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Title	Pertussis immunization in pregnancy in Canada: a cost-utility analysis
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Reviewer 1	Dena Schanzer
Institution	Infectious Disease and Emergency Preparedness Branch, Public Health Agency of Canada, Ottawa, Ont.
General comments (author response in bold)	In this study, the authors assessed the cost and cost effectiveness of universal immunization against pertussis in pregnancy. They report an additional cost of $12,987 per 1000 pregnant women vaccinated with Tdap resulting in an estimated benefit of 0.3 QALY for an incremental cost of $44,301 / QALY. Unfortunately, a number of details normally expected in a cost-effectiveness analysis are missing. While many of these items are listed in the CHEERS reporting guidelines, the required details are not provided. For example, the methods section states that “Utility values and costs were obtained from the literature through a detailed systematic review and were selected based on their fitness for purpose (i.e., relevance to the decision problem), credibility and consistency”, however the manuscript does not provide the results of the literature review nor even discuss the pros or cons of relevant studies. Rather than presenting a review of the literature on relevant parameter values, the authors seem to have selected values from one study. **Please note our responses with respect to “systematic” review above (response to editorial comments). We conducted a targeted literature search focusing on key sources for costs and utilities to employ within the model. This is standard practice for economic evaluation and we understand fully that the choice of systematic review implied methods akin to formal meta analysis. Again, apologies for the confusion.** Not only are we not provided with enough information to assess of the appropriateness of their data choice, some of their assumed ranges of uncertainty appear to be extremely narrow. For example, the range of uncertainty for pertussis incidence in 2006 is given as “Beta (359, 349219)”. I doubt that they got “Beta (359, 349219)” from the referenced document and I don’t think very many readers would understand that this suggests a standard deviation of about 5% of the incidence rate. In reality, this should be a surveillance data value for which errors in measurement are usually discussed as underreporting issues or other systematic biases that could result in a much larger uncertainty. There is, however, no discussion of underreporting. The year-to-year variation in annual incidence is significant with larger outbreaks occurring frequently enough (2 in the 10-year study period) to push the standard deviation over the study period closer to 50%. I can’t guess where the range implied by “Beta (359, 349219)” came from, and without an understanding of what uncertain is accounted for by the model, the probabilistic statements about the uncertainty in the ICER risk being misinterpreted. These are very serious concerns for an important study. **Within economic evaluation (based on the Canadian guidelines) data for which there is sample uncertainty should be represented by probability distributions. For all data within the model the probability distributions are derived from the actual data provided within the data source provided. Thus, for this example, the data comes from the reference cited: uncertainty is**

	represented by a beta distribution with alpha being the number of events and beta being the number without events. The 2018 Ontario Public Health technical document, on the recommendation to vaccinate pregnant women, outlines a number of issues that would need to be addressed in a cost-effectiveness study. This document, along the NACI statement and other provincial documents should provide a good indication of issues that need to be discussed in a cost-effectiveness study. The most obvious omission is the lack of sensitivity analysis where the parameters responsible for the most uncertainty are identified. I would imagine that VE for infants of vaccinated mothers would be a main source of uncertainty. However, I don't even see this parameter listed in Table 1 (could simply be a mislabelling issue as the referenced study does indicate that the quoted VE is for infants of vaccinated mothers). Again, one study is listed for the VE estimate, which could result in biased uncertainty ranges. The VE estimate should be based on a literature review of appropriate studies. A comparison of multiple studies suggest a broader level of uncertainty than the 95%CI for one study. If a meta-analysis is available, that would be preferred. **Vaccine effectiveness is included in the analysis and detailed in supplementary Table 2 (now clearly relabeled) with appropriate uncertainty incorporated.** **We note that a recent systematic review found that vaccine effectiveness against pertussis in infants of immunized mothers ranged from 69 to 91% for pertussis prevention and was 95% for prevention of death due to pertussis (Vygen-Bonnet, Safety and Effectiveness of Acellular Pertussis Vaccination During Pregnancy: A Systematic Review; MC Infect Dis. 2020 Feb 13;20(1):136.doi: 10.1186/s12879-020-4824-3.). This is based on the findings of four studies – the largest (n=72,781) of which we used as the basis for our estimate within our model. The lower estimate comes from a case control study (n=96). We have performed an additional scenario analysis using the lower estimate of VE (61% reduction in pertussis cases). This is now included in Page 9-10, Lines 212-220, and page 11 lines 266-267 and in Table 2.** Immunization against pertussis during pregnancy is highly effective in reducing death, with only one study reporting such estimate (VE=95%, Amirthalingam G, et al. Sustained Effectiveness of the Maternal Pertussis Immunization Program in England 3 Years Following Introduction. Clin Infect Dis 2016; 63(suppl 4): S236-S43) which we used in our modeling. The 2018 Ontario Public Health (OPH) technical document identifies international cost-effectiveness studies and discusses issues related to the Canadian context that should be addressed in your manuscript: – In noting that incidence was considerably higher in 2006 and 2012, OPH identify pertussis incidence as a key driver of cost-effectiveness. The measure of year-to-year variation in incidence does not appear to have been handled appropriately in your manuscript. In Table 1, incidence seems to be labelled as "probability of pertussis infection". Annual incidence is not a point estimate and does not have an associated probability distribution. (The Poisson distribution often associated with

	count data is used to make inference about the true rate, for example if we want to assume that the true rate is unchanged over a number of years. If you calculate the standard deviation for the annual incidence over the study period, you will notice that there is considerable extra-Poisson variation.) Rather than assigning a standard deviation to an incidence count, one would instead assess underreporting or other sources of bias. Errors associated with estimation of any systematic biases should be reported and discussed separately from surveillance data values. **Please note that we did incorporate uncertainty around pertussis incidence in two ways. First we characterized uncertainty around the incidence in each given year for which data were available. Secondly we then randomly assigned one year's incidence within the model. Please, see under Analysis on page 8.** – The CHEERS guideline requests that the data value and range be provided. It would likely be helpful to provide the annual incidence values (without a range), and an average annual incidence with an uncertainty range. There are various possibilities for the uncertainty range for the average: standard error, if you want to discuss uncertainty about an average over the specific study period; standard deviation, if you want to discuss the year-to-year variation in cost-effectiveness; or you could use bootstrapping to generate the probability distribution (to account for the non-gaussian distribution of annual incidence). **Please note this information is provided. We provide the probability distribution around pertussis incidence for each year of data and we then randomly assign one year's incidence within the model. Please, see under Analysis on page 8 and supplementary Table 2.** – CHEERS guidelines also require an explanation of how you converted estimates of precision (often 95%CI) into the distributions used. Please note that for most MDs the indicated probability distribution will not have much meaning. Please note that the guidelines require ranges in the same units as the data value or point estimate. **Please note that within the detailed Methods section and supplementary Table 2 we fully comply with the guidelines for economic evaluation in Canada and are fully transparent in the reporting of the probability distributions used.** – The OPH document also discusses some of the challenges with assessing cost. For example, they note that one dose of vaccine is already funded for all adults. This will potentially cover the cost of one dose for pregnant women for her first pregnancy, noting that the average number of children per woman is approximately two. There is also the issue of access to vaccinations during pregnancy when the pregnant patient is often transferred to an obstetrician. OPH document specifically mentions that: "Administration costs would be an important issue to consider in an Ontario-specific analysis." There is no discussion on how costs were arrived at in your manuscript. **Cost is not available because this is regarded as confidential information and is not publicly available in Canada. This is the main reason for us conducting scenario analysis around the cost of the vaccine and identifying the threshold cost at which point the decision concerning whether vaccination is cost effective would change.**

	– How much variation is there in the choice of disability weights? Again, the results of the comparison mentioned in the methods section is not provided as part of the results. Clinicians are generally interested in understanding what is accounted for when measuring the harms and benefits that go into the QALY. **Unfortunately we do not fully understand what this comment relates to. We provide the expected utility value and the parameter uncertainty.** Other specific comments: 1. Supplementary files could be used to document some of the methodological details or results of systematic reviews, or how the measures of precision/distribution were calculated. **Please see previous comments relating to systematic review.** 2. Results: Some of the listed results look like parameter estimates that were used as inputs to your model. (For example: "Vaccine effectiveness was estimated at 91% against all pertussis cases (infant and adult) and 95% against pertussis deaths."). The results section should summarize the results or outputs of your model. A table showing the rates and rate differences due to the intervention that were calculated by your model and lead into the QALY calculation should be included. **We have included in Table 1 the pertussis cases in infants and mothers for both the vaccine and no vaccine strategy.** 3. Why are most benefits expected to occur in the future? Time from vaccination of the mother to 3 months of age of the infant plus the 75 days of symptoms is likely less than a year. Perhaps more info is needed on the rates of and costs associated with chronic encephalitis? **The differences in long term outcomes comes from both the reduced mortality and reduced incidence of chronic encephalitis through vaccination. This is why more QALY gains occur beyond the one year time horizon.** 4. Where does the uncertainty with the age distribution come from? Perhaps incidence by age group should be treated as surveillance data? **We employed data which gave us the age at which children developed pertussis to allow us to characterize the time point at when the infection occurred and the differential hospitalization rates by age at infection.** 5. Please review the CHEERS checklist items and pay special attention to requests to "describe". When revising the manuscript, it would be best to assume that your response to these requests for information is insufficient. Most items do not appear to be appropriately addressed or described. **Thank you for this comment. We hope the changes made to the manuscript are satisfactory.**
Reviewer 2	Val Ginzburg
Institution	Department of Family and Community Medicine, North York General Hospital, North York, Ont.
General comments (author response in bold)	Dear authors, This is a major article that may trigger vaccination policy change therefore utmost attention should be taken when dollar value is assigned to it before it can be considered.

	Thank you. In your article for analysis of the program the cost per vaccine was used $12.5 plus added $4.5 administration cost. These do not take into account other associated costs including but not limited to distribution, transportation, administrative, storage, waste, taxes, etc. These will most likely increase the estimated cost by a significant percentage. I venture to guess at least 100%. This information may be available to you based on the previous implemented vaccinations programs in adults. 1. Could you provide this information in your analysis to estimate a real cost of this program as this may lead to a different conclusion? You have used existing data of $12.5+$4.5=17 without accounting for the real life costs and estimated that the vaccine cost would need to be less then $14.03 while this price should include at least administration costs ($4.5) as your analysis has included the administration cost in the calculation of the cost of the program. **We have incorporated a scenario analysis to identify the threshold cost of the vaccine. Unfortunately due to the commercial nature of the data the actual cost is unavailable. We have introduced the concept of these important costs within the discussion.** 2. Could you clarify your calculation and conclusion that vaccine cost should be less then $14.03? **We have clarified this in the text on page 10-11 under the section "Cost Effectiveness Results".** 3. Could you calculate the final cost per vaccine considering above additional costs to see at what cost per vaccine the program would have been cost effective every year during 2006 - 2015 period? **Unfortunately we are not sure what this comment means.** The analysis indicates that the program would be cost effective 6 out of 10 years under the simulated scenario however you have not included in your analysis who were the effected infants. This would be important to know if the infants with pertussis 71/100000 belong to a high risk population with additional comorbidities. This information would be crucial to identify high risk mothers to have vaccine vs entire population making this change in policy more cost effective. **Infants affected by pertussis during early infancy (target for maternal immunization) usually do not have comorbidities that put them at risk for pertussis and are born to pregnant women with low risk pregnancy. This is also true in the Canadian context (Abu-Raya B, Bettinger JA, Vanderkooi OG, et al. Burden of Children Hospitalized With Pertussis in Canada in the Acellular Pertussis Vaccine Era, 1999-2015. J Pediatric Infect Dis Soc 2018.).** 3. Could you provide information about subgroup analysis of the affected infants who required hospitalization, such as personal history, delivery history, pregnancy history and maternal health? Reevaluate the data if only high risk group mother were to be given vaccination would that be cost effective. **Apologies, but we are unsure what this comment relates to. Vaccination against pertussis during pregnancy is a universal recommendation that is not restricted to high risk women.**