PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Shingles, Zostavax vaccination and risk of developing dementia: a nested case-control study - results from the UK Biobank cohort.
AUTHORS	Lophatananon, Artitaya; Mekli, Krisztina; Cant, Rachel; Burns, Alistair; Dobson, Curtis; Itzhaki, Ruth; Muir, Kenneth

VERSION 1 – REVIEW

REVIEWER	Muzambi, Rutendo London School of Hygiene and Tropical Medicine
REVIEW RETURNED	29-Jan-2021

GENERAL COMMENTS	Lophatananon and colleagues aimed to investigate the association between shingles and risk of dementia using data from the UK Biobank study linked with primary and secondary care data. The authors also investigated the association between shingles and dementia in participants with and without Zostavax vaccination. The topic is of great interest and the paper is well written, however, there are several important methodological issues that the authors need to address. 1. A key issue in this study is that the authors seem to have included participants without linked primary care records in their study. The authors ascertained dementia using primary and secondary care records and participants without a dementia code were selected as controls. However, this raises issues as only 45% of the UK Biobank cohort had linked primary care records so participants without linked data may have been more likely to be coded as not having dementia due to the absence of any primary care data. Without primary care data for these individuals, it is unclear whether they had dementia or not and it is thus likely that dementia may have been misclassified. Similarly, as shingles was also ascertained using primary care data, misclassification of shingles is possibly likely among participants without linked primary care data. The authors need to address this important issue. 2. The authors could provide more information on the study population included in their Zostavax vaccination analysis. Since Zostavax vaccination was ascertained in primary care records only, were only people with linked primary care data included in this analysis? 3. How were prevalent cases defined? The authors could explicitly state whether they excluded prevalent cases, whether any other exclusions were made, and the number of participants excluded. 4. In the discussion, the authors state, “We further examined incidence in the sub-cohort aged 60-64 and found that shingles incidence rate was 7.56 per 1000 person years, which is close to

	the reported national figure." However, there seems to be no mention of this analysis in the method or results.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Ms. Rutendo Muzambi, London School of Hygiene and Tropical Medicine Comments to the Author: Lophatananon and colleagues aimed to investigate the association between shingles and risk of dementia using data from the UK Biobank study linked with primary and secondary care data. The authors also investigated the association between shingles and dementia in participants with and without Zostavax vaccination.

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1. A key issue in this study is that the authors seem to have included participants without linked primary care records in their study. The authors ascertained dementia using primary and secondary care records and participants without a dementia code were selected as controls. However, this raises issues as only 45% of the UK Biobank cohort had linked primary care records so participants without linked data may have been more likely to be coded as not having dementia due to the absence of any primary care data. Without primary care data for these individuals, it is unclear whether they had dementia or not and it is thus likely that dementia may have been misclassified. Similarly, as shingles was also ascertained using primary care data, misclassification of shingles is possibly likely among participants without linked primary care data. The authors need to address this important issue.

-We would like to thank the reviewer for their valuable comments. We have taken the comments on board and we have made changes to the dataset that we analysed and presented in the paper to reflect the central point raised by the reviewer as to the availability of outcomes.

In essence, we have now restricted analysis to a sub-cohort of subjects with primary care linkage (45%) and HES data. This sub-cohort provided a complete record of both exposures such as shingles and vaccination and dementia outcome. We ran the same analysis testing again all the potential confounders. Due to the subsequent reduced power, this has changed statistical significance of the results as summarised below but the direction of the key effects seen before remain as further described below.

In sum, before we saw a statistically significant effect with shingles before and that risk was attenuated in people that had had VZV vaccine but not to a statistically significant level. Effectively changing the focus to half the cohort with outcome data from both hospital and GP records that then reduces our power such that now see a smaller elevated risk with shingles (but now not statistically significant) and we now still that the vaccine attenuates this such that this result now becomes statistically significant. i.e. the risk gradient/relationship between the 2 factors (shingles and vaccine) remains the same but has been effectively shifted to the "left" as we have half as many events in the analysis. The pattern of results remains the same and our results remain very consistent with other recent papers coming out on the effects of shingles vaccine of dementia outcomes in other cohorts from across Europe. We believe that our paper makes an important contribution to the totality of evidence and as our results are derived from UKBiobank our paper makes an important contribution to the evidence base around this important and rapidly developing area

2. The authors could provide more information on the study population included in their Zostavax vaccination analysis. Since Zostavax vaccination was ascertained in primary care records only, were only people with linked primary care data included in this analysis?

The answer to this point is yes, and in our restricted cohort now used the analysis of Zostavax vaccination is now no longer stratified by shingles history (yes/no). We have also further adjusted for co-morbidity to minimise the chance of a "healthy cohort" effect.

3. How were prevalent cases defined? The authors could explicitly state whether they excluded prevalent cases, whether any other exclusions were made, and the number of participants excluded.

-We have added a sentence to the paper to confirm the exclusion of prevent cases and the number excluded. We have also addressed a further exclusion of any withdrawn subjects prior to the assembly of our dataset used in our analyses.

4. In the discussion, the authors state, "We further examined incidence in the sub-cohort aged 60-64 and found that the shingles incidence rate was 7.56 per 1000 person years, which is close to the reported national figure." However, there seems to be no mention of this analysis in the method or results.

- *We have removed this sentence in the discussion.*

VERSION 2 – REVIEW

REVIEWER	Muzambi, Rutendo London School of Hygiene and Tropical Medicine
REVIEW RETURNED	12-Sep-2021

GENERAL COMMENTS	The authors have adequately revised the manuscript and addressed my concerns. I just have a very minor comment relating to the first sentence of the introduction. The year in which 152 million people are projected to be living with dementia worldwide is "2050" not "2150" which is stated in the text.