Reviewer’s report

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

Version: 0 Date: 25 May 2019

Reviewer: Marc Baguelin

Reviewer's report:

The paper discusses the cost-effectiveness of a paediatric vaccination programme targeting healthy children. The study relies heavily on another modeling paper which shares some of the authors with this study (Backer et al. Epidemics 2018). The main message from the paper is that paediatric vaccination, while likely to be cost-effective, might result occasionally in massive epidemics due to the accumulation of susceptible in the youngest age groups who have escaped previous infection through vaccination or herd immunity. These results contrast with previous studies that have not shown such an effect. Overall the paper is very well written and most of the analysis very careful, but I think that the study carries three major flaws, which -in my opinion- prevent it from being used to inform policy at the moment. In particular, one of the assumption chosen is likely to drive most of the effect observed in the simulations, and I do think that this assumption is largely contradicted by current knowledge on LAIV vaccines.

I think that the way the authors have chosen to write the results in the present form is potentially dangerous. Indeed, some of the caveats from the approach are discussed and mentioned in the initial modeling paper but not in this one. Some of the policy makers are likely to read only the second paper and thus not weigh the value of the conclusions with the right amount of questioning.

Here is a brief description of the three major concerns I have with regards to the paper. Point 2 is in my opinion the most problematic.

1) The model uses only one "generic" flu strain, which means that e.g. a B strain in one season will confer immunity against an A/H3N2 year in the following seasons, while these strains should confer no cross protection. The model used in the study is thus very close from a SIR model with one strain. To sustain repeated epidemics other the years, such models need to have specific traits like forced seasonality to a level which might not be realistic. This should be explicited and could seriously bias the final conclusions.

2) The vaccine is assumed to protect for one year while natural infection protect for 5.1 years. In the first modeling study, Backer et al. actually mentioned that other modeling studies have chosen other approaches such as e.g. equal duration of protection through vaccination and natural infection, they even cite a study (Tam et al 2007) which demonstrates very good protection in year 2 after vaccination. For me this is the main assumption driving the results in
the models. To be informative, the model should be at least have a scenario with vaccine immunity equal to natural infection and one with a duration of two years. Given that the cold adapted live vaccine (the LAIV) induces a true infection in the upper respiratory track, it is likely that the resulting immunity is close to the one provided by natural infection. It is thus probable that the phenomenon of building of susceptible population is not as strong as predicted (as some of the children will remain protected for several years and compensate other individuals in the population protected through herd immunity). This might be in contrast with inactivated vaccine which are likely to provide a much shorter protection than natural infection (waning is already observed through a season).

3) The model uses a final size approach based on calculating one of the eigenvector from the Next Generation Matrix (Van de Kassteele et al.) It does not thus consider the temporal dynamics during the season. It is possible that the duration of the inferred epidemics is unrealistic and last e.g. 8 months. It is not clear to me if any filter has been implemented to prevent such unrealistic scenarios.

The authors have performed many different types of sensitivity analysis on coverage, discounting, costs and health effects. I think that this study could not be used to inform policy making without a thorough sensitivity analysis on the impact of the choice of duration of protection due to the vaccine vs natural infection.

Minor point:

"The finding that a childhood influenza vaccination program is expected to be not cost effective for the target-group itself differs from a previous dynamic modelling study for England and Wales [8]. This difference arises because we focussed on the long term impact of the childhood vaccination programme and adopted a time horizon of 20 seasons, whereas the dynamic modelling study for England and Wales focussed on the impact in the first season after implementing the childhood vaccination program, thus implicitly adopting a time horizon of one season."

I think that this unfairly caricature the previous modeling study. The model does not adopt a time horizon of one season, as it averages other several seasons (so thus reducing the variance of the impact of an individual seasonal campaign). The point below extracted from the discussion of the paper cited shows that the authors acknowledge that the potential risk for increased susceptibility should be accounted but be balanced by potential vaccination benefits being carried forward. By not accounting for this, the authors of this paper have unfortunately not fulfilled I think a fair comparison, while it is true though than an extension of the framework including propagation of immunity over several season is certainly much needed.

"The model on which this study is built considers the benefits over each individual season and averages these benefits over a 14-year period. It does not consider the impact of repeated vaccinations and the associated effect on immunity in the population. Whether there will be
additional benefits from protection carried forward from previous years, or a potential risk of increased susceptibility in the population due to a lack of exposure in the unvaccinated because of herd protection, is uncertain. An extension of our model framework to include immunity from natural exposure and vaccination and linking the seasons could potentially provide further insight."

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If not, please specify what is required in your comments to the authors.

Yes

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