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MAJOR ARTICLE

Impact of a Publicly Funded Herpes Zoster Immunization Program on the Burden of Disease in Ontario, Canada: A Population-based Study

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Background. In September 2009, a live attenuated herpes zoster vaccine (ZVL) became available in Canada. Beginning in September 2016, ZVL was made available to all Ontario residents aged 65–70 through a publicly funded immunization program. We assessed the impact of ZVL availability and its subsequent public funding on herpes zoster burden in this population.

Methods. A population-based study of Ontario residents aged 65–70 between January 2005 and September 2018. We used interventional autoregressive integrated moving average models to examine the impact of ZVL market availability and the publicly funded ZVL program on monthly incidence rate of medically attended herpes zoster, defined as an outpatient visit for herpes zoster with a prescription for a herpes zoster antiviral dispensed ≤5 days before or after the visit, or a herpes zoster–related emergency department (ED) visit or hospitalization. In secondary analyses, we examined impacts on any herpes zoster–related ED visits and hospitalizations.

Results. We found no association between ZVL market availability and monthly incidence of herpes zoster ($P = .32$) or monthly rates of ED visits and hospitalizations ($P = .88$). Conversely, the introduction of publicly funded ZVL reduced the monthly rate of medically attended herpes zoster by 19.1% (from 4.8 to 3.8 per 10 000 population; $P < .01$) and herpes zoster–related ED visits and hospitalizations by 38.2% (from 1.7 to 1.0 per 10 000 population; $P < .05$).

Conclusions. The introduction of a publicly funded immunization program for herpes zoster was associated with reduced disease burden and related acute healthcare service use.

Keywords. herpes zoster/prevention and control; vaccine; effectiveness; delivery of healthcare.

Herpes zoster, a common illness caused by the reactivation of latent varicella-zoster virus (VZV) infection, affects almost 1 in 3 adults during their lifetime. Risk factors for herpes zoster include increasing age and immune compromise [1–3]. The illness is associated with significant pain and complications, the most debilitating of which include postherpetic neuralgia, monocular blindness, and monaural deafness [1, 2]. The management of herpes zoster and its sequelae is associated with considerable cost to the healthcare system, estimated at over $1 billion annually in the United States alone [4]. Because of the individual- and system-level impacts of herpes zoster, interventions that can alleviate the clinical and economic burden of herpes zoster are needed.

Vaccination against herpes zoster is an increasingly important strategy for preventing disease, with a live attenuated unadjuvanted vaccine prepared from the Oka/Merck strain of varicella zoster virus (ZVL) and a recombinant adjuvanted subunit vaccine (HZ/su) both available for use [5]. Based on findings from the Shingles Prevention Study, a clinical trial that demonstrated a 51% reduction in the incidence of herpes zoster among adults aged 60 years and older [6], in 2010 Canada's National Advisory Committee on Immunization (NACI) first recommended ZVL for the prevention of herpes zoster and its complications in persons aged 60 years and older without contraindications [7]. Subsequently, in September 2016, Ontario became the only Canadian province to provide ZVL to all residents between the ages of 65 and 70 years free of charge through a publicly funded immunization program. Although several studies have demonstrated that ZVL reduces the incidence of herpes zoster in clinical practice by 35% to 62% [8–12], the impact of a publicly funded herpes zoster immunization program on an entire population eligible for vaccination

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remains unknown. Consequently, we studied the impact of Ontario's publicly funded herpes zoster immunization program on the incidence of herpes zoster and associated health service use among the entire population of eligible adults aged 65 to 70 years. Because ZVL was approved by Health Canada in August 2008 and made available for out-of-pocket purchase in September 2009, we also studied the impact of the period of private availability prior to the implementation of the publicly funded program on herpes zoster burden.

METHODS

Setting

We conducted a population-based time-series analysis of all residents in Ontario aged 65 to 70 years between 1 January 2005 and 30 September 2018. These individuals had universal access to physician services, hospital care, and prescription drug coverage.

Data Sources

We used the Ontario Health Insurance Plan (OHIP) database to identify outpatient physician visits for herpes zoster. We identified prescriptions for antivirals used to treat herpes zoster using the Ontario Drug Benefit (ODB) database, which contains comprehensive records of prescription drugs dispensed to Ontario residents aged 65 years and older. We used the Canadian Institute for Health Information National Ambulatory Care Reporting System (CIHI-NACRS) and Discharge Abstract Database (CIHI-DAD) to identify emergency department visits and hospital admissions related to herpes zoster, respectively. These databases contain detailed clinical information regarding all emergency department visits and hospital admissions in Ontario. We obtained basic demographic data from the Registered Persons Database, a registry of all Ontario residents eligible for health insurance. All databases were linked using unique, encoded identifiers and analyzed at ICES in Toronto, Ontario (www.ices.on.ca). Use of these databases is authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board.

Study Population and Outcomes

For each month in the study period, we defined our study population of individuals eligible for publicly funded ZVL as all Ontario residents aged 65 to 70 years who were alive on the first day of the month. Our primary outcome was the monthly rate of incident medically attended herpes zoster in our study population. We defined an incident case as an outpatient physician visit for herpes zoster (International Classification of Diseases, Ninth Revision [ICD-9], code 053) with a prescription for a herpes zoster antiviral (ie, acyclovir, famciclovir, valacyclovir) dispensed in the 5 days preceding or following the date of the physician encounter or an emergency department visit or hospital admission where the most responsible diagnosis was herpes zoster (International Classification of Diseases, 10th Revision [ICD-10], code B02). To ensure that we were identifying incident cases, we excluded individuals meeting the case definition prior to the month of interest, using a look-back window up to 1 January 2000. To prevent misclassification in our main outcome due to outpatient visits for ZVL vaccination, we excluded all physician encounters that included OHIP fee codes associated with immunization (G538, G539, G848). We also excluded all health service encounters with concurrent diagnosis codes for varicella (ICD-9 and ICD-10 codes 052 and B01, respectively). To measure the impact of publicly funded herpes zoster vaccination on severe cases of herpes zoster, we studied monthly rates of herpes zoster–related hospital admissions and emergency department visits, using both incident and prevalent events, as a secondary outcome.

Statistical Analysis

We used interventional Autoregressive Integrated Moving Average (ARIMA) models to examine the impact of private ZVL availability (September 2009 to August 2016) in Canada and the introduction of the publicly funded ZVL immunization program (September 2016 to September 2018) on rates of herpes zoster incidence [13]. We replicated this analysis for our secondary outcome of herpes zoster–related emergency department visits and hospital admissions. These models are frequently used for ecologic analyses of the introduction of new policies or programs [14, 15]. We used a ramp intervention function to test for a gradual slope change in our outcomes at the time when the ZVL became available in Canada in September 2009 and a step intervention function to test for immediate changes when Ontario's publicly funded immunization program was introduced in September 2016. Differencing was used to achieve a stationary time series and stationarity was confirmed using the augmented Dickey-Fuller test [16]. Model parameters were selected using the residual autocorrelation function (ACF), partial autocorrelation function (PACF), and inverse autocorrelation function (IACF) correlograms. Model fit was assessed using the ACF, PACF, and IACF plots; white noise probability plots and Ljung-Box chi-square test for white noise; r^2 measure of fit; and resulting forecasts [13, 17].

To explore heterogeneity in the impact of the publicly funded immunization program within the eligible population, we stratified our analyses by sex, neighborhood income quintile, and urban versus rural residence, defined on the first day of the month of interest. Neighborhood income was categorized as low (income quintiles 1 and 2), middle (income quintile 3), and high (income quintiles 4 and 5). We conducted 2 sensitivity analyses to test the robustness of our outcome definition. First, because our definition of incident herpes zoster excluded individuals who were not treated with antivirals, we also conducted a sensitivity analysis using a less restrictive definition

to capture incident herpes zoster, defined as outpatient visits for herpes zoster irrespective of receipt of antiviral therapy, an emergency department visit or hospital admission for herpes zoster, or any prescription claim for a herpes zoster antiviral. Second, we replicated our analysis using a constant 12-month look-back period for defining incident herpes zoster. All analyses were completed at ICES using SAS Enterprise Guide, version 6.1 (SAS Institute, Inc).

RESULTS

During our 14-year study period, we observed 50 740 incident cases of medically attended herpes zoster among the population of Ontario residents aged 65 to 70 years, of which 35 596 were physician visits, 14 849 were emergency department visits, and 295 were hospital admissions.

In our primary analysis, the monthly incidence of medically attended herpes zoster among individuals aged 65 to 70 years increased by 77.0% between January 2005 and August 2016, from 2.7 to 4.8 cases per 10 000 eligible population (Figure 1). We found no association between the private market availability of ZVL in September 2009 and the monthly incidence of medically attended herpes zoster in the eligible population ($P = .32$) (Table 1, Figure 1). In contrast, the monthly incidence of medically attended herpes zoster in this population decreased by 19.1% (from 4.8 to 3.8 cases per 10 000 eligible population between August 2016 and September 2018) ($P < .01$) following the introduction of the publicly funded immunization program in September 2016 (Table 1, Figure 1). We found similar results in our sensitivity analyses where the definition of herpes zoster incidence was broadened and the look-back window was changed to a consistent 12-month period (Table 1, Supplementary Figure 1). Our findings were consistent in analyses stratified by sex, neighborhood income quintile, and urban or rural residence (Table 1, Supplementary Figures 2–4). However, following an immediate decline, the monthly incidence of medically attended herpes zoster in rural settings increased to 5.5 cases per 10 000 eligible population in September 2018, which was similar to the rate observed prior to the implementation of the program (5.3 cases per 10 000 eligible population in August 2016).

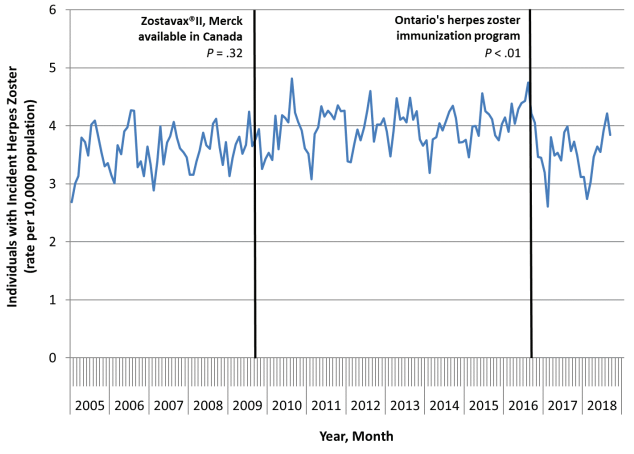

Figure 1. Monthly incidence of medically attended herpes zoster in Ontario among residents aged 65 to 70 years between January 2005 and September 2018.

In our secondary analysis, we studied 17 962 emergency department visits and 453 hospitalizations for herpes zoster. Overall, the monthly rate of these outcomes increased by 114.7% from January 2005 to August 2016 (0.8 to 1.7 emergency department visits/hospitalizations per 10 000 eligible population), with no impact of privately available ZVL ($P = .88$) (Table 1, Figure 2). Similar to our primary analysis, the introduction of publicly funded ZVL was associated with a 38.2% reduction in the monthly rate of herpes zoster–related emergency department visits and hospital admissions (from 1.7 to 1.0 per 10 000 eligible population between August 2016 and September 2018) ($P < .01$) (Table 1, Figure 2).

DISCUSSION

In our population-based study, we found that the implementation of a publicly funded herpes zoster vaccination program reduced the incidence of medically attended herpes zoster among eligible populations. This finding was consistent in analyses stratified by sex, urban and rural residence, and neighborhood income quintile. However, following an initial decline after the implementation of the publicly funded program, rates of herpes zoster increased in rural settings near the end of the study period. This finding may reflect the uneven distribution of primary care physicians across Ontario, with most family doctors concentrated within densely populated urban areas [18]. We also found decreased rates of herpes zoster–related hospital admissions and emergency department visits that were temporally associated with the publicly funded vaccination program, demonstrating the effectiveness of ZVL in reducing the incidence of the most severe forms of disease. Importantly, private availability of the vaccine did not impact rates of herpes zoster or associated health service use in eligible individuals, which continued to increase over time prior to the introduction of the publicly funded program. Increasing rates of herpes zoster have been observed internationally and have occurred independently of changes in the prevalence of immunosuppression, comorbid illness, or the introduction of varicella vaccination [19–26]. The continued increase in the incidence of herpes zoster with no known cause and the lack of impact of private vaccine availability highlight the importance of a policy intervention aimed at publicly funding ZVL in reducing the burden of herpes zoster in a large population.

Our findings complement and build upon those of earlier studies [8–12]. Most notably, ours is the first study to explore the impact of publicly funded ZVL on herpes zoster burden in an entire population of individuals eligible for the vaccine. Prior studies examining the effectiveness of ZVL have been

Table 1. Summary of ARIMA Models for Association Between Vaccine Availability and Ontario's Publicly Funded Herpes Zoster Immunization Program and Incidence Rate of Herpes Zoster and Herpes Zoster–Related Emergency Department Visits and Hospitalizations

Stratification	Rate per 10 000 Population Aged 65–70 Years			Rate per 10 000 Population Aged 65–70 Years			
	January 2005	August 2009	Impact of Vaccine Availability in Canada (September 2009), *P* Value	August 2016	September 2018	Change in Herpes Zoster Rates Following Introduction of Ontario's Publicly Funded Immunization Program (September 2016), %	Impact of Introduction of Ontario's Publicly Funded Immunization Program (September 2016), *P* Value
Incidence of medically attended herpes zoster[a]							
Overall	2.7	3.7	.32	4.8	3.8	−19.1	<.0001
Sex							
Men	2.5	3.1	.72	3.5	3.0	−15.9	.0004
Women	3.1	4.4	.36	6.1	4.8	−21.0	.0035
Rurality of residence							
Rural	2.8	4.3	.35	5.3	5.5	+4.0[b]	<.0001
Urban	2.8	3.6	.36	4.7	3.6	−22.9	<.0001
Income[c]							
Low neighborhood income	2.7	3.6	.51	5.2	4.0	−23.6	.001
Middle neighborhood income	2.0	3.6	.66	4.7	4.1	−12.4	.0230
High neighborhood income	3.2	4.1	.27	4.9	4.0	−17.8	.0003
Secondary analysis: herpes zoster–related emergency department visits and hospitalizations[d]							
Overall	0.8	1.5	.88	1.7	1.0	−38.2	.0012
Sensitivity analysis: broadened definition of incidence of medically attended herpes zoster[e]							
Overall	6.6	7.1	.27	9.0	5.0	−43.9	.0176
Sensitivity analysis: incident medical attended herpes zoster with a 1-year lookback							
Overall	2.7	3.7	.36	4.8	3.9	−17.9	<.0001

Abbreviation: ARIMA, Autoregressive Integrated Moving Average.

[a]Defined as an outpatient visit for herpes zoster with a prescription for a herpes zoster antiviral within 5 days of the visit or a herpes zoster–related emergency department visit or hospitalization.

[b]Despite the initial significant decline in rates of medically attended herpes zoster after the implementation of the publicly funded herpes zoster program, rates increased in rural settings towards the end of the study period.

[c]Defined using neighborhood income quintile and categorized as low (income quintiles 1 and 2), middle (income quintile 3). and high (income quintiles 4 and 5).

[d]Defined as all emergency department visits or hospital admissions where the most responsible diagnosis was herpes zoster (International Classification of Diseases, 10th Revision, code B02).

[e]Defined as outpatient visits for herpes zoster irrespective of receipt of antiviral therapy, an emergency department visit or hospital admission for herpes zoster, or any prescription claim for a herpes zoster antiviral.

conducted among cohorts that did not encompass the entire populations from which they were drawn. Moreover, in contrast to an earlier study examining the effectiveness of a ZVL vaccination program among eligible individuals in England [11], we were able to study separately the effects of ZVL on hospital visits related to herpes zoster across a large geographic area, extending the evidence of a beneficial effect of vaccination on more serious forms of illness. Although our estimate of ZVL effectiveness was lower than that of the study examining the population-level impact of a ZVL vaccination program in England (ie, 19% vs 35%) [11], this may reflect differences in vaccine coverage and uptake between the 2 populations. Specifically, results of a national survey found that 20.4% of Canadians aged 50 years and older had received the herpes zoster vaccine in 2016 [27], compared with an uptake of approximately 60% in the English study.

Our study has several implications for public health. Most notably, our finding that a publicly funded immunization program can reduce the burden of herpes zoster, including severe forms of the disease requiring a hospital visit, suggests that upstream interventions that remove financial barriers to vaccine access can successfully reduce the burden of herpes zoster to at-risk populations and the healthcare system. This was especially important in our population, considering that the cost of ZVL ($210 CAD) could be prohibitive to individuals without private drug insurance. However, several changes to the current policy could potentially increase the impact of universal zoster vaccination. Specifically, expanding public funding to include the HZ/su vaccine would address the limitations of ZVL, including waning efficacy with age and time and a contraindication for use in immunosuppressed individuals at greatest risk of varicella zoster reactivation and severe herpes zoster–related

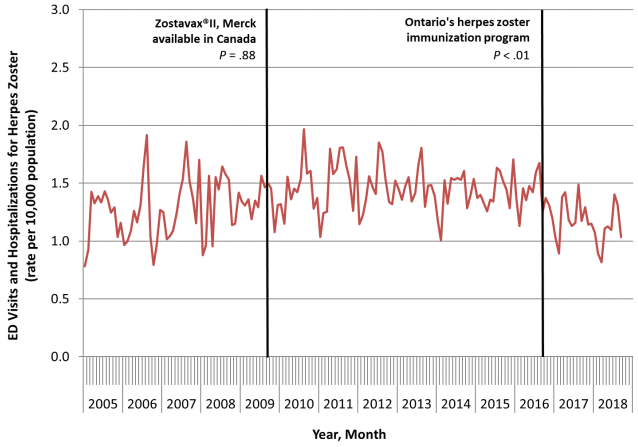

Figure 2. Monthly rate of herpes zoster–related emergency department visits and hospitalizations among residents aged 65 to 70 years between January 2005 and September 2018. Abbreviation: ED, emergency department.

complications [5, 28, 29]. This assertion is supported by a comparison of the cost-effectiveness of HZ/su and ZVL from the perspective of the Canadian health care system, in that HZ/su was more cost-effective and associated with a lower number needed to vaccinate (number of people who should be vaccinated to prevent a single case of herpes zoster, postherpetic neuralgia, ophthalmic herpes zoster, and hospitalization) than ZVL [30]. Although HZ/su is most cost-effective among adults aged 65 to 79 years, findings were consistent across all age groups, suggesting that broadening eligibility of a publicly funded HZ/su vaccination program to encompass all individuals over the age of 50 could optimize the public health impact of such an approach. These changes would align publicly funded programs with recommendations from Canada's NACI and the US Advisory Committee on Immunization Practices [31, 32].

Some limitations of our work merit emphasis. First, our definition of incident medically attended herpes zoster excludes individuals who were not dispensed an antiviral within 5 days of an outpatient encounter for herpes zoster. Consequently, our study underestimates the incidence of herpes zoster. However, we chose this approach to increase the specificity of defining a herpes zoster diagnosis from our data sources and to prevent misclassification of visits for herpes zoster vaccination as encounters for the diagnosis and treatment of active disease. Moreover, we found consistent results in a sensitivity analysis that broadened our case-finding definition to include any encounter with a diagnosis of herpes zoster or receipt of a herpes zoster antiviral. Second, our administrative databases do not permit us to determine immunization coverage and vaccine uptake. Although a national survey found that 20.4% of respondents aged 50 years and older received the herpes zoster vaccine in 2016, this figure may not reflect use among the publicly insured population in our study. However, there were no other interventions implemented during this period that could account for our findings. In addition, the burden of disease continued to increase despite the private availability of the vaccine in 2008, reinforcing the role of the publicly funded program in decreasing herpes zoster incidence. As a result, the observed relationship between the implementation of the publicly funded program and the decline in herpes zoster incidence is temporally compelling and clinically plausible. Third, our follow-up was limited to only the first 2 years following the implementation of the publicly funded program. It is unknown if the impact of this policy would change with longer follow-up, particularly because the efficacy of ZVL has been shown to wane with time [28, 29]. Fourth, our findings are based on a population of older adults with publicly funded access to physician services, hospital care, and prescription drug coverage. It is possible that our findings may not be generalizable to other contexts. Finally, we restricted our analyses to evaluations of the approval and public funding of ZVL and did not examine the impact of the subsequent availability of HZ/su in January 2018, which is not publicly funded at this time and was in limited supply during the period of our study. However, we found no change in herpes zoster incidence following the approval of ZVL, and our primary interest was an investigation of the temporal association between the publicly funded vaccine program and disease incidence.

In summary, our study suggests that the implementation of a publicly funded herpes zoster immunization program was associated with a reduction in disease incidence and serious illness requiring hospital visits among the eligible population of people aged 65 to 70 years. Expanding coverage of the policy to encompass all adults aged 50 years and older and the inclusion of the new HZ/su vaccine should be considered in an effort to optimize the impact of herpes zoster vaccination.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. Study concept and design: D. Martins, T. A. (guarantor). Analysis and interpretation of data: D. Martins, D. McCormack, T. G., M. T., S. A. B., J. C. K., M. M. M., T. A.. Acquisition of data: D. McCormack. Drafting of the manuscript: D. Martins, T. A.. Critical revision of the manuscript: D. McCormack, M. T., T. G., S. A. B., J. C. K., M. M. M.

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