PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Quantifying the incidence and burden of herpes zoster in New Zealand general practice: a retrospective cohort study utilising a natural language processing software inference algorithm.
AUTHORS	Turner, Nikki; MacRae, Jayden; Nowlan, Mary; McBain, Lynn; Stubbe, Maria; Dowell, Anthony

VERSION 1 – REVIEW

REVIEWER	Akiko Mizukami GlaxoSmithKline K.K., Japan
REVIEW RETURNED	08-Feb-2018

GENERAL COMMENTS	This study documented the incidence of HZ in Nez Zealand by the GP consultations identified using a natural language processing software inference algorithm. Overall, this manuscript is well written and organized. I only have a few comments/suggestions: 1) Setting and participants: Is there any exclusion criterion for participants? Are patients prescribed with anti-herpetic virals for preventing from herpes zoster (diagnosed as herpes zoster in claims in some countries) included in the analysis? If they are included, please describe this point. 2) Discussion P9, L7: "Furthermore, the burden of subsequent consulting was very low with 80% of zoster-related presentations requiring no follow-up and 13% requiring only a single follow-up consultation." Although there is a range of data on the number of outpatient visit, repeated visits relating to HZ on the average of 2- 6 have been reported (See references below). The reason why this low frequency of the follow-up visit was observed should be discussed. Does it base on characteristics of healthcare system in NZ or biological nature of NZ people? Is it possible to detect the burden in other database (visit to specialist, hospitalization, etc.)? It would be helpful to add discussions about this point. Cebrian-Cuenca A et al., BMC Infect Dis (2011); Gialloreti L et al., BMC Infect Dis (2010); Gater A et a., BMC Public Health (2015); Johnson B et al., J Med Econ (2016); Nakamura H et al., Drugs – Real World Outcomes (2017)

REVIEWER	Kosuke Kawai, ScD Boston Children's Hospital and Harvard Medical School, USA
REVIEW RETURNED	09-Feb-2018

GENERAL COMMENTS	Dr. Turner et al. examined the incidence of herpes zoster (shingles) in New Zealand. The incidence rate of 4.9 per 1000 patient-years is comparable to the incidence rate reported in Australia (5.6 per 1000

pys by MacIntyre et al. Plosone 2015) and other countries. I disagree with their conclusion that zoster consultations are rare. As they mentioned in the Introduction, lifetime risk of shingles is 20% to 30%. Patients with shingles can suffer from complications including post-herpetic neuralgia (a persistent painful complication) and HZ ophthalmicus with eye involvement. Recent studies also showed that shingles is associated with an increased risk of stroke in the first 3 months. The incidence of pneumonia among adults is about 25 cases per 10,000 person-years, which may be lower than the incidence of shingles, but I do not think most will consider that rare. I have several comments for consideration.

Comments

1) I appreciate their efforts in validating their NLP algorithm. PPV of 82%, specificity of 99%, and sensitivity of 84% are reasonable. The authors mentioned that they used natural language processing software for influenza and childhood respiratory diseases. I wonder how well it was performing in other diseases.

2) What about risk of post-herpetic neuralgia among patient with shingles? As they pointed out in the introduction, risk of PHN is the concerning complication. Is that something that they can assess?

3) I think just because most patients with shingles had no follow-up consultations (low healthcare utilization) do not necessary imply that shingles do not significantly affect patient's health-quality of life. I feel like the paper is written from the healthcare providers perspective, and not patient perspective. There are numerous studies showing that herpes zoster affects health-related quality of life, and complication is concerning.

4) How frequently GP refers their shingles patients with complications to dermatologist, ophthalmologist, neurologist, or ID? If that's common, the results underestimate the burden of healthcare utilization because that would not be captured in your study.

5) Figure 6 is not convincing to me. Sometimes figures can be misleading. Most of the increased visits are expected in the first two to three weeks. If you examine 12 months prior to and 12 months post-index case, the study span is wide and you may miss the increased visits occurring in the first 1 months (which we expect in the most cases).

VERSION 1 – AUTHOR RESPONSE

Reviewers' Comments to Author:

Reviewer: 1
Reviewer Name: Akiko Mizukami
Institution and Country: GlaxoSmithKline K.K., Japan Competing Interests: None declared

This study documented the incidence of HZ in Nez Zealand by the GP consultations identified using a natural language processing software inference algorithm. Overall, this manuscript is well written and organized. I only have a few comments/suggestions:

1) Setting and participants: Is there any exclusion criterion for participants? Are patients prescribed with anti-herpetic virals for preventing from herpes zoster (diagnosed as herpes zoster in claims in some countries) included in the analysis? If they are included, please describe this point.

The study aimed to assess the burden of herpes zoster (HZ) presentation on general practice, across the enrolled population, hence there are no exclusion criterion within this population.
The algorithm identifies cases from the notes within the bounds of the stated specificity and sensitivity; as such there are no exclusions – the aim is to identify all of the cases of HZ according to the algorithm criteria.

It is not common clinical practice in NZ general practice to prescribe anti-viral medications prophylactically for HZ. In terms of diagnostic criteria with the algorithm, due to the potential of anti-herpetic virals, such as acyclovir, to be used to treat genital herpes, any notes that did not also contain other identifying features of HZ would not be classified as a visit for HZ.

2) Discussion P9, L7: "Furthermore, the burden of subsequent consulting was very low with 80% of zoster-related presentations requiring no follow-up and 13% requiring only a single follow-up consultation."
Although there is a range of data on the number of outpatient visit, repeated visits relating to HZ on the average of 2- 6 have been reported (See references below). The reason why this low frequency of the follow-up visit was observed should be discussed. Does it base on characteristics of healthcare system in NZ or biological nature of NZ people? Is it possible to detect the burden in other database (visit to specialist, hospitalization, etc.)? It would be helpful to add discussions about this point.
Cebrian-Cuenca A et al., BMC Infect Dis (2011); Gialloreti L et al., BMC Infect Dis (2010); Gater A et a., BMC Public Health (2015); Johnson B et al., J Med Econ (2016); Nakamura H et al., Drugs – Real World Outcomes (2017)

This study did not look at hospitalisation or specialist visits, its objective was only to quantify the overall burden in general practice, spread across the full age range. This is lower than the Cebrian-Cuenca study, which was a very different style of study which proactively contacted patients versus this retrospective population observational study. We suggest that rates of repeat visits in GP across the whole population are likely to be relatively low. As our overall rates of ascertainment are well within the same range as other studies at 4.86/1000, our case ascertainment seems effective with this methodology.

Also it is clear that many of mentioned studies give rates by older ages; for example the review article by Gater et al in BMC Public Health 2015 that shows approx. 1.9 visits to GP for over 50 year-olds, is in line with our findings, with as much lower rates in under 50s. Furthermore we are counting repeat visits, whereas the numbers reported in the other papers are 'total' visits (e.g. should subtract one for comparison). We do not believe there is an underlying biological difference in NZ people, these differences may be due to some extent to different patterns of service utilisation, but most of the difference is likely to be in the different age distributions in the other studies with much older mean ages reported.

Reviewer: 2
Reviewer Name: Kosuke Kawai, ScD

Institution and Country: Boston Children's Hospital and Harvard Medical School, USA Competing Interests: None.

Dr. Turner et al. examined the incidence of herpes zoster (shingles) in New Zealand. The incidence rate of 4.9 per 1000 patient-years is comparable to the incidence rate reported in Australia (5.6 per 1000 pys by MacIntyre et al. Plosone 2015) and other countries. I disagree with their conclusion that zoster consultations are rare. As they mentioned in the Introduction, lifetime risk of shingles is 20% to 30%. Patients with shingles can suffer from complications including post-herpetic neuralgia (a persistent painful complication) and HZ ophthalmicus with eye involvement. Recent studies also showed that shingles is associated with an increased risk of stroke in the first 3 months. The incidence of pneumonia among adults is about 25 cases per 10,000 person-years, which may be lower than the incidence of shingles, but I do not think most will consider that rare. I have several comments for consideration.

We are reporting on the burden of HZ in general practice, which is not necessarily the same as actual incidence or burden of HZ across the population. It is difficult to define what is meant by the word 'rare'. In terms of the absolute burden on general practice workload, which is an important aim of this paper, the proportion of doctor consultations for herpes zoster is very low overall and hence we feel this is appropriately reported as rare in this context.

Comments

1) I appreciate their efforts in validating their NLP algorithm. PPV of 82%, specificity of 99%, and sensitivity of 84% are reasonable. The authors mentioned that they used natural language processing software for influenza and childhood respiratory diseases. I wonder how well it was performing in other diseases.

This methodology has been and continues to be used for other studies. (MacRAe J et al BMC Med Inform Decis Mak 2015; MacRae et al BMJ Open March 2015, Dowell et al BMJ Open 2017) Comparison cannot be made between these studies in terms of accuracy, since each time this methodology is used the PPV, specificity and sensitivities differ. In each case, validation is conducted.

2) What about risk of post-herpetic neuralgia among patient with shingles? As they pointed out in the introduction, risk of PHN is the concerning complication. Is that something that they can assess?

This study investigated the overall incidence and burden of herpes zoster visits in general practice, which would have included cases of PHN. Our aim was not to investigate PHN as an isolated issue. By investigating the frequency and number of follow-up consultations after the index presentation of HZ, we hoped to capture long lasting complications such as PHN.

A limitation of this study, is that were unable to identify the reason for the repeat visit, just that it met the criteria for being zoster-related. In the self-controlled case series part of the study, we also assessed how many non-zoster-related visits were made before and after the index presentation. The aim was to see if there was an increase in visit frequency for any reason after developing HZ, and thereby putting increased burden on the general practices. Further investigations into specialist care referrals and pain medications could help to provide further data on this. This is noted in the unanswered questions and further research comments.

2) I think just because most patients with shingles had no follow-up consultations (low healthcare utilization) do not necessary imply that shingles do not significantly affect patient's health-quality of life. I feel like the paper is written from the healthcare providers perspective, and not patient perspective. There are numerous studies showing that herpes zoster affects health-related quality of life, and complication is concerning.

We recognise, and the published literature recognises, that a patient's quality of life can be severely affected by the pain and complications of HZ. The burden of HZ on individuals is significant. However, the purpose of this study was to investigate the utilisation of services within general practice and the primary health care system associated with HZ. The data used was a collation of nearly seven million doctors' notes and as such it was not possible to analyse individual patient outcomes.
The experience of the patient would form part of a different study. Under the unanswered questions and further research heading, we note that further research needed at the community level.

4) How frequently GP refers their shingles patients with complications to dermatologist, ophthalmologist, neurologist, or ID? If that's common, the results underestimate the burden of healthcare utilization because that would not be captured in your study.

It would be very uncommon in New Zealand to refer patients to specialists, since NZ has a strong and comprehensive primary care system. Ophthalmological referrals may occur for severe cases of ocular HZ.
This study was only intended to look at the burden of HZ on primary health care, not the health service overall (which includes specialist care, hospitalisation and prescriptions).

5) Figure 6 is not convincing to me. Sometimes figures can be misleading. Most of the increased visits are expected in the first two to three weeks. If you examine 12 months prior to and 12 months post-index case, the study span is wide and you may miss the increased visits occurring in the first 1 months (which we expect in the most cases).

This figure uses a self-controlled case series approach. It considers the visit frequency for each individual both prior to and after the HZ index-visit. Effectively, the visit frequency to general practice prior to the index presentation is being used as a control for the period post the index presentation. It excludes any visits related to HZ. If visits occur more 3-4 weeks post HZ index presentation, we would expect to see this in the results still. It would only be masked if this increase in visits over this 3-4 week period had a subsequent drop in visits in the following 11 month period. Furthermore, restricting such analysis to only a 3-4 week period would be likely to introduce additional confounding, including seasonal trends.

In fact, we did see a significant number of people that did present more frequently after their HZ index presentation, but in almost all cases, there was also a comparative number of people that also presented less frequency after their HZ index presentation. Overall about 80% of 60-69 year olds presented differently before or after their HZ index presentation. Of that 80%, 40% presented more frequently, 40% less frequently.

VERSION 2 – REVIEW

REVIEWER	Kosuke Kawai
	Boston Children's Hospital and Harvard Medical School, USA
REVIEW RETURNED	08-Mar-2018

GENERAL COMMENTS	Thank you for your response. Given that the limitations I mentioned in my review have important implications, they should be incorporated into the text of the manuscript.

VERSION 2 – AUTHOR RESPONSE

Reviewers' Comments to Author:

Reviewer: 1
Reviewer Name: Akiko Mizukami
Institution and Country: GlaxoSmithKline K.K., Japan Competing Interests: None declared

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presented differently before or after their HZ index presentation. Of that 80%, 40% presented more frequently, 40% less frequently.

Following revision – Reviewer 2

Thank you for your response. Given that the limitations I mentioned in my review have important implications, they should be incorporated into the text of the manuscript.

We have further expanded information in the Study limitations part of the text to emphasise that this study was intended to consider the burden of zoster from the general practitioner's perspective rather than patients' perspectives. It was not within the scope of this study to examine specific reasons for each visit and to investigate individual experiences.