COST-EFFECTIVENESS OF UNIVERSAL OPHTHALMIA NEONATORUM PROPHYLAXIS IN CANADA

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Abstract

Background: Prophylaxis for ophthalmia neonatorum (ON) at birth is required by law in Ontario. However, declining prevalence of disease and efficacy of prophylaxis have called into question this practice. Although prophylaxis inexpensive, the cost-effectiveness of its universal application should be examined. Our modelling study will quantify the potential impact of a change in infant eye prophylaxis policy.

Methods: Our analysis compares ON prophylaxis with no prophylaxis through cost utility analysis with a lifetime time horizon, considering a provincial government payer. We assessed both the mean incremental costs of ON prophylaxis and its mean incremental effectiveness using a hybrid (part decision tree/part Markov) model. Scenario analysis examined alternative time horizons and discount rates. Threshold analysis was conducted to examine the impact of variations in the cost of prophylaxis and STI prevalence.

Results: In our model, prophylaxis for ON did not meet a willingness to pay threshold of 50,000CAD per QALY. While prophylaxis was effective in reducing morbidity associated with ON, the number needed to treat to prevent one case of ON blindness was 500,000, with an associated cost of over 4,000,000CAD. When compared to no prophylaxis, prophylaxis had an incremental cost per long term QALY gained (ICER) of CAN$ 355,798.

Interpretation: We found that ON prophylaxis, while individually inexpensive, leads to very high costs on a population level. In order for ON prophylaxis to be cost-effective, the prevalence of gonorrhea infections in pregnancy must be significantly higher. These findings contribute to the discussion on mandatory prophylaxis currently underway in several jurisdictions.

Introduction

Prophylactic treatment of ophthalmia neonatorum (ON) with topical erythromycin at birth is required by law to be applied to all newborns in Ontario(1). ON is conjunctivitis occurring in the first 4 weeks of life. Mandatory prophylaxis to prevent ON has been in place since the pre-antibiotic era when it was predominantly caused by transmission of *N. Gonorrhoeae,* leading to rapidly progressive eye infection and potential blindness(2, 3). Since the advent of antibiotic treatment for *N. Gonorrhoeae*, coupled with universal prenatal screening, rates of ON have declined significantly(3). Further, *N. Gonorrhe*a is no longer the leading cause of ON, accounting for <1% of all cases in the United states (CPS, 2018). More common aetiologic pathogens include chlamydia trachomatis, staphylococcus, streptococcus, and haemophilus spp. Erythromycin ointment does not effectively prevent these infections. There is also evidence that the efficacy of erythromycin for ON prophylaxis may be declining due to emerging resistance(4).

Several high-income countries and some Canadian provinces have repealed ON prophylaxis requirements(3). Legal mechanisms now exist for low-risk parents to opt out of prophylaxis in Ontario (1). A Canadian Agency for Drugs and Technologies in Health (CADTH) rapid response report found that evidence for or against universal screening is limited and evidence-based guidelines make conflicting recommendations(5). The Canadian Pediatric Society (CPS) advocates for focus on maternal screening rather than universal prophylaxis(6).

Our modelling study will quantify the potential impact of a change in infant eye prophylaxis policy on quality of life. Although erythromycin ointment is an inexpensive intervention, the cost-effectiveness of its universal application should be examined. This may assist the government of Ontario in choosing if it will continue to require and fund universal ON prophylaxis within provincial hospitals, or move towards relying on prenatal screening and treatment as prevention of ON, as the CPS suggests(6).

Methods

Decision Problem

The decision problem addressed by this analysis is whether a provincial government as a funder of health care should fund ON prophylaxis. Analysis compares the current ON prophylaxis regimen (base case) with no prophylaxis (alternate case). Analysis takes the form of a cost utility analysis with a lifetime time horizon. Analysis was conducted to assess both the mean lifetime incremental costs of ON prophylaxis and its mean incremental effectiveness. Effectiveness was expressed primarily by lifetime quality adjusted life years (QALYs) and with secondary outcomes, cases of blindness averted through prophylaxis and short term QALYs. Cost effectiveness was assessed using the incremental cost-effectiveness ratio (ICER). The study was conducted from the perspective of a provincial health care payer within the single payer Canadian health care context. The lifetime time horizon was used in order to capture lifetime costs of disutility through blindness from ON.

Patient population

The patient population is the Canadian population of newborns. Maternal input data from pregnant females within the Canadian population is modeled to identify neonatal exposure parameters.

Treatment comparators

This analysis compared the application of 0.5% erythromycin ointment to the eyes of newborns as prophylaxis against Ophthalmia Neonatorum to no prophylaxis. Both the base case (current universal prophylaxis practice) and the alternate case (no prophylaxis) are assessed in the context of current prenatal screening and treatment guidelines which include the treatment of chlamydia and gonorrhea detected among pregnant women as well as among infants found to have been exposed at the time of birth(6–8).

Decision analysis model

Analysis was conducted using a hybrid (part decision tree/part Markov) model constructed in Microsoft Excel 16.26 (Figure 1). The short-term decision tree model first allows determination of the proportion of mothers with chlamydia and/or gonorrhea and with prophylaxis the proportion of women who experience adverse events. The tree then simulates the impact of screening and treatment which facilitates estimation of the proportion of babies who will develop ON and the outcome of ON in terms of the proportion who develop blindness. The long-term Markov model then simulates the lifetime QALYs for infants who experience blindness and those who do not.

Risk of ON was modeled in a hypothetical population of newborns, born to mothers who had undergone prenatal screening according to current Canadian guidelines (Appendix A) and who did (base case) or did not (alternate case) receive 0.5% erythromycin ointment as ON prophylaxis at birth. Prenatal screening and obstetrical testing are assumed to modify baseline population risk of ON in the same way regardless of ON prophylaxis. Model parameters are described in Table 1.

Baseline population risk of ON is calculated based on chlamydia and gonorrhea prevalence in the Canadian female population of childbearing age(7,9), assuming a 40% probability of Gonorrhea transmission(6) and a 15% probability of chlamydia transmission from mother to newborn causing ON(10). The effectiveness of prophylaxis in decreasing this risk is calculated based on studies comparing prophylaxis to no prophylaxis(11,12).

Costs

Costs within the model were calculated for neonatal conjunctivitis treatment, erythromycin ointment and medical assessment of side effects of prophylaxis. Costs were derived from the published literature and presented in Canadian dollars (7,13–15). The costs of missed ON infection and subsequent blindness were calculated based on an expected lifetime of 82years(16) and discounted at a rate of 1.5% per annum(17). Full details of the costing methodology is provided in the appendix (Appendix B).

Utilities

Baseline health utility of a healthy term infant was taken from a meta-regression of pediatric HUI3 health utilities(16). Long term utility values assuming average health status were obtained by age from the 2014 Canadian Community Health Survey(17). Given that ophthalmia neonatorum and its treatment is not expected to have an impact on gestational age and vice versa, all infants are assumed to be born healthy at term and differential baseline health utilities of preterm and extremely preterm infants are not modelled. Disutility from ophthalmia neonatorum that is treated and cured near the time of birth is considered negligible on a lifetime time horizon, as are any disutility from adverse effects of prophylactic erythromycin ointment. The annual disutility associated with blindness from missed ON was taken from the same 2017 meta-regression for the pediatric age-group (up to age 16)(12). The disutility associated with blindness over the age of 16 was taken from a recent study (18).

Analysis

Estimates of the expected values for outcomes and costs were obtained through Monte Carlo Simulation with input parameters assigned a probability distribution based on their expected value and degree of uncertainty. Expected values were estimated based on 10000 replications which was sufficient to obtain stable estimate of the costs and QALYs for both prophylaxis and no prophylaxis. The underlying uncertainty around whether prophylaxis is cost effective was presented by a cost effectiveness acceptability curve (CEAC), illustrating the probability that prophylaxis is cost effective based on different threshold for a decision maker's willingness to pay for a QALY.

Scenario analysis

Scenario analysis addressed methodological and structural uncertainty. We reran our analyses adopting alternative discount rates (0% and 3%) and different time horizons (1 year, 10 years and 20 years).

In addition, two further threshold analyses were conducted. A simple threshold analysis was conducted to identify the cost of prophylaxis which would lead to ON prophylaxis being considered cost effective at a maximum willingness to pay for a QALY of $50,000. A further threshold analysis focussing on determining the threshold of STI prevalence in the pregnant population, or subgroup thereof, which would likewise be associated with a threshold of $50,000 per QALY.

Value of Information Analysis

Value of information analysis whereby the expected value of perfect partial information (EVPPI) was estimated for individual parameters and parameter groups using the Sheffield Accelerated Value of Information approach(19). This provides a basis for the value of further research and allows identification of the relative importance of parameter(s) with respect to the risk and consequences of basing a reimbursement decision on the current level of information. For the value of information analysis, a threshold of $50,000 per QALY was adopted.

Results

Base Case

Prophylaxis was more effective than no prophylaxis in terms of QALYs (both short and long term) and blindness prevented (Table 2). However, the gain in long term QALYs was 0.00002 and analysis suggests that the number needed to treat with prophylaxis to prevent one case of blindness was over 500,000. Prophylaxis was associated with higher lifetime costs ($7.73 versus $0.75 per patient). The cost increase was primarily due to the cost of prophylaxis plus treatment of adverse events which were only partially offset by the savings through reduced infections.

When compared to no prophylaxis, prophylaxis had an incremental cost per long term QALY gained (ICER) of CAN$ 355,798. (Table 3) For analysis restricted to short term QALY gains the ICER was CAN$ 12.3 million. Thus, prophylaxis would be cost effective, only if a decision maker's willingness to pay for a QALY was greater than CAN $355,394 per QALY.

The CEAC (Figure 2) presents the probability that prophylaxis is optimal based on the threshold value for a QALY ranging from CAN $0 to CAN $100,000. For a threshold value of a QALY of $50,000, the probability that prophylaxis would be optimal is 10.7%, whilst for a threshold of $100,000, the probability is 21.7%.

Scenario Analysis

In all scenario analyses, ON prophylaxis was associated with greater costs and greater QALYs with the ICER ranging from $207,801 to $12.3 million (Table 4). Thus, the conclusion to be drawn from each analysis did not differ from the base analysis

Based on a threshold of CAN$50,000 per QALY, there was no cost associated with ON prophylaxis whereby ON prophylaxis could be considered cost-effective, i.e. at a cost of $0 the ICER for ON prophylaxis versus no prophylaxis was CAN$ 163,885. The prevalence of Chlamydia and Gonorrhea infections prophylaxis would need to be 5.5 times higher than in our base analysis, for ON prophylaxis to be considered cost effective.

Value of Information Analysis

The value of information analysis found that only two individual parameters had non-zero EVPPI; i.e. the uncertainty around other parameters was not sufficient to change the decision with respect to whether ON prophylaxis is cost effective. The two parameters identified were the relative reduction in transmission with prophylaxis with prevalent Chlamydia and the false negative rate for prenatal STI testing.

When parameters are grouped, the value of information analysis found further research relating to two groups of parameters may have information value: the accuracy of pre-natal STI testing and the benefits (ON reduction) and risks (adverse events) from ON prophylaxis.

Discussion

Our study examined the cost-effectiveness of universal application of erythromycin ointment as prophylaxis against Ophthalmia Neonatorum in Canada. The historical impact of ON prophylaxis highlights the benefits of population-based preventative interventions(2). However, in light of declining effectiveness and changing epidemiology(20), there is reason to examine the value gained by Canadian society from such an intervention within our current health system.

Summary of Key Findings

In our model, prophylaxis for ophthalmia neonatorum did not meet a willingness to pay threshold of 50,000CAD per QALY. While prophylaxis was effective in reducing short and long-term morbidity associated with ON, the number needed to treat in order to prevent one case of ophthalmia neonatorum blindness was 500,000, with an associated cost of over 4,000,000CAD.

Our findings suggest that erythromycin eye prophylaxis, while individually inexpensive, leads to very high costs on a population level. In order for ON prophylaxis to be considered cost-effective, the prevalence of gonorrhea infections in pregnancy must be significantly higher. While prophylaxis is not cost-effective at a population-level in Ontario, there may be subgroups that benefit from this intervention.

Our value of information analysis highlights that changes in the efficacy of prophylaxis and the accuracy of prenatal STI screening could impact the results. Topical prophylaxis alone will not prevent chlamydia ON. With emerging erythromycin resistance, the efficacy of topical prophylaxis is unlikely to improve. However, future research should be undertaken if prophylaxis with other agents becomes commonplace.

The accuracy of STI screening is dependent on clinical management of individual patients and access to testing and treatment. Our analysis highlights the importance of this clinical work and that prophylaxis may be more cost-effective in settings with poor access to care and follow up.

Comparison with other literature:

Current literature on the subject of cost-effectiveness of ON prophylaxis is limited to comparisons between types of prophylaxis, rather than cost-effectiveness of prophylaxis. Generally, national guidelines in countries such as the UK, Denmark, and Sweden have been driven by risk assessment(21).

Our findings are based on theoretical outcomes and may overestimate rates of ON-related blindness. For example, there have been no reported cases of ON-related blindness in the United Kingdom at 25-year follow-up after abandoning prophylaxis (22). Additionally, a recent Cochrane meta-analysis examining rates of gonococcal conjunctivitis in infants treated with eye prophylaxis or placebo reported no cases of blindness in any study group(23).

Strengths and Limitations of the study:

An important strength of our study is that we presented results for a wide range of scenarios varying the risk stratification for our target group (possible maternal STI, including false positives and negatives, chlamydia co-infection), and a wide number of model inputs. We developed a probabilistic model, accounting for uncertainty in parameters and calibrated the model to replicate Canadian population level data.

One limitation of our study is that we did not factor antibiotic resistance to erythromycin ointment into our calculation. It is unclear how this would affect the efficacy of erythromycin-ointment ON prophylaxis. With gonococcal resistance rates of up to 30% to erythromycin(4) in some regions, antimicrobial resistance would likely reduce the efficacy of prophylaxis. This would consequently further reduce the cost effectiveness of prophylaxis and would not change our conclusions. Additionally, we modelled our study on the presumption that treatment failure or lack of treatment may lead to blindness, but that there have been no detectable cases of in developed countries in recent years(22,23). Our results may therefore overestimate the cost-effectiveness of ON prophylaxis. Additionally, we included a modelling for cost of treatment of chlamydia ON, due to CADTH definitions. However, erythromycin prophylaxis is not thought to be effective in preventing chlamydia ON, which would likely reduce the cost value of erythromycin prophylaxis even further.

Conclusions:

Our findings suggest that given a willingness-to-pay threshold of 50,000CAD per QALY, ON prophylaxis with erythromycin ointment is not cost-effective in Canada. This is particularly due to low prevalence of gonococcal infection among pregnant Canadian women. While on an individual level this is an inexpensive intervention, when applied to a population level it becomes very costly. These findings are consistent with the current Canadian Pediatric Society recommendations universal eye prophylaxis(20).

There remains a need to study the efficacy of erythromycin prophylaxis in view of current resistance patterns.

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Figure 1: Simplified representation of hybrid model

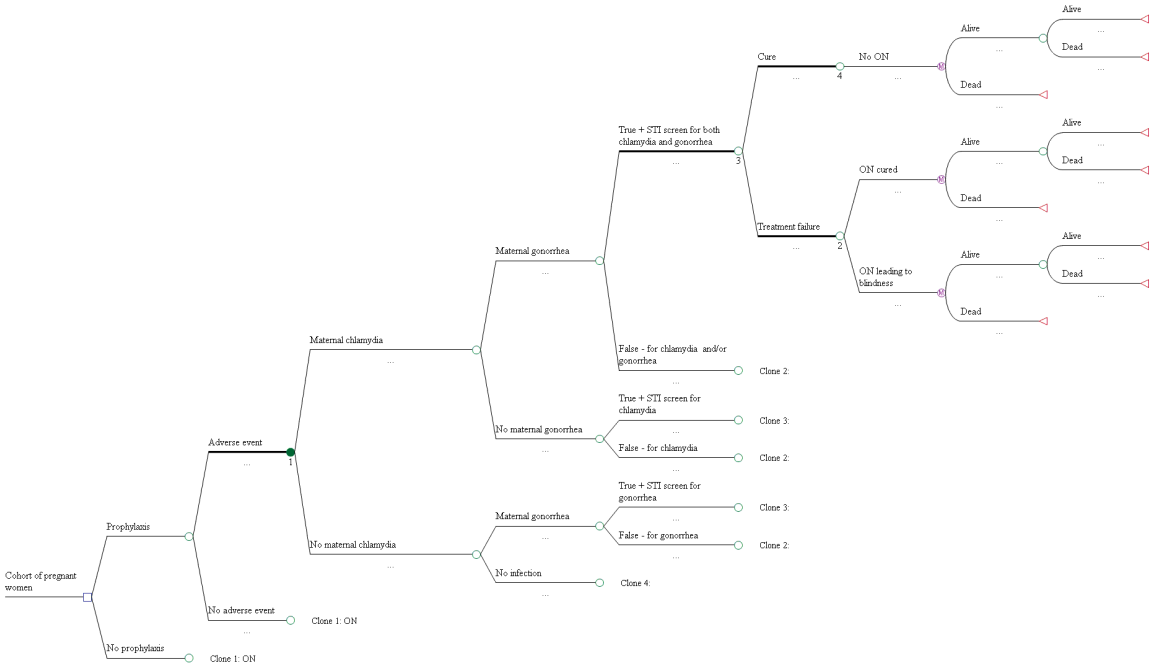

Figure 2: Cost Effectiveness Acceptability Curve

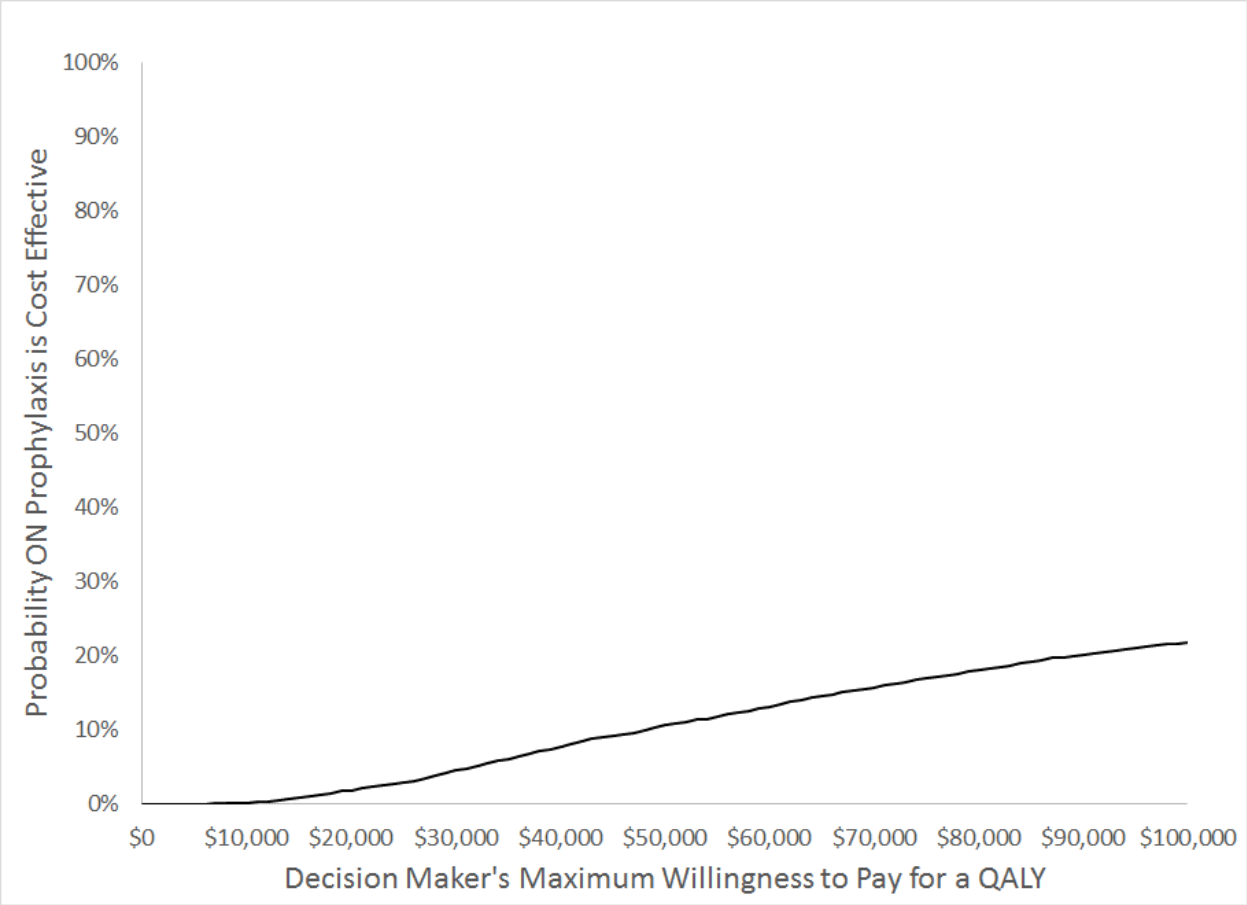

Table 1: Model Inputs

Parameter	Expected value	Probability Distribution	Source
Clinical parameters			
Prevalence of maternal infection • Chlamydia • Gonorrhea • Co-infection with Chlamydia and Gonorrhea • no maternal infection	 1.90% 0.20% 0.10% 97.90%	 Dirichlet (40,2,2,2178)	(9)
Prenatal STI screening results • False positive • False negative • True positive • True negative	 4.13% 0.12% 1.5% 94.25%	 Dirichlet(33,1,12,754)	(7)
Probability of ON in infant exposed to maternal infection • Chlamydia • Gonorrhea	 15% 40%	 Beta (156; 899) Beta (3688, 5531)	 (10) (6)
Risk of ON treatment failure and blindness • Chlamydia • Gonorrhea	 14.3% 3.46%	 Beta (326, 1850) Beta (145, 4045)	 (10) (24)
Relative Risk of ON when prophylactic erythromycin ointment used • in GC ON • in CT ON	 0.19 0.93	 LogNormal (0.07, 0,50) LogNormal (0.48, 1.79)	 (11) (12)
Probability of side effects of prophylaxis	10%	Beta (127, 1142)	(25,26)
Cost Parameters			
Erythromycin ON prophylaxis	$0.90	Fixed	(13)
Side effects of prophylaxis	$33.70	Fixed	(14)
Gonococcal ON	$2871.10	Gamma (179.44, 16)	(7)
Chlamydia ON	$574.47	Gamma (35.90, 16)	(7)
Blindness	$19,370	Gamma (4842.50, 16)	(15)
Utility Values			
Healthy term infant	0.876	Normal (0.876, 0.045)	(12)
Healthy - aged 12 +	0.912 to 0.699	Fixed	(17)
Disutility from blindness - age 0-16	0.329	Normal (0.329, 0.036)	(12)
Disutility from blindness - adult	0.208	Normal (0.208, 0.013)	(18)

Table 2: Disaggregated Results

	ON Prophylaxis	No Prophylaxis
Costs (per infant)		
Prophylaxis	$3.770	$0.000
Adverse events	$3.375	$0.000
Chlamydia transmission of ON	$0.116	$0.117
Gonorrheal transmission of ON	$0.033	$0.154
Lifetime costs of blindness	$0.440	$0.474
TOTAL COSTS	$7.734	$0.745
Outcomes		
Short term QALYs (per infant)	0.876485	0.876484
Blindness (per 1,000 infants)	0.023	0.024
Long term QALYs (per infant)	41.181768	41.181749

Table 3: Results of Base Analysis

	Total Costs	Short Term QALYs	Blindness Incidence	Long Term QALYs
ON Prophylaxis	$7.73	0.876485	0.000023	41.181768
No Prophylaxis	$0.75	0.876484	0.000024	41.181749
Difference	$6.99	0.000001	0.000002	0.000020
Incremental ratio	6	$12,348,383	$4,078.761	$355,798

Table 4: Results of Scenario Analysis

	Incremental Cost per QALY Gained for ON Prophylaxis versus No Prophylaxis
Base case	$355,798
0% discount rate	$207,801
3% discount rate	$526,467
1 Year time horizon	$12,346,383
10 Year time horizon	$1,325,046
20 Year time horizon	$826,645

Table 5: Results of Value of Information Analysis

	Expected Value of Perfect Partial Information per Woman
Individual Parameters	
Probability of false negative with STI testing	$0.0041
Relative risk of ON transmission of Chlamydia prevalent with ON prophylaxis	$0.0388
All other parameters	$0
Parameter Groups	
Accuracy of STI testing	$0.0369
Benefits and risks from ON prophylaxis	$0.0573
All other groups (disease prevalence and natural history, costs, utilities)	$0

Appendix A: Canadian Prenatal STI Screening Guidelines

Current prenatal screening guidelines recommend universal screening for chlamydia and gonorrhea among women presenting for prenatal care as well as targeted screening during the second and third trimesters for high-risk individuals. Mothers who did not receive prenatal screening should receive screening at the time of birth, and if positive, both infant and mother should be treated (2, 7, 8). When maternal chlamydia or gonorrhea is detected it is treated and a test of cure is performed to ensure that the infection has been eradicated and cannot be passed on to the infant at the time of birth(7,8).

Appendix B: Detailed Costing Methodology

Costs within the model were calculated for neonatal conjunctivitis treatment, erythromycin ointment and medical assessment of side effects of prophylaxis. Costs were derived from the published literature and presented in Canadian dollars (7,13–15). Cost of erythromycin ointment was the wholesale price provided by an Ontario hospital pharmacy in 2019(13). Application cost was assumed to be negligible given that it is performed by nursing staff in hospital at the time of birth as only one of many routine tasks. Side effects costs were based on the cost of one ambulatory care appointment with a primary care practitioner for the infant calculated from the Ontario schedule of benefits for physician services(14), given that the chemical conjunctivitis that may occur with prophylactic treatment is unlikely to require additional treatment(15).

For cases of ON, mean calculated infection treatment costs for term infants cited in the 2018 CADTH Health Technology Assessment of Prenatal STI screening(7) were used. Costs of gonococcal ON treatment, usually undertaken in hospital, were taken from bottom-up costing undertaken by CADTH(7) including the cost of hospitalization, diagnostic testing, pediatric and infectious disease specialist consultation and a single dose of intramuscular ceftriaxone. The costs of missed ON infection and subsequent blindness were calculated based on an expected lifetime of 82years(16) and discounted at a rate of 1.5% per annum(17). Costs of chlamydia ON, typically treated in the outpatient setting, were calculated using the 2016 OCCI ambulatory care case cost and include pediatric and infectious disease specialist consultation costs, as well as 14 days of oral erythromycin therapy(7).