Reviewer's report

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

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Reviewer: Chester Good

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I found this paper to be very interesting, and quite thought provoking. The authors performed a CEA for the Netherlands to examine the impact of implementing a childhood influenza vaccination program. Their dynamic transmission model improves upon previous models by accounting for both seasonal vaccine effectiveness and long-term changes in immunity following vaccination. They investigate three vaccine strategies (compared to existing strategy of vaccinating those at high risk and those over 60 years of age): 2-3 yrs, 2-12 yrs, and 2-16 years. They demonstrate that a strategy of vaccinating 2-16 year olds is very cost-effective, primarily by benefitting older patient cohorts. They also document an unexpected finding (at least to me) that a childhood vaccination program increases the likelihood of influenza pandemics in subsequent years.

General Comments

1) I find the title of this paper to be unfortunate, by highlighting the "risk of undesirable effects". In fact, the main finding of this study is that childhood influenza is very cost effective, saves lives, and improves the quality of life. I am concerned that in the current toxic environment of vaccine opponents (at least in the U.S.), that such a title draws attention to a theoretical risk of undesirable effects. I hope that the authors will reconsider the title to either balance the findings to include the positive outcomes, or simply remove "undesirable effects" from the title.

2) The most interesting and thought-provoking idea in this paper (for me) is the finding that childhood vaccination increased the likelihood of large epidemics. This hypothesis (I am not convinced that it has been scientifically proven) is built on scenarios where vaccination leads to a large accumulation of susceptible unvaccinated patients combined with years where vaccine efficacy is low (lines 88-89). This hypothesis seems to rely on prior influenza infections in unvaccinated conferring some protection in subsequent years (and the converse, that lack of influenza in previous years increases the likelihood of infections). However, lines 421-424 indicates that the model assumes no benefit from prior years of vaccination. These assumptions seem to contradict each other.

3) Following up on this issue of potential for large epidemics, the authors report an alarming (to me at least) 23.3% chance for "large epidemics"- defined as more influenza cases than any of the 11 previous years. This seems like a low bar as a definition of "large epidemic"- and based on
chance alone, there would be ~9% (1/11) chance in any subsequent year of exceeding any of the 11 previous years. In the discussion, the authors refer to the US 2017/2018 influenza epidemic—which was nearly twice the number of influenza cases as the average of the prior 7 years in the US. Might a more conservative estimate for "large epidemic" provide a more realistic metric for concern— for instance, a 25% or 50% increase in average number of cases in a given year?

a. It is not clear that the 2017/2018 influenza year is a good example to cite as a potential example of vaccination of children leading to an influenza pandemic. It appears that the pandemic 2017/2018 was mostly due to a particularly virulent strain of influenza (H3N2), and not a vaccine mismatch. Indeed, the vaccine effectiveness was reported to be 40% by the CDC (https://www.cdc.gov/flu/vaccines-work/effectiveness-studies.htm) similar or better than approximately half of the previous 13 years.

4) The focus on children as a separate entity for assessment of cost-effectiveness of childhood vaccination is also interesting and raises ethical considerations. The authors indicate that the most benefit of vaccination in children is conferred to older patient populations, and that from a children perspective, vaccination is not cost-effective. However, children do benefit from fewer cases of influenza, and improved quality of life. Moreover, the age cohort from 30-40 achieved substantial benefit from childhood vaccination- this age would likely include many parents caring for children. Did the model include consideration of the cost of sick parents being unable to care for sick children? Should the lack of cost-effectiveness (driven by the rarity for loss of life in the young from influenza) be a consideration, when overall the initiative saves lives and is cost-effective? Because children are not in a position of decision-making regarding vaccination, it raises interesting ethical concerns.

5) The authors chose several scenarios for this analysis, based on several difference age cut-points for vaccination. Of these scenarios (2-3 yrs, 2-12 yrs, 2-16 yrs), the broadest age category (2-16 yrs) was most cost-effective. It is unclear how these strategies were chosen- as opposed, say a strategy comparing 2-16 yrs, 8-16 yrs, and 12-16 yrs or some other variation. Unless these age groups were specifically being considered by the Netherlands, or a clinical rationale supports these age groups to target, I wonder the main study could simply focus on the 2-16 yr age group and move the other age groups to the supplemental material.

Specific minor comments:

1) Lines 84-86 reference studies 9 and 10- which are incompletely referenced.

2) Lines 150-151 indicate that a vaccine effectiveness of 45% was used in the model. Did the authors model the fact that patients who get influenza despite vaccination tend to have less severe disease, and also lower healthcare utilization (lines 162-166) than unvaccinated who contract influenza?
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