Author's response to reviews

Title: Disease burden of herpes zoster in Sweden - predominance in the elderly and in women - a register based study

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Author's response to reviews: see over
Dear Editor,
Thank you for the review of our manuscript “Disease burden of herpes zoster in Sweden - predominance in the elderly and in women- aregister based study”. We have now considered the reviewers opinions.

**Reviewer 1**

1. Under Background, third part, we have now added a reference on immunosenescence on line 5 and added the text “as immunosenescence progresses”

2. Under Background, first part : We have corrected the manuscript concerning the time periods:
   “The present study extracted gender-specific retrospective data from 2006-2010 concerning herpes zoster hospitalizations and drug prescriptions for antiviral medication as well as zoster-related mortality during 2006-2009.”

   In abstract the fourth sentence has been clarified:
   The herpes zoster burden of disease in Sweden was estimated by analyzing the overall, and age and gender differences in the antiviral prescriptions, hospitalizations and complications during 2006-2010 and mortality during 2006-2009.

3. This is a very interesting research question. However, this is out of the scope of the present study. A separate cost of illness study from Sweden has recently been submitted to BMC Infect Dis (Nilsson et al, 2013).

4. Thank you for your observation of the lack of the denominator under the Methods of the manuscript.
   Under Methods- Data extraction from the Swedish National Pharmacy Register, last sentence there is a description written “ For each specific calendar year within the study period, prescriptions were linked to patients and counted only once, although several prescriptions may have been assigned to the same patient”.
However for hospitalization and mortality rates we have not specified the denominator in the first submitted version. We have now clarified the denominator under Statistics with a new sentence:

“For each specific calendar year within the study period, prescriptions and hospitalizations were linked to patients and counted only once, although several events may have been assigned to the same patient.”

5.

We agree that the information on the proportion of prescriptions without text and the prescriptions with text including herpes simplex etc. is valuable to assess the predictive value of the antiviral drugs prescriptions to identify herpes zoster cases. However, patient prescription information is in many cases lacking. As a consequence, drawing conclusions from this information is connected to many uncertainties. In an attempt to minimize the overestimation of prescriptions, the analysis with exclusion using certain key words was performed. This was done by the Swedish National Pharmacy Register at the National Board Health before submitting the data to us.

6.

Unfortunately, we do not have any reference of the actual national percentage of patients with herpes zoster who are treated with antiviral drugs. However, we have unpublished data which states that approximately 72% of patients diagnosed (ICD -10) with herpes zoster in primary care receive a prescription (Dr. Lars Rombo, personal communication) (see below 7.)

7.

As stated in point 5 above, we do not think that the amount of prescriptions are overestimated, since only 72% of the patients with herpes zoster in health care facilities are prescribed an antiviral treatment. We have now added an extended discussion on the magnitude of the potential overestimation of the prescription rates due to the inclusion of non-herpes zoster cases.

We have now added two sentences to the discussion, part 3:

In the review by Pinchinat et al. [22], prescription studies were not considered as reliable as prospective studies in health care facilities or retrospective studies of herpes zoster cases identified through the review of medical files when calculation the incidence of herpes zoster.
However, an overestimation of cases in our study is less likely since only approximately 72% of the patients diagnosed (ICD-10) with herpes zoster in primary care receive a prescription of antivirals (Dr. Lars Rombo, personal communication).

8.

In the discussion, part 4, first sentence (former line 17) we have now specified that "primary and non primary diagnoses" are related to hospital cases.

”In the present study, hospital cases with non-primary and primary diagnoses of herpes zoster disease were analyzed”.

9.

We have added three sentences in the second part of the discussion about methodological differences referring to two reviews:

Recently, a review of European studies, focusing on total population incidence of herpes zoster, stated that in the 21 included studies the incidence in all ages was 2-4.6/1000 inhabitants/year which is in line with our results [22]. In the review by Thomas et al, where studies from both Europe and USA were included, the incidence in all ages varied from 3.6 to 14.2/1000 inhabitants/year [5]. However, methodological differences are frequent and direct comparisons of studies must address this circumstance.

Reviewer 2

1.

Reviewer 1 also pointed out this unclarity. Thank you for observing this. Under Methods - Data extraction from the Swedish National Pharmacy Register, last sentence ,there is a description written ”For each specific calender year within the study period, prescriptions were linked to patients and counted only once, although several prescriptions may have been assigned to the same patient”.
However for hospitalization and mortality rates we have not specified the denominator in the first submitted version. We have now clarified the denominator under Statistics with a new sentence:

“For each specific calender year within the study period, prescriptions and hospitalizations were linked to patients and counted only once, although several events may have been assigned to the same patient.”
2.

When looking at absolute numbers, the longer lifespan of females is an important factor. However, as the data in the present study is described as rates, the decreased size of the male population (due to mortality) is accounted for.

3.

We have now added a reference. It was a Swedish study comparing prescriptions of medications in general in women and men and showed that women were prescribed more medications. The end of the discussion is rewritten:

“In the European review by Pinchinat et al, the incidence rates were systematically higher in females than in men in the included studies confirming the results of this study (22, 25-28). Even though a predominance in females of antiviral prescriptions was demonstrated in several age groups in the present study, it cannot be excluded that this finding is related to a different health care seeking pattern for herpes zoster between the sexes in Sweden (29). In addition, gender difference in the incidence of herpes zoster might be due to immunological or hormonal differences between men and women. However, this issue is out of the scope of the present study and should be further explored.”

4.

This study was a register-based study where hospitalisations with herpes zoster as primary diagnoses was searched for. We agree that analysis of comorbidities would have been of interest. However, comorbidities such as pre-existing renal, liver, cardiac, pulmonary disease, endocrine disease are not accessible from the National Patient Register. When including zoster hospitalisations due to non-primary diagnoses, the primary diagnosis is accessible. However, we have not included non-primary cases in the study (it is mentioned in the Discussion). To examine comorbidities the patients records must be examined, and since this study is registerbased it is not possible to perform this analysis in this study.

5.

Yours Sincerely,

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