Estimating the Number Needed to Vaccinate to Prevent Herpes Zoster-related Disease, Health Care Resource Use and Mortality

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ABSTRACT

Background: A clinical trial has shown that a live-attenuated varicella-zoster virus vaccine is effective against herpes zoster (HZ) and post-herpetic neuralgia (PHN). The aim of the study was to estimate the number needed to vaccinate (NNV) to prevent HZ-related outcomes.

Methods: A cohort model of HZ associated disease, health care resource use and mortality was developed. Canadian population-based data were used to estimate age-specific incidence, hospitalization, quality-adjusted life-year (QALY) lost and mortality. NNV was calculated as the number of individuals needed to be vaccinated to prevent a specific HZ-related outcome during their lifetime. Different ages at vaccination were examined and probabilistic sensitivity analysis was performed.

Results: For 65 year olds, the NNV (HZ vaccine efficacy=63%, PHN vaccine efficacy=67%, no waning) to prevent a case of HZ, a case of PHN, a HZ death, a life-year lost and a QALY lost is estimated to be 11 (90%CrI: 10-13), 43 (90%CrI: 33-53), 23,319 (90%CrI: 15,312-33,139), 3,762 (90%CrI: 1,650-4,629) and 165 (90%CrI: 105-197), respectively. Results were most sensitive to the duration of vaccine protection and the age at vaccination.

Discussion: The predicted NNV to prevent HZ and PHN are low even though vaccine efficacy is between 50-70%, which reflects the high incidence of these diseases among older adults. Results clearly show that the main benefit of HZ vaccination is prevention of morbidity caused by pain (as measured by QALYs lost) rather than mortality.

Key words: Herpes zoster (HZ); post-herpetic neuralgia (PHN); vaccines; mathematical model; number needed to vaccinate

La traduction du résumé se trouve à la fin de l'article.

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Acknowledgements and financial disclosure: Dr. Brisson was an employee of Merck Frosst Canada Ltd. during the preliminary analysis. He is now associate professor at Laval University. He has consulted for Merck Frosst and has received reimbursement for travel expenses from GlaxoSmithKline. The study was funded by Merck Frosst. The contract stipulates that Dr. Brisson has absolute discretion over the contents of the publication.

Herpes zoster (shingles) is characterized by a localized and painful vesicular rash.[1,2] Its most common complication is postherpetic neuralgia (PHN), an extremely painful condition that occurs after the resolution of the herpes zoster rash. PHN lasts, on average, around 1.3 years, and the available treatments are often ineffective.[1-5] A large randomized, double-blind, placebo-controlled trial (Shingles Prevention Study) has shown zoster vaccination to reduce the incidence of PHN by 67%, and the incidence of herpes zoster by 51% in subjects ≥60 years old.[6] The number needed to vaccinate (NNV), an analogous measure to the number needed to treat (NNT),[7] can be very helpful to illustrate the potential benefit of herpes zoster vaccination as it combines both the effect of vaccine efficacy and the age-specific background incidence of disease. Although a previous study, by Skootsky,[8] has estimated the NNV to prevent a case of herpes zoster and a case of PHN, NNV for other herpes zoster health outcomes such as mortality and hospitalization have yet to be assessed. Furthermore, by estimating NNV directly from the Shingles Prevention Study,[6] Skootksy[8] did not incorporate uncertainties around the potential medium- to long-term decline in vaccine protection (maximum follow-up time in the clinical trial was 5 years (mean = 3.13 years)).[6]

In this study, we use a cohort model to estimate the NNV to prevent various herpes zoster- and PHN-related health outcomes and to quantify uncertainty around predictions.

METHODS

Model structure

We previously developed and reported a cohort model that incorporates Canadian-specific epidemiological data and the vaccine efficacy results of the Shingles Prevention Study (the full methods are described in ref. 9). The model follows a cohort of individuals through different herpes zoster states (no zoster, zoster and PHN). The model compares the age-specific incidence, health care resource use, mortality, life-years lost and quality-adjusted life-years lost (QALYs) to herpes zoster and PHN in a vaccinated cohort versus an unvaccinated one.

Model parameters

Parameter estimates and sources are presented in Table I. Herpes zoster incidence was taken from Manitoba physician billing claims.[10] We assumed that all cases were captured by the billing database. Hospitalization data were estimated from the Canadian Institute for Health Information Hospital Morbidity Database (2000-2003),[11] which provides national discharge statistics from health care facilities. In our base case, we considered a hospitalization to be attributable to zoster only if the discharge diagnosis for herpes zoster was in the first position. The PHN age-specific rates were taken directly from the Shingles Prevention Study.[6] Zoster mortality rates were taken from Statistics Canada.[12] The QALY-lost due to herpes zoster and PHN were derived from a multi-center 6-month prospective study which recruited patients ≥50 years of age presenting at their physician's office with herpes zoster rash (N=307) and PHN (N=134) (see refs. 9 and 13 for more details).

Model simulations

NNV is calculated as the number of adults that are needed to be vaccinated to prevent a herpes zoster health outcome during their lifetime.[14,15] NNV is calculated as follows:

$$NNV = N \div P \qquad (1)$$

where, N is the size of the vaccinated cohort, and P is the predicted number of herpes zoster-related events prevented in the vaccinated cohort over its lifetime. In the case of the NNV to gain a life-year or a QALY, we divided the size of the vaccinated cohort by the total number of life-years gained or QALYs gained in the cohort by preventing herpes zoster.

Vaccine characteristics

Vaccination parameters are presented in Table I. Vaccine efficacy against herpes zoster and PHN are modeled separately. Vaccine efficacy is modeled using two parameters: 1) the proportion of individuals protected following immunization (*take*), and 2) the rate of loss of protection (*waning rate*). Herpes zoster vaccine efficacy parameter values were estimated by fitting the age-specific annual incidence of herpes zoster predicted by the model with that observed in the vaccinated arm of the Shingles Prevention Study.[6,9] *Take* for vaccine efficacy against PHN was assumed to be equal to the vaccine efficacy reported in the Shingles Prevention Study and the duration of protection was assumed to be the same as for herpes zoster.

TABLE I

Model Parameter Values*

	Base	Min	Max	Reference
Vaccine efficacy against herpes zoster (Take)†				[6,8]
60 y	69%	49%	78%	
70 y	53%	43%	75%	
80 y	26%	0%	78%	
Vaccine efficacy against PHN (Take)	67%	48%	80%	[6,9]
Waning rate (per year)	0.0%	0.0%	8.3%	[9]
Herpes zoster incidence rate (per 100,000 pers-y)				[10]‡
60 to 64 y	563.4	439.8	590.4	
65 to 74 y	786.0	634.6	851.1	
75+ y	958.8	733.6	1012.0	
Consultations (per herpes zoster case)				[3,19]
60 to 64 y	1.8	1.0	2.9	
65 to 75 y	2.1	1.0	3.5	
75+ y	2.2	1.0	4.2	
Hospitalization rate (per 100,000 pers-y)				[11]§
60 to 64 y	1.2	1.2	2.3	
65 to 69 y	1.0	1.0	2.8	
70 to 74 y	3.1	3.1	9.8	
75 to 79 y	5.3	5.3	18.8	
80+ y	9.4	9.4	30.1	
Length of stay (days)				[11]§
60 to 64 y	6.6	6.6	15.3	
65 to 69 y	8.7	8.7	15.7	
70 to 74 y	8.0	8.0	15.9	
75 to 79 y	10.3	10.3	16.8	
80+ y	13.4	13.4	19.6	
Case fatality				[12]||
60 to 64 y	0.000%	0.001%	0.002%	
65 to 74 y	0.012%	0.040%	0.083%	
75+ y	0.076%	0.040%	0.083%	
PHN (per herpes zoster case)				[3,6,20]
60 to 64 y	12.0%	6.9%	11.9%	
65 to 69 y	12.0%	6.9%	11.9%	
70 to 79 y	26.0%	18.5%	33.4%	
80+ y	32.2%	25.5%	33.4%	
QALY lost per herpes zoster case				[9,13]
60 to 69 y	0.010	0.002	0.029	
70+ y	0.011	0.003	0.031	
QALY lost per PHN case				[9,13]
60 to 69 y	0.186	0.024	0.449	
70+ y	0.194	0.144	0.406	

* For vaccine efficacy parameters, the distribution used in the probabilistic sensitivity analysis are Weibull, the average of which is the base case, and the 2.5% and 97.5% percentiles of the distribution correspond to the 95%CI measured in the SPS.[6] For duration of vaccine protection, the 2.5% and 97.5% percentiles of the distribution correspond to the 95%CI measured when estimating the annual waning rate. For the epidemiological parameters, the distribution used in the probabilistic sensitivity analysis are triangular, the mode of which is the base case.

† Base case: Take for herpes zoster vaccine efficacy = -0.000541 x age2 + 0.054243 x age - 0.612759

‡ Min and Max are the minimum and maximum incidence rate observed in the Manitoba Billings data in a year between 1993-97.

§ Min and Max is zoster in the first and any diagnostic fields, respectively.

|| Min and Max are the minimum and maximum case-fatality in a year between 1991-2000 (Observed in ONS mortality statistics).

Sensitivity analysis

Multivariate probabilistic sensitivity analysis was performed to examine the uncertainty of predictions. Each parameter was assigned a probability distribution (see Table I for input distributions) and combinations of these parameter values were drawn using Latin hypercube sampling. Results are presented with the base case and 90% Credibility Intervals (CrI), which show the 5th and 95th percentile taken from the distribution of the simulation results. Credibility intervals are the Bayesian analog to confidence intervals.

RESULTS

For 65 year olds (herpes zoster vaccine efficacy (take)=63%, PHN vaccine efficacy=67%, vaccine duration=life), the NNV to prevent a case of herpes zoster, a case of PHN, a herpes zoster death, a life-year lost and a QALY lost is estimated to be 11 (90%CrI: 10-13), 43 (90%CrI: 33-53), 23,319 (90%CrI: 15,312-33,138), 3,762

TABLE II

Number Needed to Vaccinate to Prevent Herpes Zoster-related Outcomes

	Base Case*		Age at Vaccination (years)†				HZ Vaccine Efficacy		PHN Vaccine Efficacy		Waning Rate
	Base	(90%CI)	60	70	75	80	43%	76%	48%	80%	8.3%/yr
Case of HZ‡	11	(10 to 13)	9	16	27	55	16	9	11	11	22
HZ consultations	5	(* to 8)	4	7	12	25	8	4	5	5	11
Hospitalization	380	(135 to *)	374	393	410	428	380	380	526	315	1069
Inpatient day	33	(10 to *)	33	33	32	32	33	33	46	27	104
PHN‡ Case	43	(33 to 53)	41	45	55	67	43	43	59	35	104
Death	23,319	(15,312 to 33,138)	24,601	23,014	21,499	28,276	23,319	23,319	32,307	19,384	71,671
LY‡ lost	3,762	(1650 to 4629)	4187	3905	3485	5952	3762	3762	5212	3127	8233
QALY‡ lost	165	(105 to 197)	154	180	225	289	173	159	215	131	390

* Age at vaccination=65 yr old, HZ vaccine efficacy=63%, PHN vaccine efficacy=67%, Vaccine duration=life
† HZ vaccine efficacy (VE) 50 yr old=75%, HZ VE 60 yr old=69%, HZ VE 65 yr old=63%, HZ VE 70 yr old=53%, HZ VE 80 yr old=26%, PHN vaccine efficacy=67%, Vaccine duration=life
‡ HZ, Herpes zoster; PHN, Postherpetic Neuralgia; LY, Life-year; QALY, Quality-adjusted life-year

(90%CrI: 1,650-4,629) and 165 (90%CrI: 105-197), respectively (Table II). The NNVs to prevent herpes zoster, PHN and a QALY lost are low, as the incidence of disease and associated pain is high in older adults. Our model predicts that among 65 year olds, the remaining lifetime risk of having zoster and PHN is 15% and 4%, respectively. However, the NNVs to prevent a zoster-related mortality and a life-year lost are high as herpes zoster case-fatality rates are very low (Table I).

Waning vaccine efficacy and age at vaccination have the greatest impact on results (Table II). NNV estimates more than double when waning of vaccine efficacy increases from 0.0% to 8.3% per year (within the estimated 95% confidence limits of waning immunity – see Table I). Furthermore, using an average duration of five years (20% per year waning), which matches the longest length of follow-up from Shingles Prevention Study, the NNV to prevent a case of herpes zoster and a case of PHN is 41 and 229 when vaccinating 65 year olds (results not shown). Finally, NNV predictions increase with age at vaccination because vaccine efficacy decreases[6] and life expectancy shortens.

DISCUSSION

The NNV results can be used by clinicians to inform their patients on the potential benefits of herpes zoster vaccination and by public health officials as a measure of the preventable burden of disease through vaccination. We used a cohort model to estimate the NNV related to zoster vaccination. Even though vaccine efficacy is between 50-70%, the predicted NNV to prevent herpes zoster and PHN are low, which reflects the high incidence of these diseases among older adults. Results show that the main benefit of zoster vaccination is prevention of pain and suffering rather than mortality (i.e., the NNV to prevent a QALY lost is substantially less than the NNV to prevent a life-year lost). Furthermore, results suggest that the optimal age at vaccination, in terms of NNV, is between 60 and 70 years since NNV predictions increase gradually with age due to reduced vaccine efficacy and life expectancy.

Comparisons between NNV results should be performed with great care. Results must be compared using the same time frame of analysis. It has previously been suggested by Kelly et al.[16] that NNV should be calculated using the NNT formula (1 divided by the Absolute Risk Reduction (ARR) estimated in randomized clinical trials). When calculated using the NNT formula, NNV should be interpreted as the number of people needed to vaccinate to prevent one event due to disease each year. Based on the results of the Shingles Prevention Study and using the NNT formula, Skootsky[8] predicts that 175 individuals 60+ years old must be vaccinated to prevent one case of zoster per year. When using the NNT formula, we predict that 200 65-year-old adults must be vaccinated to prevent one zoster case in the first year following vaccination. We argue that the NNT formula is inadequate for vaccines as vaccination provides both short- and long-term benefits, which depend on the duration of vaccine protection. Hence, using the NNT formula, NNV will vary from year to year depending on the time since vaccination, the vaccine waning rate and variations in the background incidence of disease. For example, using the NNT formula, the NNV to prevent a case of cervical cancer per year would be infinite for the first years following HPV vaccination and would decrease gradually over time as cervical cancer occurs in older adults while the vaccine is given to young adolescent girls. Given these issues and to illustrate the full potential of vaccination (in the short and long term), we preferred to use the same NNV definition as the Centers for Disease Control and Prevention (NNV=number of persons that are needed to be vaccinated to prevent one event during their lifetime[15]). The Centers for Disease Control and Prevention predict that 17 persons (65+ years old) would need to be vaccinated to prevent one zoster case and 31 persons would need to be vaccinated to prevent one PHN case.[15] These results are comparable to our NNV predictions (see Table II).

To put the results of this analysis into perspective, we compare NNV to prevent death with varicella, human papillomavirus and influenza vaccines. For varicella vaccination, we estimate that the NNV to prevent a death is 34,000 (using mortality rates reported in Brisson et al.[17] and assuming 100% efficacy against VZV and no waning). These results are similar to our predictions of NNV to prevent a death by vaccinating 65+ year olds against zoster (23,000-28,000). On the other hand, the NNV to prevent a death with the influenza and HPV vaccines is 5,388 and 729, respectively (assuming the influenza vaccine is given to 65+ year olds[16] and the HPV vaccine is given to 12-year-old girls[14]), which is much lower than for zoster vaccination. However, the goal of the zoster vaccine is not preventing mortality but rather preventing the morbidity related to the pain caused by the disease. A common outcome measure to compare

NNV results between vaccines, which would encompass both mortality and morbidity, is needed. The NNV to prevent a QALY lost could be used for such comparisons.

Our analysis has three main strengths. First, vaccine efficacy and duration of protection were modeled directly from the Shingles Prevention Study data. Second, epidemiological and health care resource utilization were taken from Canadian-specific population-based data. Base case estimates of herpes zoster incidence and hospitalization are likely to be conservative since the first physician consultation for a herpes zoster episode was used as a proxy for incidence and we included only hospitalizations that had zoster in the first discharge diagnosis field. Finally, we performed probabilistic sensitivity analysis to identify the parameters that have the greatest impact on model predictions and to illustrate the robustness of conclusions. We show that NNV results are most sensitive to waning vaccine efficacy. Although challenging due to lack of long-term data, more studies should be focused on quantifying the rate of waning protection following vaccination against zoster.

It has been shown that the epidemiology and health care resource use associated with herpes zoster is strikingly similar between developed countries.[18] Therefore, our NNV predictions for Canada can be generalizable to other settings within the US, Europe and Australia.

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Received: July 17, 2007
Accepted: April 21, 2008

RÉSUMÉ

Contexte : Un essai clinique a montré qu'un vaccin vivant atténué contre le virus varicelle-zona est efficace contre l'herpès zoster (zona) et l'algie post-zostérienne. Nous avons cherché à estimer le nombre de personnes qu'il faudrait vacciner (NPV) pour prévenir divers problèmes liés au zona.

Méthode : Nous avons élaboré un modèle de cohorte pour la morbidité, l'utilisation des ressources en soins de santé et la mortalité associées au zona. Des données basés sur la population canadienne ont servi à estimer l'incidence selon l'âge, les hospitalisations, les années de vie perdues pondérées par la qualité, ainsi que la mortalité. Le NPV désigne le nombre de personnes à vacciner pour prévenir la manifestation d'un problème lié au zona au cours de la vie. Nous avons étudié des sujets d'âge différent lors de la vaccination et effectué une analyse de sensibilité probabiliste.

Résultats : Chez les sujets de 65 ans, nous avons estimé que le NPV (efficacité du vaccin contre le zona=63 %, efficacité du vaccin contre l'algie post-zostérienne=67 %, sans baisse de l'immunité) s'établirait à 11 pour prévenir un cas de zona (intervalle de crédibilité [ICr] à 90 %, 10-13), à 43 pour prévenir un cas d'algie post-zostérienne (ICr à 90 %, 33-53), à 23 319 pour prévenir un décès attribuable au zona (ICr à 90 %, 15 312-33 139), à 3 762 pour prévenir une année de vie perdue (ICr à 90 %, 1 650-4 629), et à 165 pour prévenir une année de vie perdue pondérée par la qualité (ICr à 90 %, 105-197). Ces résultats étaient particulièrement sensibles à la durée de la protection vaccinale et à l'âge du sujet lors de la vaccination.

Discussion : Même si le vaccin n'est efficace que dans une proportion de 50 à 70 %, il faudrait vacciner relativement peu de sujets pour prévenir le zona et l'algie post-zostérienne, un résultat qui s'explique par la forte incidence de ces deux maladies chez les personnes âgées. Il est clair que le principal avantage du vaccin contre le zona est de prévenir la morbidité causée par la douleur (mesurée en années de vie perdues pondérées par la qualité) plutôt que la mortalité.

Mots clés : herpès zoster (zona); algie post-zostérienne; vaccins; modèle mathématique; nombre de personnes qu'il faudrait vacciner