Reviewer's report

Title: Cost-Effectiveness of Increasing Vaccination in High-Risk Adults Aged 18-64 Years: A Model-Based Decision Analysis

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Reviewer: Kimberly Shea

Reviewer's report:

The authors report on the cost effectiveness of increasing influenza, pertussis, and pneumococcal vaccination in high-risk adults aged 18-64 years using their experience with the 4 Pillars Program as the basis for some of their model parameters, and data from the literature as the basis for other model parameters. I think this represents an important contribution to the literature. However, this paper could be strengthened by addressing the following comments below.

Abstract

* Please update accordingly based on comments below

Introduction

* It would be helpful to provide the actual influenza, pertussis, and pneumococcal vaccination rates among adults aged 19-64 years (overall, not worrying about "high-risk" vs. healthy) instead of saying that they are "low".

* It would also be useful to state that the 4 Pillars Program improved adult vaccination by 5-10% (+5% influenza, +10% Tdap, +10% pneumococcal vaccines), and that part of the rationale for assessing cost effectiveness is because this modest improvement carries with it a relatively high burden of investment…

Methods

* In general, I was able to follow the methods based on my existing understanding of cost effectiveness analyses. However, I found the methods to be lacking in both clarity and detail - I would like to see a more precise description of the decision tree model, as well as a much more careful explanation of the model parameters. Importantly, the authors stated that "All decision
analyses and their results are subject to the parameters selected", but did not provide robust explanations of each of the parameters that were used. Please see specific concerns below.

* It is unclear whether the baseline and end-of-4 Pillars-trial vaccine coverage estimates are for 19-64 year olds.

* It is unclear whether the absolute increase in vaccine uptake using 4Pillars are for 19-64 year olds. It should also be noted that the methods text states that the base case and end-of-trial estimates were used in the model, but Table 1 listing model parameters includes absolute increase in vaccine uptake, not end-of-trial estimates. This is confusing, and not very reader-friendly.

* It is unclear whether the range in values for vaccine coverage are attributed to different sites, different age groups, different risk groups (comorbid condition vs. healthy) or something else. The reason for the range in values should be stated.

* It is unclear whether estimates for pneumococcal VE were adjusted for pneumococcal serotypes as they were in the original cost effectiveness paper among older adults. Pneumococcal serotype is listed as a model parameter in Table 1, but it is unclear what, exactly, these parameters are (proportion of disease cases attributed to specific serotypes? Among which age groups?) or how these parameters were used.

* It is unclear why the authors assumed 0% VE against NBP? This should be explained.

* On page 4, the authors state "As reliable illness rates from the study population are not available…" the wording of this statement is confusing, perhaps because the composition of the original study population was not provided for this analysis, and I assume that the original study population did not have sufficient sample size to estimate disease rates…? The authors should clarify this in some way.

* I had some difficulty understanding the robustness of the VE estimates used for this analysis. Can the authors please clarify whether VE estimates were specific for age and/or comorbid status? In addition, it is unclear why VE for influenza was not averaged over a 10-year period as was done for pertussis and pneumococcal vaccines. Influenza VE is extremely variable over time, thereby making it the vaccine which should be averaged (or some other summary measure) over time.
I had some difficulty with the sentence "For pneumococcal vaccine, Delphi expert panel estimates of yearly effectiveness for both pneumococcal vaccines against invasive pneumococcal disease (IPD) and non-bacteremic pneumonia (NBP) were averaged over a ten-year period and adjusted for recent pneumococcal vaccine trial results" - the way this sentence is worded makes it sound as though VE estimates for IPD and non-bacteremic pneumococcal pneumonia were averaged together, which is problematic.

Can the authors please clarify whether non-bacteremic pneumonia (NBP) is non-bacteremic pneumococcal pneumonia? If so, this should be addressed throughout the entire paper, including in tables and figures.

It is unclear how probabilities for mild, moderate, and severe pertussis were assigned (there is no citation provided in the text).

In general, the overall outcomes could be stated more clearly - the original cost effectiveness model from these authors reported on Quality-adjusted life years (QALYs), public health outcomes, and costs. The intended outcomes from the current model are less clear. For example, the authors report total vaccination and illness costs as a single measure, and discuss QALYs lost per person and per lifetime (which may be the same thing, but I cannot tell).

It is currently unclear what the values presented in Table 3 represent: what is "cost"; what is "incremental cost", what is "effectiveness"; what is "incremental effectiveness", and what is an "ICER"? Each of these should be defined in the methods, and stated in the results.

It is unclear what software or cost analysis approach was used to generate these models.

Results

It is unclear how the authors arrived at the values given in the first paragraph - how, exactly, was the number of cases/hospitalizations/deaths of each disease with and without the 4 Pillars intervention estimated? I would have expected an application of model outputs to some sort of enumerated population in order to obtain estimates of persons.

Please describe the results presented in Table 3 in the results section (Table 3 is not referred to in the results - please fix this).
The current differentiation of "3rd party payer perspective" and "societal perspective" is unclear. The authors define each of these in their introduction, and then they appear to present metrics that are inconsistent with what they defined. This could be an issue with clarity of language, but I'm not sure.

Please move the sentences describing the sensitivity analysis approach to the methods:
(1) Each parameter was varied individually in 1-way sensitivity analysis over the ranges shown in Table 1. The intervention program remained favored from both third party and societal perspectives with each individual parameter variation when using a $100,000/QALY threshold, a commonly cited US benchmark. (2) All parameters were also simultaneously varied over their distributions 5,000 times in a probabilistic sensitivity analysis, with results depicted in Figure 2 as acceptability curves.

Please add some sort of qualitative assessment of how the model was impacted by altering the model parameters besides whether or not the 4 Pillars Program was favored or not. For example, was the model robust to parameter changes, etc. I see this language used in the Abstract and Discussion sections, but it is not described/explained in the Results section.

Please provide a more appropriate discussion of the study limitations. This analysis is hugely susceptible to errors in model parameters, and this should be emphasized. One way to do this would be to develop the existing discussion around the sensitivity analysis ("the results were robust" is insufficient). In addition, it the paper would be stronger if the authors could spend some time discussing how errors - big or small - in their model parameters might influence their results. Some of these errors may be related to the estimates from the original 4 Pillars trial, or limits in the ability to obtain precise measures of disease incidence and/or VE. It appears that the authors did this a little bit for influenza vaccine uptake and VE, but this does not seem sufficient.

From my perspective, one of the most concerning limitations of this analysis is the assumption that the probability of receiving one vaccine is independent of receiving the others. There is literature showing that this assumption is false. I recognize the utility of making this assumption for modeling purposes, but the authors have a responsibility to address this assumption/limitation in their discussion (minimally) and in their sensitivity analyses (ideally).

Tables and Figures

In general, please update all table and figure titles to allow each table or figure to stand alone; for example, a reader should be able to look at Table 1 and have a clear understanding that Table 1 comprises a list of parameters used in a cost effectiveness model to estimate the impact on (insert outcomes here) following implementation of the 4 Pillars Program…
* In general, please update all tables and figures to have consistent use of key words, and abbreviations. For example, pneumococcal vaccines are depicted as 'PPSV' and 'PCV13' in the text, but as 'pneumococcal polysaccharide' and 'pneumococcal conjugate' in Table 1.

* Figure 1 - In general, Figure 1 is difficult to follow. The formatting is not reader-friendly, and the figure does not really increase reader understanding of the decision tree process. The authors should consider adding values to the parameters, as well as some copy-editing.

* Figure 1 - please update vaccine names to be consistent with abbreviations used in text

* Tables 2 & 3 - I assume these tables represents adults aged 19-64 years, not persons <65 years (given that the 4 Pillars Program was tested in children as well)?

* Table 3 - Please define the following: What is "cost" measured as? Per person? ICER and "Dominated"

Discussion

* The authors state that implementing an intervention program would be "beneficial" and "economically favorable". What do these terms mean?

* I recommend that the authors include a more thorough discussion of other cost effectiveness literature related to vaccine strategies. How do the incremental costs from this program compare to others? How much "public health benefit" is generally desired? Etc.

* The conclusion should be cleaned up to more accurately reflect this particular analysis: (1) The conclusion should really refer to prevention of VPDs, not overall health; (2) "Younger adults" should probably be changed to 'younger and middle-aged adults'; and (3) high-risk medical conditions may be a stretch - for example, some chronic conditions are not ACIP-defined "high-risk" conditions.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

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

Unable to assess

Are the conclusions drawn adequately supported by the data shown?
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No

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