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QUANTITATIVE RESEARCH

Pulse oximetry screening for critical congenital heart defects in Ontario, Canada: a cost-effectiveness analysis

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Abstract

Objective Previously conducted cost-effectiveness analyses of pulse oximetry screening (POS) for critical congenital heart defects (CCHDs) have shown it to be a cost-effective endeavour, but the geographical setting of Ontario in relation to its vast yet sparsely populated regions presents unique challenges. The objective of this study was to estimate the cost-effectiveness of POS for CCHD in Ontario, Canada.

Methods A cost-effectiveness analysis, comparing POS to no POS, was conducted from the Ontario healthcare payer perspective using a Markov model. The base case was defined as a well-appearing newborn at 24 h of age. Outcome measures, including quality-adjusted life months (QALMs), lifetime costs, and incremental cost-effectiveness ratios (ICER) [ΔCost/ΔQALMs], were calculated over a lifetime horizon. All outcomes were discounted at 1.5% per year. Cost-effectiveness was assessed using an a priori ICER threshold of CAD$4166.67 per QALM (equivalent to CAD$50,000 per quality-adjusted life year). Deterministic and probabilistic sensitivity analyses were conducted to assess parameter uncertainty.

Results Implementation of POS is expected to lead to timely diagnosis of 51 CCHD cases annually. The incremental cost of performing POS was estimated to be $27.27 per screened individual, with a gain of 0.02455 QALMs. This yielded an ICER of CAD$1110.79 per QALM, well below the pre-determined threshold. The probabilistic sensitivity analysis estimated a 92.3% chance of routine implementation of POS being cost-effective.

Conclusion Routine implementation of POS for CCHD in Ontario is expected to be cost-effective.

Résumé

Objectif Les analyses coût-efficacité du dépistage par oxymétrie de pouls (DOP) des cardiopathies congénitales critiques (CCC) menées antérieurement ont montré que c'est une technique efficace par rapport à son coût, mais l'emplacement géographique de l'Ontario, avec ses vastes régions à faible densité de population, présente des difficultés particulières. Nous avons donc cherché à estimer le rapport coût-efficacité du DOP des CCC en Ontario, au Canada.

Méthode Une analyse coût-efficacité comparant le DOP à l'absence de DOP a été menée selon la perspective des contribuables payant pour les soins de santé en Ontario à l'aide d'un modèle de Markov. Le scénario de référence était celui d'un nouveau-né apparemment bien portant âgé de 24 heures. Les indicateurs de résultat, dont les mois de vie pondérés par la qualité (MVPQ), les coûts à vie et les rapports coût-efficacité différentiels (RCED) [ΔCoût / ΔMVPQ], ont été calculés pour l'horizon temporel de la vie entière. Tous les résultats ont été actualisés à 1,5 % par année. L'efficacité par rapport au coût a été évaluée a priori à l'aide

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d'un seuil de RCED de 4 166,67 $CAN par MVPQ (équivalant à 50 000 $CAN par année de vie pondérée par la qualité). Des analyses de sensibilité déterministes et probabilistes ont été menées pour évaluer l'incertitude des paramètres.
Résultats La mise en œuvre du DOP devrait mener au diagnostic opportun de 51 cas de CCC par année. Le coût différentiel du DOP était estimé à 27,27 $ par personne dépistée, avec un gain de 0,02455 MVPQ. Cela donne un RCED de 1 110,79 $CAN par MVPQ, très en-deçà du seuil prédéterminé. L'analyse de sensibilité probabiliste a estimé à 92,3 % la probabilité que la mise en œuvre systématique du DOP soit efficace par rapport au coût.
Conclusion On peut s'attendre à ce que la mise en œuvre systématique du DOP pour les CCC en Ontario soit efficace par rapport au coût.

Keywords Saturation screening · Cost-utility analysis · Health economics · Utility · Cost-effectiveness threshold

Mots-clés Dépistage par saturation · Analyse coût-utilité · Économie de la santé · Utilité · Seuil coût-efficacité

Introduction

Congenital heart defects are structural fetal malformations that occur in approximately 8–9 per 1000 live births (Hoffman and Kaplan 2002; van der Linde et al. 2011). Of these, up to 30% are "critical", associated with significant risk of mortality and morbidity (Heron and Smith 2007; Rosano et al. 2000), especially if missed (Brown et al. 2006). Routine antenatal ultrasounds can detect critical congenital heart defects (CCHDs), but many remain undiagnosed (Sharland 2012). Prior to closure of the patent ductus arteriosus, many CCHD lesions may remain without overt clinical symptoms. It has been estimated that 20–30% of CCHDs are missed by routine physical assessment in early newborn period (Meberg et al. 2009).

Screening for CCHD using pulse oximetry—henceforth referred to as pulse oximetry screening (POS)—is an attractive tool to screen for clinically undetectable CCHDs (Narayen et al. 2016). A meta-analysis of studies on POS found an overall sensitivity of 76.5% for detection of CCHD and overall specificity of 99.9% with a false positive rate of 0.14% (Thangaratinam et al. 2012). Similar sensitivity and specificity rates were reported in a more recent Cochrane review (Plana et al. 2018). Based on the evidence, the American Academy of Pediatrics as well as the Canadian Paediatric Society have endorsed routine screening for CCHD using POS (Mahle et al. 2012; Wong et al. 2017), and POS screening is being implemented in Ontario in tandem based on institutional capabilities (Newborn Screening Ontario n.d.).

POS requires real-time interpretation, and in cases of positive result, immediate action to provide timely diagnosis and appropriate management. Due to resource implications, particularly lack of availability of neonatal echocardiography at all centres as well as the burden of potentially large numbers of false positive results, there have been a number of cost-effectiveness analyses of POS for CCHD (de-Wahl Granelli et al. 2009; Knowles et al. 2005; Griebsch et al. 2007; Ewer et al. 2012; Roberts et al. 2012; Peterson et al. 2013). Details of these analyses are shown in Supplemental File 1, Table S1.1. All these models suggest that screening for CCHD is likely to be cost-effective. However, with the exception of the Swedish analysis by de-Wahl Granelli et al. (de-Wahl Granelli et al. 2009) and the US analysis by Peterson et al. (Peterson et al. 2013), all were from the United Kingdom, where availability and distribution of clinical resources are much different than in Ontario, Canada. Another limitation of previous studies is that the models represent time until diagnosis, except the study by Peterson et al. where the time horizon was first year following birth (Peterson et al. 2013). In addition, quality of life parameters associated with CCHDs have not been incorporated previously in any analyses. In light of these limitations, as well as in consideration of some unique logistical challenges towards screening for CCHDs, our objective was to determine whether POS implementation would be a cost-effective endeavour in Ontario.

Methods

A model-based cost-effectiveness analysis comparing POS to no POS was conducted from the Ontario healthcare payer perspective (Ministry of Health). A Markov model was developed to predict lifetime events, including quality-adjusted life months (QALMs), lifetime costs, and incremental cost-effectiveness ratios (ICER) [ΔCost/ΔQALMs], for a well-appearing newborn infant at 24 h of age. Ontario-specific data were used wherever possible. We followed Canadian guidelines for economic evaluations in health (Health CAfDaTi 2006). No individual patient-level data were utilized; this study was approved by the Research Oversight and Compliance Office - Human Research Ethics Program, University of Toronto, protocol reference number 32846.

Model structure

TreeAge Pro v2015 (TreeAge Software Inc., Williamstown, MA, USA) was used to develop a Markov decision model with 1-month time steps (each "cycle" representing a one-

month step), allowing lifetime follow-up. Monthly intervals were chosen as during the first years of life, there are significant variations in mortality rates, morbidities and costs that would not be ascertainable using yearly time cycles (Ohuchi et al. 2011; Simeone et al. 2014). A lifetime horizon was chosen as, increasingly, studies are reporting the longer-term outcomes of CCHDs well into adulthood (Lee et al. 2014). The following exhaustive, mutually exclusive health states were created: (1) CCHD (pre-operative); (2) no CCHD (≤ 1 month); (3) post-operative CCHD (with morbidity); (4) post-operative CCHD (no morbidity); (5) no CCHD (> 1 month); and (6) death. At any given time, a simulated individual could only be in one of the six health states.

At the beginning of the first cycle, a simulated individual could only be in one of the following: (1) CCHD (pre-operative) or (2) no CCHD (≤ 1 month). An individual with (undiagnosed) CCHD at 24 h could have the screening performed and yield a (true) positive or a (false) negative result, the latter being a case of missed CCHD. Similarly, an individual with no CCHD could have a (false) positive or a (true) negative screening result. All positive results (whether true or false) were designed to require follow-up.

In the initial cycle, the model depicted possibilities of patient location and requirement of transfer(s) in detail (Fig. 1), and in cases of confirmed CCHD, possible outcomes from surgery (Fig. 2a). The model also depicted possible outcomes in event of a missed CCHD presenting with symptoms at home (Fig. 2b). End of the first cycle resulted in an individual transitioning to 1 of the following health states: (1) Post-operative CCHD (no morbidity); (2) post-operative CCHD (with morbidity); (3) no CCHD (> 1 month); or (4) death. For purposes of this model, morbidity referred to any neurodevelopmental impairment (detailed in Supplemental File 2). In subsequent model cycles, a simulated individual could remain in the same health state, or transition to another. The cycles continued until all individuals transitioned to "Death". Figure 3 depicts possible transitions among health states in subsequent Markov cycles.

Parameter values

The definition of CCHD for the purposes of this model included any cardiac lesion that may lead to cyanosis or flow obstruction resulting in systemic hypo-perfusion. The list of all CCHD lesions included in the search is delineated in Supplementary File 2. Three major categories of variables were incorporated: (a) probabilities, (b) utilities and (c) costs. Probabilities determined the path through the decision tree during the first cycle, and transitions among health states in subsequent cycles. Utilities indicated quality of life associated with health states, as well as transfers, having POS performed and surgery. These values were used to determine the expected QALMs with either diagnostic strategy (i.e., POS implementation vs. no POS). Finally, costs associated with all procedures (including POS, echocardiograms), transfers, surgical procedures and health states (including inpatient stays and ambulatory visits) were used to estimate the comparative lifetime costs. Given the lifetime horizon, all QALMs and costs were discounted 1.5% annually, as per Canadian guidelines (Health CAfDaTi 2006).

A comprehensive targeted search of medical literature (including conduct of meta-analyses when appropriate), data abstraction from publicly available databases (including Statistics Canada), formal requests for specific data to Canadian Institute for Health Information, Ontario Case Costing Initiative, and Better Outcomes Registry & Network Ontario, and inquiry to local experts were conducted to determine point estimates and ranges for all variables. When ranges were not available for probability or utility variables, a Monte Carlo simulation with a beta distribution was

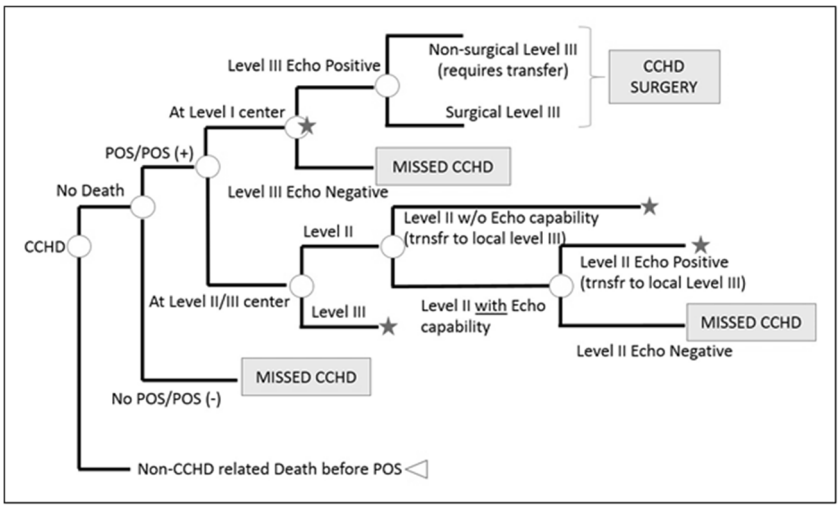

Fig. 1 Illustration of decision tree during first Markov cycle and various possible outcomes (including need for transfers) in a simulated individual who has CCHD

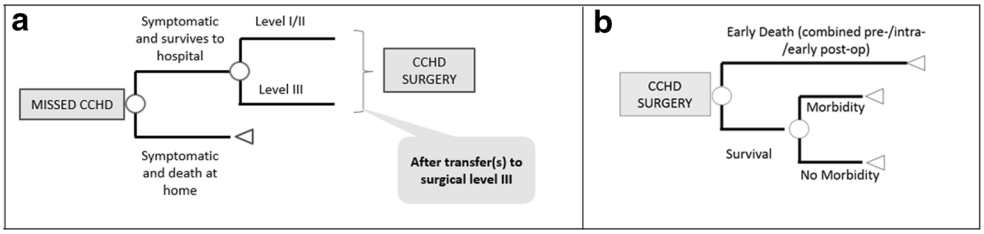

Fig. 2 Panel **a** illustrates possible outcomes after missed CCHD incorporated into first cycle of Markov decision model. Panel **b** shows the possible outcomes of CCHD surgery incorporated into first cycle of Markov model. Note than in both Figs. 1 and 2, the circles represent a "chance" node with a certain probability associated with either arm emanating from that node being chosen (determined by the values for probabilities inputted into the model) while the triangles represent a "terminal" node, culminating in the transition to another health state

conducted to yield the 2.5th and 97.5th percentile estimates. For cost variables without available ranges, the point estimate values were decreased and increased by 50%. Tables S1.2, S1.3, S1.4 and S1.5 in Supplemental File 1 delineate all variables with their point estimates and ranges. Supplemental File 2 details the comprehensive data abstraction process. When no data were available, consensus-based point estimates/ranges were utilized, indicated in Supplemental File 2.

Model outcome

Quality-adjusted life months

Quality of life in a given health state in each cycle was represented by a corresponding utility score. Utilities could range from 0 (death) to 1 (perfect health/no CCHD). Each model cycle used the incremental utility to determine the QALM for that given health state. Over a lifetime horizon, this yielded expected per patient QALMs with and without POS implementation.

Costs

The per cycle incremental costs of being in a given health state included medical costs to healthcare system. In addition, costs of POS, transports, echocardiograms and hospitalizations were incorporated. The model yielded lifetime cost per individual with either diagnostic strategy. All costs are in Canadian dollars (CAD).

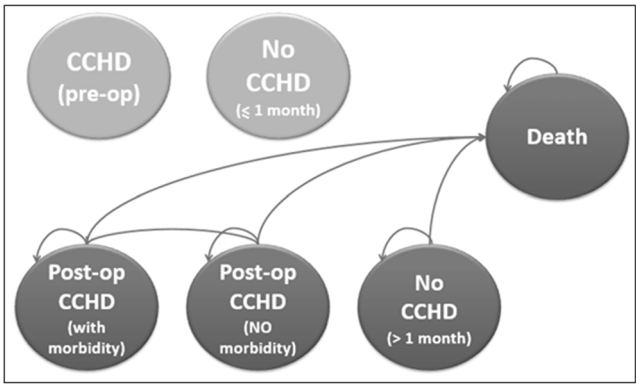

Fig. 3 Illustration of the possible transitions (denoted by arrows) among the 4 health states in subsequent Markov cycles

Cost-effectiveness (utility) analysis

Incremental cost-effectiveness ratio (ICER) expressed as added cost per QALM gained with POS (vs. no POS) was calculated. In order to determine value of POS from a healthcare payer perspective, a cost-effectiveness threshold of $4167 per QALM (equivalent to $50,000 per QALY, a commonly used cost-effectiveness threshold) (Griffiths and Vadlamudi 2016) was used.

Sensitivity analyses

For deterministic one-way sensitivity analyses, the model was run at pre-specified intervals for each included variable within their plausible range. The model was considered robust to a variable if the overall result (i.e., favourable diagnostic strategy) did not change from main analysis. Due to the importance and/or uncertainty around their point estimates/ranges, certain variables were tested for threshold values even outside estimated plausible ranges. Variables selected and ranges utilized for these "threshold analyses" are indicated under Results. Finally, a probabilistic sensitivity analysis was conducted in which multiple simulations were run where parameter values were varied simultaneously over their distribution. This was used to generate an ICER scatter plot as well as a cost-effectiveness acceptability curve.

Model validity

Validity of the model generated was assessed via face validity as the extent to which the model and its assumptions and applications correspond to current science and evidence (Karnon and Vanni 2011).

Results

In the base case of a well-appearing newborn, performing POS at 24 h of life was the superior strategy. There are approximately 150,000 births province-wide annually (Canadian Institute for Health Information; https://www.cihi.ca/en). Based on incidence of missed CCHD of 0.0004 (Cohen et al. 2015) and probability of POS detecting 0.843 of all CCHDs (Supplemental File 2), it was estimated that an additional 51 cases of CCHD will be detected annually in a timely fashion with POS implementation. The lifetime cost to the healthcare payer per individual was estimated to be $284,002.58 with POS implementation and $283,975.31 without POS implementation, yielding an incremental cost of performing POS of $27.27 per individual ($284,002.58–$283,975.31). Similarly, the expected QALMs per individual with and without POS implementation were expected to be 554.53 and 554.50, respectively, with a resulting gain of 0.03 QALMs. Based on 150,000 births per year, this would lead to an overall gain of 3682 QALMs or 307 quality-adjusted life years (QALYs) per birth cohort. The incremental cost and QALMs yielded an ICER of $1110.79, well below the cost-effectiveness threshold.

The model was not sensitive to any variable in one-way sensitivity analyses, i.e., the implementation of POS was superior for all variables across their plausible ranges. "Threshold analyses" were conducted for variables indicated in Table 1, and thresholds (where identified) above or below which POS implementation is no longer expected to be cost-effective are indicated. It was predicted that POS implementation would no longer be cost-effective if (a) POS detects < 23.2% of CCHD lesions (well below the plausible lower limit of 80.2%); (b) POS falsely positive rate exceeds 11.8% (well above the estimated upper limit of 0.994%); (c) if probability of death at home in case of missed CCHD is < 3.5%, below the estimated lower limit of 7.4%; or (d) incidence of CCHD in base case is < 0.00009 (just below the estimated lower limit of 0.0001, but well below point estimate value of 0.0004).

In probabilistic sensitivity analysis of 10,000 model simulations, POS implementation was considered cost-effective 92.3% of the time at the cost-effectiveness threshold of $4166.67 (Fig. 4). Figure 5 shows that it is more likely to be cost-effective than no POS implementation (i.e., > 50% chance) at a cost-effectiveness threshold value as low as $1175.

Discussion

Province-wide implementation of POS for CCHD in Ontario appears to be a cost-effective endeavour with an estimated 51 additional cases of CCHD diagnosed in a timely fashion annually and a 92.3% chance of being cost-effective at an ICER threshold of $4166.67 per QALM. The findings of this model are consistent with what might be expected in context of biological plausibility as patients with delayed diagnosis of CCHD are more likely to experience hemodynamic compromise, resulting in prolonged hypoxemia to vital organs. They are more likely to not survive, as well as have a higher chance of morbidity (Fixler et al. 2014).

The likelihood of POS being cost-effective, along with its safe and non-invasive method, makes it a suitable screening tool for early diagnosis of CCHD. These criteria constitute the tenets of the Wilson and Jungner screening criteria (Wilson and Jungner 1968). Our model also shows that despite many cases being detected antenatally and postnatally prior to 24 h

Table 1 Determination of threshold values for a limited set of variables

Variable*	Base case value	Lower range	Higher range	Threshold value¥
Probability that an individual patient is from the northern region that requires air transport	0.0572	0.0564	0.0581	n/a
Probability that a level 2 facility has pediatric echocardiography capability	0.22	0.11	0.34	n/a
Probability of a false negative echocardiogram result at a level 2 facility	0.0015	0.0013	0.0017	n/a
Probability of a POS screen being positive if individual has CCHD	0.843	0.802	0.878	*< 0.232*
Probability of a POS screen being positive if individual does not have CCHD	0.00966	0.00940	0.00994	*> 0.118*
Probability of home death with CCHD in 1st month in undiagnosed neonate	0.22	0.074	0.422	*< 0.035*
Probability of CCHD	0.0004	0.0001	0.0009	*< 0.00009*
Cost of echocardiogram†	213.80	106.90	320.70	n/a
Air transport‡	15,000	10,000	20,000	n/a

*All probability variables were tested from 0 to 1

¥ Variables with n/a did *not* have any threshold above or below which implementation of POS would no longer be cost-effective

†Tested from CAD$0 to CAD$10,000

‡Tested from CAD$0 to CAD$100,000

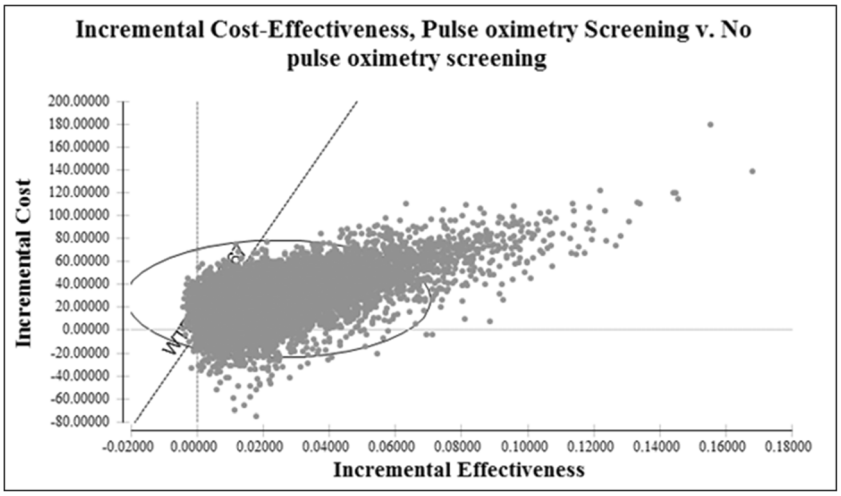

Fig. 4 Cost-effectiveness scatter plot. Note: Each dot represents the incremental cost and incremental effectiveness (QALM) from each simulation, and all simulation values "below" the line of cost-effectiveness threshold are deemed to be cost-effective, whereas the ones above the threshold line represent simulations where ICER for POS implementation was above the pre-determined threshold value

of age, POS still remains cost-effective despite the relative rarity of missed CCHD. In order to maximize effectiveness of POS, standardized guidelines for POS including recommended measurement techniques and standard procedures for follow-up are imperative (Wong et al. 2017). These procedures would minimize the cost to the healthcare system by minimizing the effect of ambiguity in steps that need to be taken and would maximize the effect of POS.

A number of studies have previously assessed the cost-effectiveness of POS implementation. Most such studies have been done in the UK (Knowles et al. 2005; Griebsch et al. 2007; Ewer et al. 2012; Roberts et al. 2012), but also in the United States and Sweden (de-Wahl Granelli et al. 2009; Peterson et al. 2013). Previous studies have evaluated a very limited time horizon, with all being until the point of diagnosis of CCHD, except the study by Peterson et al., which employed a 1-year time horizon (Peterson et al. 2013). The ICER values for these studies varied from as low as £3430 to as high as £24,900 per additional case of CCHD diagnosed. The reason for wide variability in the costs may relate to the nature of models created and data used, but all suggested that POS was likely to be cost-effective. The study by Peterson et al. determined the ICER to be $40,385 per life year gained (which converts to $3365.42 per month gained in US dollars). It should be noted that, unlike our model, none of the aforementioned studies employed utilities to account for morbidities that may be associated with CCHD and its outcomes (i.e., the various possible health states)—and as such do not present the costs for quality-adjusted life units gained and, therefore, cannot truly evaluate cost-effectiveness. In addition, our study provides a lifetime horizon which provides a clear sense of total lifetime costs and quality-adjusted life units to be gained by implementation of POS. In addition, model structures in aforementioned studies were rather simple, which did not take into account various possible pathways to the ultimate diagnosis of CCHD following a positive screen. Despite these differences from our study, these studies affirmed cost-effectiveness of POS, and our study was consistent with this in the Canadian context.

Limitations of the model framework itself relate largely to assumptions made, and include (a) assumption that individual with CCHD with positive screen would remain asymptomatic

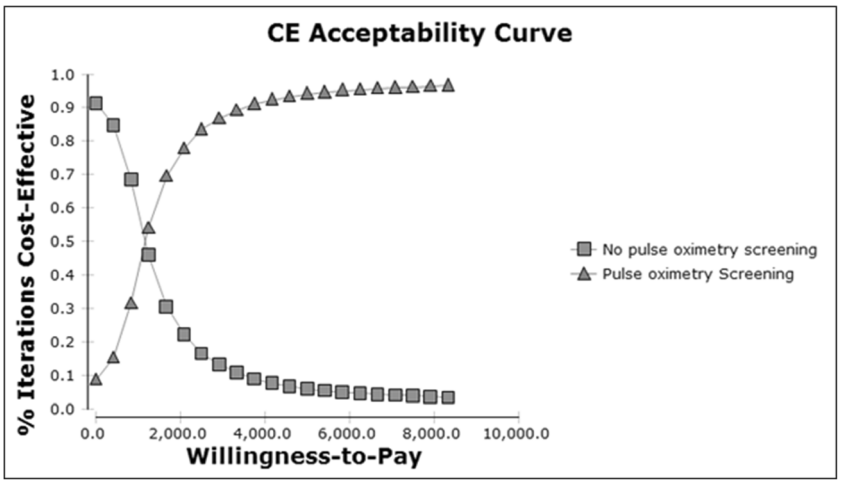

Fig. 5 Cost-effectiveness acceptability at various cost-effectiveness (or "willingness to pay") thresholds

until surgery, (b) individual with CCHD requires only 1 surgery, (c) morbidity related to CCHD limited to neurodevelopmental impairment and that no new morbidity would arise after adolescence, and (d) inability to identify values for some variables requiring assumptions regarding their point estimates and ranges. We also acknowledge that while a targeted literature search was conducted for many of the variables, these were not systematic searches (due to feasibility) and therefore may not be representative of the entire body of literature for each variable. Another important limitation is decreasing confidence in point estimates of many variables the farther out the time horizon gets, due to lack of available data. This also adds to increased uncertainty with respect to the overall results of the model. Additionally, evaluating a lifetime span, particularly when accounting for an annual discount rate, may contribute to diluting the incremental gain in QALMs. The notion of quality adjustment for pediatric population may be considered a limitation, as it is difficult to ascertain the true impact of morbidities of personal assessment of life quality at such a young age. Finally, no spillover (caregiver) effects were considered as it relates to utility and cost variables (with a few exceptions indicated previously), although this makes our analysis conservative (i.e., if including spillover effects, it would have been expected that the ICER would be lower still). The most important strength of the model is the detailed framework that represents a realistic pathway from screening to diagnosis to outcomes in the first Markov cycle. Another important strength is the employment of time-varying variables that allow the values to change over time for transitional probabilities (Supplemental File 2). This is close to the realistic progression through life following CCHD. Finally, the model is representative of Ontario's geography with a unique distribution of population (and resources)—whereby a few small areas are extremely densely populated, whereas large regions are sparsely populated.

Conclusion

POS implementation in Ontario is likely to be a cost-effective endeavour, with an estimated ICER of CAD$1110.79 per QALM gained. Despite creation of a realistic model framework, limitations in available data mean that the robustness of this analysis could be enhanced by incorporating or obtaining more local data, especially in light of POS implementation having been initiated in Ontario. In addition, it may be important to be mindful of thresholds for variables presented at which POS is no longer estimated to be cost-effective, and monitoring of these values over time may be warranted to ensure POS continues to remain a cost-effective endeavour.

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Compliance with ethical standards

This study was approved by the Research Oversight and Compliance Office - Human Research Ethics Program, University of Toronto, protocol reference number 32846.

Conflict of interest The authors declare that they have no conflicts of interest.

Disclosure Data from this study were presented at Pediatric Academic Societies Conference 2018 (Toronto, Canada). This work was part of the requirements for completion of a Master of Science degree in clinical epidemiology at the Institute for Health Policy, Management and Evaluation, University of Toronto, for A.M. The primary author (A.M.) is a recipient of an early career award from Hamilton Health Sciences Foundation (2019–2021) to support his research, although it did not directly impact the conduct of this study.

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