Reviewer's report

Title: Health-Economic evaluation of vaccination strategies for the prevention of herpes zoster and postherpetic neuralgia in Germany

Version: 1 Date: 7 June 2013

Reviewer: Mehdi Najafzadeh

Reviewer's report:

This study has estimated cost-effectiveness of HZ vaccination for individuals over 50 years old in Germany. Authors have developed a static cohort model of 50 years old with five Markov states (healthy, HZ, PHN, healthy after disease, and death) over individuals' lifetime, with fixed cycle of 3 months length and with death being the absorbing state. The number-needed-to-vaccinate (NNV), costs per HZ case avoided, cost per PHN case avoided, and cost per QALY gained have been estimated as the model outcomes and compared between those who were vaccinated vs. status quo.

Similar to previous studies, the results suggest generally increasing ICER by age at vaccination with minimum to be around 60 years old. Both deterministic and probabilistic sensitivity analyses have been performed and ICERs for different age at vaccination have been simulated.

Overall, this model has included sufficient level of details for simulating the vaccination outcomes. However, I believe there are some major issues that need to be addressed or explained.

Major compulsory revisions:

1) Average duration of PHN has been assumed to be 9 months. I understand that this is an uncertain parameter and different studies have reported different length for PHN, ranging from 8 months to more than 3 years. Have you included this uncertainty in your sensitivity analysis? This parameter is crucial in the model and in most studies turned out to cause significant variation in estimations.

2) Line 12: “We fitted the data by calculating the age-specific average utilities based on values of day 0 and day 30 as HZ-related utilities, and the age-specific average based on values of day 90 and day 180 as PHN-related utilities [14].” My concern is that the way that you have calculated these utilities, automatically results in larger utility values for PHN (i.e. over estimated PHN health state values). Looking at the estimated utilities in Table 2 confirms this issue, as all PHN utilities are larger than HZ utilities. I suspect that you have included everyone, including resolved HZ cases, in calculation of utilities from day 90 onward (that has been defined as utility of PHN). Please note that, PHN is often defined as “moderate” or “severe” pain that persists after 90 days (See definition in SPS for instance). I am wondering if you have used an acceptable definition for PHN here.
3) The other major issue is that whether they have used correct baseline utilities for those in healthy state (i.e. no HZ or PHN). EQ5D utilities are certainly lower that 1 and are decreasing by age. Therefore, age-specific baseline utilities should be used as a reference when calculating effect of HZ and PHN and need to be explicitly reported in the Table 2.

4) Based on 2 and 3, I believe both disutility and length of PHN has been underestimated in the whole analysis (and perhaps burden of HZ has been overestimated). Decreasing burden of PHN is a critical component of vaccine value since PHN cause significant morbidity over a long period.

5) I would like to have a sense of cost and QALY per person and incremental cost and QALY per person in two arms of the model as well. Also since coverage has been assumed to be 20%, the aggregate numbers that have been reported in the Tables 3 and 4 are difficult to interpret. Only 20% of the simulated cohort accrue costs and outcomes related to vaccine and outcomes related to the other 80% do not really add much information about the outcomes that we are interested in here. Please discuss otherwise. I also suggest you add this coverage rate in your Table 2 as your model assumption. Also I would add the assumption of 100% chance of VZV during the childhood in your input table.

6) Rows in Table 1 are not properly aligned which makes it difficult to comprehend the content. I had to go back and forth between Table 1 and Figure 1 to understand the notations. Please format Table 1 properly so readers can see, for example, alpha and beta both are probabilities related to “healthy” health state. Also I would consider moving Table 1 to adjacency of Figure 1.

7) I also noticed several errors in formulas that hopefully haven’t affected the actual model:

The second term of VE HZ (ij) dosen’t seem to be correct. Both indicator function range and exponential function need to be corrected. For example, if i becomes very large, the second term in the parenthesis tends toward 1. One expect that for large i’s first term and second term both go toward 0 instead. Same issue exists in VE PHN (ij) formula.

Probability of staying at PHN (# i): why you have used (1-alpha) instead of alpha? Suppose alpha is zero, then within the three cycles (that indicator function is one) the probability of staying at PHN state is zero based on your equation (instead of becoming 1).

I wouldn’t use exponential format for defining beta, delta, etc. Besides, either you are missing an integral operator behind I, or you should define I as integral of incidence rate during one cycle.

Beta, delta and epsilon seem to be defined incorrectly. For example, suppose alpha is zero. Then if I(healthy to HZ) is very large we expect to see beta get close to 1. This is not happening based on your formulation (your formula gives
minus alpha that is obviously wrong).

8) On Line 283 of the discussion, the authors say: “Interestingly, the variation in the annual waning rate of vaccine-induced immunity and the consideration of two booster scenarios had only little impact on the ICERs.” This, however, does not come as a surprise to me. You have assumed waning rate to be zero for 10 years and only then starts becoming positive. A realistic approach to model waning rate would be using a smooth functional form. Had you molded it this way, I suspect that different assumptions about waning rate would have result in a large impact on outcomes as previous studies have concluded.

9) Please give some information/numbers in Table 2 about HZ related mortality and Background mortality rates. Just pointing to a reference is not quite helpful for readers.

Discretionary Minor Revisions:

1) I would consider re-structuring section "input data" either to subsections or break it into two or more coherent sections.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.