Cost-effectiveness of neonatal ECG screening for the long QT syndrome

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Aims A significant number of preventable cardiac deaths in infancy and childhood are due to long QT syndrome (LQTS) and to unrecognized neonatal congenital heart diseases (CHDs). Both carry a serious risk for avoidable mortality and morbidity but effective treatments exist to prevent lethal arrhythmias or to allow early surgical correction before death or irreversible cardiac damage. As an electrocardiogram (ECG) allows recognition of LQTS and of some of the CHDs that have escaped medical diagnosis, and as LQTS also contributes to sudden infant death syndrome, we have analysed the cost-effectiveness of a nationwide programme of neonatal ECG screening. Our primary analysis focused on LQTS alone; a secondary analysis focused on the possibility of identifying some CHDs also.

Methods and results A decision analysis approach was used, building a decision tree for the strategies 'screening'–'no screening'. Markov processes were used to simulate the natural or clinical histories of the patients. To assess the impact of potential errors in the estimates of the model parameters, a Monte Carlo sensitivity analysis was performed by varying all baseline values by ±30%. Incremental cost-effectiveness analysis for the primary analysis shows that with the screening programme, the cost per year of life saved is very low: €11 740. The cost for saving one entire life of 70 years would be €820 000. Even by varying model parameters by ±30%, the cost per year of life saved remains between €7400 and €20 400. These figures define 'highly cost-effective' screening programmes. The secondary analysis provides even more cost-effective results.

Conclusion A programme of neonatal ECG screening performed in a large European country is cost-effective. An ECG performed in the first month of life will allow the early identification of still asymptomatic infants with LQTS and also of infants with some correctable CHDs not recognized by routine neonatal examinations. Appropriate therapy will prevent unnecessary deaths in infants, children, and young adults.

Introduction

The long QT syndrome (LQTS), a leading cause of cardiac sudden death in the young, is a genetic disease characterized by an abnormally prolonged QT interval in the electrocardiogram (ECG) and by life-threatening ventricular arrhythmias often triggered by sudden increases in sympathetic activity.1,2 When LQTS victims are infants, their deaths are often mislabelled as sudden infant death syndrome (SIDS).3

A prospective ECG study in 34 000 infants showed that QT interval prolongation in the first week of life constitutes a major risk factor for SIDS.4 Molecular evidence, initially in anecdotal cases,5 and recently in two series of 93 and 201 SIDS victims, respectively,6,7 demonstrates that ~10% of SIDS cases are actually due to LQTS. These findings and the very low mortality (<2%) among LQTS patients properly treated8–10 raised the controversial issue of neonatal ECG screening as a tool for early identification and treatment of LQTS patients.11,12 As, independently of age, sudden death is often the first manifestation of LQTS and as very effective therapies exist, early diagnosis is of paramount importance.

Some European countries are considering the possibility of introducing neonatal (days 15–25) ECG screening as part of their National Health Services, and the European Society of Cardiology, concerned with the lack of expertise of most adult cardiologists in the interpretation of neonatal ECGs, has appointed a Task Force to draw specific guidelines.13 Meanwhile, the Italian Ministry of Health has funded a currently ongoing prospective 'pilot' ECG study in 50 000 infants to assess the feasibility and outcome of a nationwide neonatal ECG screening.14 Even though the
primary objective of this prospective study is identifying early those with QT prolongation, the results on over 30,000 infants already analysed have unexpectedly revealed four cases of still asymptomatic life-threatening congenital heart diseases (CHDs) [three cases of coarctation of the aorta and one of anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA)] which escaped the initial medical visit.

Cost-effectiveness data are essential if similar programmes have to be considered by appropriate governing bodies. Accordingly, we performed a cost-effectiveness study based on the latest data regarding LQTS prevalence and management with the primary analysis focused on the impact of identifying early the infants affected by LQTS. As a direct consequence of the unexpected finding of our uniquely large prospective study, we performed a secondary analysis considering the impact of identifying early not only the infants affected by LQTS but also those with some life-threatening CHDs.

Methods

Diseases under study

Although the main focus of the present study is the early diagnosis of LQTS, we considered the possibility that ECG screening could also identify anomalies related to CHDs which had escaped routine neonatal examinations, namely coarctation of the aorta and ALCAPA. This choice was due to our direct experience based on over 30,000 infants studied prospectively and to the fact that these conditions are the most frequently undetected CHDs at the two traditionally recommended examinations, i.e. before first discharge from hospital and at 6 weeks of age.

As to ALCAPA, abnormal Q-waves in leads I, aVL, and precordial leads V5–V7 will be present in all affected infants and should be detected by ECG screening, thus leading to surgery. As to coarctation of the aorta, ~50% of all those affected are likely to become symptomatic by the third week of age; another 25–30% will develop major symptoms or will die during the first year of life and should be detected by ECG analysis.

Decision analysis

The assessment of the cost-effectiveness of prevention programmes in the pediatric population is complex, as benefits and costs take place over several decades. As an alternative, or surrogate, to a prospective randomized controlled study, unethical and unfeasible, we used a decision-analytic approach and built a predictive model, a decision tree (DT), largely based on information, published and unpublished, drawn from our own large LQTS database.

Effectiveness is expressed in life year saved (LYS), and costs (Euros) have been considered from the National Health System point of view. Thus, loss of productivity was not taken into account. The time horizon of the analysis is a person’s life.

As the computational tool, we used TreeAge Pro Suite® (TreeAge Software Inc.), a software package to build and analyse DTs.

Decision tree

A DT is a probabilistic formalism representing the consequences of various options. Its first node, the ‘decision node’, has as many branches as the options to be compared. Each branch is then split according to possible events arising from the option it represents. Events are quantified by the corresponding probability of occurrence. Thus, a DT is composed of a number of paths, each ending with an outcome, in our case years of life, number of lives saved, or sustained cost.

Solving the DT requires calculating the expected values of outcomes for each option. If some options are both less expensive and more effective than others, they are defined as ‘cost-saving’ options. More often, effectiveness and cost are directly correlated, and from these figures incremental cost-effectiveness ratios can be calculated. This ratio is the cost to save 1 year of life by implementing a more effective, but more expensive option, compared with a less effective and less expensive option. The lower the ratio the more favourable the intervention (for quantitative considerations on thresholds, see Discussion).

A simplified version of the actual DT is shown in Figure 1. The two options, screening and no screening, are drawn from the square node. Newborns may be healthy or affected by LQTS or by one of the two CHDs under consideration: coarctation of the aorta and ALCAPA. Branches are annotated with their probability of occurrence, here reported as percentages, e.g. 0.04% means that one out of 2500 newborns is affected by LQTS. In the case of screening, the result can be positive or negative. In the case of no screening or false negative results, newborns affected by a severe pathology have a greater probability of dying in their first year of life.

To represent the natural history of both affected and healthy infants, we used Markov processes which are stochastic processes modelling transitions between different states over a finite or infinite time interval. States are ‘health states’, and the time horizon is the individual’s life. The calculation of the cost/LYS requires to run the model until death occurs. Also, as certain costs hold for the entire life, to cut the time horizon before death would introduce a bias. Markov models are based on time-varying transition probabilities to account for the fact that risks change with age and that clinical manifestations decrease with increasing age.

Through Markov models, it is possible to obtain estimates of life expectancy, time spent in each state, average time to enter a certain state, and probability of being in a particular state after a certain amount of time. If an economic cost is associated to each health state, the expected total cost (i.e. the cost sustained throughout the entire life) can also be calculated. As an example, the upper-right portion of Figure 1 shows the Markov model for healthy infants. Here, only two states (‘alive’ or ‘dead’) were used because what is modelled is the life of the general population. First, the two states are listed, with their initial probability of 100 and 0%, respectively. Note that ‘100% alive’ in the Markov process refers to the initial state of the healthy. As to LQTS-affected infants, we used Markov processes which are stochastic processes modelling transitions between different states over a finite or infinite time interval. States are ‘health states’, and the time horizon is the individual’s life. The calculation of the cost/LYS requires to run the model until death occurs. Also, as certain costs hold for the entire life, to cut the time horizon before death would introduce a bias. Markov models are based on time-varying transition probabilities to account for the fact that risks change with age and that clinical manifestations decrease with increasing age.

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Starting from the 'asymptomatic' state, LQTS could be detected in several ways: by chance (e.g. by an ECG performed for other reasons), by the occurrence of syncope or cardiac arrest (usually before age 20), or by an established diagnosis of LQTS among family members. When this happens and LQTS is recognized, the patient is treated. The most frequent transition in this case is to \( \beta B \). We assume that \( \beta B \) therapy, once initiated, continues through life and that other treatments may be added. In the case of screening-detected disease, a similar Markov process will represent the 'therapy-modified LQTS history'.

*Figure 1* is a simplified view of the real DT, which represents the diagnostic strategy also, based on recent guidelines. The complete tree is composed of almost 35 paths, each ending in a Markov process as described.

**Data used in analysis**

Table 1 shows the baseline values adopted for the probabilities in the DT. They originate largely from our own data, published or unpublished. When the literature reports different values, based on valid data, they are listed as 'range' and their source is indicated. Some of the reported probabilities have been used directly in the DT (for example, the prevalence of diseases and the ECG false negative rate), others have been used to calculate the
annual transition probabilities for the Markov model. For example, knowing that 40% of patients with LQTS become symptomatic during their life and knowing that this happens mostly during the first decade of life, we calculated the annual risk of developing LQTS symptoms, assuming a two-exponential risk model, with a higher risk before age 20.

Table 2 shows the costs of diagnostic tests and treatments, based on DRGs and the reimbursement rates of the Italian National Healthcare System.

The attribution of a given value to any parameter listed in the DT carries an unavoidable degree of uncertainty. To assess the impact of potential errors in our estimates, we performed a sensitivity analysis by varying the baseline values in a range of ±30% using the Monte Carlo simulation which allows to change all the parameters simultaneously. Uniform distributions were used to sample variable values. We have chosen a range of variation of ±30% as a safe approximation of the maximal variation for each parameter; as a consequence, the resulting distribution of the estimated cost-effectiveness ratios should provide a consistent estimate of the distribution of these rates across European countries.

To obtain valid estimates, useful for policy makers, we applied the results of the DT to the number of newborns per Italy, ≈550,000.

Results

Primary analysis (LQTS only)

Table 3 reports the life expectancy and expected cost for both the screening and no-screening options, together with 95% confidence intervals (CIs), of the primary analysis

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**Table 1** Values and sources of the DT quantification

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline value (range) (%)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of LQTS in general population</td>
<td>1/2500</td>
<td>Goulene et al., Crotti et al., Schwartz et al.</td>
</tr>
<tr>
<td>False negative LQTS*</td>
<td>20 (8–29)</td>
<td>Priori et al., Zareba et al.</td>
</tr>
<tr>
<td>Symptomatic LQTS patients</td>
<td>40 (36–61)</td>
<td>Priori et al., Garson et al.</td>
</tr>
<tr>
<td>On treatment</td>
<td>85</td>
<td>Calculated by difference</td>
</tr>
<tr>
<td>Asymptomatic LQTS patients</td>
<td>60</td>
<td>Moss et al., Priori et al.</td>
</tr>
<tr>
<td>On treatment</td>
<td>50 (36–53)</td>
<td>Crotti et al.</td>
</tr>
<tr>
<td>Proportion of LQTS patients receiving cardiac treatments for LQTS</td>
<td>64% (50–82)</td>
<td>Priori et al., Zareba et al.</td>
</tr>
<tr>
<td>Modality of treatment</td>
<td>βB 56</td>
<td>On the basis of several studies showing βB therapy as the most common modality of treatment (80–90% of treated LQTS patients)</td>
</tr>
<tr>
<td>LCSD</td>
<td>2</td>
<td>International Registry (5.4% of symptomatic LQTS patients)</td>
</tr>
<tr>
<td>ICD</td>
<td>6</td>
<td>International Registry (12% of symptomatic LQTS patients); our data on all genotyped patients (6–7%)</td>
</tr>
<tr>
<td>Non-LQTS-related death</td>
<td>3</td>
<td>ISTAT</td>
</tr>
<tr>
<td>LQTS-related death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic LQTS patients*</td>
<td>11 (9–14)</td>
<td>Priori et al., Garson et al.</td>
</tr>
<tr>
<td>On βB therapy</td>
<td>2 (1–2.8)</td>
<td>Moss et al., Priori et al., Schwartz et al.</td>
</tr>
<tr>
<td>Following LCSD</td>
<td>0.1</td>
<td>Schwartz et al.</td>
</tr>
<tr>
<td>Following ICD implant</td>
<td>0.02 (0–0.8)</td>
<td>Zareba et al., Crotti et al.</td>
</tr>
<tr>
<td>Prevalence of CHDs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coarctation of the aorta*</td>
<td>1/5000</td>
<td>McBride et al.</td>
</tr>
<tr>
<td>ALCAPA</td>
<td>1/50,000</td>
<td>Rosen et al.</td>
</tr>
</tbody>
</table>

*Silent mutation carriers, with a normal ECG, mostly asymptomatic or with a benign phenotype, e.g. one previous undiagnosed syncope.

*Eighty-five per cent of symptomatics (40%) + 50% of asymptomatics (60%) = 64% treated patients.

*Sudden cardiac death as first event in previously asymptomatic LQTS patients, probably untreated.

In our analysis, we considered 50% of all cases, which correspond to the percentage of all those affected likely to become symptomatic after 3 weeks of age.

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**Table 2** Costs

<table>
<thead>
<tr>
<th>Cost</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>€12</td>
<td>ECG</td>
</tr>
<tr>
<td>€12,000</td>
<td>ICD implantation</td>
</tr>
<tr>
<td>€23, two times per year</td>
<td>ICD interrogation</td>
</tr>
<tr>
<td>€4000</td>
<td>LCSD intervention</td>
</tr>
<tr>
<td>€62</td>
<td>Holter monitoring</td>
</tr>
<tr>
<td>€0.20 per die</td>
<td>βB therapy</td>
</tr>
<tr>
<td>€17,435</td>
<td>Correction intervention for ALCAPA</td>
</tr>
<tr>
<td>€7269 calculated by averaging the DRG reimbursements for intervention with and without complications (€6289) and including the cost for an angiography (€980)</td>
<td>Correction intervention for AC</td>
</tr>
<tr>
<td>€56; treated individuals make a stress test every 2 years from 6 years of age till 40 years of age. After 40 years of age, the test is made every 3 years</td>
<td>Stress test</td>
</tr>
<tr>
<td>€52</td>
<td>Echocardiogram</td>
</tr>
<tr>
<td>€21</td>
<td>Cardiological visit</td>
</tr>
</tbody>
</table>

AC, coarctation of the aorta.
limited to LQTS. Obviously, screening rare diseases increases modestly the life expectancy of the entire population; in this case, by only 1 day with a cost increase of €35. When focusing on the patients identified by the screening, the expected survival of LQTS patients increases by almost 7.6 years. The primary incremental cost-effectiveness analysis shows that the cost/LYS is very low, €11 740. Differently expressed, the cost for saving one entire life of 70 years would be approximately €820 000.

The impact of screening can be usefully expressed also as lives saved, i.e. the number of deaths prevented before age 40. Figure 3 helps to understand the process. It illustrates the Markov cohort analysis, i.e. the probability distribution of the different health states as a function of age. Markov cohort analyses were performed at the Markov node in the no-screening strategy and at the therapy node in the screening strategy. In the no-screening strategy (Figure 3A), most of the cohort is initially in the asymptomatic undiagnosed LQTS state; when these asymptomatic individuals are identified for whatever reason as affected by LQTS, the corresponding cohort moves to another state. As the Markov process lasts from 0 to 119 years (with life expectancy for the general population of 79.7 years), at the end, the cohort falls into two states: LQTS-related death and non-LQTS-related death. In the screening strategy (Figure 3B), the model assumes that diagnosed individuals are immediately treated with βB, thus most of the cohort is in the βB state from the beginning. Very few individuals are initially in the non-LQTS-related death state (4.3/1000), whereas almost 20% are false negatives who follow a process similar to the no-screening strategy but with a lower risk of cardiac death because their disease is less severe, as their QT interval is normal or borderline.26

The percentages of the cohort in the different states at age 40 and according to the two different strategies are shown in Table 4. The main finding is that, by screening, early mortality due to LQTS decreases from 13.5 to 3.2%. With 550 000 newborns per year, ~220 infants per year are affected by LQTS (prevalence of 1/2500). Without screening, 13.5% of them (n = 30) will die early. In the case of screening, early mortality will be 3.2% (seven deaths). Accordingly, the screening strategy would save 23 lives per year.

Albeit traditional in economic evaluation of healthcare programmes, the opportunity of discounting future costs and benefits for prevention programmes is questionable because in this way such programmes will always be disadvantaged in comparison to programmes that produce immediate benefits. Nonetheless, we took into account some discounting strategies. First, we discounted only costs at the 3% rate, resulting in a cost-effectiveness ratio of €11 577 and then we discounted benefits as well at the same rate. This increased the incremental cost-effectiveness ratio to €21 530, a higher figure but still well within acceptable boundaries of cost-effectiveness. Raising this discount rate from 3 to 5%, the ratio becomes €38 648.

Finally, the sensitivity analysis with 30% variation around the baseline value of all parameters concurrently, performed to cover for the possibility that some of our estimates might have been too optimistic or incorrect, shows that the incremental cost-effectiveness ratio remains between €7400 and €20 400 (95% CI), still a very low cost to save 1 year of life. When the sensitivity analysis takes
into account also the 3% discounting rate for both costs and benefits, the incremental cost-effectiveness ratio ranges between €7800 and €43 300 (95% CI).

Secondary analysis (LQTS + CHDs)

Table 3 reports the results of the incremental cost-effectiveness analysis for the combination of LQTS and the two CHDs. The life expectancy of the patients with ALCAPA and the coarctation of the aorta identified by the screening increases by almost 27 and 13 years, respectively, as a consequence of preventing their early deaths. The cost/LYS, €7022 (95% CI 4000–14 200), is lower compared with that of the primary analysis. The cost for saving one entire life of 70 years would be approximately €490 000.

With 550 000 newborns per year, ~121 infants are expected to be affected by the two considered CHDs (110 coarctation of the aorta + 11 ALCAPA). Among these, the 11 with ALCAPA and 55 infants affected by coarctation of the aorta are likely to escape diagnosis within the first 3 weeks of age. Without screening, five (7.6%) of these 66 newborns will die early, whereas this figure decreases to one (1.5%) in the case of screening. Added to the 23 lives saved among the LQTS patients identified by the screening, these other four lead to 27 the total number of lives that the screening strategy would save per year.

Applying discounting at the 3% rate for costs only and for costs and benefits, in the secondary analysis, the incremental cost-effectiveness ratios become, respectively, €6997 (95% CI 3900–13 900) and €16 208 (95% CI 7900–38 400). Raising the discount rate to 5%, the ratio becomes €21 000.

Discussion

The present data show that a programme of neonatal ECG screening performed in a large European country is
cost-effective. The main finding is that the cost per year of life saved would be less than €12 000.

Our initial objective was the early identification of infants affected by LQTS. Our reasoning was that early diagnosis would have led to proper therapy and thus to prevention of some of the SIDS deaths, and especially of many more sudden deaths occurring later on in childhood and young adulthood. This led to our primary analysis. However, we soon13 realized that by casting the large net of ECG screening, we would have had the opportunity to identify other life-threatening conditions. For the present analysis, we focused on just two major CHDs and this led to our secondary analysis. This selection actually underestimates the number of early diagnoses of correctable cardiac diseases that will result from ECG screening, including the short QT syndrome, some cases of the Brugada syndrome, and other CHDs.

The implications of this study are wide. Therefore, its main features need to be examined and discussed prior to draw the logical consequences.

Standards of evaluation of cost-effectiveness

Healthcare programmes have been classified in five grades of recommendation, from A to E.27 Grade A programmes are both more effective and cheaper than the existing ones, whereas grade E programmes are less or equally effective and more expensive. Grades B through D identify more effective but more expensive programmes. Grade B programmes cost less than $20 000 per quality-adjusted life-year (QALY) and are rated as 'highly cost-effective'; grade C programmes cost from $20 000 to $100 000/QALY and are rated as 'cost-effective', whereas grade D programmes cost more than $100 000/QALY, and their cost-effectiveness is questionable. When interventions, such as the present ECG screening programme, do not affect significantly the quality of life of the target population, QALYs and years-of-life saved are very similar.

More recent analyses have not challenged these thresholds, as health interventions are considered cost-effective in the USA at $50 000–$100 000 per LYS28 and in Europe in a range between €43 00029 and €100,000.22

Thus, the incremental cost-effectiveness ratio of approximately €12 000 has to be rated as 'highly cost-effective'. Not even the possible variations due to different discounting rates (up to 5%) nor the probability of errors in the estimates for the model parameters cause the incremental cost-effectiveness ratio to fall outside the accepted thresholds.

Previous studies

Only the study by Zupancic et al.30 has previously examined the cost-effectiveness of neonatal ECG screening. Using a different approach, they concluded that the cost/LYS by universal screening would be $18 465. It has to be noted that they rested on the widespread but incorrect assumption that LQTS has a prevalence of 1/10 000, four times lower than real; that their study aimed specifically at prevention of SIDS, a small fraction of the potential benefit; that they did not consider the secondary benefit of identifying other CHDs; and that they assumed that ECGs would be performed on day 3 of life, when the number of spurious QT prolongation is very high and produces many false positives.13 This is why the European Society of Cardiology recommended to perform ECG screening during weeks 3–4 of life.

Validity of the estimates

The model used requires estimates of the probability of the patients to be in any given state. The strength of our analysis lies in being able to use not only published information including that coming from our International Registry for LQTS2 but, above all, also unpublished data from our own large database for LQTS patients progressively accrued since 19711 and from our uniquely large prospective study with ECGs performed in 45 000 infants.14 The latter provides unprecedented information, not yet available in the medical literature, on what neonatal electrocardiography can reveal. Although Table 1 provides a succinct description of the sources of each estimate, here we discuss two important ones.

The literature offers several estimates concerning the prevalence of LQTS, ranging from 1/5000 to 1/20 000; however, none of them is based on actual data. A meaningful estimate of the prevalence of LQTS requires a large prospective study based on an unselected population. We performed an ECG between days 15 and 25 in 45 000 infants, and in the first 33 000 ECGs analysed, we observed a markedly prolonged QTc (≥470 ms) in 0.9/1000.15 Molecular screening performed in this subgroup indicates >50% of positive genotyping. Assuming that indeed half of the infants with a QTc ≥470 ms carry LQTS mutations, the prevalence of LQTS would be 1/2000. This is certainly an underestimate because among the infants with a QTc between 440 and 470 ms (1.3% of the entire population), there will undoubtedly be additional LQTS mutations carriers. For further caution, in the present analysis, we have conservatively assumed the prevalence of LQTS to be 1/2500. The prevalence of the two CHDs under considerations is derived from the literature21,32 and supported by our prospective study.14 Another critical issue is the percentage of LQTS patients who die suddenly as first manifestation of the disease. One study in a large pediatric population13 indicated a figure of 9%, whereas the most recent study on

| Table 4 Summary of the results for the two strategies |
|---------------------------------|------------------|------------------|
| Model states | Percentage at 40 years of age |
|-----------------|------------------|------------------|
| No screening | Screening |
|--------------------------------------------------|
| Asymptomatic LQTS (and no therapy) | 13 | 3 |
| Asymptomatic LQTS with previous unrecognized syncpe (and no therapy) | 5 | 1 |
| ββ therapy | 58 | 82.8 |
| ββ + ICD | 5.5 | 5 |
| ββ + LCSD | 2 | 2 |
| Non-LQTS-related death | 3 | 3 |
| LQTS-related death | 13.5 | 3.2 |
| In the first year of life ~3% |
| Asymptomatic LQTS ~9% |
| During ββ therapy ~2% |
| During ββ + ICD 0.02% |
| During ββ + LCSD 0.1% |
over 600 genotyped patients shows a 13% incidence of sudden death among patients prior to diagnosis. To the latter figure, one would have to add the infants with de novo mutations who are usually labelled as SIDS victims. Accordingly, we have used the intermediate figure of 11%.

In any such ECG screening, there will be false negatives and false positives. Again on the basis of our own prospective study in 45,000 infants, 14 values exceeding the traditional normal parameters, 13 a fact which per se does not imply the presence of a disease, are observed in 18% of cases. Accordingly, for such a number, we have calculated the cost of a second ECG and of a cardiological visit, and for 20% of these also of an echocardiogram. As to the false outcomes, the situation differs for LQTS and for the two CHDs under analysis. In LQTS, there is ~20% of silent mutation carriers and their risk for major cardiac events is very low; in our analysis, they follow the no-screening strategy. As to ALCAPA, we expect no false negatives at the ECG screening. 19 As to coarctation of the aorta, we expect to miss ~20–25% of cases. It is worth stressing here that we are not at all advocating ECG screening to detect CHDs but that we simply recognize and accept that some cases, which do escape initial medical examinations, can be identified by the ECG screening.

It is critically important that the sensitivity and the Monte Carlo analyses showed that even wide variations (±30%) in these estimates had a small effect on the cost-effectiveness outcome.

Limitations of the study

Although the clinical data will be the same across Europe, there could be some difference for specific costs. We considered and discarded the option of attempting to define an ‘average’ cost for European countries; it would have been cumbersome, fraught with likely errors, and with results not immediately transferable to specific countries. We have chosen instead to make accurate calculations for Italy, one of the European countries with the largest population, and then to test the robustness of the results through sensitivity analysis. This was done by varying every single parameter (probabilities and costs) by ±30%.

In this way, we should have covered the inter-countries cost variations and have provided a cost-effectiveness figure for the screening programme valid for all, or most, European countries.

The ‘cost components’ of an economic evaluation of a healthcare programme depend on the point of view of the analysis, which in our case was that of the National Healthcare System, because in Italy it holds for all the direct costs. We did not consider overhead costs, for example those associated with training of adult cardiologists in reading pediatric ECG, because guidelines for interpretation have already been published. 13 neither did we consider compliance issues in performing the ECG. This could introduce some bias in favour of the screening, but we assume full compliance because the ECG is available everywhere, it does not present any health risk, and especially because the direct experience with our large pilot study in 45,000 infants has shown complete and favourable acceptance by the families.

Also, we did not examine the quality of life. On one hand, the quality of life of the target population, i.e. patients with LQTS or CHDs, could be negatively affected by the screening because more people than necessary (particularly false positives) could be treated, with some minor but unavoidable side effects; on the other hand, the quality of life of the parents would have a dramatic benefit by the prevention of a premature death of one of their children. Had these issues been considered, and other CHDs been considered, the cost-effectiveness of the screening programme would probably have been even greater.

Implications

The concept of introducing neonatal ECG screening as a programme of cardiovascular prevention has resulted from the evidence that some of the deaths due to LQTS, a life-threatening disease diagnosed by an ECG and for which very effective therapies do exist, occur in infancy and are diagnosed as SIDS or, more frequently, occur in early childhood. This proposal generated a controversy based partly on fears of medico-legal consequences for missed diagnoses and partly on concerns for its economic cost. When objectively examined, it became evident that ECG screening, initiated with the goal of identifying early the infants likely to be affected by LQTS, had the potential of producing the following clinically relevant benefits: (i) the affected infants could be treated and protected from life-threatening arrhythmias, thus reducing LQTS-related deaths in childhood and in later years as well; (ii) additional family members (children, teenagers, and adults) also affected by LQTS and thus at risk of sudden death could be identified; (iii) by treating all infants affected by manifest LQTS, we would also protect those at risk of dying in the first few months of life and whose deaths would be labelled as ‘SIDS’. In addition, the unexpected finding observed in our ongoing prospective neonatal ECG study has prompted a fourth benefit, namely the identification of the few but important cases of CHDs that might escape the routine medical visits, 21,34 for which surgical correction can radically change prognosis.

The present study demonstrates that neonatal ECG screening is highly cost-effective and that a significant number of lives can be saved for an objectively small cost. The time is ripe for those involved in the administration of public health to consider the implementation by the National Health Services of such a programme with the objective of reducing the number of preventable sudden cardiac deaths in infants, children, and young adults. It is also time for the European citizens and taxpayers to be informed about what is possible to do, and at what cost, for reducing the tragic burden of sudden deaths in the young.

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References


2. Moss AJ, Schwartz PJ. 25th Anniversary of the international Long QT Syndrome Registry: an ongoing quest to uncover the secrets of LQTS.


25. ISTAT. Tavole di Mortalità per la popolazione italiana, a cura di M. Marsili e M. Battaglini, collana “Istat”, n. 9, 2006.


