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Title: Universal ophthalmia neonatorum prophylaxis in Canada: a cost-effectiveness analysis
Authors: Ellen C. Rowlands Snyder MD MSc, Elspeth McGregor BASc MBBS, Doug Coyle PhD

Reviewer 1: Dorothy Moore
Institution: Pediatrics, McGill University
General comments (author response in bold)

This is a model-based cost utility analysis comparing the outcomes of newborns receiving ophthalmia neonatorum ocular prophylaxis with those receiving no prophylaxis. The mean lifetime incremental costs of ON prophylaxis and the mean incremental effectiveness are assessed. Prophylaxis had an incremental cost per long term QALY gained of CAN$ 355,798. The conclusion is that given a willingness-to-pay threshold of 50,000 CAD per QALY, ON prophylaxis with erythromycin ointment is not cost-effective in Canada. This information will be relevant to decision-makers responsible for public health preventive protocols and programs.
The methodology appears to be sound. I have concerns about the model parameter used to determine risk of blindness. The data on this point in Table 1 is quite confusing and may be an important overestimate of the risk of this outcome. See comment re Table 1, below.
An important limitation is the sparsity or lack of data concerning (i) the long term consequences of neonatal gonococcal ophthalmia, especially blindness, in countries where rapid diagnostic techniques and effective treatment are available, and (ii) on the effectiveness of ocular prophylaxis with erythromycin in preventing gonococcal ophthalmia.
Thank you for this feedback and these comments. The limitations in the data available are highlighted in our limitations sections of the discussion and are certainly one of the challenges facing decisionmakers. Our probabilistic model accounts for some of the uncertainty in the data that is available and our value for information analysis sheds light on the impact of some of this uncertainty.

Specific comments, most of which are minor editorial issues:
ABSTRACT

Line 33: …Although prophylaxis “is” inexpensive…
Line 29 (and elsewhere in the manuscript): Suggest use “ocular prophylaxis” instead of “eye prophylaxis” (more conventional term)
Thank you for these suggestions. We have made the suggested changes.

INTRODUCTION

Lines 54-58, also elsewhere in the document: Note format for names of microorganisms: If Genus and species given, italics, and with small letter for species: <i>N. gonorrhoeae, Chlamydia trachomatis;
Thank you for these suggestions. We have made the suggested changes.

Line 57: “(CPS, 2018)”. What does this refer to? (CPS statement was 2015 and is ref. 6)
We have changed the reference (CPS, 2018) to ref. 6

METHODS

Page 3 line 103: “proportion of women who develop adverse events”. I think this should read ‘proportion of newborns…”
Thank you for this suggestion. We have made this change.

Line 114: should read “gonorrhea”
Did not see a change to be made on line 114, but changed Gonorrhea to gonorrhea in line 120.

Line 117: Ref 11 re effectiveness for prevention of GC ophthalmia: Note that for this study both silver nitrate and erythromycin were used alternatively and results for the two products are not separated. If silver nitrate is superior to erythromycin, effectiveness of the latter may be overestimated. I realize that there are no data specific to erythromycin and GC, but this limitation should be mentioned, perhaps in the discussion.
Added to the discussion “there is limited data on the real-world effectiveness of erythromycin ointment in the prevention of ON. The effectiveness parameter used came from a study which pooled data from silver nitrate and erythromycin ointment use and therefore could overestimate the effectiveness of erythromycin alone.”p6
Note that the possibility that our study overestimates the cost effectiveness of ON is already discussed.

Line 135: Ref 12. I think the ref. here is 16 (Kwon) not 12 (Chen)
Thank you for this correction. We have made this change

RESULTS

Page 4 line 176: “$355,394” ? Is this the correct number?
Thank you for noting this typo. We have made the correction to 355798.

Page 5 line 188: should read “chlamydia and ”gonorrhea”
Thank you for this suggestion. We have made this change.

Line 189: “… infections prophylaxis..” delete “prophylaxis”
Thank you for this suggestion. We have made this change.

DISCUSSION

Page 5 line 223: “With emerging erythromycin resistance…” – re-word to indicate that erythromycin resistance refers to N. gonorrhoeae, not chlamydia.
Thank you for this suggestion. We have altered the wording to indicate the resistance is specific to gonorrhea.

Page 6 line 225 – 226: Should mention that screening needs to be repeated during pregnancy for women with negative results on initial screening but at high risk of acquisition of infection during pregnancy; rigour with which this is done will influence transmission risk.
Thank you for this comment. The section has been edited to more explicitly refer to the pre-natal screening guidance that the reviewer is highlighting

"The accuracy of STI screening is dependent on universal access to STI testing and treatment as well as rigorous application of pre-natal screening guidelines including identification and follow up of high-risk individuals (8)." P6. The value of information analysis indeed highlights how important this is when considering risk of ON.

Page 6 line 233: "Generally, national guidelines in countries such as the UK, Denmark, and Sweden have been driven by risk assessment (21).". The reference cited does not support this statement.
Thank you for this comment, we have adjusted the wording as follows: " While national guidelines in countries such as the UK, Denmark, and Sweden have recommended discontinuing ON prophylaxis(21), the United States as well as many provinces in Canada continue the practice(5)." P6

Line 239: "…reported no cases of blindness in any study group". This review (ref 23, 2020 version as 2015 version is no longer available) states that "none of the studies collected data on blindness".
Reference updated to 2020 version: "Additionally, a recent Cochrane meta-analysis examining rates of gonococcal conjunctivitis in infants treated with ophthalmic prophylaxis or placebo indicated that the studies reviewed did not report on blindness as an outcome and that the effect of prophylaxis on ON had low to very low certainty of evidence (23)."

Line 252: "would likely reduce". Suggest replace with something like "might reduce". Resistance is determined by levels of an antibiotic achievable in the blood stream. Application to the eye will provide very high levels locally. It is not known if this will be sufficient to overcome resistance.
Thank you for the suggestion. We have made the recommended change and certainly agree that that there is considerable uncertainty in how resistance to systemic antibiotics translates to topical/ophthalmic applications.

Reviewer 2: Shehzad Ali
General comments (author response in bold)

This is an important study that evaluates the cost-effectiveness of universal ophthalmia neonatorum prophylaxis in Canada. The economic evaluation is well-conducted and clearly described. The study uses a lifetime perspective and uses a combination of decision tree and Markov model. The authors conducted a probabilistic analysis and also reported scenario analyses. Overall, this is a well-conducted study.
However, I have a few queries and suggestions.
- The authors have found that, given the current prevalence, prophylaxis is not cost-effective. If prophylaxis is stopped, the number of cases will rise. At what point would prophylaxis become cost-effective again?
Thank you for your comments!
Our model identifies the expected rise in ON following cessation of prophylaxis without other changes in STI management in Canada. Our study indicates that prophylaxis is not cost effective in the current context.

- The authors mention that more common pathogens include chlamydia trachomatis, staphylococcus, streptococcus, and haemophilus spp. Given that erythromycin is less

effective against them, should the comparator not include other antibiotics for prophylaxis?
Universal mandatory ON prophylaxis currently uses erythromycin. There are jurisdictions that have stopped requiring ON prophylaxis and there is currently debate as to whether Ontario should do the same. While the differential effectiveness of antibiotic ointments on less virulent ocular pathogens is interesting, it was not the focus of this paper. A future paper could look at the cost effectiveness of different regiment, should an alternative become the recommended clinical practice.

- For additional analysis, did the authors consider specific subgroups in which the prevalence of ON is higher?
As described, our scenario analysis looked at the cost effectiveness in a theoretical population with higher prevalence of ON. Analysing subgroup data for our input parameters would not be feasible given the very small numbers within the whole population already.

Minor points:
- Introduction should include more information on what CPS recommends. Consider moving Appendix A to the main text.
We aim to keep within the word limit, but acknowledge the need for clarity and relevant details within the main body of the text. As such we have added a few details to the introduction as follows: "The Canadian Pediatric Society (CPS) advocates for focus on prenatal maternal screening for N. gonorrhoeae and C. trachomatis rather than universal ophthalmic prophylaxis for the newborn(4)."p2

- Decision tree is a little confusing – specific thoughts are below:
o 'maternal chlamydia' splits into 'maternal gonorrhea' or 'no maternal gonorrhea'. I understand this is to capture co-infection but this can be labelled better.
Thank you for these helpful comments. We have made some changes to help with clarity.

o Same goes for the next split: 'true +STI screen' and 'false –'. If you mean true positive and false negative, what about the true negative and false positive?
At the branch of the tree the reviewer refers to, individuals have infections. Therefore, the probabilities relate to whether these infections are detected – hence, the only relevant probabilities relate to true positive and false negative.

o Then 'cure' and 'treatment failure': the treatment is not clear.
Footnote added to figure to clarify that this refers to treatment of maternal STI (and therefore newborn exposure)

o Node 2: 'ON cured' after 'treatment failure' – does this imply spontaneous recovery or a second line treatment?
With the clarifying footnote it should now be clearer that ON cured refers to treatment of ON in the infant, while the preceding node refers to the treatment of the maternal STI.

- Results section: when utility and cost values are presented, you should also include the confidence intervals, or justify not including them.

Thank you for this comment. The probability distribution is presented in table 1 for these parameters in the format that is standard this type of study.