Reviewer’s report

Title: Vaccinating children against influenza: overall cost-effective with potential for undesirable outcomes

Version: 0 Date: 26 May 2019

Reviewer: Nick Scott

Reviewer's report:

This study uses a mathematical model to assess the health impacts and cost-effectiveness of introducing a childhood vaccination program in the Netherlands. The article is well written, and the figures, tables and messaging are clear. The conclusions follow from the scenarios modelled. I have the following considerations for the authors.

Main comments:

1. The finding that such a program could lead to increased likelihood of above-average seasons, and hence the possibility of health losses, is new. This appears to be driven by the relative difference in vaccine-derived immunity and natural immunity. Given the implications of this finding, additional analyses are warranted to determine thresholds for these parameters where this is no longer the case. For example, if natural immunity following infection were less than X years, then would this outcome no longer occur in the model?

2. Related, is that much of the sensitivity analysis is focused on the impact of individual parameters on the ICER, which is useful. However, given the finding above, it would also be worth understanding which parameter inputs can mitigate the probability of net QALY losses (e.g. is there a threshold vaccination coverage in children (90%?) after which there are no longer likely to be any QALY losses among children? If the existing vaccine coverage among the general adult population were higher, would this influence the probability of QALY losses [such as if parents were vaccinated as well - this could be tested by just varying the input parameter for coverage in adults]?). This is necessary to help policy-makers better understand whether there are any factors that are likely to mitigate such risks.

3. Model description:
   a. The structure of the model itself is not clear, and a diagram would be beneficial. For example, the model uses annual time steps, but also appears to account for social contact patterns? How is transmission modelled among each age group?
   b. The model appears to be age structured, but what groups are considered? Is it by year or by age category (and what are the categories)?
4. Has this type of work been assessed for other influenza vaccination programs? For example, many workplaces have influenza vaccination programs. What is the usual process considered before implementing these? - if information is available this would be worth mentioning in the intro or discussion.

5. It is not clear what the authors mean by the five-year stabilization period, after the vaccine is introduced. What happens in the model in this period?

6. What is the current vaccination coverage among the different age groups?

7. Inputs around immunity (e.g. vaccine efficacy, natural immunity efficacy and duration of protection) should be summarized in one of the tables

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Not applicable

Are the conclusions drawn adequately supported by the data shown?
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Yes

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