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Title: Cost-effectiveness modelling of birth and infant dose vaccination in Ontario from 2020 to 2050

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Reviewer 1

General comments (author response in bold)

I appreciate the invitation to review this paper, and congratulate the authors on tackling an important topic.

This is an economic evaluation, examining the impact of changing vaccination for hepatitis B from adolescent to infant vaccination approaches in Ontario.

Hepatitis B remains an important infectious disease, particularly outside of Canada. Given that Canada – and Ontario in particular – receives large numbers of immigrants from areas where hepatitis B is more prevalent, this will be useful for policymakers in provinces/territories that do not yet use an infant vaccination strategy.

My major concerns:

1. Did the authors use the CHEERS reporting guideline? I did not see this in the materials I reviewed, and it would help increase the transparency around reporting elements of the model.

Yes, CHEERS was followed.

2. I know the Abstract has a tight word count but it would be important to provide more information on what type of model / approach was used.

Now included, “The PRoGReSs model (1), a dynamic HBV model that incorporates population by year, disease stage, sex, and the influence of immigration, was used to quantify the disease and economic burden of chronic HBV infection in Ontario from 2020-2050.” Page 3: lines 8-9.

3. In the Intro or Discussion: My understanding is that in Ontario, part of the reason for HBV vaccination to happen in adolescents is the identification of HBV as a sexually transmitted infection. As the authors note, of course, there is vertical transmission and other forms of exposure. Will this need to be addressed to get buy-in from families? Will a communications plan be necessary to reframe HBV?

We have revised the introduction to better frame this, in line with comments from another reviewer above. A public education campaign would undoubtedly accompany the rollout of the change in policy, and could involve both the use of social media and signage in clinical settings. As well, primary care providers (and in this case obstetrical providers) are typically the most common mechanism to introduce new vaccinations (or vaccinations that were not previously publicly funded, but now are), and get parental buy-in. A communications plan would likely come from Ontario Health to disseminate information to the Ontario Health Teams. Large professional associations such as the Ontario Medical Association, the Nurse Practitioners’ Association of Ontario, and the Registered Nurses’ Association of Ontario, and The Association of Ontario Midwives would also likely

disseminate to members. As an example, this recently occurred when Tdap was added to the publicly funded schedule for third trimester dosing (long-standing in the US).

4. In the Methods or Discussion: If a dose is given at birth, are there any considerations in terms of rollout and training staff around implementation? How would parents react, and what can be learned from other provinces that already have an infant strategy? **In terms of skills, RNs/RPNs in labour and delivery units are already administering intramuscular vitamin K shortly following birth, so certainly this would not be a new skill, and HBV immunization could be done at the same time. Furthermore, children born to HBV-positive mothers are already vaccinated at birth and it is routine in Ontario for children who need immunizations and are in the hospital to receive them while they are inpatients, so birth dose vaccination is already part of the skillset of obstetrical, neonatal, and pediatric nurses. We do not anticipate that an immunization that has been available for several decades and used in other provinces and the US in newborns and infants would present the same concerns regarding vaccine hesitancy as we have seen for COVID-19 or other vaccinations. As we reference in the discussion, vaccination uptake in infancy is the highest among all age groups – 90% in Ontario. As a comparison of a fairly new addition to pediatric immunizations in Ontario, the rollout of rotavirus vaccination occurred in 2011, and has had excellent uptake. By the third year of roll-out there was an uptake of 84% (Wilson et al. PLoS One, 2018). Although we cannot exactly predict how parents in Ontario would react, however, what we do know from our clinical practice is that many parents pay out of pocket to provide HBV vaccination to their children prior to adolescence. Finally, as clinicians who see HBV-positive patients, we can also say that parents or family members who are diagnosed with HBV years after their children are born (fathers, grandparents, etc) are quite worried that they could have infected the child and are/were frustrated that their child was not offered birth dose HBV vaccination in Ontario. Universal vaccination would fix this. A public education campaign would undoubtedly accompany the rollout of the change in policy.**

5. Methods: Please mention discounting and the rate in the Methods.

We have updated the methods to include discount and rate with citation. “All costs were inflated to 2020 Canadian dollars (CAD) based on the consumer price index for health care (24), and indirect costs were discounted at a standard 3% rate (23).” Page 7: lines 20-21.

6. Methods: Please update the model input table to reflect the literature sources used. Can the authors provide more details on “expert consensus”? Who were the experts – the authors?

We have added a new table to the Supplement that outlines the Delphi process used to gain expert consensus. Table 1S.

7. For Table 3: Is it missing scenario 5?

Yes, this was in error, and has been corrected.

My minor concerns:

1. In the introduction, can the authors briefly compare Canada to other OECD countries with a similar healthcare system?

We have added a brief mention of other countries with similar healthcare systems. “However, even after 30 years and adoption among 100+ countries (including the US, UK, Australia) (4), only 3 provinces/territories in Canada provide birth dose vaccination, 5 vaccinate in infancy, and 5 in adolescence; including Ontario (5).” Page 4: lines 9-10.

2. Results: this sentence was confusing: “... were projected to decrease approximately 50%, partially as the result of an annual 3% discount rate, but largely due to a decrease in prevalence with any vaccination strategy.”

This has been split into two sentences. “For all proposed scenarios, annual direct medical costs were estimated at \$142 M (2020 CAD) in 2020 and were projected to decrease by approximately 50%. This is partially as the result of an annual 3% discount rate, but would occur due to a decrease in prevalence with any vaccination strategy.” Page 8: lines 18-21.

3. Some of the tables in the supplement have incorrect titles, and the first graph has a confusing y-axis (no label, unclear from title).

We have updated the graph in the supplement to clarify the y-axis and title.

4. I think it would be useful to be consistent when reporting of costs, instead of \$3,334 M just state \$3.3 B.

Most values were reported in the text and figures in millions, and now this is consistent throughout.

Reviewer 2: Carla Ginn, Associate professor; co-completed by Grace Perez, Biostatistician, University of Calgary

Institution: Faculty of Nursing, University of Calgary; University of Calgary

General comments (author response in bold)

Abstract

1. Background– please include more information regarding all Canadian provinces/territories and birth dose vaccination for HBV.

Modified to include HBV immunization across provinces. “However, even after 30 years and adoption among 100+ countries (including the US, UK, Australia) (4), only 3 provinces/territories in Canada provide birth dose vaccination, 5 vaccinate in infancy, and 5 in adolescence; including Ontario (5).” Page 4: lines 9-10.

2. Methods – please describe the type of model used.

We have now included that the PProGRess model was used that that incorporates population by year, disease stage, sex, and the influence of immigration.

3. Interpretation – has thought been given to focusing on addressing vaccine hesitancy in new parents?

Unfortunately, due to space limitations, are not able to include discussion on this in the manuscript. However, we do not anticipate that an immunization that has been available for several decades and used in other provinces in newborns and infants would present the same concerns regarding vaccine hesitancy as we have seen for COVID-19 and some other vaccines. As we reference in the discussion,

infant vaccination uptake is the highest among all age groups – 90% in Ontario. That being said, as a comparison of a fairly new addition to pediatric immunizations in Ontario, the rollout of rotavirus vaccination occurred in 2011, and has had excellent uptake. By the third year of roll-out had an uptake of 84% (Wilson et al. PLoS One, 2018).

4. This is a very interesting, well-written, and methodologically sound paper. It would be helpful if the Figures were attached and/or referred to in order within the paper. The number of Figures could be reduced for clarity.

We have ensured that all figures appear in the order in which they are presented in the text and removed unnecessary supplemental figures.

5. Does Figure 1S take into account the potential of adolescent immunization coverage (may only be 67%) in comparison to the potentially higher uptake (90%) in infancy?

Figure 1S represents the prevalence with the base case scenario, i.e. prevalence will decrease over time even with continued adolescent immunization. However, we have removed in line with comment #4.

6. Table 1S title is missing a word or two after the word “Grade.”

Corrected, as above.

7. Table 2 – why do the percentage coverages fluctuate over time?

We suspect this comment is with respect to Table 1, and not Table 2. The coverage rates are ramped up over time under the assumption that nearly full coverage will take a least several years to achieve.

This paper provides a potentially positive impact on cost-benefit, policy development, and health outcomes in Ontario, throughout Canada, and globally.

Reviewer 3: Dr. Graham

Institution: Viral Hepatitis, Infectious Disease, Beth Israel Deaconess Medical Center
General comments (author response in bold)

1. This manuscript takes a comprehensive modeling approach to determine the value of a change in policy for HBV vaccinations. It notes that the WHO has advocated universal birth-dose HBV vaccination but does not clearly explain why, which would have been important in the context of the global controversy around hexavalent infant vaccination starting at 2 months.

This was not included due to space limitations. However, we have now included this in the background. “The rationale for adolescent vaccination was based on four assumptions: that all pregnant women are screened, that all infants born to positive mothers receive postexposure immunization, that sexual contact is the only other risk factor, and that immunity from birth and infant vaccination wanes.”

Page 4: lines 11-15.

2. The authors detail the lapses in care that should drive a change in policy, but they are not presented in an easy-to-follow way. Readers should take away that birth-dose vaccine is necessary because 1) not all pregnant women are tested for HBsAg; 2) not all HBsAg+ pregnant women and infants receive all required care; 3) not all household members of every baby are tested for HBV; and 4) any health plan that involves the

cooperation of adolescents is bound to have gaps. The paper does not make clear why several provinces delay HBV vaccination until adolescence.

We have modified the background to include this. As above. Page 4: lines 11-15.

3. The focus on cost implies that cost is a factor, or that describing a less-expensive approach would convince people to change the policy, but the modest expense of these vaccine programs makes this concern hard to believe. What is the root cause that needs to be addressed in order to effect a change in policy?

This is a fair point, and we have now included this perspective in the conclusion. “We have demonstrated previously that children born in Canada and living in Ontario are acquiring HBV prior to adolescent immunization, a lifelong disease that is completely preventable. Here we show that birth dose vaccination is cost-effective and infant immunization is cost-saving. Considering the minimal increase in cost, it may be reasonable to shift to birth dose to attempt to achieve the fewest number of preventable new infections in children. Based on these data, a policy shift to include birth dose HBV immunization is required and should become the standard of care and publicly funded.” Page 14: lines 1-7.

4. My impression is the authors favor the hexavalent 2, 4 and 6 month vaccine series, although this approach does not address a couple of gaps meant to be addressed by the birth dose vaccine (without making this clear). In addition, most countries that use the hexavalent vaccine do so because of cost and the difficulty accessing babies at birth for vaccination. These challenges should not be issues in Canada. A critical element of this model is the cumulative burden of HBV detailed in Table 3. I don't understand why scenario 5 is not listed here, since cost-saving with scenario 5 needs to be balance by any increase in cases due to babies who would be missed between birth and 2 months. **Our original objective was to present the data as is, and not to overinterpret, or make a recommendation. However, as suggested by this reviewer and others, we have now taken a stance in the conclusion as above. The reason to compare birth to infant immunization was in fact because 5 provinces in Canada vaccinate in infancy, and at least BC has data on the benefits of this (referenced in the discussion). However, when we speak with experts in HBV from those provinces, there is not a clear reason why the provinces made the switch. Not including the hexavalent scenario was described in the text, but not in the table. This was a formatting error, and it has been added.**

5. The fact that prevalence drove most of the uncertainty in scenario 5 is worrisome since over 50% of persons with HBV have not been diagnosed.

The uncertainty is measured around cost-effectiveness (cost per DALY averted), and the greatest driver of this uncertainty in most regions is the prevalence of chronic HBV. We agree that low rates of diagnosis are worrisome, as the undiagnosed portion of prevalent cases is typically the reason for having a large range around total prevalence. That being said, it is very likely that the prevalence is higher than our base case, rather than lower, which would make infant/birth dose vaccination more cost-effective.

Minor comments

6. The legends for Tables and Figures are either missing or sparse.

We have revised figure legends, table titles and footnotes.

7. I cannot tell if “infant vaccination” refers to the hexavalent 2, 4, 6 schedule and “birth dose vaccination” refers to all schedules that include at least one individual HBV vaccine, with one given at birth.

Exactly, the infant schedule does not include a birth dose. We have clarified in the abstract and throughout the manuscript.