Author's response to reviews

Title: Cost-effectiveness analysis of quadrivalent seasonal influenza vaccines in England

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Reviewer 1

The authors examine the incremental cost-effectiveness of using quadrivalent influenza vaccines rather than trivalent vaccines in various age and risk groups in England, finding that use of quadrivalent vaccines in pediatric groups was most likely to be cost-effective (i.e., with the greatest incremental cost per quadrivalent dose), with extending quadrivalent vaccination to high risk adults or to the elderly having less of an incremental cost per dose margin to maintain cost-effectiveness at £20,000-30,000/QALY thresholds. Their modeling exercise and results are clearly reported overall, but would benefit from some clarification on trivalent vaccine effectiveness values used in the model, the rationale for no consideration of vaccination at ages <2 years, and justification for using a 90% criterion for cost-effectiveness acceptability, along with some more minor issues.

1. The authors use values for trivalent vaccine efficacy against influenza B representing efficacy during a year where there is a poor match between the circulating influenza B strain and the B strain in the trivalent vaccine. However, this circumstance is relatively rare - the vaccine included strain typically matches up fairly well with the predominant circulating influenza B. Thus, trivalent vaccine efficacy in the model represents, in my view, a worst-case scenario. This, however, is fine if the intent is to show what the maximum incremental cost per quadrivalent dose is under best-case scenarios for quadrivalent vaccines. If this is the intent, then the authors should state this and justify this choice. If this is not the intent, then sensitivity analyses varying trivalent vaccine efficacy should be considered.

+ Yes, this perhaps requires more information to be clear to the reader.
The original analysis by Baguelin et al assumed a mis-matched vaccine against the B strains for all 14 years in the model based on virological characterisation done at Public Health England during the corresponding seasons. We kept this assumption in the new manuscript. We agree that this presents the best-case scenario for quadrivalent vaccines.

We have expanded on our logic for this assumption in line 292 in the Discussion (see below) and hope that this clears things up.

“We assumed that existing trivalent vaccines were poorly-matched to the dominant circulating B strain in each influenza season. Whilst this assumption allowed us to maintain a consistent modelling approach with Baguelin et al. we recognise that it presents the best-case scenario for introducing quadrivalent vaccines. In addition, other countries have reported some vaccines were well-matched against the dominant circulating influenza B strains with little activity for the unmatched B strain [20,21], which would reduce the maximum incremental cost-per-dose of quadrivalent vaccines in our analysis. However, our approach allows us to report the maximum incremental cost in the best possible scenario for quadrivalent vaccines with the understanding that any previous years with a better strain match in vaccines reduces the cost effectiveness of quadrivalent vaccines. Indeed, the estimated proportion of influenza B infections between 2000 and 2010 caused by vaccine mismatched strains was 52.4% [22] presenting an encouraging opportunity for quadrivalent vaccines to reduce the public health impact of seasonal influenza.”

2. Other countries routinely vaccinate children against influenza at ages <2 years, while the authors consider no policy that includes these children. Some mention should be made regarding this policy choice and the choice of the modelers to not consider potential policies that include the youngest age group.

The existing vaccination programme using live-attenuated vaccine is unsuitable for children <2 years old due to safety concerns. Only the inactivated vaccine is licensed for children in this age group from 6 months of age but we did not consider it an option for our analysis. We have added a brief discussion point in line 306:

+ We did not consider extending eligibility to children aged under two years old, in contrast to vaccination programmes in other countries. The live-attenuated vaccine is not licensed for children in this age group, as the effectiveness of current inactivated vaccines is lower [23] and implementation of an injectable vaccine would represent considerable additional workload, this has not yet been recommended in the UK

3. The authors state, "The criteria to be cost-effective was that 90% of simulations had an incremental cost-effectiveness ratio below the willingness-to-pay threshold." (lines 179-181) They use no reference for this value. Although it seems reasonable, the authors should justify this value.

+ We sought to take a conservative approach to our economic evaluation so opted for this high threshold of cost-effectiveness and the proportion of simulations that fell below the £20,000/QALY limit. The JCVI recommends that mathematical modelling analyses to support the decision to implement new vaccination programmes should use a threshold of 90% of

“The level of risk aversion that the committee should demonstrate is a difficult judgement, but we recommend that the JCVI should require that their estimate of the likelihood that the true ICER exceeds £30,000 per QALY is no more than 10%.”

To make our approach clearer in the manuscript, we’ve added the following line to the Methods section in line 180:

“The criteria to be cost-effective was in line with recommendations from the JCVI that 90% of simulations had an incremental cost-effectiveness ratio below the willingness-to-pay threshold [17].”

Minor issues

- Showing cost differences between trivalent and quadrivalent vaccines from other countries could be useful to readers in understanding the maximum incremental cost per quadrivalent dose values mentioned in the paper.

  + This is a helpful suggestion, thank you. Since submitting our manuscript a systematic review on economic evaluations of quadrivalent influenza vaccines has been published which reports these values. We have cited the review in line 338, restructuring the paragraph comparing our results to the literature.

“The de Boer et al. review reported the range of incremental cost-per-dose of quadrivalent vaccines over existing trivalent equivalents for all studies was $1.25 to $7.14 in 2015 US dollars [25], though there was variation in the perspective for which economic evaluations were performed, the WTP thresholds for each country and the requirement of the proportion of simulations that should be below those WTP thresholds. Many studies reported that quadrivalent vaccines are cost effective with an emphasis of the sensitivity of these estimates to the parameters for the cost of vaccines and the efficacy of vaccines considered against the circulating influenza B strains. We adopted a conservative approach to our economic evaluation and feel that our conservative incremental cost-per-dose estimates for each proposed programme compare well to the studies featured in this review, with similar findings from our sensitivity analysis to those featured in the review.”

Other CEAs, like You et al. from Hong Kong conducted a similar threshold analysis and did not use the list price for each vaccine, so we did not include these studies in our Discussion section.

- "Clinical risk groups" should be briefly defined.
+ This is a helpful suggestion, thank you. We have listed the top-level clinical risk groups on line 86. We had already cited The Green Book, the guide for healthcare practitioners on immunisation and infectious diseases, which lists these comorbidities in more detail but it may be helpful to the reader to see the list explicitly.

Reviewer 2

I have difficulties to follow the methods of the paper hence find the current manuscript difficult to assess for several reasons. The underlying model for this analysis is based on Baguelin et al. 2015. The methods section should describe in more detail what the main features of the Bequalin model are in terms of model design/structure, assumptions etc. since I am not familiar with this work in the UK.

+ We have added additional details about the modelling approach of Baguelin et al 2015 to our methods section. See line 106:

We used the same mathematical model as [3] and [11], used to recommend the introduction of the paediatric seasonal influenza vaccination programme in the United Kingdom. The model brings together surveillance data from a variety of primary care, secondary care and sentinel data sources in addition to data on social contact patterns and seroepidemiological data and uses these data in a Bayesian approach, specifically adaptive MCMC techniques, to reconstruct epidemics using a transmission model for three influenza subtypes over fourteen years.

We’re hesitant to add more details on the modelling approach adopted by Baguelin et al 2015 for a few reasons, namely brevity and the avoidance of repeating the publication of the description of methods that is already in the public domain.

The cost structure is not clear - in order to reach the adolescents between 12-16 years old more activities are required for social mobilization and education hence more operational delivery costs would be expected.

+ The cost of vaccination per dose administered was assumed to include all administration and delivery costs in addition to the price of the vaccine, as assumed in the previous modelling work that introduced our model in 2015. If resources required per vaccinated child are higher to reach the secondary school population then this would affect both trivalent and quadrivalent, and should not therefore alter our findings. The key parameter here is the cost difference between the two programmes when the vaccine is changed. We have included a brief explanation in the manuscript on line 277:

Any additional resources required to implement the paediatric influenza vaccination programme would be the same whether the programme used a trivalent or quadrivalent live-attenuated vaccine, so we did not consider this potential additional cost in our analysis.

In line 148 it stated that "the additional cost of the QIIV pain in reimbursements to GPs and Pharmacists". I am not sure from what perspective the analysis (governmental versus societal,
financial versus economic) was performed. It would be useful to explicitly mention the perspective and scope of the analysis.

+ The analysis was performed from the perspective of the healthcare provider, as specified at the end of the second paragraph of the Methods section:

Costs and health benefits from the perspective of the healthcare provider were discounted an annual rate of 3.5%.

We have also discussed this in the Strengths and Weaknesses sub-section of the Discussion:

Our economic evaluation of the vaccination programmes followed the guidelines recommended by the National Institute for Health and Clinical Excellence (NICE) in evaluating the costs of the programme from the perspective of the health care provider

The programmes assessed are confusing. In line 155 you state that all four scenarios (i.e. baseline, programme 1, 2 and 3) including all children 2-16 were also assessed. However, in the results section I only found the three programmes without 2-16 year old. It would be useful to have a schematic overview of the comparators assessed in this study and how it compares to previous studies to understand what this study adds to the current discussions/publications in the UK

+ For all four scenarios we assumed that the childhood vaccination programme had been rolled-out to include all 2-11 year olds, not 2-16 year olds. We also assumed that the existing at-risk programme and elderly adults programmes continued. We then simulated the introduction of quadrivalent vaccines to the different cohorts.

We will include the following schematic diagram in the manuscript to clarify the scenarios explored. We thank the reviewer for this suggestion:

Finally, we re-ran all of the simulated programmes listed above but assumed that the childhood vaccination programme had been rolled-out to all 2-16 year olds, rather than just 2-11 year olds. We considered this minor change to all simulated programmes to assess the sensitivity of our results to the scope of the childhood vaccination programme.

Overall

Observational studies must adhere to the preferred reporting guidelines: STROBE. Please ensure this study complies with these guidelines, and include a completed checklist with your revised manuscript (available checklists can be found here: https://www.strobe-statement.org/index.php?id=available-checklists).

+ We will upload a completed checklist for cohort, case-control and cross-sectional studies combined.