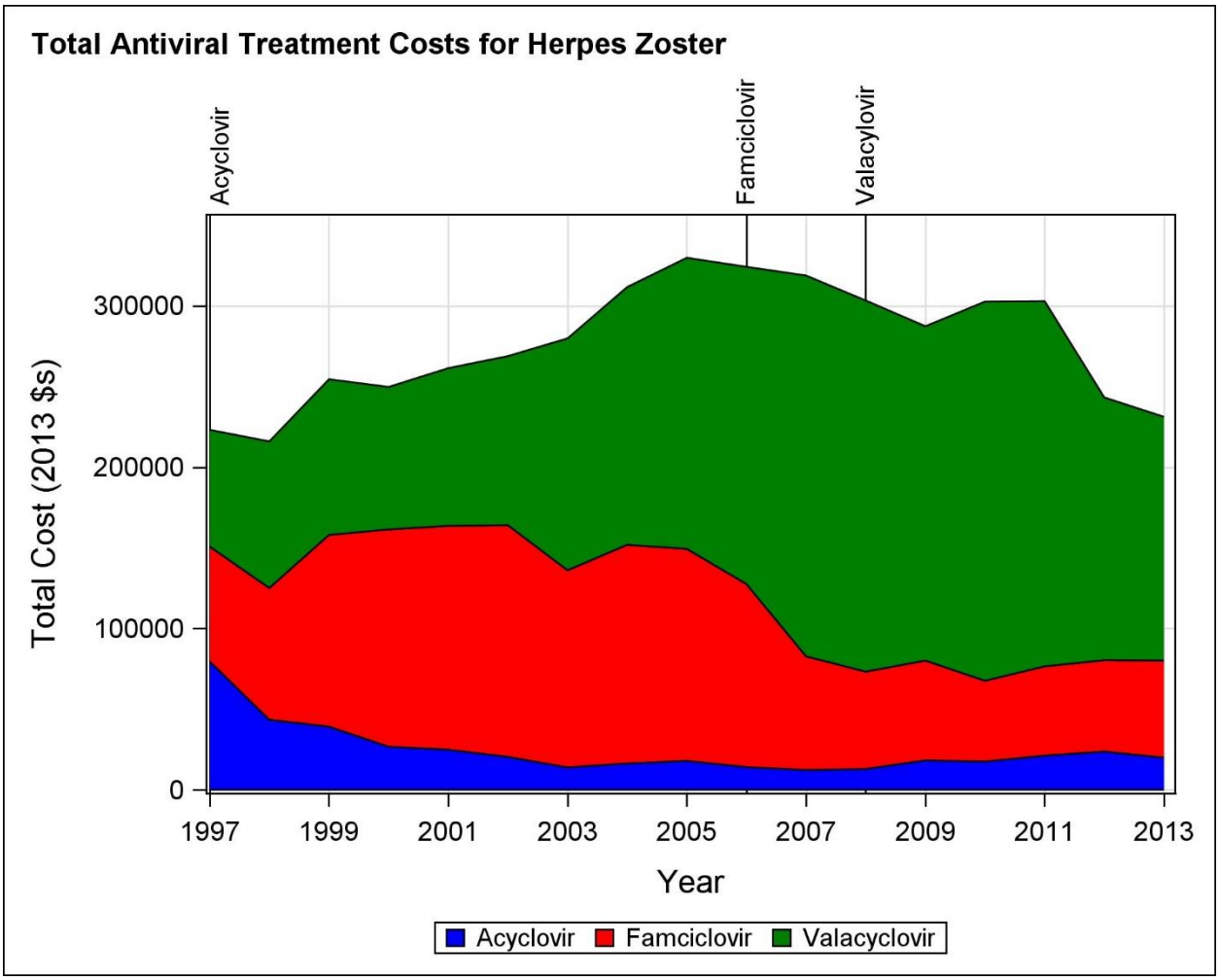


Figure 4.9-4 Summed costs of antiviral treatment of herpes zoster.

Vertical lines indicate date generic versions of labelled drug introduced.

4.10. References

1. Schmader KE, Dworkin RH. Natural history and treatment of herpes zoster. J Pain. 2008;9(1 Suppl 1):S3-S9.

2. Gnann JW, Whitley RJ. Clinical practice. Herpes zoster. N Engl J Med. 2002;347(5):340-346.

3. Hope-Simpson RE. the Nature of Herpes Zoster: a Long-Term Study and a New Hypothesis. Proc R Soc Med. 1965;58(January):9-20.

4. Brisson M, Edmunds WJ, Law B, et al. Epidemiology of varicella zoster virus infection in Canada and the United Kingdom. Epidemiol Infect. 2001;127(02):305-314.

5. Fairley CK, Miller E. Varicella-zoster virus epidemiology--a changing scene? J Infect Dis. 1996;174 Suppl(Suppl 3):S314-S319.

6. Brisson M, Edmunds WJ, Gay NJ, Law B, De Serres G. Modelling the impact of immunization on the epidemiology of varicella zoster virus. Epidemiol Infect. 2000;125(3):651-669.

7. Gialloreti LE, Merito M, Pezzotti P, et al. Epidemiology and economic burden of herpes zoster and post-herpetic neuralgia in Italy: a retrospective, population-based study. BMC Infect Dis. 2010;10:230.

8. Lionis CD, Vardavas CI, Symvoulakis EK, et al. Measuring the burden of herpes zoster and post herpetic neuralgia within primary care in rural Crete, Greece. BMC Fam Pract. 2011;12(1):136.

9. Massengill JS, Kittredge JL. Practical considerations in the pharmacological treatment of postherpetic neuralgia for the primary care provider. J Pain Res. 2014;7:125-132.

10. Dworkin RH, Johnson RW, Breuer J, et al. Recommendations for the management of herpes zoster. Clin Infect Dis. 2007;44 Suppl 1:S1-S26.

11. Ono F, Yasumoto S, Furumura M, et al. Comparison between famciclovir and valacyclovir for acute pain in adult Japanese immunocompetent patients with herpes zoster. J Dermatol. 2012;39(11):902-908.

12. Gauthier a, Breuer J, Carrington D, Martin M, Rémy V. Epidemiology and cost of herpes zoster and post-herpetic neuralgia in the United Kingdom. Epidemiol Infect. 2009;137(1):38-47.

13. Ultsch B, Köster I, Reinhold T, et al. Epidemiology and cost of herpes zoster and postherpetic neuralgia in Germany. Eur J Health Econ. 2013;14(6):1015-1026.

14. Horien C, Grose C. Neurovirulence of varicella and the live attenuated varicella vaccine virus. Semin Pediatr Neurol. 2012;19(3):124-129.

15. Drug Products Database. Healh Canada Drug Products Directorate (web based database). http://webprod5.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp. Accessed November 2, 2015.

16. Oxman MN, Levin MJ. Vaccination against Herpes Zoster and Postherpetic Neuralgia. J Infect Dis. 2008;197 Suppl(Suppl 2):S228-S236

17. Schmader KE, Johnson GR, Saddier P, et al. Effect of a zoster vaccine on herpes zoster-related interference with functional status and health-related quality-of-life measures in older adults. J Am Geriatr Soc. 2010;58(9):1634-1641.

18. Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med. 2005;352(22):2271-2284.

19. Statistics Canada. Annual Demographic Estimates: Canada, Provinces and Territories. (webpage) Ottawa, ON; 2015. http://www.statcan.gc.ca/pub/91-215-x/91-215-x2014000-eng.pdf. Accessed November 17th 2015.

20. Roos LL, Brownell M, Lix L, Roos NP, Walld R, Macwilliam L. From health research to social research : Privacy , methods , approaches. Soc Sci Med. 2008;66:117-129.

21. Bilcke J, Ogunjimi B, Marais C, et al. The health and economic burden of chickenpox and herpes zoster in Belgium. Epidemiol Infect. 2012;140(11):2096-2109.

22. Tanuseputro P, Zagorski B, Chan KJ, Kwong JC. Population-based incidence of herpes zoster after introduction of a publicly funded varicella vaccination program. Vaccine. 2011;29(47):8580-8584.

23. Brisson M, Gay NJ, Edmunds WJ, Andrews NJ. Exposure to varicella boosts immunity to herpes-zoster: implications for mass vaccination against chickenpox. Vaccine. 2002;20(19-20):2500-2507.

24. Horn J, Karch A, Damm O, et al. Current and future effects of varicella and herpes zoster vaccination in Germany – insights from a mathematical model in a country with universal varicella vaccination. Hum Vaccin Immunother. 2016;5515(February):00-00.

25. Damm O, Ultsch B, Horn J, Mikolajczyk RT, Greiner W, Wichmann O. Systematic review of models assessing the economic value of routine varicella and herpes zoster vaccination in high-income countries. BMC Public Health. 2015;15(1):533.

26. Wormsbecker AE, Wang J, Rosella LC, et al. Twenty years of medically-attended pediatric varicella and herpes zoster in Ontario, Canada: A population-based study. PLoS One. 2015;10(7):5-11.

27. Ogunjimi B, Van Damme P, Beutels P. Herpes Zoster Risk Reduction through Exposure to Chickenpox Patients: A Systematic Multidisciplinary Review. PLoS One. 2013;8(6).

28. Klompas M, Kulldorff M, Vilk Y, Bialek SR, Harpaz R. Herpes Zoster and Postherpetic Neuralgia Surveillance Using Structured Electronic Data. Mayo Clin Proc. 2011;86(12):1146-1153.

Chapter 5. Price of Pain: Population Based Cohort Burden of Disease Analysis of Medication Cost in Herpes Zoster and Postherpetic Neuralgia

5.1. Chapter Introduction

The second paper in this thesis examines the pharmacological treatment of both acute zoster associated pain, and the more chronic condition of PHN. The pain of HZ is frequently the symptom that prompts people to seek medical treatment, and can range in intensity from moderate to severe. PHN is the most feared complication of HZ, and can be difficult to treat. While only about 10% of patients convert from acute HZ to PHN, it accounts for the vast majority of drug costs.

The results reported in the paper span the period from 1997/98 to 2011/12. The incidence of HZ, and rates of conversion to PHN are reported, along with total annual costs and the mean costs per episode of pharmacotherapy. Trends over time in the use of different drug classes used are also analyzed and discussed.

5.2. Manuscript Cover Page

Price of Pain: Population Based Cohort Burden of Disease Analysis of Medication Cost in Herpes Zoster and Postherpetic Neuralgia

Kevin J Friesen BSc (Pharm)[1], Jamie Falk BSc (Pharm) PharmD [1], Silvia Alessi-Severini BSc (Pharm) PhD[1], Dan Chateau PhD[2], Shawn Bugden MSc. Pharm.D[1]

[1]College of Pharmacy, Rady Faculty of Health Sciences, University of Manitoba, 750 Bannatyne Ave, Winnipeg, MB, R3E 0T5. [2]Assistant Professor, Department of Community Health Sciences, College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Mb, R3E 3P5

This work was published in the Journal of Pain Research in August 3rd, 2016, volume 2016(9): 543-550 https://dx.doi.org/10.2147/JPR.S107944

Running Header: Cost of treating Herpes Zoster Pain and Postherpetic Neuralgia

Keywords: Herpes zoster, burden, economics, postherpetic neuralgia, gabapentin

Contributions: Kevin Friesen designed the study, analysed the data, and wrote the manuscript. Shawn Bugden assisted in study design, provided guidance during the analytical phase of the study, and critically reviewed the study. Silvia Alessi-Severini was involved in the initiation of this research program and critically reviewed the manuscript. Dan Chateau and Jamie Falk both provided guidance and extensively reviewed and commented on this manuscript throughout the editing process.

Price of Pain: Population Based Cohort Burden of Disease Analysis of Medication Cost in Herpes Zoster and Postherpetic Neuralgia

5.3. Abstract

Background:

Pain is a main symptom of herpes zoster (HZ), and postherpetic neuralgia (PHN) is a frequent complication occurring in 5% to 15% of cases, causing moderate to severe neuropathic pain. A population-based observational study was conducted to evaluate the treatment patterns and economic burden of prescription drug treatment of HZ and PHN pain in the province of Manitoba (Canada) over a period of 15 years.

Methods:

Administrative health care data, including medical and hospital separation records, were examined to identify episodes of HZ using International Classification of Diseases-9/10 codes between April 1, 1997 and March 31, 2014. Episodes of PHN were identified using medical and prescription claims. Incident use of analgesic, antidepressant, or anticonvulsant drugs was used to determine prescription pain costs.

Results:

The age-adjusted incidence of HZ increased from 4.7 episodes/1,000 person-years in 1997/98 to 5.7/1,000 person-years in 2013/14. PHN occurred in 9.2% of HZ cases, a rate that did not change over the study period (P=0.57). The annual cost to treat HZ pain rose by 174% from 1997/98, reaching CAD $332,981 in 2011/12, 82.8% (95% confidence interval [CI] 81.2%, 84.3%) of which was related to PHN. The per episode cost of HZ rose by 111% from $31.59 (95% CI $25.35, $37.84) to $66.81 (95% CI $56.84, $76.78) and by 94% for PHN from $292 (95% CI $225, $358) to $566 (95% CI

$478, $655). These increases were driven by increasing use of anticonvulsants, primarily gabapentin, which accounted for 57% of the increase in cost.

Conclusions:

There has been an increase in the incidence of HZ and PHN and in the average cost associated with the prescription treatment of their resultant neuropathic pain. The primary driver of the increased episodic cost is the increased use of gabapentin. These changes have resulted in a substantial increase in the economic burden associated with HZ and PHN.

Price of Pain: Population-Based Cohort Burden of Disease Analysis of Herpes Zoster and Postherpetic Neuralgia

5.4. Background

Herpes zoster (HZ) is an infectious disease caused by reactivation of latent varicella zoster infection. This common viral disease afflicts between 20-30% of the population at some point in their lifetime; up to 50% of individuals over 80 years of age are affected.[1,2] The dermatological symptoms of HZ are typically preceded by prodromal symptoms that range from a tingling or burning sensation to sharp stabbing pain. This is followed by a raised, reddish rash and vesicular lesions, typically over the region of skin affected by prodromal symptoms, 2 to 3 days later. This rash typically affects singular dermatomes resulting in a unilateral, stripe-like appearance that is diagnostic of HZ. Lesions continue to erupt for several days before the rash crusts over, generally within 7 to 10 days. Symptoms then begin to subside and total resolution generally occurs within 3 to 4 weeks.[3] While HZ is generally self-limiting, longer lasting complications can occur.

The most common complication of zoster is postherpetic neuralgia (PHN). PHN is defined as pain that persists after the resolution of the dermatological symptoms of HZ. It is caused by damage to sensory neurons sustained during the initial active infection with pain persisting even after the virus has returned to its dormant state.[4] There is no single standard definition of PHN. Pain persisting at 30 to 120 days measured from onset of HZ or from healing of rash are used in the literature.[5–7] Pain persisting at 90 days from initial HZ diagnosis is the most commonly used definition.[5–7]

The incidence of HZ is estimated at 3.5 to 7 cases per 1000 person-years (PY), with the incidence in females slightly higher than males.[8,9] The incidence of HZ increases steadily with age, rising to 6-7/1000 PY by 60 years, and continuing to increase thereafter.[2,10,11] The rate of conversion to PHN has been estimated at anywhere from 5% to 60% of HZ cases.[7,11,12] This wide range is partially explained by the lack of standard diagnostic criteria. Studies that used pain persisting at 90 days to define PHN have a more conservative conversion rate with a narrower range of between 5% and 15%.[7–9,11–13]

PHN is a challenging condition to treat, and the effectiveness of pharmacological therapy is limited. The Canadian Pain Society consensus statement on the treatment of neuropathic pain recommends as first line therapy for PHN one of tricyclic antidepressants (TCAs), gabapentin, or pregabalin.[14] Opioids and topical lidocaine are listed as second line alternatives. The European Federation of Neurological Societies 2010 treatment guidelines for neuropathic pain largely echo these recommendations. Opioids, while effective, are not recommended as first line therapy due to side effects, the development of tolerance, and the risk of dependency.[15] A variety of other drugs are also discussed in the literature, including a number used for other forms of neuropathy, although their efficacy for PHN is disputed. These include valproic acid/divalproex sodium, duloxetine, venlafaxine, carbamazepine, tramadol, NSAIDs, and selective serotonin reuptake inhibitors.[6,14–18]

While treatment of PHN remains difficult, it is possible to reduce the risk of HZ, and with it PHN, with the HZ vaccine (Zostavax®, Merck & Co., Inc., Kenilworth, NJ, USA). This vaccine has been shown to reduce the relative risk of HZ by 51%, and of PHN by

almost 67%. While this makes it possible to decrease the chance of developing HZ and PHN, these conditions will continue to result in a significant burden to society in the near future.

To determine the incidence of HZ and rates of PHN, a retrospective cohort study was conducted in Manitoba, Canada over a period of 17 years. The objectives were to determine the burden of disease of zoster-related pain, and to understand the major cost drivers in the changing cost of treating HZ.

5.5. Methods

A population based cohort study was conducted in Manitoba (Canada) using administrative healthcare data from Manitoba's universal public health care system gathered from April 1st 1995 to March 31st 2014 in the course of providing routine medical care. These data were accessed via the Manitoba Centre for Health Policy (MCHP) Population Health Research Data Repository, a collection of databases containing records of contacts of Manitoba residents with the health care system.[19] Databases utilized included the Drug Program Information Network (DPIN), which processes all community-pharmacy based prescriptions for insurance coverage and drug utilization review; the Medical Services database which contains records of all fee-for-service medical provider claims; hospital discharge abstracts containing separations data for all hospitalizations; and the Manitoba Health Registry which contains basic demographic information on all persons registered with Manitoba Health, Healthy Living and Seniors. All records are de-identified but contain a unique scrambled personal health number allowing for the cross-linkage of records over time and across data sets.

Episodes of zoster were identified using diagnostic codes in medical claims and hospital separations. Individuals with one or more International Classification of Diseases (ICD) 9 codes starting with 053, or ICD-10-CM codes starting with B02 were considered as HZ cases, the date of the first being the episode start date. The use of ICD diagnostic codes to diagnose zoster is both highly selective (positive predictive value 93%) and sensitive (97.5%).[20] Multiple episodes per individual were allowed if 2 years had elapsed between episodes. To ensure only incident episodes were included in the analysis a two year washout period was used, thus any episodes identified prior to 1997/98 were excluded. Episodes where individuals were under 20 years at diagnosis were excluded to avoid misclassification of VZ cases as HZ. Cases of PHN were identified by HZ pain drug treatment or medical claims with HZ ICD codes appearing past 90 days from diagnosis. Ongoing treatment is defined below.

Drug treatment was categorized using Anatomical Therapeutic Chemical (ATC) classes. Prescriptions for opioids (ATC codes starting with N02A), NSAIDS (M01), anticonvulsants (N03A), antidepressants (N06A), nabilone (A04AD), local anesthetics (D04A), glucocorticoids (H02AB), and ASA and acetaminophen (N02B) associated with HZ episodes identified in the previous step were collected. Those dispensed between 90 days pre-HZ diagnoses and two years post-diagnosis were evaluated against several criteria to assess if they were related to HZ or PHN or were only coincident.

Use of each drug class was categorized as either incident or prevalent for that episode by evaluating prescriptions in the 90 days preceding diagnosis. A drug class was categorized as prevalent if a person received a total of 30 days' supply or more within those 90 days, and all within-class prescriptions were excluded from analysis for that

episode. From the remaining incident class, all prescriptions from diagnosis to the later of a) 90 days post-diagnosis or b) date of last HZ medical claim, were classified as HZ-PHN treatment. Prescriptions with dispensation dates outside this window had to meet the continuous use criteria. A grace period of 100% of the prescription duration was added to its duration to create an end date. To be considered continuous treatment there could be no gaps between the end date of previous prescriptions and receipt of the next. Discontinuity signaled the end of drug treatment and of that episode; all later prescriptions were removed from further analysis of this episode.

Data were summarized by Manitoba Health fiscal years, which run from April 1st to March 31st for each year. Results are reported as occurring within the fiscal year of diagnosis. Incidence rates for HZ were calculated for 1997/98 through to 2013/14, and age adjusted using the population of Manitoba in 1997 as our standard. As 2 years follow-up was required to capture all data related to episodes of HZ with PHN, only episodes diagnosed from 1997/98 to 2011/12 contributed to the PHN analysis. Regression analysis was conducted on rates of conversion from HZ to PHN across this interval.

Drug costs were calculated directly from prescription records, included cost of both drug and dispensing fee, and were adjusted to 2013 Canadian dollars using Statistics Canada's consumer price index (CPI) for prescription drug costs in Manitoba. Annual total prescription costs were tabulated for all HZ episodes, as well as within HZ episodes that converted to PHN (HZ-PHN). Prescription costs per episode were calculated and t-tests conducted to determine significance of differences between mean costs in 1997/98 and 2011/12. Regression on the proportion of total cost due to HZ-

PHN was used to look for trends over time. The relationship between age at diagnosis and mean treatment cost was examined by regression analysis.

Prescription data was stratified by drug class for HZ-PHN episodes, looking at anticonvulsants, antidepressants, NSAIDs, and opioids. The number of treated episodes was determined for each year. Regressions on number of class-wise treated episodes were used to examine trends over time.

SAS version 9.4 (SAS Institute, Cary NC) was used for all data analysis. Approvals were granted by the University of Manitoba Health Research Ethics Board (HREB) and the Manitoba Health Information Privacy Committee (HIPC).

5.6. Results

Between April 1st, 1997 and March 31st, 2014 there were 73,893 episodes of HZ diagnosed in Manitoba resulting in a mean of 4347 (95% confidence interval (CI) 4067, 4626) episodes per year. There were 5749 episodes of HZ diagnosed in 2013/14, a 50% increase from the 3844 episodes diagnosed in 1997/98. The age standardized incidence rate of HZ increased by 21%, from 4.70 episodes/1000 PY in 1997/98 to 5.70 episodes/1000 PY in 2013/2014.

Total prescription costs for treating pain from HZ and PHN are shown in Table 1. The annual cost of prescription drugs used to treat all HZ-related pain rose by over 174%, from $121,438 in 1997/98 to $332,981 in 2011/12. The drug cost of HZ-PHN episodes rose by 191%, from $96,554 to $281,342. PHN accounted for a mean of 82.8% (95% CI 81.2%, 84.3%) of drug costs. This percentage did not change significantly over the course of the study period ($p=0.57$, $R^2=0.026$).

From 1997/98 through to 2011/12, the period for which full PHN results could be obtained, there were 6038 episodes of HZ that met study criteria for PHN, corresponding to a conversion rate of 9.6 %. A linear regression analysis on conversion rates revealed no significant trend over this period of time ($p=0.45$ $R^2= 0.046$). However, the increase in the total number of HZ episodes resulted in a greater number of PHN cases over time, rising from 331 in 1997/98 to 497 in 2011/12.

The mean cost of treating HZ-related pain increases linearly with age at diagnosis, each additional year increasing the mean episode cost by $1.04 ($p<0.0001$ $R^2= 0.65$). (Figure 1) The mean cost for persons aged 20 to 29 years was $24.15 (95% CI $19.95, 28.34), while for persons aged 60 to 69 the cost was 143% higher at $58.72 (95% CI $52.92, $64.53).

The average cost of treating an episode of HZ, and separately those episodes with PHN, increased over the study period (Table 1). The mean cost per episodes to treat all HZ-related pain rose significantly by 111% ($t=5.369$, $p<0.0001$) from 1997/98 to 2011/12; and by 94% for HZ-PHN episodes ($t=4.36$, $p<0.0001$).

Changes in the drug classes used to treat of HZ-PHN were evaluated examining the number of treated episodes by class over time using linear regression. (Figure 2) Only anticonvulsant use changed significantly with a 212% increase in the number of anticonvulsant treated episodes from 1997/98 to 2011/12 ($p<0.0001$, $R^2=0.92$).

The duration of treatment for HZ-PHN varied widely between drug classes. (Figure 3) The median days supplied was highest for antidepressants (178 days), and anticonvulsants (134 days), with shorter durations for NSAIDs (50 days) and opioids (28

days). The median duration of anticonvulsant treatment increased from 55 days to 141 days between 1997/98 and 2011/12. There was much less change observed in the median treatment duration of other drug classes, with antidepressants increasing from 161 days to 190 days, opioids remaining relatively stable with an increase from 26.5 days to 27 days, and NSAIDS decreasing from 38.5 days to 30 days.

The overall annual cost of opioid, NSAID and antidepressant prescriptions underwent a moderate increase with antidepressants increasing by 91%, opioids by 67%, and NSAIDs by 35% (Table 2). However, these changes were small compared to the increase in anticonvulsant use, which underwent a 755% rise in class cost, increasing from $15,520 to $132,685. This increase accounts for 56% of the total increase in prescription spending for the treatment of all HZ associated pain.

The most frequently prescribed anticonvulsant drug for HZ-PHN also changed over time. In 1997 carbamazepine prescriptions accounted for 62% (260 prescriptions) of all anticonvulsant prescriptions, while gabapentin accounted for only 21% (89 prescriptions). In contrast, in 2011 only 3.2% (80 prescriptions) of all anticonvulsant prescriptions were for carbamazepine. Gabapentin accounted for 73% (1798) of prescriptions, while pregabalin, which was not available in 1997, accounted for 9.2% (226).

5.7. Discussion

The economic burden of treating HZ associated pain, and PHN in particular, increased significantly from 1997/98 to 2011/12 (Table 1). This increase is the combined result of increases in both the incidence of diagnosed HZ and in mean episode cost of

prescription drug treatment of pain. A dramatic increase in gabapentin was found to be a primary driver of mean episode cost.

Over the seventeen year period of 1997/98 to 2013/14 there has been a sustained increase in the incidence of herpes zoster, with a resulting increase in the number of PHN cases. Changes in size and increasing age[21] of the provincial population explain the majority of this increase. However, after taking both these factors into account, a significant 21% increase in the age-adjusted incidence per thousand people remains. As the rate of conversion from HZ to PHN did not change over the study period, the increased number of HZ episodes resulted in an increase in the number of PHN cases. This increase in PHN is an important factor in determining the economic burden of HZ as these cases were responsible for over 80% of HZ-related analgesic prescription costs.

Not only were there more HZ and PHN cases, there was also a significant increase in the mean cost per episode related to the treatment of pain. This higher episode cost was driven by the increased use of anticonvulsant drugs, primarily gabapentin. While the number of users of anticonvulsants rose, the use of other classes of drugs remained relatively unchanged (Table 2). Not only did the number of persons using anticonvulsant drugs increase, the median duration of treatment with them increased as well.

From an evidence-based perspective this change might seem surprising. There is considerable debate on whether this increased expenditure is justified. There is limited evidence demonstrating superior efficacy, and a much greater cost compared to the other first line therapy such as TCAs.[22] In fact, one systematic review estimated the NNT for a 50% reduction of pain of gabapentin to be 4.39 (95%CI 3.34-6.07), while that

of TCAs was 2.64 (95% CI 2.1-3.54).[23] Gabapentin was introduced to the Canadian market in December 1994 when it was approved for the adjunctive treatment of partial seizures.[24] It was aggressively marketed to physicians for a number of non-approved indications, including PHN, by Parke Davis. This promotion eventually lead to a US federal lawsuit against the company for off-label marketing in 1996.[25] It was not until 2004 that the FDA approved gabapentin for PHN, [25] although it has never received this indication in Canada. Some of this promotion suggested that TCA use for PHN was inappropriate in older patients from a safety perspective.[22] However, gabapentin is not without its own adverse effects and a systematic review suggests the number needed to harm (NNH) for major harms is actually similar for gabapentin (NNH= 12.25, 95% CI 7.69-30.2) and TCAs (NNH= 16.9, 95% CI 8.85-178).[23]

Concerns have been raised about the use of opioids in non-cancer pain.[26] These include the risk of dependency, the development of tolerance, and the potential for abuse, and are part of the rationale for listing opioids as second line PHN treatment options.[15,27] However, opioids were used frequently to treat HZ-PHN episodes (Figure 2). While the high rate of use may be concerning, the median of duration of opioid treatment (Figure 3) reveals generally short-term use, possibly reflecting appropriate opioid stewardship.

This study has a number of strengths and limitations. Population level data from a universal single payer health-care system ensures virtually all contacts of residents with this healthcare system and all prescription dispensations are captured in the study. These data sets also allow us to directly measure health system costs rather than inferring results from survey data or sampling, as it has been done in many previous

studies.[12,28–30] There are also several limitations to this study. We are unable to measure the true incidence of HZ in the population as only persons who sought medical treatment appear in the administrative data. However, previous studies have reported that up to 95-99% of persons with HZ will seek medical attention.[8,28] Second, HZ diagnostic codes or prescription treatment past 90 days post diagnosis were used as a proxy for a PHN diagnosis as we only had access to the first three digits of ICD codes in our data. Thus rates reported are of HZ cases requiring ongoing medical management, sometimes referred to as clinically significant PHN. This methodology is common in administrative data studies looking at PHN.[8] Lastly, the use of non-prescription medications, including low dose ibuprofen and naproxen, acetaminophen, ASA, and topical treatments is not captured. However, these costs are outside the scope of this study.

The total costs of treating pain associated with HZ and PHN rose by 174% between 1997/98 and 2011/12. There are two primary components to this increasing economic burden. The first is the increasing number of HZ cases. While some of this can be attributed to an aging population, the age standardized incidence of HZ has increased. The second component is the increasing average cost of treating an episode of HZ-PHN driven by the use of higher cost anticonvulsants for longer periods of time. Management of the economic burden of HZ-PHN analgesic treatment should include use of evidence-based cost effective therapies, and measures such as vaccination which can help reduce the incidence of HZ.

5.8. Acknowledgments

The authors acknowledge the Manitoba Centre for Health Policy for use of data contained in the Population Health Research Data Repository under project #H2014:411 (HIPC# 2014/2015-35). The results and conclusions are those of the authors and no official endorsement by the Manitoba Centre for Health Policy, Manitoba Health, Seniors and Active Living, or other data providers is intended or should be inferred. Data used in this study are from the Population Health Research Data Repository housed at the Manitoba Centre for Health Policy, University of Manitoba and were derived from data provided by Manitoba Health, Seniors and Active Living. We would also like to thank Heather Prior from the Manitoba Centre for Health Policy for her assistance and preliminary data extraction.

5.9. Tables and Figures

	Herpes Zoster Episodes				Herpes Zoster with PHN			
Year	Cases	Rxs	Total Cost	Mean Cost (95% CI)	Cases	Rxs	Total Cost	Mean PHN Cost (95% CI)
1997/98	3844	6082	$121,438	$31.59 ($25.35, $37.84)	331	3925	$96,555	$291.71 ($225.45, $357.96)
1998/99	3781	6309	$130,276	$34.46 ($28.38, $40.53)	349	4229	$107,007	$306.61 ($248.06, $365.16)
1999/00	3941	7820	$245,329	$62.25 ($50.74, $73.76)	367	5526	$215,149	$586.24 ($475.95, $696.53)
2000/01	3954	7629	$224,626	$56.81 ($46.70, $66.92)	399	5440	$192,830	$483.28 ($393.34, $573.23)
2001/02	4060	8282	$271,792	$66.94 ($52.67, $81.22)	429	6064	$236,570	$551.45 ($425.20, $677.69)
2002/03	4126	8015	$254,967	$61.80 ($52.07, $71.52)	410	5554	$215,795	$526.33 ($440.91, $611.75)
2003/04	4070	7783	$231,833	$56.96 ($47.57, $66.35)	375	5541	$191,562	$510.83 ($421.55, $600.12)
2004/05	4087	7070	$194,372	$47.56 ($40.78, $54.34)	379	4670	$153,891	$406.05 ($343.97, $468.12)
2005/06	4131	7886	$214,436	$51.91 ($44.30, $59.51)	432	5581	$172,052	$398.27 ($334.80, $461.74)
2006/07	4143	7918	$207,393	$50.06 ($42.52, $57.60)	377	5586	$165,257	$438.35 ($366.84, $509.86)
2007/08	4207	7968	$193,942	$46.10 ($39.89, $52.31)	377	5674	$152,928	$405.64 ($348.23, $463.06)
2008/09	4295	9435	$252,994	$58.90 ($50.77, $67.04)	440	7147	$209,013	$475.03 ($407.32, $542.74)
2009/10	4584	9393	$267,865	$58.43 ($49.20, $67.67)	427	7024	$222,968	$522.17 ($434.64, $609.71)
2010/11	4622	9102	$276,383	$59.80 ($49.42, $70.17)	449	6617	$230,827	$514.09 ($416.88, $611.30)
2011/12	4984	11065	$332,981	$66.81 ($56.84, $76.78)	497	8398	$281,342	$566.08 ($477.51, $654.66)

Table 5.9-1 Total and cost per episode of treating herpes zoster related pain by year

Total prescription cost per episode. , and include prescriptions for postherpetic neuralgia when present. Costs are reported in 2013 Canadian dollars. Abbreviations: HZ, herpes zoster; PHN, postherpetic neuralgia; Rxs, prescriptions; CI, confidence interval

	Antidepressants		Anticonvulsants		NSAIDs		Opioids		Miscellaneous	
Year	Users	Cost	Users	Cost	Users	Cost	Users	Cost	Users	Cost
1997	348	$35,607	153	$15,520	400	$23,122	866	$33,208	544	$13,980
1998	378	$29,458	168	$29,124	380	$34,326	838	$23,896	520	$13,471
1999	404	$39,612	235	$83,398	475	$64,916	893	$43,752	571	$13,651
2000	424	$46,315	250	$64,642	479	$66,661	893	$34,441	505	$12,567
2001	440	$48,663	293	$85,722	469	$47,112	885	$70,139	544	$20,157
2002	435	$52,683	298	$82,635	453	$48,795	920	$56,048	574	$14,806
2003	425	$46,661	303	$71,625	398	$32,101	819	$62,947	532	$18,498
2004	444	$49,589	326	$63,383	368	$28,335	889	$36,793	552	$16,273
2005	445	$44,140	364	$78,247	377	$29,826	902	$40,096	540	$22,127
2006	419	$49,873	389	$70,737	364	$27,909	848	$31,437	502	$27,437
2007	396	$37,136	485	$86,579	325	$24,099	829	$31,008	501	$15,119
2008	397	$51,837	533	$112,910	389	$27,118	828	$35,141	515	$25,988
2009	430	$54,128	540	$122,855	348	$24,299	866	$41,026	518	$25,558
2010	428	$49,949	581	$123,577	326	$23,549	853	$42,545	526	$36,763
2011	447	$67,903	694	$132,685	383	$31,252	926	$55,318	582	$45,824

Table 5.9-2 Treatment of herpes zoster related pain by drug class.

Total treated herpes zoster episodes (users) and drug class cost by year. Numbers are for all herpes zoster related pain, including post-herpetic neuralgia. A single episode can be treated with more than one class of drug, possibly contributing data to multiple categories.

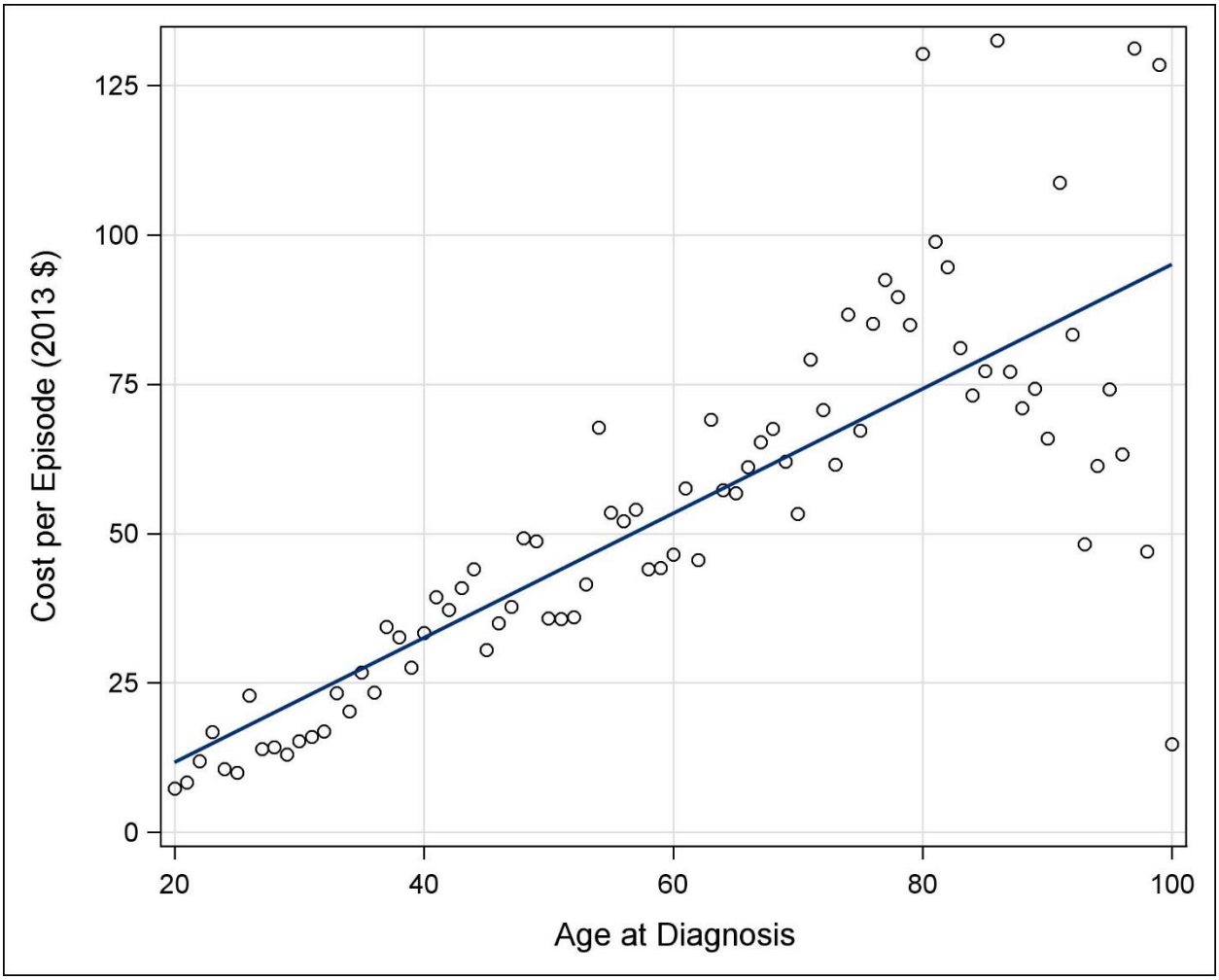


Figure 5.9-1 Mean cost of herpes zoster pain treatment by age.

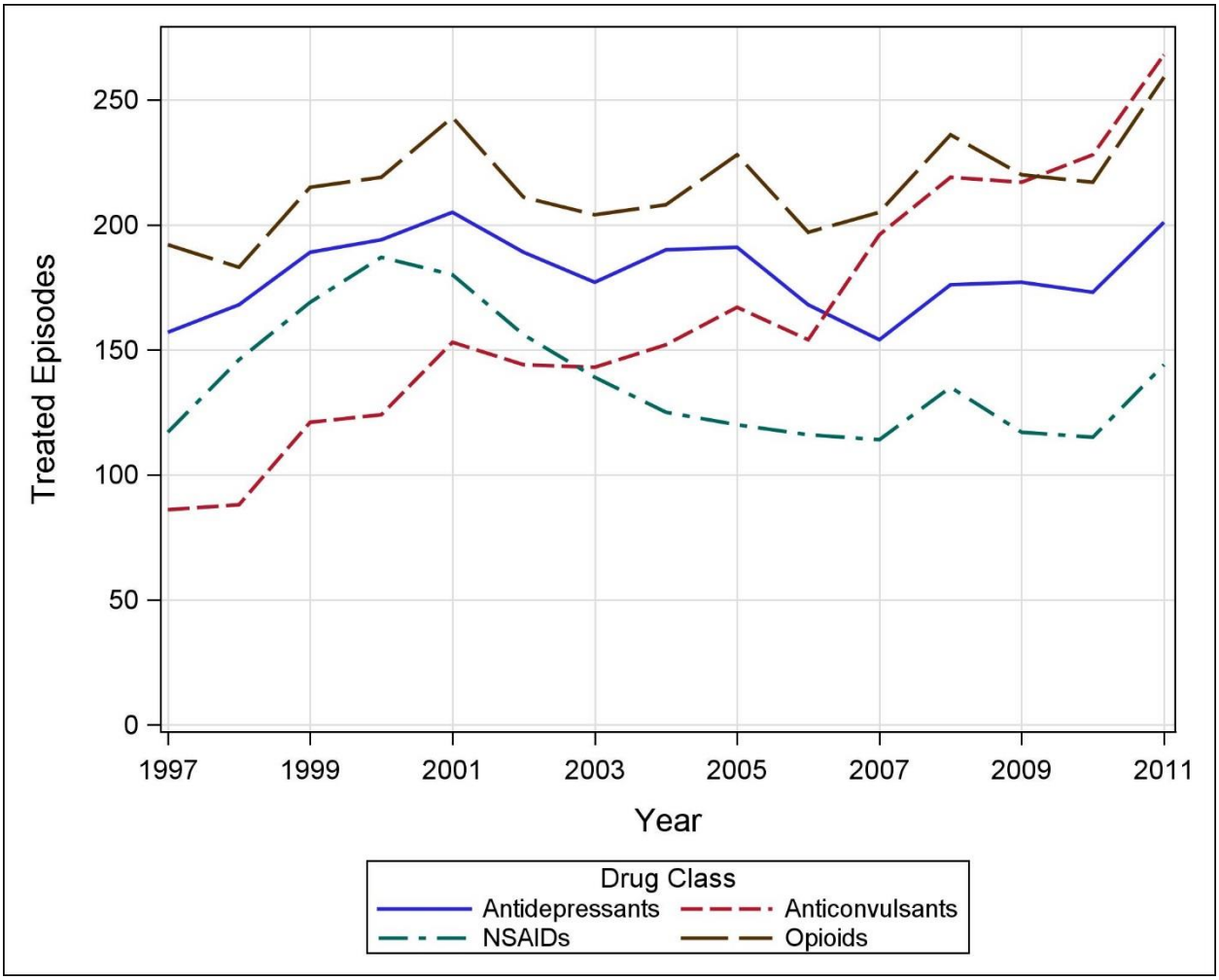


Figure 5.9-2 Treatment of Post-Herpetic Neuralgia Episodes by Drug Class

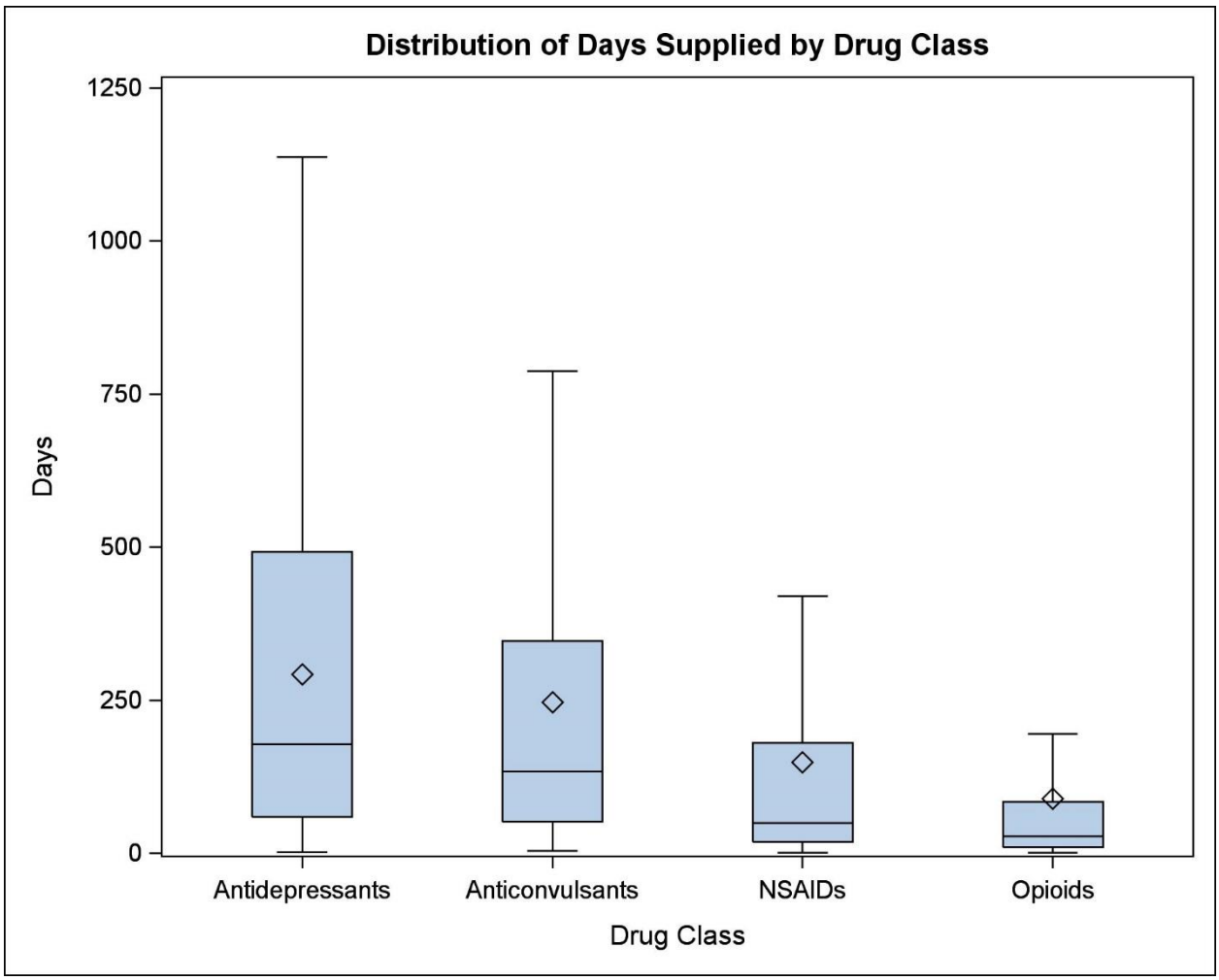


Figure 5.9-3 Distribution of days of drug treatment per episode

5.10. References

1. Brisson M, Edmunds WJ, Law B, et al. Epidemiology of varicella zoster virus infection in Canada and the United Kingdom. Epidemiol Infect. 2001;127(02):305-314.

2. Johnson RW, Alvarez-Pasquin M-J, Bijl M, et al. Herpes zoster epidemiology, management, and disease and economic burden in Europe: a multidisciplinary perspective. Ther Adv vaccines. 2015;3(4):109-120.

3. Dworkin RH, Johnson RW, Breuer J, et al. Recommendations for the management of herpes zoster. Clin Infect Dis. 2007;44 Suppl 1:S1-S26.

4. Bennett G, Watson C. Herpes Zoster and Postherpetic Neuralgia: Past, present and future. Pain Res Manag. 2009;14(4):275-282.

5. Snedecor SJ, Sudharshan L, Cappelleri JC, et al. Systematic review and meta-analysis of pharmacological therapies for pain associated with postherpetic neuralgia and less common neuropathic conditions. Int J Clin Pract. 2014;68(7):900-918.

6. Tontodonati M, Ursini T, Polilli E, et al. Post-herpetic neuralgia. Int J Gen Med. 2012;5:861-871

7. Gauthier a, Breuer J, Carrington D, Martin M, Rémy V. Epidemiology and cost of herpes zoster and post-herpetic neuralgia in the United Kingdom. Epidemiol Infect. 2009;137(1):38-47.

8. Ultsch B, Köster I, Reinhold T, et al. Epidemiology and cost of herpes zoster and postherpetic neuralgia in Germany. Eur J Health Econ. 2013;14(6):1015-1026.

9. Weitzman D, Shavit O, Stein M, Cohen R, Chodick G, Shalev V. A population based study of the epidemiology of Herpes Zoster and its complications. J Infect. 2013;67(5):463-469.

10. Tanuseputro P, Zagorski B, Chan KJ, Kwong JC. Population-based incidence of herpes zoster after introduction of a publicly funded varicella vaccination program. Vaccine. 2011;29(47):8580-8584.

11. Edmunds WJ, Brisson M, Rose JD. The epidemiology of herpes zoster and potential cost-effectiveness of vaccination in England and Wales. Vaccine. 2001;19(23-24):3076-3090.

12. Cebrián-Cuenca AM, Díez-Domingo J, San-Martín-Rodríguez M, Puig-Barberá J, Navarro-Pérez J. Epidemiology and cost of herpes zoster and postherpetic neuralgia among patients treated in primary care centres in the Valencian community of Spain. BMC Infect Dis. 2011;11(1):302.

13. Gialloreti LE, Merito M, Pezzotti P, et al. Epidemiology and economic burden of herpes zoster and post-herpetic neuralgia in Italy: a retrospective, population-based study. BMC Infect Dis. 2010;10:230.

14. Moulin D, Boulanger A, Clark a J, et al. Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society. Pain Res Manag. 2014;19(6):328-335.

15. Attal N, Cruccu G, Baron R, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol. 2010;17(9):1113-e88.

16. Boivin G, Jovey R, Elliott CT, Patrick DM. Management and prevention of herpes zoster: A Canadian perspective. Can J Infect Dis Med Microbiol. 2010;21(1):45-52.

17. Philip A, Thakur R. Post Herpetic Neuralgia. J Palliat Med. 2011;14(6):765-773. doi:10.1089/jpm.2011.9685.

18. Massengill JS, Kittredge JL. Practical considerations in the pharmacological treatment of postherpetic neuralgia for the primary care provider. J Pain Res. 2014;7:125-132.

19. Roos LL, Brownell M, Lix L, Roos NP, Walld R, Macwilliam L. From health research to social research : Privacy , methods , approaches. Soc Sci Med. 2008;66:117-129.

20. Klompas M, Kulldorff M, Vilk Y, Bialek SR, Harpaz R. Herpes Zoster and Postherpetic Neuralgia Surveillance Using Structured Electronic Data. Mayo Clin Proc. 2011;86(12):1146-1153.

21. Statistics Canada. Annual Demographic Estimates: Canada, Provinces and Territories. (webpage) Ottawa, ON; 2015. http://www.statcan.gc.ca/pub/91-215-x/91-215-x2014000-eng.pdf. Accessed November 2, 2015.

22. O'Connor AB, Noyes K, Holloway RG. A Cost-Effectiveness Comparison of Desipramine, Gabapentin, and Pregabalin for Treating Postherpetic Neuralgia. J Am Geriatr Soc. 2007;55(8):1176-1184.

23. Hempenstall K, Nurmikko TJ, Johnson RW, A'Hern RP, Rice ASC. Analgesic therapy in postherpetic neuralgia: A quantitative systematic review. PLoS Med. 2005;2(7):0628-0644.

24. Drug Products Database. Health Canada Drug Products Directorate (web based database). http://webprod5.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp. Accessed November 2, 2015.

25. Torborg DS. The Dark Side of the Boom : The Peculiar Dilemma of Modern False Claims Act Litigation. J Law Health. 2013;26:181-218.

26. National Opioid Use Guideline Group. Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain - Part A Executive Summary. 2010:1-38 (website) http://nationalpaincentre.mcmaster.ca/documents/opioid_guideline_part_a_v4_5.pdf. Accessed November 2, 2015.

27. Moulin DE, Clark a. J, Gilron I, et al. Pharmacological management of chronic neuropathic pain - Consensus statement and guidelines from the canadian pain society. Pain Res Manag. 2007;12(1):13-21.

28. Bilcke J, Ogunjimi B, Marais C, et al. The health and economic burden of chickenpox and herpes zoster in Belgium. Epidemiol Infect. 2012;140(11):2096-2109.

29. Di Legami V, Gianino MM, Atti MCD, et al. Epidemiology and costs of herpes zoster: Background data to estimate the impact of vaccination. Vaccine. 2007;25(43):7598-7604.

30. Lionis CD, Vardavas CI, Symvoulakis EK, et al. Measuring the burden of herpes zoster and post herpetic neuralgia within primary care in rural Crete, Greece. BMC Fam Pract. 2011;12(1):136.

Chapter 6. Cost of Shingles: Population Based Burden of Disease Analysis of Herpes Zoster and Postherpetic Neuralgia

6.1. Chapter Introduction

The third and final thesis paper looks at the overall healthcare system burden of HZ and PHN in Manitoba. This is done by examining the results of the previous two papers with the two other main treatment modalities: medical care and hospitalization.

Hospitalization is an infrequent result of HZ, but has an oversize impact on the total disease burden due to its high cost, with a typical HZ-related stay costing upwards of $12,000. The provision of medical care is also extremely important and is similar in scale to the cost of pharmacotherapy. Trends in the total annual, and mean episode costs for each of the three pillars of treatment are reported for both HZ in general, and episodes of HZ with PHN specifically for the period of 1997/98 to 2011/13.

In addition, a more in depth analysis of changes in the age-adjusted incidence of HZ over the period of 1997/98 to 2013/14 is reported. A piecewise regression analysis is used to examine an apparent breakpoint in incidence of HZ.

6.2. Manuscript Cover Page

Cost of Shingles: Population Based Burden of Disease Analysis of Herpes Zoster and Postherpetic Neuralgia

Kevin J Friesen BSc (Pharm)[1], Dan Chateau PhD[2], Jamie Falk BSc (Pharm) PharmD [1], Silvia Alessi-Severini BSc (Pharm) PhD[1], Shawn Bugden MSc. Pharm.D[1]

[1]College of Pharmacy, Rady Faculty of Health Sciences, University of Manitoba, 750 Bannatyne Ave, Winnipeg, MB, R3E 0T5. [2]Assistant Professor, Department of Community Health Sciences, College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Mb, R3E 3P5

Running Header: Burden of Herpes Zoster and Postherpetic Neuralgia

Keywords: Herpes zoster, burden, economics, postherpetic neuralgia

Contributions:
Kevin Friesen designed this study, analysed the data, and wrote this manuscript. Shawn Bugden assisted in study design, provided guidance during the analytical phase of the study, and critically reviewed the study. Silvia Alessi-Severini was involved in the initiation of this research program and critically reviewed the manuscript. Dan Chateau and Jamie Falk both provided guidance and extensively reviewed and commented on this manuscript throughout the editing process.

Cost of Shingles: Population Based Burden of Disease Analysis of Herpes Zoster and Postherpetic Neuralgia

6.3. Abstract

Background:

Herpes zoster (HZ) is a dermatological disease that results in significant pain and distress, and is frequently complicated by postherpetic neuralgia (PHN). Together, these illnesses produce a significant economic burden to the healthcare system.

Methods:

Administrative healthcare data collected over the period of April 1st 1997 to March 31st 2014 were analyzed to determine the burden of HZ, looking at three primary treatment domains: prescription drugs, medical care, and hospitalization.

Episodes of HZ were identified using international classification of disease (ICD) codes. Piecewise regression was used to examine the age-adjusted (AA) incidence of HZ from 1997/98-2013/14. Costs analysis was restricted to 1997/98-2011/12 to allow for equal follow-up time for all episodes. All amounts were adjusted for inflation and expressed in 2013 Canadian dollars.

Results:

A total of 73,886 episodes of HZ were identified between 1997/98 and 2013/14. The annual number of HZ increased by 49.5% over this period. Piecewise regression on the AA-incidence of HZ revealed a breakpoint in 2008/09 ($F_{(3,13)}$=59.6, p<0.0001). The pre-breakpoint incidence was stable at 4.7 episodes/1000 person-years (PY). Post-breakpoint, the incidence began to climb reaching 5.7 episodes/1000 PY in 2013/14.

The cost of pharmacotherapy rose significantly (p <0.03) from $89.77/episode (95% CI: $82.96, $96.59) to $127.34/episode (95% CI: $117.24, $137.44). Mean medical costs also rose significantly (p <0.0001) from $57.98/episode (95% CI; $55.26, $60.70) to $78.84/episode (95% CI; $74.08, $83.61). Hospitalization rates declined from 3.10% in 1997/98 to 1.36% in 2011/12, with mean per-episode cost dropping from $397/episode (95% CI; $284, $511) to $195/episode (95% CI; $129, $260).

Total annual costs of HZ and PHN were $1,997,183 in 2011/12, 4.7% lower than the 1997/98 costs of $2,095,633.

Conclusion:

A significant increase in annual number of HZ cases was observed, driven largely by demographic factors. However, the 21% increase in the AA-incidence reveals changes in HZ rates beyond those expected by population shifts.

The increase in HZ cases and rising medical and prescription costs were offset by the dramatic drop in HZ-related hospitalizations rates of hospitalization. What is not clear is whether offsetting cost reductions (declining hospitalizations, introduction of generic drugs) can be maintained in the future. Ultimately, it is the balance of these trends that

have left the total burden of disease unchanged, but this will likely be challenged by increasing rates of disease.

Cost of Shingles: Population Based Burden of Disease Analysis of Herpes Zoster and Postherpetic Neuralgia

6.4. Background

The varicella zoster virus (VZV) causes varicella zoster (VZ) upon initial infection, affecting the skin and its sensory neurons. As VZ resolves, the virus enters a latent state in neuronal ganglia, remaining there for life.[1–3] Reactivation of VZV, typically within singular ganglia, causes herpes zoster (HZ), a dermatological condition similar in symptoms to VZ but causing moderate to severe pain.[4,5] A potential complication of HZ is postherpetic neuralgia (PHN), a longer-lasting pain syndrome caused by inflammation or virus-induced nerve damage.[4–6]

Before a VZ vaccine became available in 1999 (Varivax, Merck Frosst Canada & Co), nearly all persons were infected with VZV, typically as a child. By the age of 40, VZV prevalence was 95%-97%.[7,8] Virtually this entire pre-VZ vaccine population is at risk of developing HZ, with an incidence estimated at between 1.2 and 6.3 cases per 1000 person years (PY), with rates increasing with age. The lifetime prevalence of HZ is between 20-30%, rising to 50% by age 80. [2,7,9,10]

The antiviral drugs acyclovir, valacyclovir, and famciclovir are the cornerstone of HZ treatment and reduce the duration and severity of symptoms, including pain.[11] Treatment should begin within 72 hours of the onset of symptoms and continue for 7 days.[2,6,12] Antiviral drugs have been reported to account for 50-70% of the drug cost for treated cases of HZ.[13–16] Other drugs used to treat HZ pain include analgesics, opioids, glucocorticoids, and topical lidocaine.

Despite being relatively common, there is no a standard definition of PHN, particularly in reference to the duration of pain which differentiates continuing HZ pain from PHN. One of the more common criteria used is the persistence of pain for 90 days or more post-HZ diagnosis. Studies using this definition report that 5%-15% of HZ cases convert to PHN.[13–15,17–19] PHN is a challenging condition to treat. The Canadian Pain Society consensus statement and the European Federation of Neurological Societies (EFNS) treatment guidelines list tricyclic antidepressants (TCAs), gabapentin, and pregabalin as first line; and opioids or topical lidocaine as second line treatment options for PHN.[20,21]

In randomized controlled trials, the HZ vaccine (Zostavax®, Merck), introduced to Canada in September 2009, has been shown to reduce the burden of HZ by 61%, decrease the relative risk of HZ by 51%, and that of PHN by almost 67%.[16,22–24]

A number of recent studies have looked at the burden of HZ-PHN in a variety of health care systems, including Belgium,[25] France,[26] Germany,[14,27] Greece,[28] Italy,[13,29] Spain,[18] the United Kingdom,[15] and Israel.[17] However, little recent Canadian data have been published. To establish the current burden of HZ and PHN in the setting of a universal healthcare system, and to look at long term trends in their treatment costs, a retrospective, population based study was conducted over the 15 year period from 1997/98 to 2011/12 in Manitoba, Canada.

6.5. Methods

Using an observational, cohort-based methodology, the incidence and burden of HZ and PHN were examined from April 1st 1997 to March 31st 2014 using administrative healthcare data from the province of Manitoba, Canada. Data was obtained from the

Manitoba Centre for Health Policy (MCHP), which maintains a data repository containing records of virtually every contact between Manitoba residents and the province's universal healthcare system.[30,31] All records are de-identified but contain a unique number that allows researchers to link individual patient records across databases.

Databases used included the Drug Program Information Network (DPIN), a community-pharmacy based prescription processing system that enables submission of online insurance claims by pharmacies, the Medical Services database which contains records of fee-for-service medical claims, Hospital Discharge Abstracts containing summary data of each hospital stay; the Manitoba Immunization Monitoring System (MIMS) database which contains records on vaccines administered in the population, and the Manitoba Health Registry from which population counts and basic demographics on individuals can be obtained.

Cases of HZ were identified using International Classification of Diseases (ICD) diagnostic codes. This method has been shown to be highly selective (positive predictive value 93%) and sensitive (97.5%).[32] Individuals with one or more ICD-9-CM (Clinical Modification) codes starting with '053', or ICD-10-CA (Canadian enhancement) codes starting with 'B02' were classified as HZ cases, with episodes starting on the date of the first code. HZ was considered to have converted to PHN when medical services claims or prescriptions for HZ were received 90 days or more after diagnosis.

Multiple episodes of HZ were allowed provided two conditions were met: 1) a minimum of 2 years had elapsed since the start, and 2) a minimum of 180 days had elapsed since the last HZ ICD code from the preceding episode. To avoid misclassification of

prevalent episodes, episodes with start dates prior to April 1st 1997 were discarded. Episodes in individuals under 20 years of age were excluded from the analysis to avoid misclassification of potentially miscoded VZ cases. Furthermore, to avoid misclassification of physician visits regarding HZ vaccine as episodes, the MIMS database was searched for HZ vaccination records. As MIMS does not capture all HZ vaccinations we also used DPIN to search for vaccine prescriptions, and medical claims to find vaccination tariff codes, using these as surrogate markers of vaccination. Any HZ episode starting within 30 days of vaccination was excluded.

Pharmacotherapy was assessed using DPIN. Prescriptions for acyclovir, valacyclovir, and famciclovir dispensed in the first 30 days of an episode were classified as HZ antiviral treatment. DPIN was searched by Anatomical Therapeutic Chemical (ATC) class. Prescriptions for nabilone (ATC class A04AD), local anesthetics (D04A), systemic corticosteroids (H02A), NSAIDS (M01), opioids (N02A), ASA, acetaminophen (N02B), anticonvulsants (N03A), and antidepressants (N06A) were categorized as HZ pain prescriptions, provided that several conditions were met: 1) treatment of pain with any drug class began within 90 days following diagnosis; 2) use of a class was incident to diagnosis; and 3) use after the later of 90 days post-diagnosis and date of last ICD code for HZ was continuous. Use within a drug class was considered incident if less than 30 of the 90 days pre-diagnosis had prescription coverage from that class. Continuous use was defined as no gaps between prescription dispensations greater than 200% the duration of the previous prescription.

All costs were adjusted for inflation to 2013 Canadian dollars using the Statistics Canada consumer price index.

HZ episodes were further stratified into two subcategories based on PHN status: HZ episodes with no diagnosis of PHN (HZ-only), and HZ episodes that converted to PHN (HZ-PHN). Costs were analyzed across all HZ episodes, and then within each strata separately. The Manitoba Pharmacare fiscal year (April 1st to March 31st) was used for analysis over time. All costs and events were considered to have been incurred in the fiscal year of diagnosis.

Due to observation time required, two separate reporting periods are used. Epidemiology is reported from 1997/98-2013/14 as a follow-up period is not required. For burden analysis, two years of observable time is required to capture costs accruing over episodes, especially for HZ-PHN. These results are reported for 1997/98- 2011/12

Statistical Analysis

The number of episodes and incidence rate of HZ, and PHN conversion rates were calculated for each study year. The age-adjusted incidence was determined using the 1997 Manitoba population as our standard. A segmented regression analysis was conducted to examine an apparent change in incidence of HZ. Ordinary least sum of squares (OLS) regression analysis was used for trend analysis of costs and utilization. Due to non-linearity and high variance, OLS regression was not suitable for hospitalization costs. Instead, a t-test was used to compare annual hospital costs over the first (1997/98-2003/04) and last (2004/05-2011/12) halves of the study period.

SAS® version 9.4 (SAS Institute, Cary, NC) and Microsoft Excel 2013® (Microsoft Corporation, Redmond WA) were used for data analysis. Approvals were granted by the University of Manitoba Health Research Ethics Board (HREB) and the Manitoba Health Information Privacy Committee (HIPC).

6.6. Results

6.6.1. Trends over time

A total of 73,886 episodes of HZ were diagnosed between 1997/98 and 2013/14, an overall crude incidence of 4.99 cases/1000 person-years (PY). A sustained upward trend in the annual numbers of HZ episodes was observed across the study period (Table 1). There were 5,746 episodes of HZ identified in 2013/14, a 49.5% increase from 1997/98.

To adjust for the effects of an increase in the size and age distribution, the age-adjusted (AA) incidence was calculated and plotted (Figure 1). This revealed two linear trends that appeared to converge between 2009/10 and 2010/11. Piecewise regression on the AA-incidence revealed a breakpoint in July 2009 ($F_{(3,13)}$=59.6 p<0.0001). Prior to 2009/10, the incidence of HZ remained relatively steady (p=0.96) at 4.70 cases/1000 PY (95% confidence interval (CI): 4.65, 4.75). Starting in 2009/10 the AA-incidence began increasing on average by 0.29 cases/1000 PY/year (95% CI: 0.20, 0.37), reaching 5.70 cases/1000 PY in 2013/14, a 21% increase from pre-2009/10 level.

Pharmacotherapy

Trends in drug utilization, medical claims cost, hospitalizations, and total cost were examined over the period from 1997/98 to 2011/12.

Antiviral treatment rates increased from 41.7% to 62.9% ($F_{(1,13)}$= 220 p<0.0001 R^2= 0.94) over this period. The cost per treatedepisode dropped from $139.61 to $96.20 due to the introduction of generic antiviral drugs. The mean cost of pain treatment per episode increased by over 111% for HZ, rising from $31.59 (95% CI: $25.35, $37.84) to

$66.81 (95% CI: $56.84, $76.79), and by 94% for HZ-PHN, from $291 (95% CI: $225, $358) to $566 (95% CI: $478, $655) over the same interval. On average, HZ-PHN episodes were responsible for 83% of pain-related drug costs, a proportion that remained unchanged over time (p=0.57).

The mean cost for all drug treatment rose significantly ($F_{(1,13)}$=6 p<0.03 R^2=0.32), from $89.77 (95% CI: $82.96, $96.59) to $127.34 (95%CI: $117.24, $137.44), with the majority of this increase occurring in the first three study years (Figure 2). There was a significant upward linear trend in the total annual drug cost ($F_{(1,13)}$= 30.4 p<0.0001 R^2=0.70), a result of the increase in the number of HZ cases and the rise in mean per episode cost (Figure 3).

Medical Services Utilization.

An upward trend in utilization of medical services was observed ($F_{(1,13)}$= 59.5 p<0.0001 R^2=0.82), The number of medical claims per episodes of zoster rose slightly from 2.53 claims/episode (95% CI: 2.41, 2.65) to 2.80 claims/episode (95% CI: 2.67, 2.93), while the costs per medical claim rose 23% ($F_{(1,13}$=59.9, p<0.0001 R^2= 0.82). Together, these trends produced a linear increase in the per episode cost ($F_{(1,13}$= 48.0 p<0.00001 R^2=0.76) from $57.98/episode (95% CI: $55.26, $60.70) in 1997/98, to $78.84/episode (95% CI: $74.08, $83.61) in 2011/12 (Figure 2). The effect of these trends is amplified by the increase in HZ cases resulting in a significant increase in total annual medical costs ($F_{(1,13}$=182.0 p<0.0001 R^2= 0.93)(Table 1).

Hospitalization

The cost per HZ related hospitalization did not change significantly over the study period with a mean of $12,038/ hospitalization (95% CI: $11,068, $13,007). The overall

mean length of stay was 13.95 days (95% CI: 12.71, 15.19) and did not change significantly (1997/98 vs 2011/12 t=-1.62, p=0.11). There was a sharp drop in the rate of HZ-related hospitalization across the study period ($F_{(1,13)}$= 49.6 p<0.0001 R^2= 0.79), from 3.10% in 1997/98 (119 hospitalizations) to 1.36% in 2011/12 (68 hospitalizations). This resulted in the mean per episode cost of hospitalization dropping significantly (F=25.0 p=0.0002 R^2= 0.62) from $397 (95% CI: $284, $511) to $195 (95% CI: $129, $260), a decline of 51.0%.

Hospitalization costs accounted for 48.5% of total costs in 2011, down from 72.9% in 1997/98. The mean annual cost over the first half of the study (1997/98-2003/04) was $1,145,074 (95% CI: $968,817, $1,321,331), significantly higher than the mean cost of $710,400 (95% CI: $560,336, $860465) seen over last half of the study (2004/05-2011/12) ($t_{(13)}$=4.55, p=0.0005).

Total Cost

The annual total health care costs of treating HZ are shown in Table 1. Linear regression analysis revealed no significant trend across the study period (p= 0.25) with the total health system burden of HZ and PHN being 4.7% lower in 2011/12 than in 1997/98.

6.6.2. Herpes Zoster Burden and Mean Costs 2011/12

There were 4984 diagnosed episodes of HZ in 2011/12, an incidence of 5.3 episodes/1000 PY. Of these, 497 went on to develop PHN, a conversion rate of 10.0%. Hospitalization accounted for 49% of total cost, medical services for 20%, and prescription drug costs for 32%. Although PHN occurred in only a tenth of all episodes,

they were responsible for 41.6% of hospital costs, 21.3% of medical cost, and 49.7% of drug costs. Overall, HZ-PHN episodes accounted for 38.5% of total HZ-related costs.

Mean Cost per Episode

The mean cost of an episode of HZ in 2011/12 was $401 (95% CI: $318, $484). The mean cost for HZ that converted to PHN (HZ-PHN), including the cost of treating PHN, was $1614 (95% CI: $1009, $2220). HZ episodes not associated with PHN (HZ-only) had a mean cost of $266 (95% CI: $204, $329), 16.5% of HZ-PHN episodes.

Pharmacotherapy:

The mean cost of treating an episode of HZ with prescription drugs in 2011/12 was $127.34. Of this, 52.5% was from the treatment of pain with a mean cost of $66.81 (95% CI: $56.84, $76.78), the remainder arising from antiviral treatment at a mean of $60.53 (95% CI: $60.43, 59.92). For HZ-PHN episodes the mean drug cost was $635 (95% CI: $547, $723) with pain treatment accounting for 89% of this cost at $566/episode (95% CI: $478, $655). HZ-only episodes had a mean drug cost of $71.12 (95% CI: $69.18, $73.05), over 83% of which was due to antiviral prescriptions treatment.

Medical Services Utilization

The average HZ episode in 2011/12 resulted in 2.80 (95% CI: 2.67, 2.93) medical claims for a mean cost of $78.84 (95% CI: $74.08, $83.61). The average HZ-PHN episodes resulted in 5.57 claims (95% CI: 4.86, 6.29) with a mean cost of $168.30 (95% CI: $128.79, $207.81), while the average HZ- only episodes resulted in 2.49 claims (95% CI: 2.38, 2.60) with a mean cost of $68.93 (95% CI: $66.08, $71.79).

Hospitalization

HZ-related hospitalization was uncommon, and occurred in 1.36% of episodes in 2011/12 with a mean cost per stay of $14,258/hospitalization (95% CI: $9,461, $19,056). HZ-PHN episodes were more frequently hospitalized at a rate of 5.0%, whereas HZ-only episodes had a hospitalization rate of 1.0%. There was no significant difference in the cost per hospitalization between HZ-PHN and HZ-only episodes so these results were combined. The cost of hospitalization averaged across all HZ episodes was $194.54 (95% CI: $115.90, $273.17).

6.7. Discussion

This study explored the burden of HZ in terms of healthcare system costs. A significant increase in the incidence of HZ, independent of demographic shifts in the population, was found to begin in 2009/10. The medical cost per episode increased, as did total annual costs. Aside from the increase occurring within the first three study years, the per-episode drug costs remained relatively constant, with the increased mean costs of treating pain offset by decreases in antiviral cost per treatment. The combination of increase per-episode medical costs, and constant per-episode drug costs were multiplied by increasing numbers of episodes, causing total outpatient costs to increase. However, this was offset by a dramatic drop in rates of hospitalization.

Although hospitalization is uncommon in HZ patients, at a cost of $12,000 per stay, it has a disproportionate impact on the total burden. In 1997/98, hospital costs accounted for almost three quarters of total HZ costs, this proportion had dropped to 40%-50% over the final study years. This is a result of a dramatic change in rates of

hospitalization, which dropped from 3.10% in the first study year to 1.36% in the last year. However, it appears that this is the floor to hospitalization rates, as the downward trend appears to have ended midway through the study.

The same is not true regarding the trends seen in number of cases, prescription drug costs, and medical service utilization. The number of HZ cases increased by 50% from 1997/98 to 2013/14, largely driven by demographic changes. The cost per episode of medical care has also seen sustained increases. Increasing costs of pain treatment were offset by drops in antiviral costs leaving the per-episode drug cost steady, however, the increasing number of episodes has resulted in increasing total drug costs. These trends do not appear to be slowing down, and if hospitalization rates have indeed plateaued, it may be the case that the burden of zoster will increase in the future.

The increase in the incidence of HZ, which began in 2009/10, is one of the most interesting results of this analysis. The 21% increase in the age-adjusted incidence is not explained by demographic changes as changes in size and age distribution are controlled for. Exposure to wild VZV circulating in the population acts as an exogenous boost to HZ cell-mediated immunity in latently infected adults.[33–35] It has been proposed that an unintended consequence of VZ vaccination programs could be an increase in HZ rates. However, researchers have found mixed evidence when searching for such an effect at the population level.[33,36–41] While this study was not designed to examine such a relationship, it is interesting to note that the VZ vaccinations were added to the routine schedule of universally provided childhood vaccinations in 2004, just 5 years before the increase began.

An important limitation to our results on the burden of HZ is that only direct medical expenses have been considered. There are other sources of burden for both patient and society outside of this narrow focus, perhaps the most important being changes to individuals quality of life, especially for those individuals affected by PHN. Societal costs such as lost productivity, disability payments, and opportunity costs are also outside of the scope of this study. However, this analysis has numerous strengths, including the fact that costs are not estimated based on models nor inferred from a sample but rather directly measured across the entire provincial population. This study examined 15 years of healthcare data, allowing us to see changes over an extend period of time.

6.8. Conclusion

This study explored the burden of HZ in terms of healthcare system costs. A significant increase in the incidence of HZ, independent of demographic shifts in the population, was found to begin in 2009/10. The medical cost per episode increased, as did total annual costs. Per-episode drug costs remained level, with increased mean costs of treating pain offset by decreases in antiviral cost per treatment. The combination of increase per-episode medical costs, and constant per-episode drug costs were multiplied by increasing numbers of episodes, causing total outpatient costs to increase. However, this was offset by a dramatic drop in rates of hospitalization.

6.9. Acknowledgments

The authors acknowledge the Manitoba Centre for Health Policy for use of data contained in the Population Health Research Data Repository under project #H2014:411 (HIPC# 2014/2015-35). The results and conclusions are those of the

authors and no official endorsement by the Manitoba Centre for Health Policy, Manitoba Health, Seniors and Active Living, or other data providers is intended or should be inferred. Data used in this study are from the Population Health Research Data Repository housed at the Manitoba Centre for Health Policy, University of Manitoba and were derived from data provided by Manitoba Health, Seniors and Active Living.

I would also like to thank Heather Prior from the Manitoba Centre for Health Policy for her assistance and preliminary data extraction.

This work was supported by a grant from Merck Canada.

6.10. Tables and Figures

FY Year	Cases		Medical Services		Hospitalization		Drugs		Annual Totals	
	HZ	PHN	Visits	Cost	Stays	Cost	Rxs	Cost	Overall	PHN Only
1997/98	3844	331	9738	$222,864	119	$1,527,684	7842	$345,085	$2,095,633	$625,970
1998/99	3781	349	9311	$216,567	94	$947,462	8139	$346,495	$1,510,524	$521,352
1999/00	3941	367	9645	$240,928	97	$1,176,332	9927	$498,362	$1,915,623	$852,724
2000/01	3954	399	9981	$252,837	80	$978,360	9758	$475,111	$1,706,307	$622,177
2001/02	4060	429	10218	$268,900	95	$1,171,142	10548	$532,201	$1,972,243	$809,190
2002/03	4126	410	10549	$262,471	78	$1,116,598	10350	$523,136	$1,902,205	$507,749
2003/04	4070	375	10191	$275,353	83	$1,097,938	10169	$511,907	$1,885,197	$820,833
2004/05	4087	379	10291	$277,410	61	$621,227	9578	$504,787	$1,403,424	$406,629
2005/06	4131	432	10828	$286,785	49	$443,617	10507	$543,196	$1,273,598	$455,895
2006/07	4143	377	10849	$297,755	67	$924,959	10551	$530,623	$1,753,338	$473,495
2007/08	4207	377	11360	$314,783	72	$704,245	10679	$512,113	$1,531,142	$469,445
2008/09	4295	440	11615	$310,292	59	$809,855	12265	$555,622	$1,675,768	$400,491
2009/10	4584	427	12561	$355,407	58	$582,423	12456	$553,298	$1,491,129	$559,819
2010/11	4622	449	12998	$363,637	58	$627,314	12217	$578,973	$1,569,924	$633,618
2011/12	4984	497	13945	$392,947	68	$969,563	14439	$634,674	$1,997,183	$768,050

Table 6.10-1 Overall health system burden of herpes zoster and postherpetic neuralgia in Manitoba, Canada

Results were summarized by fiscal year with individuals episodes data considered to have occurred in year of diagnosis. All costs have been adjusted to 2013 Canadian dollars using Statistics Canada consumer price index. Abbreviations: FY, fiscal year; HZ, herpes zoster; PHN, postherpetic neuralgia

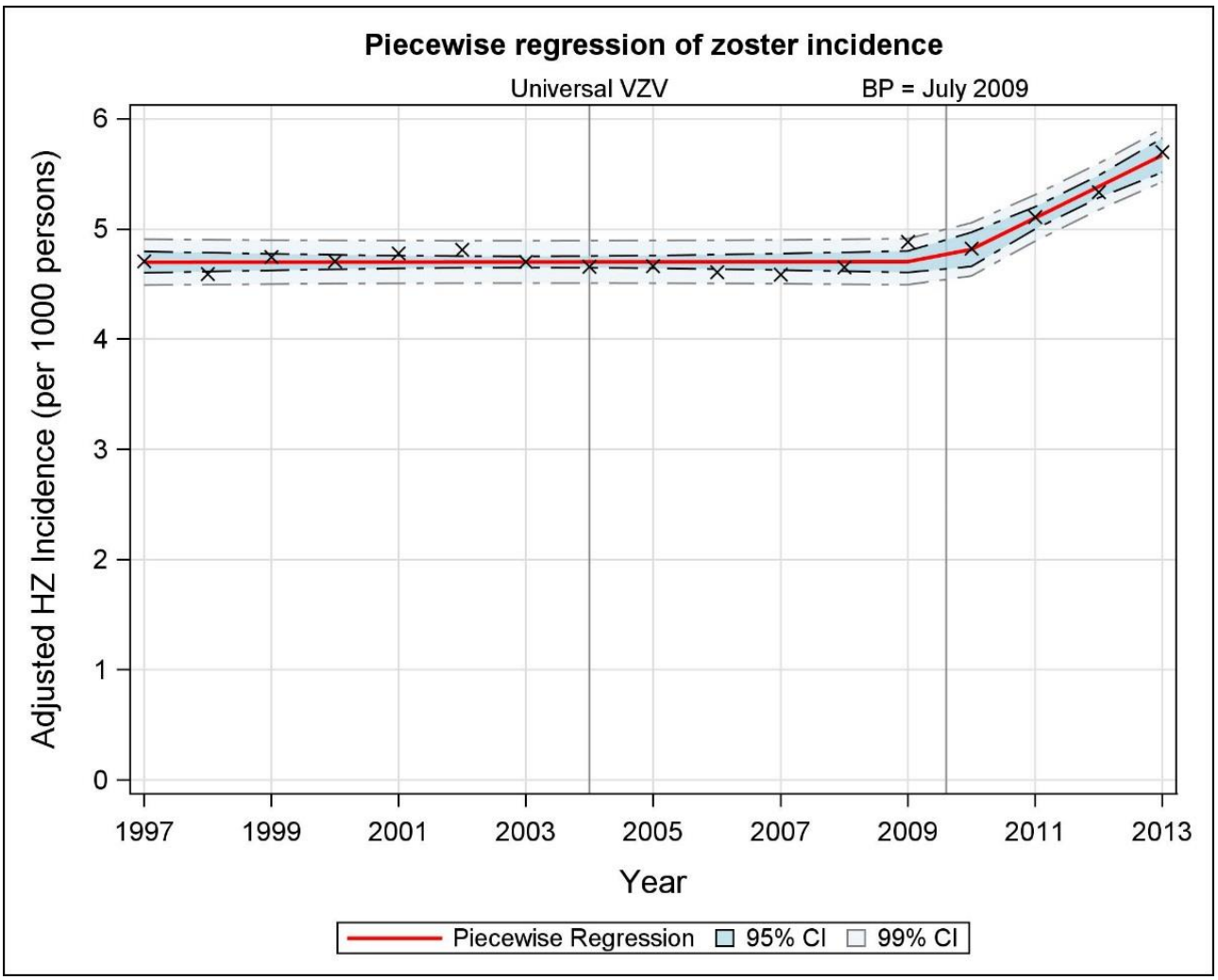


Figure 6.10-1 Piecewise regression on age adjusted incidence of herpes zoster

The age adjusted incidence of herpes zoster was calculated using 1997 as the reference year for age standardization. A highly significant breakpoint was found in July 2009 ($p<0.0001$). Varicella zoster vaccinations were added to the routine childhood vaccination schedule in 2004. **Abbreviations**: VZV, varicella zoster vaccinations; BP, breakpoint; HZ, herpes zoster; CI, confidence interval.

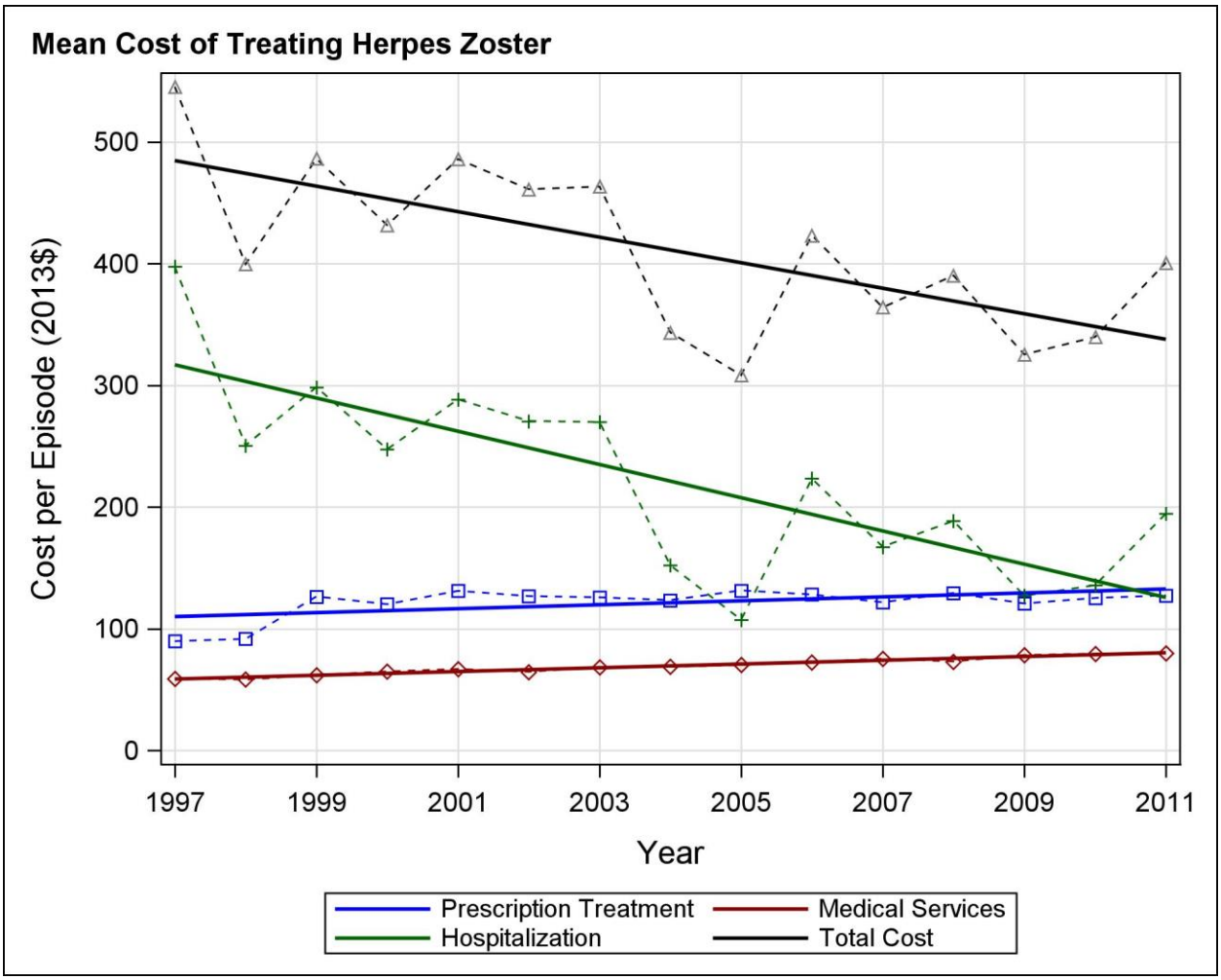


Figure 6.10-2 Cost per episode of herpes zoster by treatment modality.

The mean cost of treating herpes zoster was determined within each year and regression analysis performed (solid lines). Significant trends were found for all modalities: prescription and medical costs $p<0.0001$; hospitalization $p<0.0002$. All costs have been adjusted to 2013 Canadian dollars using Statistics Canada consumer price index.

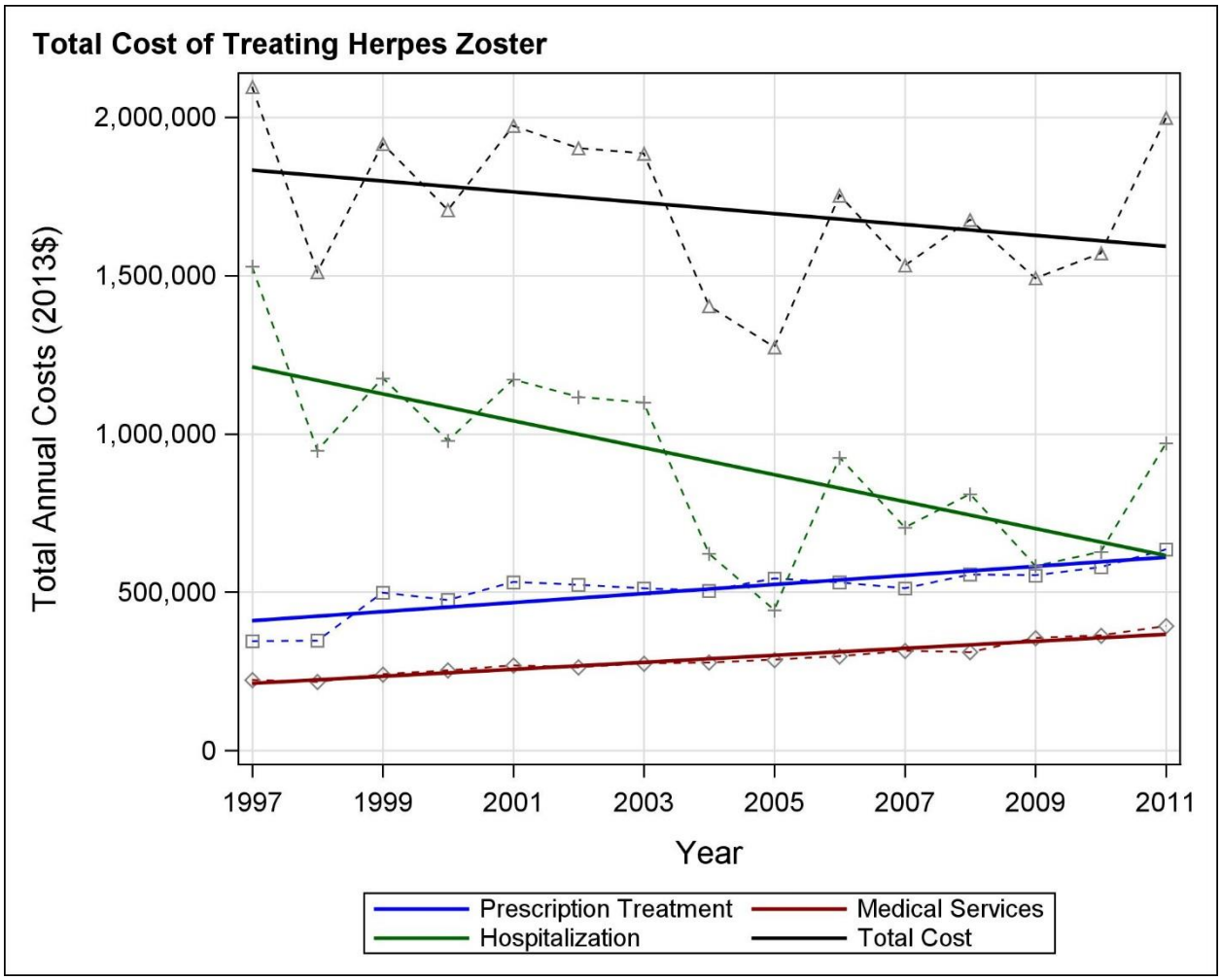


Figure 6.10-3 Totals Costs of Treating Herpes Zoster by Modality.

The total cost of treating herpes zoster was determined within each year and regression analysis performed (solid lines). Significant trends were found for all modalities: prescription costs non-significant and medical costs $p<0.0001$; hospitalization $p<0.0002$. All costs have been adjusted to 2013 Canadian dollars using Statistics Canada consumer price index

6.11. References

1. Hope-Simpson RE. the Nature of Herpes Zoster: a Long-Term Study and a New Hypothesis. Proc R Soc Med. 1965;58(January):9-20.

2. Schmader KE, Dworkin RH. Natural history and treatment of herpes zoster. J Pain. 2008;9(1 Suppl 1):S3-S9.

3. Gnann JW, Whitley RJ. Clinical practice. Herpes zoster. N Engl J Med. 2002;347(5):340-346.

4. Gershon A a, Gershon MD, Breuer J, Levin MJ, Oaklander AL, Griffiths PD. Advances in the understanding of the pathogenesis and epidemiology of herpes zoster. J Clin Virol. 2010;48 Suppl 1:S2-S7

5. Mueller NH, Gilden DH, Cohrs RJ, Mahalingam R, Nagel M a. Varicella zoster virus infection: clinical features, molecular pathogenesis of disease, and latency. Neurol Clin. 2008;26(3):675-697, viii.

6. Dworkin RH, Johnson RW, Breuer J, et al. Recommendations for the management of herpes zoster. Clin Infect Dis. 2007;44 Suppl 1:S1-S26.

7. Brisson M, Edmunds WJ, Law B, et al. Epidemiology of varicella zoster virus infection in Canada and the United Kingdom. Epidemiol Infect. 2001;127(02):305-314.

8. Fairley CK, Miller E. Varicella-zoster virus epidemiology--a changing scene? J Infect Dis. 1996;174 Suppl(Suppl 3):S314-S319.

9. Johnson RW, Alvarez-Pasquin M-J, Bijl M, et al. Herpes zoster epidemiology, management, and disease and economic burden in Europe: a multidisciplinary perspective. Ther Adv vaccines. 2015;3(4):109-120.

10. Brisson M, Edmunds WJ, Gay NJ, Law B, De Serres G. Modelling the impact of immunization on the epidemiology of varicella zoster virus. Epidemiol Infect. 2000;125(3):651-669.

11. Massengill JS, Kittredge JL. Practical considerations in the pharmacological treatment of postherpetic neuralgia for the primary care provider. J Pain Res. 2014;7:125-132.

12. Ono F, Yasumoto S, Furumura M, et al. Comparison between famciclovir and valacyclovir for acute pain in adult Japanese immunocompetent patients with herpes zoster. J Dermatol. 2012;39(11):902-908.

13. Gialloreti LE, Merito M, Pezzotti P, et al. Epidemiology and economic burden of herpes zoster and post-herpetic neuralgia in Italy: a retrospective, population-based study. BMC Infect Dis. 2010;10:230.

14. Ultsch B, Köster I, Reinhold T, et al. Epidemiology and cost of herpes zoster and postherpetic neuralgia in Germany. Eur J Health Econ. 2013;14(6):1015-1026.

15. Gauthier a, Breuer J, Carrington D, Martin M, Rémy V. Epidemiology and cost of herpes zoster and post-herpetic neuralgia in the United Kingdom. Epidemiol Infect. 2009;137(1):38-47.

16. Oxman MN, Levin MJ. Vaccination against Herpes Zoster and Postherpetic Neuralgia. J Infect Dis. 2008;197 Suppl(Suppl 2):S228-S236.

17. Weitzman D, Shavit O, Stein M, Cohen R, Chodick G, Shalev V. A population based study of the epidemiology of Herpes Zoster and its complications. J Infect. 2013;67(5):463-469.

18. Cebrián-Cuenca AM, Díez-Domingo J, San-Martín-Rodríguez M, Puig-Barberá J, Navarro-Pérez J. Epidemiology and cost of herpes zoster and postherpetic neuralgia among patients treated in primary care centres in the Valencian community of Spain. BMC Infect Dis. 2011;11(1):302

19. Edmunds WJ, Brisson M, Rose JD. The epidemiology of herpes zoster and potential cost-effectiveness of vaccination in England and Wales. Vaccine. 2001;19(23-24):3076-3090.

20. Attal N, Cruccu G, Baron R, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol. 2010;17(9):1113-e88.

21. Moulin D, Boulanger A, Clark AJ, et al. Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society. Pain Res Manag. 2014;19(6):328-335.

22. Schmader KE, Oxman MN, Levin MJ, et al. Persistence of the efficacy of zoster vaccine in the shingles prevention study and the short-term persistence substudy. Clin Infect Dis. 2012;55(10):1320-1328.

23. Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med. 2005;352(22):2271-2284.

24. Drug Products Database. Heal Canada website. http://webprod5.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp. Accessed November 2, 2015.

25. Bilcke J, Ogunjimi B, Marais C, et al. The health and economic burden of chickenpox and herpes zoster in Belgium. Epidemiol Infect. 2012;140(11):2096-2109.

26. Blein C, Gavazzi G, Paccalin M, Baptiste C, Berrut G, Vainchtock A. Burden of herpes zoster: the direct and comorbidity costs of herpes zoster events in hospitalized patients over 50 years in France. BMC Infect Dis. 2015;15(1):350.

27. Ultsch B, Siedler A, Rieck T, Reinhold T, Krause G, Wichmann O. Herpes zoster in Germany: quantifying the burden of disease. BMC Infect Dis. 2011;11(1):173.

28. Lionis CD, Vardavas CI, Symvoulakis EK, et al. Measuring the burden of herpes zoster and post herpetic neuralgia within primary care in rural Crete, Greece. BMC Fam Pract. 2011;12(1):136.

29. Di Legami V, Gianino MM, Atti MCD, et al. Epidemiology and costs of herpes zoster: Background data to estimate the impact of vaccination. Vaccine. 2007;25(43):7598-7604.

30. Roos LL, Brownell M, Lix L, Roos NP, Walld R, Macwilliam L. From health research to social research : Privacy , methods , approaches. Soc Sci Med. 2008;66:117-129.

31. Jutte DP, Roos LL, Brownell MD. Administrative record linkage as a tool for public health research. Annu Rev Public Health. 2011;32:91-108.

32. Klompas M, Kulldorff M, Vilk Y, Bialek SR, Harpaz R. Herpes Zoster and Postherpetic Neuralgia Surveillance Using Structured Electronic Data. Mayo Clin Proc. 2011;86(12):1146-1153.

33. Brisson M, Gay NJ, Edmunds WJ, Andrews NJ. Exposure to varicella boosts immunity to herpes-zoster: implications for mass vaccination against chickenpox. Vaccine. 2002;20(19-20):2500-2507.

34. Solomon BA, Kaporis AG, Glass AT, Simon SI, Baldwin HE. Lasting immunity to varicella in doctors study (L.I.V.I.D. study). J Am Acad Dermatol. 1998;38(5 Pt 1):763-765.

35. Thomas SL, Wheeler JG, Hall AJ. Contacts with varicella or with children and protection against herpes zoster in adults: a case-control study. Lancet. 2002;360(9334):678-682.

36. Chao DY, Chien YZ, Yeh YP, Hsu PS, Lian IB. The incidence of varicella and herpes zoster in Taiwan during a period of increasing varicella vaccine coverage, 2000-2008. Epidemiol Infect. 2012;140(6):1131-1140.

37. Edmunds WJ, Brisson M. The effect of vaccination on the epidemiology of varicella zoster virus. J Infect. 2002;44(4):211-219.

38. Russell ML, Dover DC, Simmonds KA, Svenson LW. Shingles in Alberta: Before and after publicly funded varicella vaccination. Vaccine. 2014;32(47):6319-6324.

39. Tanuseputro P, Zagorski B, Chan KJ, Kwong JC. Population-based incidence of herpes zoster after introduction of a publicly funded varicella vaccination program. Vaccine. 2011;29(47):8580-8584.

40. Leung J, Harpaz R, Molinari NA, Jumaan A, Zhou F. Herpes zoster incidence among insured persons in the united states, 1993-2006: Evaluation of impact of varicella vaccination. Clin Infect Dis. 2011;52(3):332-340.

41. Ogunjimi B, Van Damme P, Beutels P. Herpes Zoster Risk Reduction through Exposure to Chickenpox Patients: A Systematic Multidisciplinary Review. PLoS One. 2013;8(6).

Chapter 7. Thesis Conclusions

This thesis explored the burden of HZ and PHN from a healthcare system perspective. One of our initial hypotheses was that the absolute number of HZ episodes would rise over time as a direct result of a population aging and growth (Appendix A) [78,79]. Our results confirmed this hypothesis, finding a 49.5% increase in the annual number of HZ episodes. Further, we found an increase in age-adjusted incidence of HZ of 21%, an upward shift that cannot be explained by the demographic factors mentioned above. This trend was not seen over the first 12 years of the study period, but only began after 2009. It is interesting that this upward trend began five years after the VZ vaccine was added to the provinces schedule of routine childhood vaccinations. The observation fits with the exogenous boosting hypothesis, which suggests that decreasing levels of wild-VZV circulating in the population could have deleterious effects on HZ rates in those already latently infected with VZV.[42,55,57]

Assuming that treatment costs would either increase with time or remain constant, we also hypothesized that the burden of HZ and PHN should increase with time due to the increasing number of affected individuals. However, this was not observed in our study. We did observe an upward trends in mean medical and prescription costs that, left unopposed, combined with the increasing rate of HZ, would have resulted in an increase healthcare system burden of illness. However, these upward trends were counteracted by the dramatic decrease in HZ-related hospitalization rates, which fell by half.

While hospitalization is an infrequent outcome of HZ, its average cost of over $12,000 per stay gives it tremendous leverage to affect the overall burden of disease. Hospital costs account for 48% (in 2011/12) to 73% (in 1997/98) of total burden. The drop in hospitalization rates occurred during the first half of the study period, after which rates stabilized, and it may be the case that this is the floor below which rates can no longer continue to fall.

The increasing cost of pharmacotherapy was itself the result of a mixture of additive and opposing trends. The rate of antiviral treatment of HZ rose by over 50% over the study period. Combined with the increasing number of episodes, this resulted in more than twice as many treated episodes in 2013/14 than in 1997/98, yet the total cost of antiviral drugs rose by only 2.6%. This is due to the introduction of generic versions of antiviral drugs, with acyclovir going generic in 1997, famciclovir in 2006, and valacyclovir in 2008, resulting in the cost per treated episode dropping to less than half of the initial cost by 2013/14.

The introduction of generic drugs used to treat HZ and PHN pain helped offset some of the increases drug cost, changes in prescribing patterns for PHN, in particular the large increase in gabapentin use, completely overwhelmed this offset. This lead to the per-episode cost of treating pain to rise by 111%, and the total annual cost to rise by 174%.

The future burden of HZ and PHN will depend on the balance between the factors identified and how they change. Whether the upward trend in the AA-incidence of HZ observed continues or not is unclear. However, it seems certain that the absolute number of HZ cases will continue to increase, driven by demographic changes. Population models project that the population of Manitoba will continue to grow, with an

increasing proportion represented by aged persons.[74] The drugs used to treat HZ and PHN are all now available in generic formulations, and hospitalization rates appear to have plateaued, thus their ability to further buffer future increases in cost may be limited. While the burden of HZ has not increased over the fifteen years between 1997/98 and 2011/12, the direction the burden of disease charts over the next fifteen seems likely to increase.

THESIS REFERENCES

1. Gershon A a, Gershon MD, Breuer J, Levin MJ, Oaklander AL, Griffiths PD. Advances in the understanding of the pathogenesis and epidemiology of herpes zoster. *J Clin Virol*. 2010;48 Suppl 1:S2-S7.

2. Brisson M, Edmunds WJ, Law B, et al. Epidemiology of varicella zoster virus infection in Canada and the United Kingdom. *Epidemiol Infect*. 2001;127(02):305-314.

3. Chapman RS, Cross KW, Fleming DM. The incidence of shingles and its implications for vaccination policy. *Vaccine*. 2003;21(19-20):2541-2547.

4. Edmunds WJ, Brisson M, Rose JD. The epidemiology of herpes zoster and potential cost-effectiveness of vaccination in England and Wales. *Vaccine*. 2001;19(23-24):3076-3090.

5. Weitzman D, Shavit O, Stein M, Cohen R, Chodick G, Shalev V. A population based study of the epidemiology of Herpes Zoster and its complications. *J Infect*. 2013;67(5):463-469,

6. Cebrián-Cuenca AM, Díez-Domingo J, San-Martín-Rodríguez M, Puig-Barberá J, Navarro-Pérez J. Epidemiology and cost of herpes zoster and postherpetic neuralgia among patients treated in primary care centres in the Valencian community of Spain. *BMC Infect Dis*. 2011;11(1):302.

7. Tontodonati M, Ursini T, Polilli E, et al. Post-herpetic neuralgia. *Int J Gen Med*. 2012;5:861-871.

8. Philip A, Thakur R. Post Herpetic Neuralgia. *J Palliat Med*. 2011;14(6):765-773.

9. Schmader KE, Dworkin RH. Natural history and treatment of herpes zoster. *J Pain*. 2008;9(1 Suppl 1):S3-S9.

10. Gialloreti LE, Merito M, Pezzotti P, et al. Epidemiology and economic burden of herpes zoster and post-herpetic neuralgia in Italy: a retrospective, population-based study. *BMC Infect Dis*. 2010;10:230.

11. Mueller NH, Gilden DH, Cohrs RJ, Mahalingam R, Nagel M a. Varicella zoster virus infection: clinical features, molecular pathogenesis of disease, and latency. *Neurol Clin*. 2008;26(3):675-697, viii.

12. Wilson JF. Herpes zoster. *Ann Intern Med*. 2011;154(5):ITC31-15; quiz ITC316.

13. Gilden DH, Mahalingam R, Cohrs RJ, Tyler KL. Herpesvirus infections of the nervous system. *Nat Clin Pract Neurol*. 2007;3(2):82-94.

14. Grinde B. Herpesviruses: latency and reactivation - viral strategies and host response. *J Oral Microbiol*. 2013;5(5):1-9.

15. Horien C, Grose C. Neurovirulence of varicella and the live attenuated varicella vaccine virus. *Semin Pediatr Neurol*. 2012;19(3):124-129.

16. Fairley CK, Miller E. Varicella-zoster virus epidemiology--a changing scene? *J Infect Dis*. 1996;174 Suppl(Suppl 3):S314-S319.

17. Hunt R. Virology - Herpes Virus. In: Hunt RC, ed. *Microbiology and Immunology On-Line*. Vol University of South Carolina School of Medicine; 2010. http://pathmicro.med.sc.edu/virol/herpes.htm. Accessed November 4, 2015

18. Zerboni L, Sen N, Oliver SL, Arvin AM. Molecular mechanisms of varicella zoster virus pathogenesis. *Nat Rev Microbiol*. 2014;12(3):197-210.

19. Weaver BA. The burden of herpes zoster and postherpetic neuralgia in the United States. *J Am Osteopath Assoc*. 2007;107(3 Suppl 1):S2-S7. http://www.ncbi.nlm.nih.gov/pubmed/17488884. Accessed October 19, 2014.

20. Dworkin RH, Barbano RL, Tyring SK, et al. A randomized, placebo-controlled trial of oxycodone and of gabapentin for acute pain in herpes zoster. *Pain*. 2009;142(3):209-217.

21. Solomon CG, Cohen JI. Herpes Zoster. *N Engl J Med*. 2013;369(3):255-263.

22. Gnann JW, Whitley RJ. Clinical practice. Herpes zoster. *N Engl J Med*. 2002;347(5):340-346.

23. Boivin G, Jovey R, Elliott CT, Patrick DM. Management and prevention of herpes zoster: A Canadian perspective. *Can J Infect Dis Med Microbiol*. 2010;21(1):45-52.

24. Schmader KE, Sloane R, Pieper C, et al. The Impact of Acute Herpes Zoster Pain and Discomfort on Functional Status and Quality of Life in Older Adults. *Clin J Pain*. 2007;23(6):490-496.

25. Gharibo C, Kim C. Postherpetic Neuralgia: An overview of the pathophysiology, presentation, and management. *Pain Med News*. 2011;(April):1-8.

26. Dworkin RH, Johnson RW, Breuer J, et al. Recommendations for the management of herpes zoster. *Clin Infect Dis*. 2007;44 Suppl 1:S1-S26.

27. CPhA. *E-CPS*. Ottawa, ON: Canadian Pharmacists Association; 2014. http://www.e-cps.ca.

28. Gnann JW. Antiviral therapy of varicella-zoster virus infections. In: Arvin A, G C-F, E M, eds. *Human Herpesviruses: Biology, Therapy, and Immunoprophylaxis*. Vol Cambridge: Cambridge University Press; 2007.

29. Bruxelle J, Pinchinat S. Effectiveness of antiviral treatment on acute phase of herpes zoster and development of post herpetic neuralgia: review of international publications. *Médecine Mal Infect*. 2012;42(2):53-58.

30. Bennett G, Watson C. Herpes Zoster and Postherpetic Neuralgia: Past, present and future. *Pain Res Manag*. 2009;14(4):275-282.

31. Wareham DW, Breuer J. Herpes zoster. *Bmj*. 2007;334(June):1211-1215.

32. Wood MJ, Johnson RW, McKendrick MW, Taylor J, Mandal BK, Crooks J. A randomized trial of acyclovir for 7 days or 21 days with and without prednisolone for treatment of acute herpes zoster. *N Engl J Med*. 1994;330(13):896-900.

33. Whitley RJ, Weiss H, Gnann JW, et al. Acyclovir with and without prednisone for the treatment of herpes zoster. A randomized, placebo-controlled trial. The National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. *Ann Intern Med*. 1996;125(5):376-383.

34. Moulin D, Boulanger A, Clark AJ, et al. Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society. *Pain Res Manag*. 2014;19(6):328-335.

35. Attal N, Cruccu G, Baron R, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol*. 2010;17(9):1113-e88.

36. Massengill JS, Kittredge JL. Practical considerations in the pharmacological treatment of postherpetic neuralgia for the primary care provider. *J Pain Res*. 2014;7:125-132.

37. Merck Canada. Varivax product monograph. http://www.merck.ca/assets/en/pdf/products/VARIVAX_III-PM_E.pdf. Accessed Jan 17, 2016.

38. Drug Products Database. *Health Canada website*. http://webprod5.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp. Accessed November 2, 2015.

39. Sweet L, Gallant P, Morris M, Halperin S a. Canada's first universal varicella immunization program: Lessons from Prince Edward Island. *Can J Infect Dis*. 2003;14(1):41-44.

40. Hilderman T, Katz A, Derksen S, et al. *Manitoba Immunization Study*. Winnipeg: Manitoba Centre for Health Policy; 2011. http://mchp-appserv.cpe.umanitoba.ca/reference/MB_Immunization_Report_WEB.pdf. Accessed March 27 2016.

41. Pubilc Health Agency of Canada. Varicella (Chickenpox). 2012. http://www.phac-aspc.gc.ca/im/vpd-mev/varicella-eng.php. Accessed March 27, 2016.

42. Ogunjimi B, Van Damme P, Beutels P. Herpes Zoster Risk Reduction through Exposure to Chickenpox Patients: A Systematic Multidisciplinary Review. *PLoS One*. 2013;8(6).

43. Merck Canada. Zostavax product monograph. 2014. http://www.merck.ca/assets/en/pdf/products/ci/ZOSTAVAX_II-CI_E.pdf. Accessed Jan 17, 2016.

44. Oxman MN, Levin MJ. Vaccination against Herpes Zoster and Postherpetic Neuralgia. *J Infect Dis*. 2008;197 Suppl(Suppl 2):S228-S236.

45. Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med*. 2005;352(22):2271-2284.

46. Schmader KE, Oxman MN, Levin MJ, et al. Persistence of the efficacy of zoster vaccine in the shingles prevention study and the short-term persistence substudy. *Clin Infect Dis*. 2012;55(10):1320-1328.

47. Morrison VA, Johnson GR, Schmader KE, et al. Long-term Persistence of Zoster Vaccine Efficacy. *Clin Infect Dis*. 2015;60(6):900-909. doi:10.1093/cid/ciu918.

48. Lal H, Cunningham AL, Godeaux O, et al. Efficacy of an Adjuvanted Herpes Zoster Subunit Vaccine in Older Adults. *N Engl J Med*. 2015:1-10.

49. Kawai K, Preaud E, Baron-Papillon F, Largeron N, Acosta CJ. Cost-effectiveness of vaccination against herpes zoster and postherpetic neuralgia: a critical review. *Vaccine*. 2014;32(15):1645-1653.

50. Najafzadeh M, Marra C a., Galanis E, Patrick DM. Cost effectiveness of herpes zoster vaccine in Canada. *Pharmacoeconomics*. 2009;27(12):991-1004.

51. Peden AD, Strobel SB, Forget EL. Is herpes zoster vaccination likely to be cost-effective in Canada? *Can J Public Health*. 2014;105(4):e287-e295.

52. Hornberger J, Robertus K. Cost-effectiveness of a vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *Ann Intern Med*. 2006;145(5):317-325.

53. Damm O, Ultsch B, Horn J, Mikolajczyk RT, Greiner W, Wichmann O. Systematic review of models assessing the economic value of routine varicella and herpes zoster vaccination in high-income countries. *BMC Public Health*. 2015;15(1):533.

54. Hope-Simpson RE. the Nature of Herpes Zoster: a Long-Term Study and a New Hypothesis. *Proc R Soc Med*. 1965;58(January):9-20.

55. Brisson M, Gay NJ, Edmunds WJ, Andrews NJ. Exposure to varicella boosts immunity to herpes-zoster: implications for mass vaccination against chickenpox. *Vaccine*. 2002;20(19-20):2500-2507.

56. Edmunds WJ, Brisson M. The effect of vaccination on the epidemiology of varicella zoster virus. *J Infect*. 2002;44(4):211-219.

57. Horn J, Karch A, Damm O, et al. Current and future effects of varicella and herpes zoster vaccination in Germany – insights from a mathematical model in a country with universal varicella vaccination. *Hum Vaccin Immunother*. 2016;5515(February):

58. Solomon BA, Kaporis AG, Glass AT, Simon SI, Baldwin HE. Lasting immunity to varicella in doctors study (L.I.V.I.D. study). *J Am Acad Dermatol*. 1998;38(5 Pt 1):763-765.

59. Thomas SL, Wheeler JG, Hall AJ. Contacts with varicella or with children and protection against herpes zoster in adults: a case-control study. *Lancet*. 2002;360(9334):678-682.

60. Russell ML, Dover DC, Simmonds KA, Svenson LW. Shingles in Alberta: Before and after publicly funded varicella vaccination. *Vaccine*. 2014;32(47):6319-6324.

61. Brisson M, Edmunds WJ, Gay NJ, Law B, De Serres G. Modelling the impact of immunization on the epidemiology of varicella zoster virus. *Epidemiol Infect*. 2000;125(3):651-669.

62. Pinheiro P, Plaß D, Kr A. The Burden of Disease Approach for Measuring Population Health. In: Krämer A, Khan MH, Kraas F, eds. *Health in Megacities and Urban Areas*. Vol Contributions to Statistics. Heidelberg: Physica-Verlag

Heidel; 2011:21-38.

63. Gold MR, Stevenson D, Fryback DG. HALYS and QALYS and DALYS, Oh My: similarities and differences in summary measures of population Health. *Annu Rev Public Health*. 2002;23:115-134.

64. Murray CJ. Quantifying the burden of disease: the technical basis for disability-adjusted life years. *Bull World Health Organ*. 1994;72(3):429-445.

65. Segel JE, Economics HP. Cost-of-Illness Studies — A Primer. 2006;(January):1-39.

66. Stewart A, Honeycutt AA, Hardee A. An Assessment of the State of the Art for Measuring Burden of Illness An Assessment of the State of the Art for Measuring Burden of Illness Final Report. 2011;(0212050).

67. Kay D, Prüss A, Corvalán C. Methodology for assessment of Environmental burden of disease. 2000;(August):23-24.

68. Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol*. 2015;44(3):827-836.

69. Gauthier a, Breuer J, Carrington D, Martin M, Rémy V. Epidemiology and cost of herpes zoster and post-herpetic neuralgia in the United Kingdom. *Epidemiol Infect*. 2009;137(1):38-47.

70. Lionis CD, Vardavas CI, Symvoulakis EK, et al. Measuring the burden of herpes zoster and post herpetic neuralgia within primary care in rural Crete, Greece. *BMC Fam Pract*. 2011;12(1):136.

71. Di Legami V, Gianino MM, Atti MCD, et al. Epidemiology and costs of herpes zoster: Background data to estimate the impact of vaccination. *Vaccine*. 2007;25(43):7598-7604.

72. Ultsch B, Siedler A, Rieck T, Reinhold T, Krause G, Wichmann O. Herpes zoster in Germany: quantifying the burden of disease. *BMC Infect Dis*. 2011;11(1):173.

73. Ultsch B, Köster I, Reinhold T, et al. Epidemiology and cost of herpes zoster and postherpetic neuralgia in Germany. *Eur J Health Econ*. 2013;14(6):1015-1026.

74. Yan L, Lix L, Jiang D, Einarson K, Dube S. *Manitoba Population Projections 2013-2042*. Winnipeg; 2014.

75. Panatto D, Bragazzi NL, Rizzitelli E, et al. Evaluation of the economic burden of Herpes Zoster (HZ) infection: A systematic literature review. *Hum Vaccin Immunother*. 2015;11(1):239-238.

76. Klompas M, Kulldorff M, Vilk Y, Bialek SR, Harpaz R. Herpes Zoster and Postherpetic Neuralgia Surveillance Using Structured Electronic Data. *Mayo Clin Proc*. 2011;86(12):1146-1153.

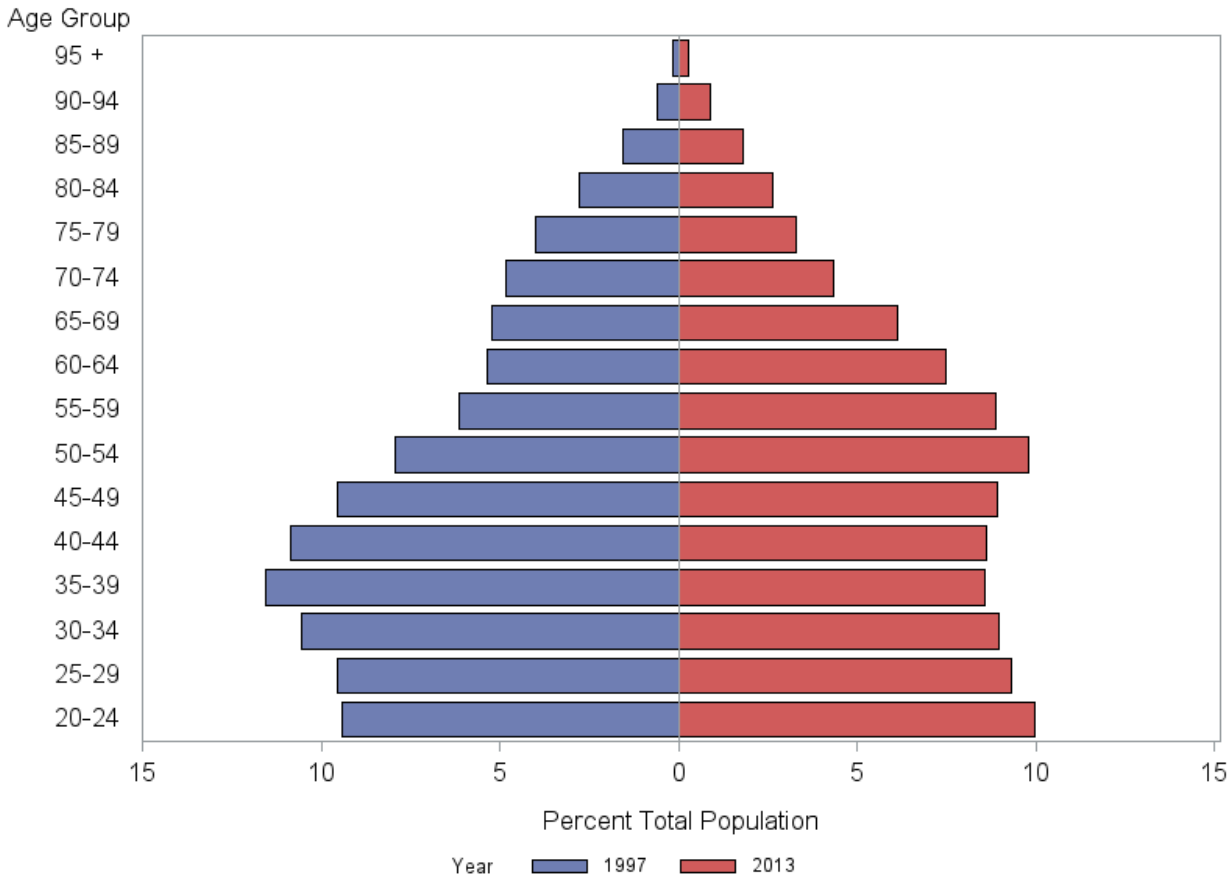
77. Bilcke J, Ogunjimi B, Marais C, et al. The health and economic burden of chickenpox and herpes zoster in Belgium. *Epidemiol Infect*. 2012;140(11):2096-2109.

78. Milan A. *Report on the Demographic Situation in Canada*.; 2010. http://www.statcan.gc.ca/pub/91-209-x/2011001/article/11511-eng.pdf. Accessed March 17, 2016.

79. Statistics Canada. *Annual Demographic Estimates: Canada, Provinces and Territories*. Ottawa, ON; 2015. http://www.statcan.gc.ca/pub/91-215-x/91-215-x2014000-eng.pdf. Accessed March 17, 2016.

APPENDIX A: AGE DISTRIBUTION TORNADO PLOT

Age Distribution of Manitoba: 1997 versus 2013



The age distribution of Manitoba was determined for the years 1997 and 2013 using the Manitoba Health registry to obtain population counts in 5 year age intervals for persons age 20 and above. The above tornado plot illustrates the changing demographics of Manitoba, with a shift towards an older population clearly seen.

APPENDIX B: RESEARCH APPROVALS AND ACKNOWLEDGEMENTS

Prior to beginning the research presented in this thesis, and to gaining access to the Population Health Research Data Repository approvals were needed from the Manitoba Centre for Health Policy (MCHP), the University of Manitoba Health Research Ethics Board (HREB), and from Manitoba Health, Seniors and Active Living's Health Information Privacy Committee (HIPC), and a pledge of confidentially in accordance with the Personal Health Information Act (PHIA).

Acknowledgements

Manitoba Centre for Health Policy

The authors acknowledge the Manitoba Centre for Health Policy for use of data contained in the Population Health Research Data Repository under project #2015-007 (HIPC#2014/2015-35). The results and conclusions are those of the authors and no official endorsement by the Manitoba Centre for Health Policy, Manitoba Health, or other data providers is intended or should be inferred. Data used in this study are from the Population Health Research Data Repository housed at the Manitoba Centre for Health Policy, University of Manitoba and were derived from data provided by Manitoba Health, Seniors, and Active Living.

SAS

The data analysis for this thesis was generated using SAS/STAT software, Version 9.4 of the SAS system for Windows. Copyright © 2002-2012 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

Manitoba Centre for Health Policy Approval Letter

UNIVERSITY OF MANITOBA | Faculty of Health Sciences

College of Medicine
Manitoba Centre for Health Policy
Community Health Sciences
408-727- McDermot Ave Winnipeg MB
Canada R3E 3P5
Phone (204) 789-3819
Fax (204) 789-3910
Email info@cpe.umanitoba.ca

February 27, 2015

Kevin Friesen
Apotex Centre
750 McDermot Ave.
Winnipeg, Manitoba R3E 0T5

Dear: Kevin

Re: Assessment of health and economic burden of herpes zoster and post-herpetic neuralgia in Manitoba: A population-based study
MCHP project number: 2015-007

Enclosed is a copy for your records of the fully executed Researcher Agreement, representing approval to proceed with the above research project at the Manitoba Centre for Health Policy (MCHP) using Manitoba Health data. It is important that the requirements outlined in this agreement be shared with all members of your project team, specifically Section 5 obligations respecting use and disclosure and Section 6 regarding reports, monitoring and enforcement. It is also important that all correspondence with MCHP relating to this project reference the MCHP project number.

We look forward to facilitating access to the Population Health Research Data Repository for your project. To proceed, please contact Charles Burchill (Manager, Program and Analysis System) at charles_burchill@cpe.umanitoba.ca. Sophie Buternowsky, Senior grants Accountant, at MCHP will be contacting you regarding invoicing for your project.

If any changes are made to the original approved study protocol, they must be submitted to the Health Research Ethics Board for approval and the data providers. A copy of the submissions and approvals must also be sent to MCHP.

We would be glad to assist you in meeting ongoing project requirements for maintaining access to the data, as outlined at our website:
http://umanitoba.ca/faculties/medicine/units/community_health_sciences/departmental_units/mchp/resources/access.html

Should you have any questions, please do not hesitate to contact me at (204) 975-7770.

Sincerely,

Jo-Anne Baribeau
Repository Access Coordinator

cc Sophie Buternowsky, Senior Grants Accountant
Shawn Bugden, MSc Thesis Supervisor

University of Manitoba Health Ethics Review Board Approval

P126-770 Bannatyne Avenue
Winnipeg, Manitoba
Canada R3E 0W3
Telephone 204-789-3255
Fax 204-789-3414

UNIVERSITY OF MANITOBA | BANNATYNE CAMPUS
Research Ethics Board

HEALTH RESEARCH ETHICS BOARD (HREB)

CERTIFICATE OF FINAL APPROVAL FOR NEW STUDIES

Delegated Review

PRINCIPAL INVESTIGATOR:	INSTITUTION/DEPARTMENT:	ETHICS #:
Mr. Kevin Friesen	U of M/College of Pharmacy	H2014:411
APPROVAL DATE: December 19, 2014	**EXPIRY DATE:** December 19, 2015	
STUDENT PRINCIPAL INVESTIGATOR SUPERVISOR (If applicable): Dr. S. Bugden		

PROTOCOL NUMBER:	PROJECT OR PROTOCOL TITLE;
N/A	Assessment of Health and Economic burden of Herpes Zoster and Post-Herpetic Neuralgia in a Manitoba: A Population-Based Study
SPONSORING AGENCIES AND/OR COORDINATING GROUPS: Merck	

Submission Date of Investigator Documents:	HREB Receipt Date of Documents:
December 10, 2014	December 10, 2014

THE FOLLOWING ARE APPROVED FOR USE:

Document Name	Version(if applicable)	Date
Protocol: Proposal		December 10, 2014
Consent and Assent Form(s):		
Other: Data Extraction Sheet		submitted November 24, 2014

CERTIFICATION

The above named research study/project has been reviewed in a ***delegated manner*** by the University of Manitoba (UM) Health Research Board (HREB) and was found to be acceptable on ethical grounds for research involving human participants. The study/project and documents listed above was granted final approval by the Chair or Acting Chair, UM HREB.

HREB ATTESTATION

The University of Manitoba (UM) Research Board (HREB) is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement 2, and the applicable laws and regulations of Manitoba. In respect to clinical trials, the HREB complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations of Canada and carries out its functions in a manner consistent with Good Clinical Practices.

QUALITY ASSURANCE

The University of Manitoba Research Quality Management Office may request to review research documentation from this research study/project to demonstrate compliance with this approved protocol and the University of Manitoba Policy on the Ethics of Research Involving Humans.

CONDITIONS OF APPROVAL:

1. The study is acceptable on scientific and ethical grounds for the ethics of human use only. ***For logistics of performing the study, approval must be sought from the relevant institution(s).***
2. This research study/project is to be conducted by the local principal investigator listed on this certificate of approval.
3. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to the research study/project, and for ensuring that the authorized research is carried out according to governing law.
4. **This approval is valid until the expiry date noted on this certificate of approval. A Bannatyne Campus Annual Study Status Report** must be submitted to the HREB within 15-30 days of this expiry date.
5. Any changes of the protocol (including recruitment procedures, etc.), informed consent form(s) or documents must be reported to the HREB for consideration in advance of implementation of such changes on the **Bannatyne Campus Research Amendment Form.**
6. Adverse events and unanticipated problems must be reported to the HREB as per Bannatyne Campus Research Boards Standard Operating procedures.
7. The UM HREB must be notified regarding discontinuation or study/project closure on the **Bannatyne Campus Final Study Status Report.**

Sincerely,

John Arnett, PhD. C. Psych.
Chair, Health Research Ethics Board
Bannatyne Campus

Please quote the above Human Ethics Number on all correspondence.
Inquiries should be directed to the REB Secretary **Telephone:** (204) 789-3255/ **Fax:** (204) 789-3414

University of Manitoba Health Ethics Review Board Annual Renewal

UNIVERSITY OF MANITOBA | Research Ethics - Bannatyne
Office of the Vice-President (Research and International)

P126-770 Bannatyne Avenue
Winnipeg, Manitoba
Canada, R3E 0W3
Telephone : 204-789-3255
Fax: 204-789-3414

HEALTH RESEARCH ETHICS BOARD (HREB)

CERTIFICATE OF ANNUAL APPROVAL

PRINCIPAL INVESTIGATOR:	INSTITUTION/DEPARTMENT:	ETHICS #:
Mr. Kevin Friesen	U of M/College of Pharmacy	HS17918 (H2014:411)
HREB MEETING DATE (If applicable):	**APPROVAL DATE:** November 25, 2015	**EXPIRY DATE:** **December 19, 2016**
STUDENT PRINCIPAL INVESTIGATOR SUPERVISOR (If applicable): Dr. S. Bugden		

PROTOCOL NUMBER:	PROJECT OR PROTOCOL TITLE:
NA	Assessment of Health and Economic Burden of Herpes Zoster and Post-Herpetic Neuralgia in a Manitoba: A Population-Based Study
SPONSORING AGENCIES AND/OR COORDINATING GROUPS: Merck Canada	

Submission Date of Investigator Documents:	HREB Receipt Date of Documents:
November 6, 2015	November 9, 2015

REVIEW CATEGORY OF ANNUAL REVIEW: **Full Board Review** ☐ **Delegated Review** ☒

THE FOLLOWING AMENDMENT(S) and DOCUMENTS ARE APPROVED FOR USE:

Document Name(if applicable)	Version(if applicable)	Date

Annual approval

*Annual approval implies that the most recent **HREB approved** versions of the protocol, Investigator Brochures, advertisements, letters of initial contact or questionnaires, and recruitment methods, etc. are approved.*

Consent and Assent Form(s):

CERTIFICATION

The University of Manitoba (UM) Health Research Board (HREB) has reviewed the annual study status report for the research study/project named on this ***Certificate of Annual Approval*** as per the category of review listed above and was found to be acceptable on ethical grounds for research involving human participants. Annual approval was granted by the Chair or Acting Chair, UM HREB, per the response to the conditions of approval outlined during the initial review (full board or delegated) of the annual study status report.

HREB ATTESTATION

The University of Manitoba (UM) Health Research Board (HREB) is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement 2, and the applicable laws and regulations of Manitoba. In respect to clinical trials, the HREB complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations of Canada and carries out its functions in a manner consistent with Good Clinical Practices.

QUALITY ASSURANCE
The University of Manitoba Research Quality Management Office may request to review research documentation from this research study/project to demonstrate compliance with this approved protocol and the University of Manitoba Policy on the Ethics of Research Involving Humans.

CONDITIONS OF APPROVAL:

1. The study is acceptable on scientific and ethical grounds for the ethics of human use only. ***For logistics of performing the study, approval must be sought from the relevant institution(s).***
2. This research study/project is to be conducted by the local principal investigator listed on this certificate of approval.
3. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to the research study/project, and for ensuring that the authorized research is carried out according to governing law.
4. **This approval is valid until the expiry date noted on this certificate of annual approval. A Bannatyne Campus Annual Study Status Report** must be submitted to the REB within 15-30 days of this expiry date.
5. Any changes of the protocol (including recruitment procedures, etc.), informed consent form(s) or documents must be reported to the HREB for consideration in advance of implementation of such changes on the **Bannatyne Campus Research Amendment Form.**
6. Adverse events and unanticipated problems must be reported to the REB as per Bannatyne Campus Research Boards Standard Operating procedures.
7. The UM HREB must be notified regarding discontinuation or study/project closure on the **Bannatyne Campus Final Study Status Report.**

Sincerely,

John Arnett, PhD., C. Pysch.
Chair, Health Research Ethics Board
Bannatyne Campus

Please quote the above Human Ethics Number on all correspondence.
Inquiries should be directed to the REB Secretary **Telephone:** (204) 789-3255/ **Fax:** (204) 789-3414

Manitoba Health Information Privacy Committee Approval

Manitoba
Health, Healthy Living and Seniors
Health Information Management
4040-300 Carlton Street, Winnipeg, Manitoba, Canada R3B 3M9
T 204-786-7139 F 204-944-1911
www.manitoba.ca

January 7, 2015

Kevin Friesen
Faculty of Pharmacy
University of Manitoba
750 McDermott Avenue
Winnipeg, MB R3E 0T5

HIPC No. 2014/2015 – 35
File number to be quoted on correspondence

Dear Kevin,

RE: Assessment of Health and Economic Burden of Herpes Zoster and Post-Herpetic Neuralgia in Manitoba: A Population-Based Study

Thank you for submitting the requested documentation and providing clarification for the above named project. The Health Information Privacy Committee has now *approved* your request for data for this project.

Any significant changes to the proposed study design should be reported to the Chair/HIPC for consideration in advance of their implementation. Also, please be reminded that any manuscripts and presentation materials resulting from this study must be submitted to Manitoba Health, Healthy Living and Seniors for review. Specifically, *manuscripts must be submitted at least 30 calendar days prior to publication and presentation materials must be submitted at least 10 calendar days prior to presentation.*

Please note that a Researcher Agreement will need to be completed before work on this project can commence. This will be initiated by **MCHP**. If you have any questions or concerns, please do not hesitate to contact Marc Silva, Acting Committee Coordinator at (204)786-7229.

Yours truly,

Dr. Biehl, MD, FRCP
Chair, Health Information Privacy Committee

c.c. D. Malazdrewicz

Manitoba
spirited energy