COST-EFFECTIVENESS OF CARRIER SCREENING FOR CYSTIC FIBROSIS IN AUSTRALIA

Short title: Cost-effectiveness of CF carrier screening

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The impact of information retention on the cost-effectiveness of carrier screening for Cystic Fibrosis

Background: Carrier screening for cystic fibrosis is not widely available in Australia, partly due to concerns regarding its cost-effectiveness. The benefit of information from pregnancy to pregnancy has not been widely considered in existing cost-effectiveness analyses.

Methods: A decision tree was constructed estimating costs and outcomes from screening, including both initial and subsequent pregnancies. Effectiveness was expressed in terms of CF births averted. Costs were collected using a health service perspective. All costs and outcomes were discounted at 5% per annum.

Results: Screening reduced the annual incidence of CF births from 34 to 14/100,000 births (an aggregate number of CF births of 100.9 and 41.9 respectively). In initial pregnancies, costs in the screening arm (A$16.6 Million/100,000 births) exceed those in the non-screening arm (A$13.4 Million/100,000 births). The incremental cost per CF birth in initial pregnancies is therefore approximately A$150,000. However, this was reversed for subsequent pregnancies, in that the pre-collected information reduces the incidence of CF in subsequent pregnancies at low additional costs. When aggregated, the results suggest screening is likely to be cost-saving.

Conclusions: The introduction of national carrier screening for cystic fibrosis should be considered, as it is likely to reduce CF incidence at an acceptable (potentially negative) cost.

Keywords: Cystic Fibrosis; Australia; screening; cost-effectiveness; economic evaluation
Introduction

Carrier screening for cystic fibrosis (CF) has been possible since the discovery of the cystic fibrosis transmembrane conductance regulator (CFTR) gene.\textsuperscript{1,2} Despite this technological advance, there have been few population-based carrier screening programs introduced. An early pilot program in Edinburgh used a couple screening model and halved the live birth incidence of CF.\textsuperscript{3} Fee for service pre-conception and prenatal screening are widely practiced in the United States, but do not receive government subsidy. Recent guidance from the American College of Obstetricians and Gynecologists suggested that CF screening continues to be offered to women of reproductive age.\textsuperscript{4} A small fee for service program has been operating in Victoria, Australia since 2006 but does not attract government financial support.\textsuperscript{5}

A key factor for policy makers in funding decisions is an understanding of the economic implications of screening. In a resource-constrained environment, social decision-making has become increasingly reliant on the evaluation of costs and outcomes in parallel, as typified by the Pharmaceutical Benefits Advisory Committee’s (PBAC) central role in determining public subsidy of new pharmaceuticals in Australia.

There are several cost-effectiveness analyses of CF carrier screening, that have been summarised in a systematic review.\textsuperscript{6} The review found that these analyses occurred across a range of settings and screening strategies (e.g. stepwise, prenatal, pre-conceptional). The review also demonstrated heterogeneity in study design, model inputs and outcome measurement, making generalisability of results difficult. Based on the findings of this review, it is apparent that there is wide divergence in results. For example, the cost per CF
baby averted through prenatal screening in a primary care setting ranges from negative (i.e. it is cost-saving)\(^7\) through to US$386,773.\(^8\) At the time of the review, no study explored the costs and benefits of CF screening in Australia. However, a subsequent cost-effectiveness analysis did investigate prenatal screening in Australia.\(^9\) This concluded that prenatal screening using a range of different timing strategies was unlikely to be cost-saving.

One important consideration in this study which was not addressed in the studies reported in the systematic review\(^6\) (and also the more recent Australian study)\(^9\) is to evaluate the impact of screening on subsequent reproduction decisions. This is important as providing parents with information in initial pregnancies impacts on their decisions in any subsequent pregnancies. For example, if a couple knows they are both carriers, they may decide to pursue in vitro fertilisation (IVF), or use prenatal diagnosis or to abstain from reproduction. It would be expected that parents taking up these options would lead to a reduction in the number of CF infants, and also the costs of treating CF and associated conditions (although IVF and prenatal diagnosis involve other costs). Similarly, identifying parents as non-carriers has implications for subsequent pregnancies, not in terms of reducing CF incidence, but in eliminating the need for subsequent testing.

The aim of this study is to provide information to decision makers regarding the optimal approach to CF screening within a resource-constrained environment. In particular, we aim to explore the impact of information retention on the cost-effectiveness of carrier screening. The screening options considered in this study are (i) no screening, (ii) optional pre-conceptional screening followed by optional prenatal screening for those who do not take up pre-conceptional screening. We present a decision tree contrasting costs and outcomes associated
with carrier screening approaches for CF based on the experience in Victoria that could be used across Australia.

Methods

The economic evaluation consisted of two components. The first component considered the costs and outcomes accruing to infants whose parents had no information regarding their carrier status from previous pregnancies (i.e. a screening naïve population). This population was termed initial pregnancies in this study. The second component of the economic evaluation considered the costs and outcomes accruing to any subsequent infants. For these infants, parents have prior knowledge regarding their carrier status, and this was reflected in the pathways followed by these infants. This population was termed subsequent pregnancies.

Initial Pregnancies

A decision tree was built based on the Victorian pilot program. A decision tree is a technique commonly used in cost-effectiveness analysis to describe the pathways an individual can follow with respect to a condition, and then to ascribe probabilities, costs and outcomes to each of the possible pathways (also called branches). Using these estimates of probabilities, costs and outcomes, two or more competing strategies (such as screening and not screening) can be compared. In this decision tree, both pre-conceptional and prenatal screening were offered. The key elements of the tree are reproduced in Figure 1. The decision tree was built in TreeAge Pro 2011, a software designed specifically for this type of conceptual problem.

Figure 1 here
Figure 1 is simplified, as it does not show the pathways occurring following a false negative result (or a false positive, but the model assumes 100% specificity). While these are included in the model (available on request), existing studies generally assumed high sensitivity, meaning that very few couples would populate those branches of the decision tree.

Screening prenatally and pre-conceptionally have a number of similar features. The key difference between the arms is that the latter allows for IVF or abstention from reproduction in the first instance for couples identified as being carriers. For prenatal screening, these options only exist for subsequent pregnancies.

To complete this analysis, we had to make a number of simplifying assumptions. We assumed parenting partnerships are stable; carrier status information is remembered for subsequent pregnancies; and following a negative test result, couples proceed with pregnancy rather than pursuing further testing (e.g. chorionic villus sampling (CVS)).

Model Inputs

The parameters required to populate the model are presented in Table 2. All costs are in Australian 2010 dollars unless stated.

Table 2 here

Screening Costs
The international evidence on the cost of screening is variable, providing a broad range of values. This is partly due to different cost bases in different countries and settings, but also reflects the different cost components included in the estimates. Existing Australian evidence regarding the marginal cost of screening suggests a figure of $116.77 per test for pre-natal screening. This consisted of blood collection ($10), DNA extraction ($11.27), screening test consumables ($31.95) and screening test labour ($63.77). These figures are based on a 10-mutation panel as recommended by the Human Genetics Society of Australasia CF carrier screening position statement (available at www.hgsa.org.au). These figures are likely to represent an overestimate for a national screening program as they are both likely to include aspects of fixed costs which could be shared, and would be subject to economies of scale under a larger program. Thus, the analysis biases in favour of not screening as economies of scale would be likely to reduce the average cost.

Other Medical Costs

The cost of termination was estimated using Australian Diagnosis-Related Group data from 2008-9. These data provide an estimate of the total cost of managing a specific type of patient including a wide range of different types of cost. In this case, we used DRG O05Z, which estimates the total cost of a termination to be $1,708. CVS costs are estimated using Medical Benefits Schedule Item number 16603 ($115.20). The costs of an IVF cycle were estimated to be between $6,000 and $9,000; for the model we assumed a midpoint of $7,500. We do not know the number of IVF cycles per couple contingent on choosing IVF as a result of CF screening results. It is likely to be below the general IVF population as these couples are less likely to have fertility barriers; in our analysis, we have conservatively assumed one cycle per couple and tested the sensitivity of the result to this.
Lifetime CF management costs were estimated by Van Gool et al.\textsuperscript{11} In this, the lifetime costs of management of a CF patient were estimated using Australian registry data of CF patients in 2003-2005. The lifetime cost of managing a CF patient was estimated to be $336,000, assuming a 5% discount rate. This includes costs incurred in the inpatient setting (58%) and pharmaceuticals (29%), with the remainder consisting of medical services (including transplants), diagnostic testing and complications management.

\textit{Outcomes}

A screening program has a variety of relevant outcomes, including carrier status detection, reassurance to non-carrier parents, identification of fetuses with CF, reassurance of parents with a non-CF baby, information to all prospective parents, or something more general such as (quality-adjusted) years of life. For this study, the cost per CF birth averted was specified as the primary outcome of interest. Using CF births as an outcome measure is limited as it is not comparable to outcomes in other areas of medicine (and health more generally). This means it is difficult to interpret for a policy maker facing a wide range of possible uses of scarce resources. While quality-adjusted life years (QALYs) represent the gold-standard outcome measure for economic evaluation, they include some ethically questionable assumptions in situations in which termination can occur.\textsuperscript{6} For example, can we reasonably assume that a CF-baby averted will be followed by a healthy infant (either through CVS testing of subsequent pregnancies or IVF)? This is clearly contentious and we therefore do not follow this approach.

\textit{Perspective and discount rate}
Costs were collected from a healthcare system perspective. Thus, issues such as productivity were excluded. With the exception of the costs of treating people with CF, all costs are immediate so are not discounted. The lifetime costs of managing patients with CF were generated using a 5% discount rate; the reason for doing this is that it is the standard discount rate recommended in Australian economic evaluations of health technologies.12

Sensitivity Analysis

A univariate sensitivity analysis was conducted, varying each model parameter within a range representing plausible high and low values (reported in Table 2). The systematic review of Radhakrishnan et al. provides ranges for many of the parameters.6 The discount rate applied to the future healthcare costs of treating an individual with CF is not considered in the sensitivity analysis. This is because the range of discount rates (i.e. 0-10%) considered by Van Gool et al. produce lifetime costs of care similar to those outlined in Table 2 (i.e. increasing or decreasing the cost by 50%). The results are presented in a Tornado plot identifying the parameters to which the conclusion is most sensitive. The analysis was repeated including and excluding the effect of information from initial infants on reproductive choices in subsequent infants.

Subsequent Pregnancies

To model subsequent pregnancies, we categorised these into three groups defined by common patterns of screening and risk within each group. We constructed three supplementary decision trees A, B and C identifying the likelihood of a CF baby (as well as
any other options available to these parents, such as abstention from reproduction) in subsequent pregnancies based on screening results from a previous pregnancy. These sub-trees consist solely of the probability of a CF infant (which is described below), and the costs associated with each group. If parents cannot have a CF infant in subsequent pregnancies (because at least one of the parents is a non-carrier), they enter sub-tree A. If both parents received a positive test result (in the sense that they are identified as carriers) for the initial pregnancy (and hence are carriers as we assumed specificity to be 1), they enter sub-tree B. In sub-tree B, couple choose between no further reproduction, becoming pregnant and use prenatal diagnosis, or IVF (with pre-implantation genetic diagnosis, (PGD)). It was therefore assumed that no parents both identified as carriers would pursue a pregnancy without at least prenatal testing of the infant. Also, if parents have a CF child irrespective of the screening results from an initial pregnancy, they enter model B. If the female receives a false negative (and hence her partner is not invited for screening), the couple may enter sub-tree C in which no screening is undertaken in subsequent pregnancies but there remains a chance of a CF baby. This occurs if the father is a carrier (a 4% chance in the base case). If the parents are not screened, all parents who are both carriers, but did not have a CF baby in the initial pregnancy, enter sub-tree C. This allocation of parents to these options is presented in Table 1.

Table 1 here

Infants in each of the three supplementary decision trees have different probabilities of CF than those screened in the initial program (termed initial infants). This is because their parents’ carrier status has been identified (or not in the case of sub-tree C). To identify the importance of these changing probabilities, it is first necessary to identify the relative
numbers of initial and subsequent infants. Australian Bureau of Statistics data (2068.0 – 2006 Census tables) were used to identify the mean number of infants per mother contingent on having at least one child. Data from the 44-49 year old cohort was used as they are the youngest cohort likely to have no additional children. For this cohort, the average mother had 1.484 subsequent children after their first born. The total number of subsequent children per year is then divided between the terminal (right-hand side) nodes in the decision tree, assigned to one of the sub-trees A-C, and the number of CF infants and costs associated with subsequent pregnancies were estimated. Note that we have assumed that parents with positive CF status will decide to have a similar number of children compared to the general population. This assumption is to some extent verified by results from the Australian Cystic Fibrosis Data Registry (ACFDR) that show that 20% of CF patients have siblings with CF (available at [http://www.cysticfibrosis.org.au/pdf/Cystic_Fibrosis_in_Australia_2009.pdf](http://www.cysticfibrosis.org.au/pdf/Cystic_Fibrosis_in_Australia_2009.pdf)). Given that parents with positive carrier status have a 1 in 4 chance of having a baby with CF, this would suggest that most CF patients have a sibling. The results including subsequent pregnancies are considered in univariate sensitivity analysis using the same approach as that undertaken for initial pregnancies.

**Results**

In the initial child cohort, prenatal screening was estimated to reduce the number of CF births by approximately 53%. For subsequent children, 117.0/100,000 couples ended in group B, in which any future reproduction was assumed to take place using IVF or PND. This compared with 40.0/100,000 in the No Screening group, reflecting the CF births \((0.25\times\text{carrier rate}^2)\). Screening reduced the population in group C from 120.0/100,000 to 43.3/100,000. In this group, subsequent pregnancies have a 25% chance of being CF as both parents are carriers.
If no screening occurs, the number of CF infants in Australia is estimated to be 40.0/100,000 in initial pregnancies, and 30.0/100,000 in subsequent pregnancies (as one quarter of carrier couples will have their carrier status revealed by having a CF baby). Given the relative size of the two groups, this equates to 34.0/100,000 in all pregnancies, or 100.9 per year in Australia.

The model predicts that, under the screening program, the number of CF babies in Australia is reduced to 14.0 CF infants per 100,000 pregnancies or 41.4 per annum (from 100.9), a 59% reduction. The proportion of initial and subsequent children with CF, and the cost of screening for and managing CF in both initial and subsequent populations are provided in Table 3.

The incremental cost of screening first children is estimated to be $16.6 Million - $13.4 Million = $3.2 Million/100,000 (i.e. the cost offset of reduced treatment of CF does not outweigh the cost of screening). The incremental cost per CF birth averted in initial pregnancies is $150,000. Whether this represents value for money is uncertain as no threshold for this outcome measure exists. However, the reduced treatment costs in subsequent births are significant, particularly since a large proportion of identified non-carriers are not screened in subsequent pregnancies. When weighted to reflect the relative sizes of the first and subsequent infant populations, the model estimates a net cost saving associated with a national screening program of $2.5 Million/100,000 pregnancies.

Sensitivity Analysis
The model was insensitive to the cost of CVS and termination, the infant mortality risk of CVS, and the assumptions concerning whether parents abstain, pursue IVF or PND. The results for the remaining parameters for the initial infant only are presented graphically in Figure 2.

If subsequent infants are included in the sensitivity analysis, all scenarios are cost saving with the exception of two. First, if the lifetime cost of CF management is reduced by 50% (to $168,000), the cost of the screening program per infant across both initial and subsequent births is $9.99. The cost per CF birth averted in this case is $49,928. Second, if the carrier rate is reduced to 2% (instead of the baseline rate of 4%), the cost is $23.95, with a cost per CF birth averted of $478,946.

Discussion and Conclusions

We have shown that CF carrier screening can reduce CF in Australia. While carrier screening results in an incremental increase in cost per CF birth averted for the first pregnancy screened, substantial savings in subsequent pregnancies are likely. The sensitivity analysis suggests that the base case result is most sensitive to the cost of the test, the probability of termination following a positive CVS test, the lifetime cost of CF management and the carrier rate. Of these, the cost of the test is the most uncertain parameter. In this study, no reduction in cost has been made to reflect economies of scale; doing so would reduce the incremental cost associated with testing in initial pregnancies, and increase the expected cost saving.
across all pregnancies. When considering initial pregnancies only, the cost of the test would have to fall to $80 to make the program cost-saving.

Relative to the work of Maxwell et al., the findings in this study are more suggestive of a screening program recouping costs in terms of reduced incidence of CF, and hence reduced costs of care. The reason for this divergence is two-fold. Firstly, we have included the impact of information on subsequent pregnancy choices. This is important as many parents will require no screening for subsequent pregnancies, and those who are carriers may make decisions which reduce the overall prevalence of CF births. The second reason is that we have employed new data relating to the cost of treating a CF individual. In some regards, the estimates of Van Gool et al. are likely to underestimate the cost of a CF case as they ignore issues surrounding productivity, both of the CF individual and their parent or carer; however, since this is only of relevance if a societal perspective is taken.

An associated practical issue which might be considered in future work is whether public subsidy of the sequalae of a carrier screening program is appropriate. For example, if a couple are identified to be carriers, should society meet the costs of IVF if the couple choose to pursue assisted reproduction? This issue is beyond the scope of this work, but is an important philosophical and practical issue which may stem from a universal screening program.

This work illustrates the difficulties of economic evaluation in this type of intervention. The choice of outcome is contentious for two reasons. Firstly, a screening program provides information likely to be valued independent of health gain (e.g. through reassurance). Within standard health economic evaluation frameworks, health is the core outcome resulting from
an intervention, thus ignoring these non-health benefits. The second reason is that the changes in behaviour resulting from screening occur in multiple dimensions. Screening for CF reduces CF incidence, but also impacts on the number of terminations and couples abstaining from reproduction. Economic evaluation is usually reliant on combining all outcomes into a common outcome measurement, (e.g. the QALY). However, estimating QALYs based on CF babies averted, or couples abstaining from reproduction is almost impossible and would involve a series of unpalatable or unrealistic assumptions.

In conclusion, when initial and subsequent pregnancies are considered together, carrier screening for CF is cost-effective when analysed in the context of the Australian health care system. The generalisability of the conclusion to other countries is uncertain, due to different practices towards the management of people with CF, or couples planning or going through pregnancy. Costs differ between countries, as do conventions regarding discounting of future events. However, our model can be easily replicated and adopted by future researchers to examine the cost-effectiveness of carrier screening in other settings. Translating this information to healthcare policy is the next challenge.

Bibliography


Figure 2: Univariate sensitivity analysis (initial infant only)

Note that the order of the values of parameters within the brackets indicates the value which gives the lower and upper estimate of cost / CF birth averted.
Table 1: Model Memory

<table>
<thead>
<tr>
<th></th>
<th>Male carrier</th>
<th>Male not carrier</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>True positive</td>
<td>False negative</td>
</tr>
<tr>
<td>Female carrier</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B</td>
</tr>
<tr>
<td>Female not carrier</td>
<td></td>
<td>A*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B</td>
</tr>
</tbody>
</table>

*: Males are not screened following a negative female result

A: All subsequent babies do not have CF so no further costs are incurred

B: All subsequent babies are dependent on choice between IVF, becoming pregnant and using prenatal screening or abstaining from reproduction

C: All subsequent babies are not subject to screening, and have a 25% chance of having CF (i.e. probability of baby with two carrier parents having CF)
### Table 2: Model Parameters and Assumptions for Sensitivity Analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Source</th>
<th>Range (for use in sensitivity analysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrier Rate</td>
<td>0.04</td>
<td>Massie et al. 2000</td>
<td>±50%</td>
</tr>
<tr>
<td>Cost of CVS</td>
<td>$115.20</td>
<td>MBS item number</td>
<td>±50%</td>
</tr>
<tr>
<td>Cost of lifetime CF treatment</td>
<td>$336,000</td>
<td>Van Gool et al. 2010</td>
<td>±50%</td>
</tr>
<tr>
<td>Cost of testing</td>
<td>$116.77</td>
<td>Maxwell et al. 2010</td>
<td>±50%</td>
</tr>
<tr>
<td>Cost of termination</td>
<td>$1,708</td>
<td>AR-DRG</td>
<td>±50%</td>
</tr>
<tr>
<td>Cost of IVF</td>
<td>$7,500</td>
<td>Chambers et al. 2008</td>
<td>±50%</td>
</tr>
<tr>
<td>Probability mortality (CVS)</td>
<td>0.013</td>
<td>Lieu 1994</td>
<td>0.0075-0.013 (Radhakrishnan et al. 2008)</td>
</tr>
<tr>
<td>Probability CVS test if 2+ve</td>
<td>0.9</td>
<td>Radhakrishnan et al. 2008¹</td>
<td>0.75-1 (Radhakrishnan et al. 2008)</td>
</tr>
<tr>
<td>Probability male tests if female +ve</td>
<td>0.94</td>
<td>Nielsen 2002</td>
<td>0.84-1.00 (assumption)</td>
</tr>
<tr>
<td>Probability female tests (prenatal)</td>
<td>0.80</td>
<td>Nielsen 2002</td>
<td>0.5-1 (Radhakrishnan et al. 2008)</td>
</tr>
<tr>
<td>Probability female tests (preconceptional)</td>
<td>0.20</td>
<td>Assumption</td>
<td>0.1-1 (Radhakrishnan et al. 2008)</td>
</tr>
<tr>
<td>Probability termination if CVS+ve</td>
<td>0.90</td>
<td>Radhakrishnan et al. 2008²</td>
<td>0.3-1 (Radhakrishnan et al. 2008)</td>
</tr>
<tr>
<td>Sensitivity CVS</td>
<td>1</td>
<td>Radhakrishnan et al. 2008</td>
<td>Not considered as all existing studies</td>
</tr>
<tr>
<td>Specificity CVS</td>
<td>1</td>
<td>assume 1</td>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
<td>---------</td>
<td>--------------------</td>
<td></td>
</tr>
<tr>
<td>Test Sensitivity</td>
<td>0.9</td>
<td>Radhakrishnan et al. 2008</td>
<td>0.85-1 (Radhakrishnan et al. 2008)</td>
</tr>
<tr>
<td>Test Specificity</td>
<td>1</td>
<td>Radhakrishnan et al. 2008</td>
<td>0.99-1 (Radhakrishnan et al. 2008)</td>
</tr>
<tr>
<td>Prob (IVF) if both +ve</td>
<td>0.2</td>
<td>Assumption</td>
<td></td>
</tr>
<tr>
<td>Prob (abstain) if both +ve</td>
<td>0.2</td>
<td>Assumption</td>
<td></td>
</tr>
<tr>
<td>Prob (postnatal diagnosis) if both +ve</td>
<td>0.6</td>
<td>Assumption</td>
<td></td>
</tr>
</tbody>
</table>

1 Radhakrishnan et al. identified that assumptions of foetal diagnosis following confirmation of carrier status ranged from 75% to 100%. A figure of 90% was selected to represent a typical value.

2 Radhakrishnan et al. identified that assumptions of termination following identification of a CF fetus ranged from 80% to 95%. A figure of 90% was selected to represent a typical value.

3 Radhakrishnan et al. identified that assumptions of test sensitivity in a general population ranged from 85% to 100%. A figure of 90% was selected to represent a typical value.

4 As these probabilities are mutually exhaustive, increasing one probability has to be reflected in a reduction in one or both of the other two. For the sensitivity analysis, this study explores the effect of extreme distributions between the three, assuming in turn that all parents enter IVF, that all parents abstain, and that all parents use prenatal diagnosis.
Table 3: Estimated reduction in CF under screening programs

<table>
<thead>
<tr>
<th></th>
<th>Initial child</th>
<th>Subsequent children</th>
<th>All children*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No screening</td>
<td>Screening</td>
<td>No screening</td>
</tr>
<tr>
<td>CF infants per 100,000 births</td>
<td>40.00</td>
<td>18.79</td>
<td>30.00</td>
</tr>
<tr>
<td>Cost (screening and sequelae included) per 100,000 births</td>
<td>$13.4 Million</td>
<td>$16.6 Million</td>
<td>$10.1 Million</td>
</tr>
<tr>
<td>Incremental screening cost / CF birth averted</td>
<td>$150,000</td>
<td>-$339,000 (cost saving)</td>
<td>-$125,000 (cost saving)</td>
</tr>
</tbody>
</table>

* This is a weighted mean of the initial and subsequent children, allowing for the relative sizes of the two populations