Reviewer's report

Title: Cost-effectiveness evaluation of quadrivalent influenza vaccines for seasonal influenza prevention: A dynamic modeling study of Canada and the United Kingdom

Version: 3
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Reviewer: Koen B. Pouwels

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Major compulsory:

The model was calibrated using US unvaccinated influenza attack rates and year-to-year relative amount of influenza A compared to influenza B. The validity of this approach is dependent on several assumptions.

To better enable the reader to evaluate whether the attack rates that are used for calibration are likely valid, the authors should instead of just referring to a systematic review that includes several comparisons, specify which specific studies/numbers are used. For example in the previously published description of the model (Vaccine 2014;32:5098-5117), the authors stated that they used information about unvaccinated persons in vaccine efficacy trials obtained from the meta-analysis. However, it is not clear whether the authors used indeed only the RCTs that evaluated vaccine efficacy (and excluded the RCTs about antiviral efficacy (e.g. Clover et al. Am J Dis Child 1986;140:706-9, appendix table 142-144 of the referenced meta-analysis) or both vaccine and antiviral efficacy.

Obviously, the validity of the calibration depends on the degree of herd protection. If herd protection differs between the different included trials and the modelled US population, the validity of the calibration is compromised. The trials from the meta-analysis are from different years (1980-1998 if all are included), with likely different vaccination coverages among the population and consequently different degrees of herd immunity. Hence, the authors should at least mention this potential limitation in the discussion and preferably provide some information that could potentially support the assumption that the degree of herd immunity will be similar.

Since the data are calibrated on attack rates from a different country and the number of outcomes are obtained by multiplying the number of influenza cases by an outcome probability, the authors should add some references or information that could support the estimated number of influenza-related GP visits, ER visits, hospitalizations and deaths in the UK and Canada.

The vaccine efficacy against influenza A was assumed to be identical for both TIV and QIV. Could the authors provide any evidence to support this essential assumption?
Minor essential:

For Canada cost were inflation-adjusted to 2013 using the Canadian CPI. Does this mean that all 2013 costs were available for the UK?

The same list-price for LAIV and QLAIV is modelled. But is not it reasonable that the price could be lowered more for LAIV than for QLAIV when used for a routine vaccination programme?

It is stated that the conclusion is shown to be robust against uncertainty in the natural history parameters of influenza. However, this is only true if the uncertainty about the validity of the calibrating is ignored. The posterior distribution obtained for the natural history parameters do not reflect uncertainty about comparability of the different populations etc.

…. the slower antigenic drift of influenza may result in some carry-over of influenza B protection to subsequent seasons, thus further increasing the benefit of QIV relative to TIV. However, does this necessarily mean that the benefit will be larger? In a purely hypothetical situation that TIV induces two year full-protection, one could just change the B component every year and obtain very good protection. In that situation, changing to QIV would not necessarily be better, especially not in terms of cost-effectiveness terms.

Level of interest: An article of importance in its field

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