# Newborn screening for congenital heart defects: a systematic review and cost-effectiveness analysis

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November 2005

**Health Technology Assessment
NHS R&D HTA Programme**

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**Declared competing interests of authors:** none

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The research reported in this monograph was commissioned by the HTA Programme as project number 99/45/01. The contractual start date was in March 2001. The draft report began editorial review in February 2004 and was accepted for publication in February 2005. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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# Abstract

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**Objectives:** To provide evidence to inform policy decisions about the most appropriate newborn screening strategy for congenital heart defects, identifying priorities for future research that might reduce important uncertainties in the evidence base for such decisions.

**Data sources:** Electronic databases. Groups of parents and health professionals.

**Review methods:** A systematic review of the published medical literature concerning outcomes for children with congenital heart defects was carried out. A decision analytic model was developed to assess the cost-effectiveness of alternative screening strategies for congenital heart defects relevant to the UK. A further study was then carried out using a self-administered anonymous questionnaire to explore the perspectives of parents and health professionals towards the quality of life of children with congenital heart defects. The findings from a structured review of the medical literature regarding parental experiences were linked with those from a focus group of parents of children with congenital heart defects.

**Results:** Current newborn screening policy comprises a clinical examination at birth and 6 weeks, with specific cardiac investigations for specified high-risk children. Routine data are lacking, but under half of affected babies, not previously identified antenatally or because of symptoms, are identified by current newborn screening. There is evidence that screen-positive infants do not receive timely management. Pulse oximetry and echocardiography, in addition to clinical examination, are alternative newborn screening strategies but their cost-effectiveness has not been adequately evaluated in a UK setting. In a population of 100,000 live-born infants, the model predicts 121 infants with life-threatening congenital heart defects undiagnosed at screening, of whom 82 (68%) and 83 (69%) are detected by pulse oximetry and screening echocardiography, respectively, but only 39 (32%) by clinical examination alone. Of these, 71, 71 and 34, respectively, receive a timely diagnosis. The model predicts 46 (0.5%) false-positive screening diagnoses per 100,000 infants with clinical examination, 1168 (1.3%) with pulse oximetry and 4857 (5.4%) with screening echocardiography. The latter includes infants with clinically non-significant defects. Total programme costs are predicted of £300,000 for clinical examination, £480,000 for pulse oximetry and £3.54 million for screening echocardiography. The additional cost per additional timely diagnosis of life-threatening congenital heart defects ranges from £4900 for pulse oximetry to £4.5 million for screening echocardiography. Including clinically significant congenital heart defects gives an additional cost per additional diagnosis of £1500 for pulse oximetry and £36,000 for screening echocardiography. Key determinants for cost-effectiveness are detection rates for pulse oximetry and screening echocardiography. Parents and health professionals place similar values on the quality of life outcomes of children with congenital heart defects and both are more averse to neurological than to cardiac disability. Adverse psychosocial effects for parents are focused around poor management and/or false test results.

**Conclusions:** Early detection through newborn screening potentially can improve the outcome of congenital heart defects; however the current programme performs poorly, and lacks monitoring of quality assurance, performance management and longer term outcomes. Pulse oximetry is a promising alternative newborn screening strategy but further evaluation is needed to obtain more precise

estimates of test performance and to inform optimal timing, diagnostic and management strategies. Although screening echocardiography is associated with the highest detection rate, it is the most costly strategy and has a 5% false-positive rate. Improving antenatal detection of congenital heart defects increases the cost per timely postnatal diagnosis afforded by any newborn screening strategy but does not alter the relative effects of the strategies. An improvement of timely management of screen positive infants is essential. Further research is required to refine the detection rate and other aspects of pulse oximetry, to evaluate antenatal screening strategies more directly, and to investigate the psychosocial effects of newborn screening for congenital heart defects.

# Contents

# Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review. Information has been adapted from references 1–3.

## Glossary

**Aneurysm**   A ballooning enlargement of an area of a blood vessel or part of the heart wall. Blood does not flow smoothly through aneurysms and this may lead to blood clots forming within them.

**Aorta**   The main artery which takes blood from the heart into the circulation around the body (systemic circulation).

**Arrhythmia**   A disturbance in the normal heart rhythm.

**atresia** (adjective: atretic)   Complete obstruction to a valve or blood vessel, which may be due to poor development. Blood cannot flow past this blockage point in the circulation.

**atrium** (plural: atria)   The right atrium and the left atrium are the two chambers at the top of the heart, which collect blood returning through veins from the body and lungs.

**Balloon septostomy**   During cardiac catheterisation, an inflated balloon is pulled across the atrial septum to make an artificial hole. This procedure is used in cases of transposition of the great arteries and tricuspid atresia to create a hole through which oxygenated and deoxygenated blood can mix. This temporarily relieves the heart problem and allows corrective surgery to be undertaken later.

**Banding**   An operation used to palliate problems where pulmonary flow and pressure are high.

**Bicuspid**   Heart valves have three 'leaflets', or cusps, and are called tricuspid valves. An abnormal variant is the 'bicuspid' valve, which has only two cusps.

**Bronchiolitis**   A respiratory infection caused by respiratory syncytial virus and more prevalent in the winter months. The infection is likely to be most severe in infants under 1 year of age and is characterised by wheezing.

**Cardiac catheterisation**   A 'catheter' or tube is inserted through an artery or vein into the heart, where it is used to measure pressures and inject X-ray contrast media (angiography).

**Cardiopulmonary bypass**   A 'heart lung bypass' machine takes over the function of the heart and the lungs, pumping blood around the body and supplying oxygen to the blood, while open-heart surgery takes place. The extracorporeal circuit can be used to cool the body.

**Chamber**, as in 'four chamber'   This refers to the four internal chambers of the heart – the two atria and two ventricles. Congenital heart defects may affect the chambers of the heart or affect blood vessels external to the heart. Examples of four-chamber defects would be hypoplastic left heart and septal defects. During an echocardiogram, an attempt is made to look at all four chambers of the heart, and this is called a 'four-chamber view'.

**Circulatory arrest**   Some elements of some procedures, particularly inside small hearts, can only be achieved if the central circulation is drained of blood and the heart stopped from beating for a short period.

**Congestive heart failure**   A build-up of fluid, predominantly in the lungs and liver, which occurs when the heart is unable to pump effectively. Children with heart failure may be breathless and have difficulty feeding.

*continued*

# Glossary *continued*

**Cyanosis** A lowered oxygen level (saturation) in the blood, leading to a purple–blue colour of the skin and nails.

**Decision analysis** A process that involves identifying all available choices and potential outcomes in a series of decisions that have to be made about patient care. The range of outcomes can be plotted on a decision tree. The relative worth of each outcome is preferably described as a utility or quality of life.

**Dilated/dilatation** This is when the blood vessel, heart chamber or an orifice is stretched or enlarged beyond its normal size.

**Ductus arteriosus** The blood vessel connecting the pulmonary artery with the aorta before birth, which usually closes soon after birth. If the ductus remains open after the early weeks of life, allowing blood to flow between the aorta and the pulmonary artery, this is not normal and it is called a 'persistent (patent) ductus arteriosus' (PDA). Duct-dependent congenital heart defects are ones in which infants become unwell as the ductus closes.

**Echocardiogram (ECHO)** An ultrasound scan produces a moving picture of the heart and can provide detailed information about the type of congenital heart defect. Doppler technology can be combined with echo to provide information about velocity and pattern of blood flow.

**Eisenmenger's syndrome** See 'Pulmonary vascular obstructive disease'.

**Electrocardiogram (ECG)** A recording of the heart's electrical activity.

**Endocarditis prophylaxis** The use of antibiotics to prevent infective endocarditis at times when infection might be expected to enter via the blood.

**Fontan operation** This operation connects the main veins from the systemic circulation to the lung arteries so that blood returning from the body flows directly into the lung circulation without passing through the right ventricle as in a normal heart. This operation is used for complex congenital heart defects when the heart structure cannot be corrected.

**Foramen ovale** The hole between the two atria, which is present at birth. This may remain open ('patent foramen ovale') in about one-fifth of normal adults but rarely needs treatment.

**Heart sounds** These are the sounds made by the closure of the heart valves with each heart beat and are usually heard with a stethoscope.

**Hypoplasia** (adjective: hypoplastic) A term used to describe incomplete development or underdevelopment of a structure.

**Incompetent** A term used to refer to 'leakage' at a heart valve. The flow of blood backwards through a leaky valve is also called 'regurgitation'.

**Infective endocarditis** An infection of the endocardium (internal lining of the heart), which is more common if there are existing abnormalities of the heart, particularly the valves and ventricular septum.

**Innocent murmur** A murmur heard in healthy children, which does not signify any underlying heart disease or defect. These soft heart murmurs are very common and are of no significance.

**Lead time** The time gained in treating or controlling a disease when detection is earlier than usual, for example, in the presymptomatic stage, as when screening is used for detection.

**Lead time bias** Overestimation of survival time due to measuring from a starting point of early detection by screening procedures rather than from clinical symptoms and signs.

**Murmur** A noise, heard with the doctor's stethoscope, which results from disturbance in the flow of blood through the heart. Murmurs may be due to an abnormal heart structure disturbing blood flow, or may occur in a normal heart ('innocent murmur').

**Outlet defects** This refers to heart defects which affect the blood vessels leaving the heart – the aorta and pulmonary artery. Examples of such defects would be transposition of the great arteries and coarctation. During an echocardiogram, an attempt is made to look at the vessels leaving the heart, but this is technically more difficult than a four-chamber view.

*continued*

## Glossary *continued*

**Pacemaker (artificial)**   An electronic device used to stimulate the heart and regulate the heart rhythm.

**Palliation** (adjective: palliative)   The term used to describe a treatment or operation that does not correct the heart problem but reduces the detrimental effects and slows clinical deterioration.

**Pulmonary**   A term for anything to do with the lungs.

**Pulmonary artery**   The main artery carrying blood from the heart to the lungs.

**Pulmonary vascular obstructive disease**
Cardiac failure and cyanosis due to higher pressure on the right side of the heart and caused by the abnormally high pulmonary pressure and blood flow associated with some congenital heart defects. It is a rare complication that develops in later childhood and adulthood.

**Pulse oximetry**   A non-invasive measurement of blood oxygen level (saturation) which involves placing an oximeter against an area of translucent skin, such as a finger, toe or earlobe.

**Respiratory failure**   This occurs when breathing mechanisms start to fail and the main signs are breathlessness and cyanosis. This may be due to many different diseases affecting the lungs or heart.

**Septum**   The wall within the heart separating the left and right sides. The atria are separated by the 'atrial septum' and the ventricles by the 'ventricular septum'. A 'septal defect' is an abnormal hole allowing blood to flow across a septum.

**Shunt**   This may refer to either (1) blood flow through an abnormal communication (e.g. septal defect) or (2) a surgically created communication between two blood vessels through an artificial tube. Surgical shunts are inserted to improve circulation through the lungs in children with low pulmonary blood flow.

**Stenosis**   A term to describe the narrowing of a heart valve or blood vessel.

**Subacute bacterial endocarditis**   See 'infective endocarditis'.

**Systemic circulation**   A term to describe blood flow, from the left ventricle of the heart and aorta, to the body and brain.

**Valve**   A structure in a blood vessel or the heart which allows blood to flow only one way through the circulation with no backflow of blood. The main heart valves are the 'atrioventricular valves' (mitral and tricuspid valves) controlling blood flow from the atria to the ventricles, the 'pulmonary valve' (controlling blood flow into the pulmonary artery) and the 'aortic valve' (controlling blood flow into the aorta).

**Valvotomy**   A procedure which involves cutting through a tight cardiac valve to relieve the obstruction.

**Ventilate**   A term to describe the use of a machine (mechanical ventilator) to help a patient who cannot breathe adequately.

**Ventricle**   One of the two muscular chambers at the bottom of the heart which pump blood out to the body or the lungs with each heart contraction.

# List of abbreviations

| | |
|---|---|
| ACE | angiotensin-converting enzyme |
| ANNP | advanced neonatal nurse practitioner |
| AS | aortic stenosis |
| ASD | atrial septal defect |
| AVSD | atrioventricular septal defect |
| BPA | British Paediatric Association |
| CAVSD | complete atrioventricular septal defect |
| COA | coarctation (of the aorta) |
| EVI | expected value of information |
| EVPI | expected value of perfect information |
| EVSI | expected value of sample information |
| HLH | hypoplastic left heart |
| HRQoL | health-related quality of life |
| HUI | Health Utility Index |
| IAA | interrupted aortic arch |
| ICD | International Classification of Diseases |
| ICER | incremental cost-effectiveness ratio |
| ICU | intensive care unit |
| IQR | interquartile range |
| IVS | intact ventricular septum |
| MA | mitral (valve) atresia |
| NSC | National Screening Committee |
| NT | nuchal translucency |
| NYHA | New York Heart Association |

| | |
|---|---|
| OPCS | Office for Population Censuses and Surveys |
| PA | pulmonary atresia |
| PDA | persistent (patent) ductus arteriosus (not preterm) |
| PFO | patent foramen ovale |
| PS | pulmonary stenosis |
| PVOD | pulmonary vascular obstructive disease |
| QALY | quality-adjusted life-year |
| RCOG | Royal College of Obstetricians and Gynaecologists |
| RCT | randomised controlled trial |
| SG | standard gamble |
| SHO | senior house officer |
| TA | tricuspid atresia |
| TAPVC | total anomalous pulmonary venous connection |
| TGA | transposition of the great arteries |
| TOF | tetralogy of Fallot |
| Truncus | truncus arteriosus |
| TTO | time trade-off |
| UVH | univentricular heart (mitral atresia, tricuspid atresia, common ventricle) |
| VAS | visual analogue scale |
| VSD | ventricular septal defect |

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

# Executive summary

## Objectives

The objectives of this study were to provide evidence to inform policy decisions about the most appropriate newborn screening strategy for congenital heart defects and to identify priorities for future research that might reduce important uncertainties in the evidence base for such decisions.

Specifically the study aimed to:

- systematically review the epidemiology, natural history, treatment and outcomes of congenital heart defects, as well as the performance, effects and costs of current and alternative newborn screening strategies
- classify congenital heart defects for newborn screening taking into account clinical features, presymptomatic interval, prevalence, natural history and treatment
- evaluate effects, costs and cost-effectiveness of alternative newborn screening strategies
- explore the values of parents and health professionals towards the quality of life of children with congenital heart defects
- explore parental experiences of newborn screening for, and diagnosis of, congenital heart defects.

## Methods

A systematic review of the published medical literature concerning outcomes for children with congenital heart defects was carried out. The results of this review were then used in the decision analytic model, based on a population of 100,000 live-born infants, developed to assess the cost-effectiveness of alternative screening strategies for congenital heart defects relevant to the UK.

A study was then carried out exploring the perspectives of parents and health professionals towards the quality of life of children with congenital heart defects. Eight health state descriptions of degrees of cardiac and neurological disability resulting from congenital heart defects were developed and these were presented with a self-administered anonymous questionnaire to two groups of respondents: parents of a child with a congenital heart defect and the health professionals who care for them. Respondents were asked to rank and then score these health states on a visual analogue scale; they then marked the state 'death' on the scale. The views of health professionals and parents about the quality of life of children with congenital heart defects, as represented by these typical health states, were compared.

Finally, a structured review was carried out of the medical literature regarding parental experiences of newborn screening with relevance to screening for congenital heart defects. The findings from the literature review were linked with those from a focus group set up by the study with parents of children with congenital heart defects.

## Results

### Epidemiology
Congenital heart defects affect 7–8 per 1000 live-born infants and account for 3% of all infant deaths and 46% of deaths due to congenital malformations. Around 18–25% of affected infants die in the first year, with 4% of those surviving infancy dying by 16 years.

### Outcomes
Long-term sequelae include cardiac arrhythmias, infective endocarditis and pulmonary vascular obstructive disease.

The study found that long-term outcome studies addressing physical disability, neurodevelopmental, cognitive or psychosocial outcomes and the capacity to participate in normal childhood activities are lacking. Severe neurological deficits affect 5–10% following surgery and milder neurological problems occur in up to one-quarter of children.

### Classification of congenital heart defects
Congenital heart defects can be classified into three main types.

- Life-threatening congenital heart defects are structural cardiac malformations in which collapse is likely and comprise: transposition of the great arteries, coarctation/interrupted aortic arch, aortic stenosis, pulmonary atresia and hypoplastic left heart/mitral atresia.
- Clinically significant congenital heart defects are structural cardiac malformations that have effects on heart function but where collapse is unlikely or its prevention unlikely to be feasible. The most common defects in this group are ventricular septal defect, complete atrioventricular septal defect, atrial septal defect and tetralogy of Fallot.
- Clinically non-significant congenital heart defects are anatomically defined cardiac malformations that have no functional clinical significance. They include ventricular septal defects only detectable with echocardiography and requiring no treatment.

## Screening

The primary objective of newborn screening is the presymptomatic identification of life-threatening congenital heart defects to achieve a timely diagnosis, defined as a preoperative diagnosis before collapse or death occurs. A secondary objective is the detection of clinically significant congenital heart defects.

Current newborn screening policy comprises a clinical examination at birth and 6 weeks, with specific cardiac investigations for specified high-risk children. Routine data are lacking, but under half of affected babies, not previously identified antenatally or because of symptoms, are identified by current newborn screening. There is evidence that screen-positive infants do not receive timely management.

Pulse oximetry and echocardiography, in addition to clinical examination, are alternative newborn screening strategies but their cost-effectiveness has not been adequately evaluated in a UK setting.

## Decision analysis

In a population of 100,000 live-born infants, the model predicts:

- 121 infants with life-threatening congenital heart defects undiagnosed at screening, of whom 82 (68%) and 83 (69%) are detected by pulse oximetry and screening echocardiography, respectively, but only 39 (32%) by clinical examination alone. Of these, 71, 71 and 34, respectively, receive a timely diagnosis
- 46 (0.5%) false-positive screening diagnoses per 100,000 infants with clinical examination, 1168

(1.3%) with pulse oximetry and 4857 (5.4%) with screening echocardiography. The latter includes infants with clinically non-significant defects
- total programme costs of £300,000 for clinical examination, £480,000 for pulse oximetry and £3.54 million for screening echocardiography.

The additional cost per additional timely diagnosis of life-threatening congenital heart defects ranges from £4900 for pulse oximetry to £4.5 million for screening echocardiography. Including clinically significant congenital heart defects gives an additional cost per additional diagnosis of £1500 for pulse oximetry and £36,000 for screening echocardiography. Key determinants for cost-effectiveness are detection rates for pulse oximetry and screening echocardiography.

## Valuing quality of life

Parents and health professionals place similar values on the quality of life outcomes of children with congenital heart defects and both are more averse to neurological than to cardiac disability.

## Parental views

Adverse psychosocial effects for parents are focused around poor management and/or false test results.

# Conclusions

The main conclusions of the study are as follows.

- Early detection through newborn screening potentially can improve the outcome of congenital heart defects.
- The current programme performs poorly, and lacks monitoring of quality assurance, performance management and longer term outcomes.
- Pulse oximetry is a promising alternative newborn screening strategy but further evaluation is needed to obtain more precise estimates of test performance and to inform optimal timing, diagnostic and management strategies.
- Although screening echocardiography is associated with the highest detection rate, it is the most costly strategy and has a 5% false-positive rate.
- Improving antenatal detection of congenital heart defects increases the cost per timely postnatal diagnosis afforded by any newborn screening strategy but does not alter the relative effects of the strategies.
- Timely management of screen-positive infants is essential if outcomes are to improve.

## Implications for health care

The findings suggest the following:

- Broadly, newborn screening for congenital heart defects meets the National Screening Committee criteria for a screening programme.
- There is a strong case for modifying the current policy of clinical screening of the newborn and 6-week-old infant to include other more effective tests.
- The review and the decision analysis suggest that pulse oximetry in addition to clinical examination appears to be a strong candidate for screening, but would require further research evaluation to inform policy.
- Adequate diagnostic and management services are essential to ensure good outcome.
- Information for parents and health professionals is needed across the antenatal and newborn continuum, as is a training curriculum for midwives and others involved in screening.
- Routine data systems, currently lacking, are required for audit, quality assurance and to assess longer term follow-up, as are clearly defined process and outcome measures.

## Recommendations for further research

The following areas are suggested for further study:

- Refining the detection rate and other aspects of pulse oximetry.
- More direct evaluation of antenatal screening strategies.
- Investigating the psychosocial effects of newborn screening for congenital heart defects.

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# Chapter 1

# Introduction

Congenital heart defects are the most common group of congenital anomalies, affecting between 7 and 8 per 1000 live-born infants.[4] Included in this figure are heart defects that contribute importantly to infant mortality and morbidity and which may only be recognised when the affected infant develops life-threatening symptoms of cardiovascular collapse. For these defects, timely recognition in the newborn period is vital to prevent death or cardiovascular collapse with its attendant morbidity. Hence, clinical examination of the cardiovascular system at the time of routine clinical newborn examination has been practised for more than 30 years and is considered to form part of newborn screening. Current guidance recommends a routine clinical examination for all in the newborn period and again at 6–8 weeks of age.[5] However, evidence to suggest that this has been an effective strategy in improving outcome for infants with congenital heart defects is lacking. Although in the UK information about test performance and longer term outcomes have not been systematically collected at a national level, it is nonetheless clear that a negative newborn and 6-week examination is not necessarily reassuring for parents or health professionals. In one population-based study, more than half of babies with undiagnosed congenital heart defects were missed by routine neonatal examination, and more than one-third by 6 weeks.[6] Can this be improved and, if so, how?

One strategy is to advance the time of diagnosis from postnatal to fetal life. Antenatal screening programmes to detect fetal anomalies by ultrasound were introduced in the early 1980s.[7] Although these have the potential to identify congenital heart defects, existing evidence suggests that these have variable success in recognising fetuses with serious congenital heart defects: nationally a fetal diagnosis was made in 23% of all affected pregnancies and 12% of all affected live births.[8] While those centres with above-average detection rates diagnosed around 63% of all affected pregnancies, the extent to which the national picture has improved over the 10 years since this national study was carried out is unclear as data to evaluate the antenatal screening programme are not routinely collected. However,

the authors of a recent Health Technology Assessment review of ultrasound screening in pregnancy, published in 2000, concluded that detection rates were low for cardiac abnormalities.[7]

It is likely, therefore, that some form of newborn screening for congenital heart defects will continue for the foreseeable future. Technological developments in echocardiography and pulse oximetry mean that their application to newborns at the population level can be considered feasible: a number of studies have been published suggesting that these technologies merit further evaluation as newborn screening tests.[9]

Impetus to examine these alternative strategies in the UK has been provided by the Bristol Royal Infirmary Inquiry, which recommended in 2001 that "National standards should be developed, as a matter of priority, for all aspects of the care and treatment of children with congenital heart disease. The standards should address diagnosis, surgical and other treatments, and continuing care."[10] Newborn screening provides one route to diagnosis and it is therefore timely to consider national policies in this light. Further impetus is provided by the work of the National Screening Committee (NSC), which assesses proposed new screening programmes against a set of internationally recognised criteria to ensure that they do more good than harm at a reasonable cost (www.nsc.nhs.uk/pdfs/Criteria.pdf). In 1996, the NHS was instructed not to introduce any new screening programmes until the NSC had reviewed their effectiveness (www.nsc.nhs.uk/uk_nsc/uk_nsc_main.htm).

The evaluation of newborn screening for congenital heart defects presents several challenges. The term encompasses a spectrum of malformations which have varying prevalence, natural history and treatments and hence anticipated benefit from screening. Since they are associated with different clinical features, a single screening test is unlikely to identify all defects. Echocardiography in early life has revealed a high prevalence of structural heart malformations that are of no functional or clinical consequence and which, for the most part, resolve spontaneously. It

therefore follows that clarity regarding the precise objectives of newborn screening is required if the optimal screening strategies are to be selected and evaluated: which defects matter, which defects can be detected and for which defects can early intervention alter outcome?

Which outcomes should and can newborn screening influence? Congenital heart defects account for about 3% of deaths in infancy, so reduction in mortality, assuming this is feasible, is an indisputable objective. The Bristol Inquiry noted the lack of information about longer term outcomes for congenital heart defects: what longer term outcomes should we aim to influence through newborn screening and whose values should that choice reflect? In arriving at a decision, policy makers require estimates of effectiveness, absolute costs and cost-effectiveness. They also need to understand the potential disbenefits to the whole population of introducing a new screening programme or modifying an existing one.

We have addressed these questions in this report. The objective of this study was to provide evidence to inform policy decisions about the most appropriate newborn screening strategy for congenital heart defects and to identify priorities for future research that might reduce important uncertainties in the evidence base for such decisions. The study has five parts: the development of a screening classification for congenital heart defects based on a review of their epidemiology, natural history and treatment; a systematic review of the childhood outcomes of congenital heart defects; an evaluation of the effects, costs and cost-effectiveness of alternative newborn screening strategies using a decision analytic model; an exploration of the perspectives of parents and health professionals towards the quality of life of children with congenital heart defects; and a review of parental experiences of newborn screening based on literature review, together with a focus group involving parents of children with congenital heart defects carried out in conjunction with Heartline.

# Chapter 2
# What are congenital heart defects?

**Chapter outline**

In this chapter, we provide an overview of congenital heart defects and the associated burden of disease from clinical and epidemiological viewpoints. The normal heart and changes that occur in the fetal circulation at birth are described. We then summarise the clinical features of 13 of the most common or severe congenital heart defects in terms of their anatomical description, prevalence at birth, natural history, clinical presentation, management, childhood outcome and the potential benefit of early diagnosis. Finally, classification systems for grouping congenital heart defects are considered and the difficulty of using current systems to understand the potential benefit of early detection for specific heart defects is highlighted.

**Key messages**

- Congenital heart defects affect 7–8 per 1000 live-born infants, three-quarters of whom will be diagnosed by 1 year of age.
- This prevalence estimate increases at least 10-fold if small muscular ventricular septal defects and other functionally unimportant anatomical abnormalities, detectable largely only by echocardiography, are included.
- The most prevalent life-threatening defects are coarctation of the aorta (COA) and critical aortic stenosis (AS) and the most prevalent clinically significant malformation is ventricular septal defect (VSD).
- Overall 18–25% of affected infants die in the first year of life, with a further 4% of those surviving infancy dying by 16 years of age. Congenital heart defects account for 3% of all infant deaths. Not all congenital heart defects may be diagnosed before or at death.
- Specific defects with a high first-year mortality include hypoplastic left heart (HLH), interrupted aortic arch (IAA), transposition of the great arteries (TGA), total anomalous pulmonary venous connection (TAPVC), AS and pulmonary atresia (PA). Although individually rare, taken together these defects contribute significantly to death in infancy from congenital heart defects.
- Congenital heart defects which are likely to result in collapse early in the newborn period include HLH, IAA, TGA, TAPVC and PA.
- Congenital heart defects such as atrial septal defect (ASD), complete atrioventricular septal defect (CAVSD), pulmonary stenosis (PS), tetralogy of Fallot (TOF) and ventricular septal defect (VSD) are unlikely to benefit from early diagnosis in infancy.

## The anatomy of the normal heart (*Figure 1*)

The 'right' heart (right atrium and right ventricle) pumps 'blue' deoxygenated blood around the lungs where oxygen diffuses from the air into the blood. 'Red' oxygenated blood returns to the 'left' heart (left atrium and left ventricle), which pumps it out through the aorta and around the body to deliver oxygen. Once the body organs and tissues have extracted oxygen from the blood, the deoxygenated blood returns through large veins to the right heart. Each side of the normal heart has a reservoir (atrium) and a pumping chamber (ventricle) separated by an 'atrioventricular valve' (the 'tricuspid valve' on the right and the 'mitral valve' on the left). The pulmonary and aortic valves, situated at the entrance to the pulmonary artery and aorta respectively, improve cardiac efficiency by preventing backflow into the heart as the ventricles relax. Although the mechanics of the ventricles are organised so that they contract
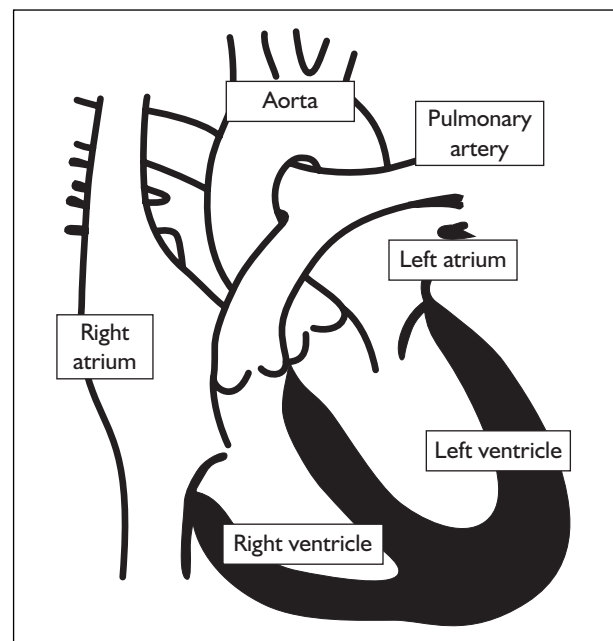


**FIGURE 1** *The normal heart*

together, they are separated by walls (septa) which prevent mixing of the blue and red blood. Relative to the body, the lungs are a low-pressure circuit and the normal right ventricular muscle is thinner than the left ventricular muscle.

## The biology and physiology of the heart: changes at birth

The fetal heart is 'built' by about 8 weeks gestation and remains responsible for providing the growing fetus' circulatory requirements. Hearts that are too defective to do this – perhaps because of leaky valve mechanisms – are not compatible with fetal progress and it is likely that a proportion of first trimester miscarriages are associated with cardiac abnormalities. By 11–13 weeks gestation fetal heart failure is in the differential diagnosis of causes of increased nuchal translucency. In specialist hands, the detailed structure of the fetal heart becomes visible to trans-vaginal ultrasound techniques by around 14 weeks gestation and soon after to trans-abdominal ultrasound. However, fetal anomaly screening, which includes screening for congenital heart disease, is timed at around 18–20 weeks gestation, partly because the structures can be delineated by trained ultrasonographers in a large proportion of pregnancies.

*In utero*, oxygenation and many transfer functions are provided by the placenta, which receives about 40% of the combined fetal right and left ventricular output. This returns via the umbilical vein and ductus venosus to the right heart. The lungs have no oxygenating function and receive only about 7% of cardiac output, the rest of the right ventricular output being diverted via the arterial duct (ductus arteriosus) to the descending aorta, that is, in a direction which postnatally would be called 'right to left'. In addition, blood flows 'right to left' through the oval fossa in the atrial septum. With the two sides of the heart in free communication, the left and right hearts are able to interrelate so that a wide variety of anomalies that are very serious postnatally are able to sustain an adequate fetal circulation.

After birth, the placenta is taken out of the circulation as the umbilical cord is tied and the lungs are recruited progressively with the first few breaths. With the abrupt decrease in return via the venous duct and the increase in return from lungs to left atrium, the flap-like oval fossa virtually closes, removing any potential for intracardiac communications between the two sides of a normal heart. Over the first 24 hours or so, and

triggered by a prostaglandin-dependent mechanism in its wall, the arterial duct also closes, leaving the right and left hearts to function independently. Closure of the arterial duct will generally occur even if it decompensates an abnormal circulation.

Infants with congenital heart defects associated with duct-dependent pulmonary or systemic blood flow or with transposition streaming become at risk of collapse as they fail to make adequate transition from their fetal to postnatal circumstances (streaming is the term used when the 'blue' deoxygenated and 'red' oxygenated blood are pumped through the wrong circuits). Infants whose malformation requires continuing ductal patency to perfuse the whole or even just the lower body (HLH, critical AS, IAA or COA) become progressively acidotic as the duct constricts, perfusion falls and their pulses become impalpable. Infants with duct-dependent pulmonary blood supply or transposition streaming suffer from progressive cyanosis as systemic oxygenation falls. Newborn infants are able to tolerate much lower oxygen saturations than older children or adults because their whole intrauterine physiology is adapted to hypoxic circumstances.

The variety of congenital heart defects is enormous, partly because of the number of permutations and combinations of defects which can affect the atria, ventricles, septa, veins or great arteries.

In the following section we describe the major categories of congenital heart defects, and summarise their prevalence, natural history, management and outcome, ending with a brief comment on the perceived benefits of early diagnosis. A summary is given in *Table 1*.

## Descriptions of congenital heart defects

### Aortic valve stenosis (aortic stenosis) (*Figure 2*)
#### Description
The term aortic valve stenosis describes a restriction to blood flow through the aortic valve. It may present throughout infancy and childhood and, indeed, throughout life. Inevitably those presenting early in the newborn period are at the severe end of the spectrum, both morphologically and physiologically. The stenosed or narrowed aortic valve is usually small and dysplastic and is

**TABLE 1** *Summary of congenital heart defects and their prevalence*

| Name of congenital heart defect | Description | Median prevalence per 100,000 live births (*lower quartile, upper quartile*)[11] | Prevalence per 100,000 live births[11–13] |
|---|---|---|---|
| Aortic (valve) stenosis (AS) | Narrowed aortic valve | 26 (16, 39) | 20 |
| Atrial septal defect (ASD) | Hole in atrial septum allowing blood flow from left to right atrium | 56 (37, 106) | 28 |
| Coarctation of the aorta (COA) | Narrowing of the distal aortic arch | 36 (29, 49) | 35 |
| Complete atrioventricular septal defect (CAVSD) | Lower atrial septum, inlet ventricular septum and atrioventricular valves are all malformed | 34 (24, 40) | 27 |
| Hypoplastic left heart (HLH) syndrome | Aortic valve atresia, possible mitral atresia (MA) and small left ventricle | 23 (15, 28) | 14 |
| Interruption of the aortic arch (IAA) | Part of the aorta fails to develop. Always associated with another major heart defect | Not cited | 8 |
| Persistent (patent) ductus arteriosus (PDA) | Fetal connection between pulmonary artery and aorta persisting after 6–12 weeks of age | 57 (32, 78) | 50 (adjusted for late diagnoses) |
| Pulmonary atresia (PA) | Pulmonary valve is closed. May have VSD or intact ventricular septum (IVS) | 8 (8, 15) | 21 (4.8 intact ventricular septum; 10.0 with ventricular septal defect; 6.6 complex pulmonary atresia) |
| Pulmonary stenosis (PS) | Narrow malformed pulmonary valve | 53 (35, 84) | 65 |
| Tetralogy of Fallot (TOF) | Subaortic VSD with anterior displacement of aorta and right ventricular outflow obstruction | 35 (29, 58) | 31 |
| Total anomalous pulmonary venous connection (TAPVC) | Pulmonary veins do not connect with left atrium and blood flows directly into systemic circulation | 9 (6, 12) | 9 |
| Transposition of the great arteries (TGA) | Pulmonary artery arises from left ventricle and aorta from right ventricle | 30 (23, 29) | 30 |
| Ventricular septal defect (VSD) | Hole(s) in the interventricular septum. Often associated with other heart defects | Over 4000 (if series involving routine echocardiography at birth are included) | 197 (echocardiography not used to screen) |
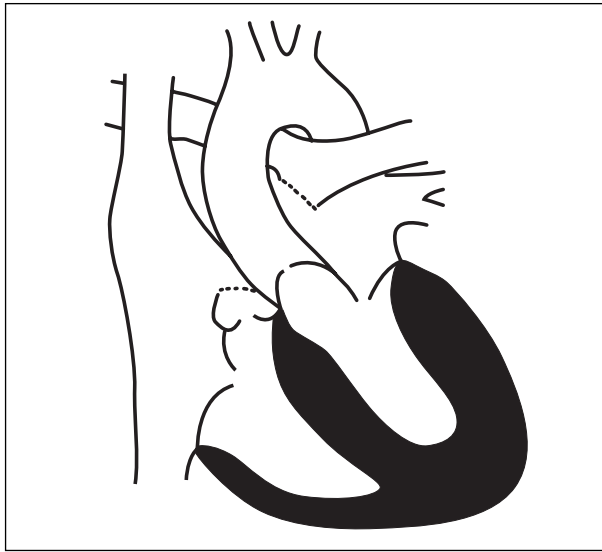
**FIGURE 2** *Aortic stenosis*

often bicuspid. The left ventricle may be dilated with poor contraction or hypertrophied with preserved systolic function. Sometimes the aortic valve and left ventricle are underdeveloped, bordering on hypoplastic left heart syndrome.

### Prevalence at live birth
In Hoffman and Kaplan's review of 37 papers, a prevalence of 26 per 100,000 live births was reported (lower quartile 16, upper quartile 39).[11] This is comparable to an earlier report from the North East of 20 per 100,000 live births.[4] In a later report from the same centre, the prevalence was cited as 19.6 per 100,000 live births in infancy (during the first year of life) with an additional 57% of diagnoses made post infancy in childhood.[12] These later presenting cases are generally less severe.

### Natural history
This depends entirely on the severity of AS and the presence of associated abnormalities such as COA or subaortic stenosis. More severe stenosis presents with heart failure, cardiovascular collapse or early death.[14]

### Presentation
Few infants are diagnosed early. Of those diagnosed in the first year of life, 84% are discharged home without the problem being recognised and 54% are still undiagnosed at 12 weeks of age.[6]

### Management
The management depends on the severity of the stenosis. Severe stenosis, heart failure or other

symptoms all require palliation of the stenosis by valvotomy. This can be achieved surgically or with a balloon catheter with similar morbidity and mortality.

### Outcome
Most reports are of selected surgical or balloon catheter series. Wren and colleagues reported a 21% mortality for individuals not recognised in the first year of life.[6]

### Benefit of early diagnosis
Recognition of the abnormality before symptomatic deterioration or death will inevitably lead to an improved outcome.

## Atrial septal defect (*Figure 3*)
### Description
The commonest type of ASD, the so-called 'ostium secundum' defect, is a central hole in the atrial septum. It varies considerably in size and permits left to right flow at atrial level, producing right atrial and right ventricular volume loading. Less common types of atrial defect include the 'sinus venosus' defect, which is high in the atrial septum and is associated with a partially anomalous connection of the right upper or right pulmonary vein(s). An 'ostium primum' defect is more correctly classified as a partial atrioventricular septal defect.

### Prevalence at live birth
This depends on the type of ascertainment. Hoffman and Kaplan, in their review of 43 papers, quote a median prevalence at live birth of 56 per 100,000 (lower quartile 37, upper quartile 106).[11]



**FIGURE 3** *Atrial septal defect*

In the North East the prevalence at live birth diagnosed in infancy was 28 per 100,000.[4] Because many defects are not diagnosed until later in childhood or even in adult life, prevalence is higher if it includes ascertainment beyond infancy. Thus, in a later study from the North East,[12] 59% of all ASDs recognised in childhood were diagnosed after the age of 12 months. The incidence of new diagnoses in adult life is unknown.

### Natural history
Symptoms early in life are rare, even in the presence of a large left to right shunt. There is often a subjective symptomatic improvement after ASD closure in childhood. However, in the majority, true symptoms will not develop until adult life when the chronic effects of right heart volume loading take their toll, leading to the development of congestive heart failure, atrial fibrillation and, in some cases, pulmonary hypertension. In a review of the literature, Hoffman reported an average age at death in patients with large ASD of 40 years, with a 6% annual mortality.[15]

### Presentation
In the absence of symptoms, the normal mode of presentation is with a murmur emerging beyond the neonatal period. An ASD is sometimes recognised at birth during echocardiographic assessment for other reasons.

### Management
An intervention is required to close all but the smallest ASDs. This was one of the first malformations to be closed by surgery. In more recent years, transcatheter closure has been an alternative. Surgical closure is usually undertaken before school age if the diagnosis has been made by then.

### Outcome
Surgical closure of the ASD in childhood will usually lead to a normal life expectancy and quality of life. A minority of patients will experience atrial arrhythmias as an associated problem. The long-term performance of transcatheter closure is unknown but is likely to be as good as surgery.

### Benefit of early diagnosis
There is no real benefit to early diagnosis of ASD in infancy. Rarely, some ASDs will result in the development of irreversible pulmonary vascular obstructive disease (PVOD) in later childhood or adulthood.

## Coarctation of the aorta (*Figure 4*)
### Description
This is the commonest cause of heart failure or cardiovascular collapse in the newborn infant. There is narrowing of the distal aortic arch, usually in the vicinity of the ductus. In newborn infants, it is often accompanied by hypoplasia of the proximal aorta and sometimes of the aortic arch. If the stenosis is severe the circulation to the lower half of the body will be duct dependent and symptoms will develop as the duct starts to close. There is an associated cardiac malformation in about 40% of infants (and in more than half of those presenting during the newborn period). The commonest association is a VSD or bicuspid aortic valve, but AS, mitral valve problems and more complex cardiac malformations are also common.

### Prevalence at live birth
This depends on the hierarchical method of classification in infants with more than one cardiovascular malformation. Most anatomical or embryological hierarchies will lead to under ascertainment of COA. In Hoffman's review of 39 papers, a prevalence of 36 per 100,000 live births (lower quartile 29, upper quartile 49) is quoted.[15] In the series by Wren and colleagues the prevalence of isolated coarctation in infancy was 24 per 100,000, but another 11 cases per 100,000 were associated with a more significant cardiac abnormality giving an overall prevalence at live birth of 35 per 100,000.[4] In another report reviewing post-infant presentation of cardiovascular malformations, it was estimated that one-third of cases will present beyond infancy.[12]

### Natural history
COA may present with heart failure, collapse or even death in the newborn period, with heart
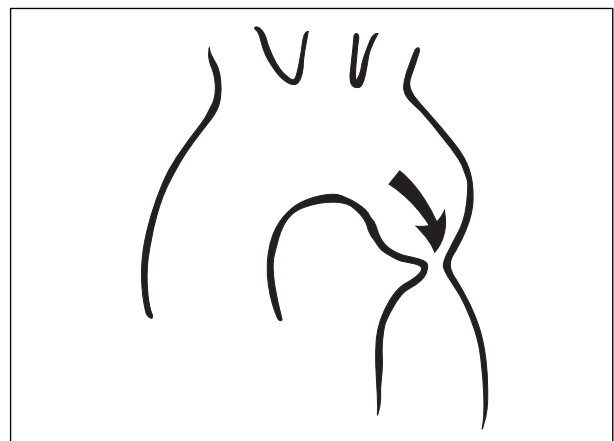


**FIGURE 4** *Coarctation of the aorta*

failure or failure to thrive in infancy, and with failure to thrive or hypertension beyond infancy. In a report from Oxford, collapse or death occurred in 40% of infants with a postnatal diagnosis.[16]

### Presentation
While a few infants (14%) present before the routine newborn examination, this is often because of another associated malformation such as TGA.[6] In the Northern Region study, 76% of affected infants were discharged from the maternity unit undiagnosed and 27% remained unrecognised by 6 weeks of age.[6] In the Oxford series, 9% of those diagnosed in infancy but after birth were diagnosed at autopsy.[16]

### Management
Early presentation in the newborn period implies that the situation is duct dependent and infants improve with prostaglandin infusion. Definitive early surgical repair is preferred.

### Outcome
In the North East series there was 16% mortality in infancy. The surgical mortality of COA repair is low and the overall outcome will be influenced by associated malformations.

### Benefit of early diagnosis
In the Oxford report, cardiovascular collapse or death did not occur among the 10 infants with an antenatal diagnosis, but occurred in 10 of the 25 infants with a postnatal diagnosis.[16] COA was also one of the main causes of death before diagnosis in the review of deaths from congenital heart defects in infancy by Abu-Harb and colleagues.[14]

## Complete atrioventricular septal defect (*Figure 5*)
### Description
This is a major malformation of the inlet of the heart, affecting the lower part of the atrial septum, the inlet part of the ventricular septum and the atrioventricular valve(s). The inlet VSD is usually unrestrictive, producing pulmonary hypertension. There is a common atrioventricular valve in place of the mitral and aortic valves. The common valve usually has five leaflets and is often regurgitant.

### Prevalence at live birth
In Hoffman and Kaplan's review of 40 papers, a median prevalence of 34 per 100,000 live births (lower quartile 24, upper quartile 40) was cited.[11] In the North East series, the prevalence was 27 per 100,000 and 63% of cases were associated with Down's syndrome.[6]



**FIGURE 5** *Complete atrioventricular septal defect*

### Presentation
The majority of infants will present with heart failure in infancy, or sometimes earlier with a murmur. It is recommended that infants with Down's syndrome be referred for early echocardiography, hence some infants will be diagnosed in the absence of cardiac symptoms and/or signs. Some infants with a relatively high pulmonary resistance remain well with no murmur and no heart failure and the defect may not be recognised until they are inoperable (see below). Around 40% remain unrecognised at 6 weeks of age, with or without Down's syndrome.[6]

### Natural history
Without treatment, the natural history is premature death. This is either from heart failure in infancy, or heart failure with an associated infection (such as bronchiolitis) in infancy, or from irreversible pulmonary vascular disease (Eisenmenger's syndrome) in later childhood or early adult life.

### Management
The preferred option is primary surgical repair which involves patch closure of the VSD, division of the common atrioventricular valve into left and right atrioventricular valves with adequate function and patch closure of the ASD. The mortality from this operation has fallen dramatically over the past 10–20 years. In most cases postoperative atrioventricular valve function is good although long-term surveillance is required and reoperation for atrioventricular valve regurgitation is sometimes necessary.

### Outcome
In the North East series,[12] the infant mortality in infants with complete atrioventricular septal defects born in 1985–94 was 44%. This reflects both the seriousness of the cardiac condition and the frequency of associated non-cardiac malformations including lethal trisomy. The predicted further survival to 16 years was 96% as late problems are few.

### Benefits of early diagnosis
There is no definable survival benefit to early presymptomatic diagnosis of complete atrioventricular septal defect in infancy. An unknown proportion of babies with complete atrioventricular septal defect remain asymptomatic with no murmur as pulmonary resistance remains high and, if they are not recognised, they are at risk of developing irreversible PVOD in later childhood or adulthood. The majority of infants with complete atrioventricular septal defect become increasingly breathless and are thus recognised at a stage of their natural history when surgery is beneficial, or are recognised during cardiac investigations for associated Down's syndrome. Corrective surgery carries the lowest mortality and best long-term outcome if it is undertaken by about 6 months of age.

## Hypoplastic left heart syndrome (*Figure 6*)
### Description
HLH syndrome encompasses aortic valve atresia and some forms of MA. There is no forward flow through the left heart. The aortic valve is usually small and imperforate, the left ventricle is underdeveloped to a variable, and often extreme,
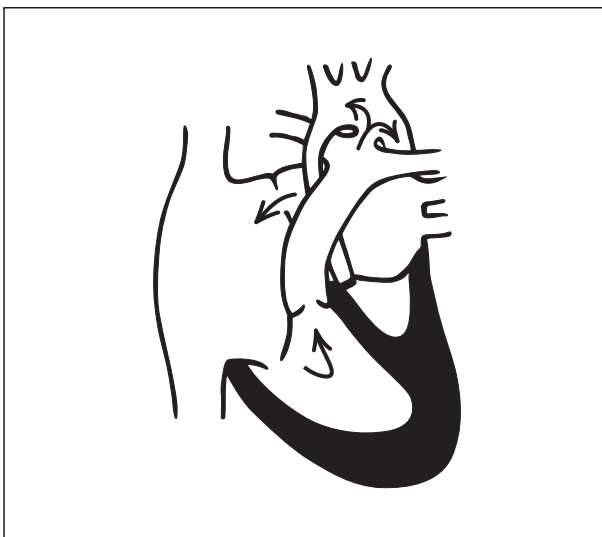


**FIGURE 6** *Hypoplastic left heart*

extent and the mitral valve is hypoplastic or atretic. Pulmonary venous return enters the right atrium from the left atrium and the only outlet from the heart is through the pulmonary artery. The systemic circulation is totally duct dependent. The aortic arch is usually hypoplastic and the ascending aorta is very small, acting simply as a conduit for flow into the coronary arteries.

### Prevalence at live birth
In Hoffman and Kaplan's review of 36 papers, the prevalence was 23 per 100,000 live births (lower quartile 15, upper quartile 28).[11] In the North East series, the prevalence was 14 per 100,000 live births.[4] Live birth prevalence is likely to be influenced by antenatal diagnosis and termination of pregnancy.

### Natural history
The natural history is early death with almost no prospect of prolonged natural survival.[17] Half of those affected present with symptoms before the routine newborn examination but another one-third go home with the problem unrecognised.[6,18] All affected infants present or die before 6 weeks of age.

### Presentation
Presentation is with early heart failure or early death. The median age at diagnosis is about 2 days in those diagnosed postnatally.

### Management
A prostaglandin infusion is given on presentation and continued after diagnosis pending a management plan. In previous years infants were often allowed to die because of the poor results of intervention. More recently, radical palliative surgery (the Norwood operation and variants) has become more widespread and results have improved. Primary transplantation is a theoretical option but is not employed in the UK for lack of suitable donors.

### Outcome
This is very variable but still poor. In the Birmingham series, infants undergoing a Norwood operation had an actuarial 4-year survival of 44%.[19] In another report from the same centre there was a 25% 6-month survival among live-born affected infants and a 15% 6-month survival (taking into account termination of pregnancy) in infants diagnosed antenatally.[20] In a recent report from Guy's Hospital, only one-third of antenatally diagnosed infants were live-born and 50% of the latter survived the first stage of palliation.[21]

***Benefit of early diagnosis***
Experience in San Francisco suggests an improved survival after antenatal diagnosis and treatment from birth to prevent haemodynamic deterioration.[22] However, another report from Boston failed to show a benefit.[23]

## Interruption of the aortic arch (*Figure 7*)
***Description***
In interruption of the aortic arch a portion of the aorta fails to develop. The descending aorta is entirely supplied via the ductus. The interruption may be distal to the left subclavian artery (type A) or between the left carotid and the left subclavian arteries (type B). Interruption of the aortic arch is always associated with a major cardiac abnormality such as VSD, aortopulmonary window, truncus arteriosus (truncus), or other complex malformations. Type B interruption is strongly associated with 22q11 deletion (Di George syndrome).

***Prevalence at live birth***
The prevalence at live birth is difficult to ascertain as interruption of the aortic arch is considered as a secondary or subsidiary diagnosis in most hierarchies. In Hoffman and Kaplan's review, no estimate of prevalence is cited.[11] In the North East, the prevalence was 8 per 100,000 live births.[4] In Iowa and Minnesota in 1982–91 it was 6.6 per 100,000 live births.[24] The Baltimore–Washington Infant Study reported 3.4 per 100,000 live births.[25]

***Natural history***
Presentation is early because the lower half of the body has an entirely duct-dependent circulation.
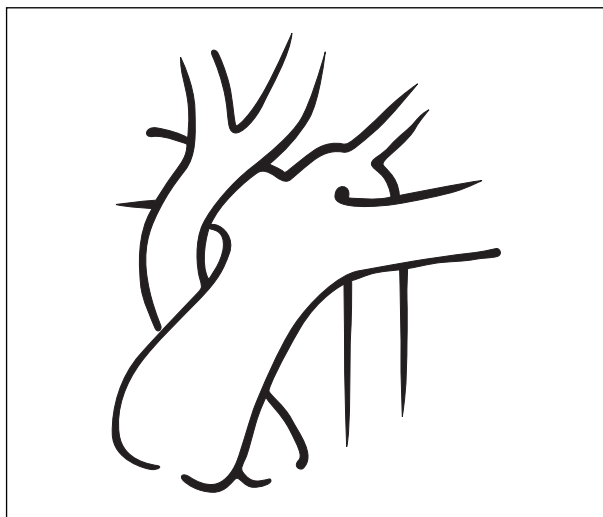


**FIGURE 7** *Interruption of the aortic arch*

Affected infants present with heart failure, collapse or death.

***Presentation***
One-third of infants present before the routine newborn examination but this may be because of associated cardiac disease. Patients with interruption of the aortic arch deteriorate very quickly once their duct begins to close, with initial breathlessness, worsening into collapse and death within hours. About half go home without recognition of the problem, but all present with heart failure or death before 6 weeks of age.[6]

***Management***
Resuscitation includes prostaglandin infusion. The surgical aim is primary repair of the aortic arch and what else is done depends on associated diagnoses. In the presence of an aortopulmonary window, VSD or truncus, the usual choice would be primary repair of both the arch and the heart problem. In the presence of a double inlet ventricle or complex transposition, it would be more common to perform pulmonary artery banding for palliation.

***Outcome***
Most reports are of surgical series and deal only with surgical mortality. In a multi-centre series from the USA concerning births from 1983 to 1993, there was a surgical mortality of 35%.[24] In the report by Wren and colleagues the mortality throughout infancy in 1987–94 was 67%.[6] Late follow-up studies are not available but the aortic arch repair is not always corrective in the long term. The risks associated with residual or recurrent arch obstruction and with revision procedures will impair life expectancy for this group relative to normal children.

***Benefit of early diagnosis***
Early diagnosis will inevitably lead to a better outcome, although published evidence is limited owing to small sample sizes and variable ascertainment.

## Persistent (patent) ductus arteriosus (*Figure 8*)
***Description***
The ductus is a normal component of the fetal circulation, serving to divert most of the right ventricular outflow away from the lungs and towards the placenta. It is programmed to close soon after birth. If the ductus remains patent or open beyond 6–12 weeks post-term, it is described as 'persistent' and will not close spontaneously thereafter. Patency of the ductus is common in premature infants.
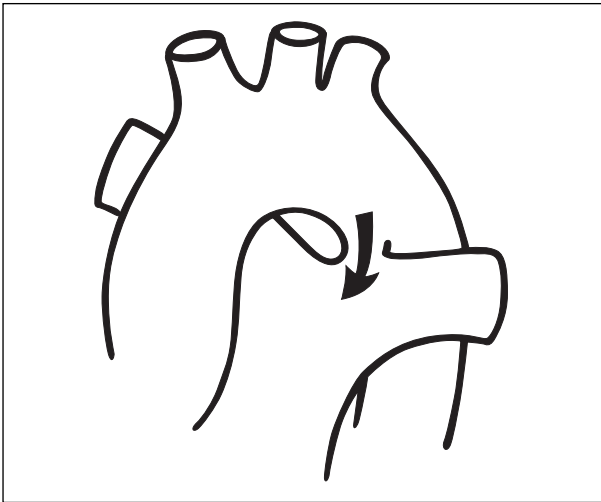
**FIGURE 8** *Persistent ductus arteriosus*

### Prevalence at live birth

This depends mainly on the method of case ascertainment as the duct very often does not cause symptoms early in life in babies who are born at term. Hoffman and Kaplan report a median prevalence at live birth of 57 per 100,000 (lower quartile 32, upper quartile 78).[11] In the North East of England, the prevalence at live birth with diagnoses made during infancy was 23 per 100,000.[4] However, diagnosis is often delayed until later in childhood because of the relative lack of symptoms and signs. In a further study from the North East with ascertainment beyond infancy, only 41% of diagnoses were made in infancy, giving an adjusted prevalence at live birth of around 50 per 100,000.[12] Persistence of the ductus is three times as common in girls as in boys.

### Natural history

Symptoms early in life are rare, other than in association with prematurity. The natural history is difficult to determine as treatment is always offered nowadays, but Campbell writing in 1968 concluded that if untreated, 80% of patients would survive to 30 years of age but only 40% to 60 years of age.[26] This attrition may be an overestimate as small asymptomatic ducts are likely to have been underascertained in the pre-echocardiography era. If the duct is small the only significant problem in the long run is the development of infective endarteritis. If it remains medium or large, eventually congestive heart failure, atrial fibrillation or pulmonary vascular disease may develop.

### Presentation

Infants with a medium or large duct present during infancy with heart failure or signs of a significant shunt. More commonly, the duct is small and is detected in an asymptomatic child with a murmur.

### Management

Detection of a ductus almost universally leads to its closure. This is still accomplished surgically in premature infants but in term infants is now virtually always managed by transcatheter closure.

### Outcome

Closure of the duct is effectively curative, leading to a normal quality of life and life expectancy.

### Benefit of early diagnosis

A symptomatic large duct is an indication for early surgery but most are asymptomatic and are closed with a transcatheter technique when the child's body weight is >10 kg (around 10–12 months old). Occasionally, a large duct is not recognised in infancy and causes irreversible PVOD. Although detection of large ducts does not need to occur in the neonatal period, there can still be a benefit from early diagnosis.

## Pulmonary atresia

### Description

The term 'pulmonary atresia' describes a group of malformations which have in common the absence of a direct connection between the heart and the lungs. They otherwise differ with variable morphology and natural history. The two main types are pulmonary atresia with intact ventricular septum (PA/IVS) (*Figure 9*) and pulmonary atresia with ventricular septal defect (PA/VSD) (*Figure 10*). In PA/IVS the right ventricle and tricuspid valve are usually severely hypoplastic, and the pulmonary arteries are usually well developed and supplied by a patent ductus. In PA/VSD, sometimes known as tetralogy of Fallot with pulmonary atresia, there are usually two good-sized ventricles with a single subaortic VSD and very variable pulmonary artery blood supply. There is sometimes a single ductus, but more often a group of collateral vessels arising from the descending aorta. PA may also be a component of more complex malformations such as double-inlet left ventricle, congenitally corrected TGA or hearts with atrial isomerism.

### Prevalence at live birth

Hearts characterised by pulmonary atresia are relatively rare. In Hoffman and Kaplan's review of 11 papers, a median prevalence of 8 per 100,000 but a mean of 13 per 100,000 is cited (lower quartile 8, upper quartile 15).[11] In the North East of England, the prevalence at live birth of all

**FIGURE 9** *Pulmonary atresia with intact ventricular septum*
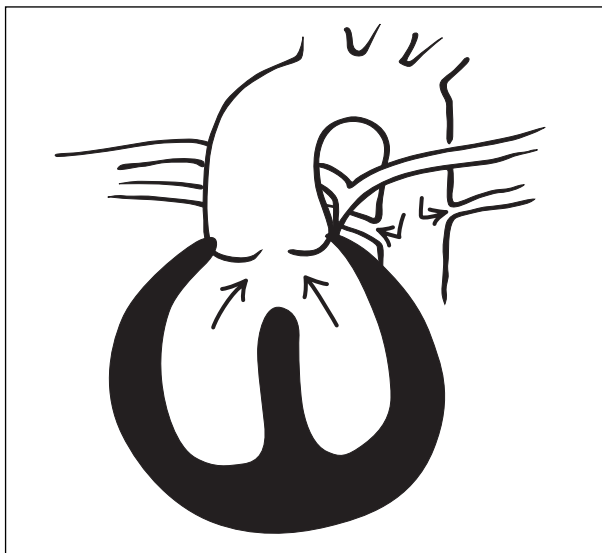


**FIGURE 10** *Pulmonary atresia with ventricular septal defect*

forms of pulmonary atresia was 21 per 100,000, with 5 per 100,000 with PA/IVS, 10 per 100,000 with PA/VSD and 7 per 100,000 with more complex PA.[13] However, the reported prevalence depends on the hierarchy used to describe infants with more than one cardiac malformation. An 'anatomical' or 'embryological' hierarchy will lead to under reporting of PA by 27% when compared with a 'physiological' hierarchy.[4]

### Natural history
Infants with PA/IVS will die very early without treatment. The natural history of PA/VSD is more variable and depends on the pulmonary blood supply. Affected infants are symptomatic but can easily survive into adult life, even without any intervention if the pulmonary blood supply is

fairly balanced. Pulmonary vascular disease and other problems are likely to develop in adult life, leading to a diminished quality of life and shortened survival.

### Presentation
Almost all affected infants present early in life. In those with PA/IVS, a critically 'duct-dependent' malformation, this is usually in the first few hours of life with cyanosis. In those with PA/VSD, which is less often duct dependent, this is with cyanosis later in infancy. Wren and colleagues[6] reported that 50% of cases (probably including most of those with PA/IVS) were recognised before the routine newborn examination, although by contrast 31% were not recognised before discharge from hospital.

### Management
Infants with PA/IVS have a functional single ventricle and the eventual aim is usually some kind of 'Fontan' operation, more often a cavopulmonary connection achieving a right heart bypass. Early palliation involves creating a shunt to replace the ductus. Management of PA/VSD depends on the pulmonary blood supply. About half of those affected will eventually be suitable for definitive surgical repair with closure of the VSD and placement of a conduit to connect the right ventricle to the pulmonary arteries.

### Outcome
Leonard and colleagues[13] report a total mortality of 56% with one-fifth of deaths occurring in the first week and two-thirds within the first year (for infants live-born in 1980–95). One-year mortality was 52% for PA/IVS, 25% for PA/VSD and 48% for PA associated with more complex abnormalities.

### Benefit of early diagnosis
Babies with PA have a duct-dependent pulmonary blood flow, so they become more cyanosed as the ductus closes and eventually will collapse and perhaps die. Although some infants may become rapidly unwell in the first hours of life before a screening opportunity, the timely diagnosis of less symptomatic infants with PA could avert deaths, particularly as some of these babies currently collapse at home after discharge from maternity hospital.

## Pulmonary stenosis (*Figure 11*)
### Description
This is most often an isolated abnormality, with incomplete opening of the pulmonary valve caused by fusion of the valve cusps. The valve may be bicuspid, or sometimes more dysplastic, so that
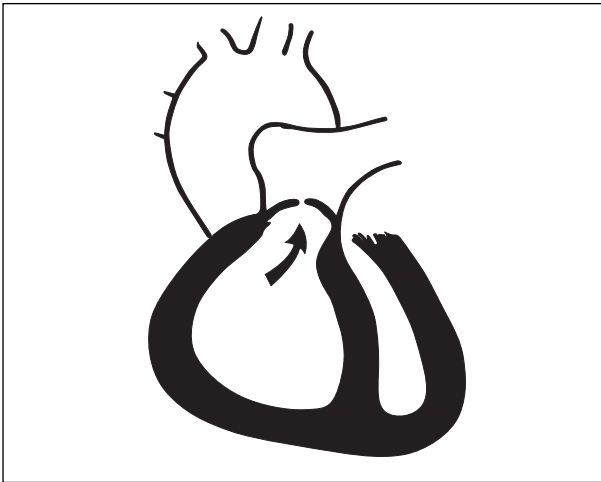
**FIGURE 11** *Pulmonary stenosis*

its true structure is not easy to recognise. The right ventricular pressure is higher to overcome the obstruction and the pressure difference between right ventricle and pulmonary artery is usually taken as the most accurate measure of the severity of stenosis.

### Prevalence at live birth
This depends on the mode of ascertainment as not all cases are recognised in infancy. Hoffman and Kaplan, in a review of 39 papers, report a median prevalence of 53 per 100,000 (lower quartile 35, upper quartile 84).[11] In the North East of England, the prevalence at live birth of those recognised in infancy was 44 per 100,000.[4] In a later report, 24% of all diagnoses were made beyond infancy, giving an adjusted prevalence at live birth of around 65 per 100,000.[12]

### Natural history
This is variable and depends on the severity of the stenosis. Most commonly the valve is mildly narrowed and children are asymptomatic. With more severe stenosis there is restricted right ventricular output with cyanosis soon after birth. There have been few population-based studies to give an accurate picture of the natural history.[15] Apart from severe stenosis in infancy, congestive heart failure is rare until the fourth decade of life.

### Presentation
Most commonly this is with a murmur. In the North East study, 80% of cases were not diagnosed before discharge from hospital after birth, despite the fact that the routine newborn examination was abnormal in about 60% of cases. About 60% of those recognised in infancy remain undiagnosed by 6 weeks of age and 43% still unrecognised by 12 weeks of age.

### Management
This depends on the severity of the stenosis. Mild stenosis is left untreated because there are no symptoms and the long-term outlook is good. Moderate or severe stenosis is treated with a valvotomy. This is almost always accomplished by a transvenous balloon dilation rather than surgery.

### Outcome
The results of valvotomy, whether achieved surgically or via balloon dilation, are good. Pulmonary regurgitation may be detectable on echocardiography but is rarely clinically significant.

### Benefit of early diagnosis
There appears to be no benefit to early diagnosis for infants with pulmonary valve stenosis and treatment after clinical presentation is appropriate. An exception may be the unusual case of a very severe PS which mimics PA/IVS and is duct-dependent.

## Tetralogy of Fallot (*Figure 12*)
### Description
This is the commonest type of cyanotic heart disease overall, although cyanosis is often not a prominent feature in early infancy. It is a combination of a large subaortic ventricular septal defect with anterior displacement of the aorta which produces complex right ventricular outflow obstruction. This varies considerably in severity and in anatomical detail between patients and this variability mainly explains the broad spectrum of natural history. With severe obstruction the picture is dominated by early cyanosis. With little obstruction, the haemodynamic situation is more like that of a large VSD.



**FIGURE 12** *Tetralogy of Fallot*

*Prevalence at live birth*

In the North East series the prevalence was 31 per 100,000 live births[4] with only 3% of cases being first diagnosed after infancy.[12] In Hoffman and Kaplan's review of 41 papers, the median prevalence was 35 per 100,000 (lower quartile 29, upper quartile 58).[11]

*Natural history*

The natural history is determined by the severity and rate of progression of the right ventricular outflow obstruction. This tends to progress, especially when there is a significant subpulmonary component to the stenosis. Affected infants and children become progressively more cyanosed. Samanek reports a 1-year unoperated survival of 84% and a 5-year survival of 78%.[17] Hoffman reports a median age at death of 2–7 years with only 10% of untreated patients surviving for 20 years.[15] Survivors would experience moderate to severe disability because of cyanosis and impaired exercise tolerance.

*Presentation*

Almost all diagnoses are made in infancy after recognition of cyanosis or a heart murmur. In the North East series, 12% of affected infants were diagnosed before the routine newborn examination. Although this examination was abnormal in 70%, 57% of all cases were not diagnosed before discharge from hospital, and 28% were still unrecognised at 6 weeks of age.[6]

*Management*

This again depends on the severity of the outflow obstruction. Excessive or increasing cyanosis, or hypercyanotic 'spells', are generally managed by an early palliative aortopulmonary shunt, which increases the pulmonary artery flow. The eventual aim is definitive repair, with closure of the ventricular septal defect and relief of the pulmonary outflow obstruction. Surgical repair of TOF was one of the first cardiopulmonary bypass operations and the age at operation has come down dramatically over the years. A generation or more ago surgery was usually performed at school age. The median age at repair now in many units is around 1 year but in some the policy is repair during infancy.

*Outcome*

Current surgical mortality is low, of the order of 1%. The results of surgery are generally good with relatively few further problems during childhood. The surgery often produces pulmonary regurgitation, which may cause further problems and require further surgery in some patients in adult life.

*Benefit of early diagnosis*

Even after clinical presentation, definitive surgery may be delayed electively until a child is over 1 year of age. Hypercyanotic spells which are not recognised and treated can cause neurological injury but this is rare nowadays and there is no benefit to early diagnosis in the majority of cases.

## Total anomalous pulmonary venous connection (*Figure 13*)

*Description*

This is usually an isolated malformation. The pulmonary veins fail to make a direct connection with the left atrium; all the pulmonary venous blood ends up in the systemic circulation. There is an ASD with obligatory blood flow from right to left. The pulmonary venous connection is variable in position and in degree of obstruction. The connection may be supracardiac to the innominate vein, infradiaphragmatic to the hepatic or portal vein (*Figure 13*) or intracardiac to the coronary sinus. The second of these is most often obstructed and the third rarely so.

*Prevalence at live birth*

In Hoffman and Kaplan's review of 25 papers, a prevalence of 9 per 100,000 live births is quoted (lower quartile 6, upper quartile 12).[11] This is comparable to the prevalence in the North East of England of 9 per 100,000 live births.[4]

*Natural history*

Samanek reports a 50% 1-month and 0% 12-month survival without treatment.[27]

*Presentation*

The timing and mode of presentation depend on whether the anomalous connection is obstructed.
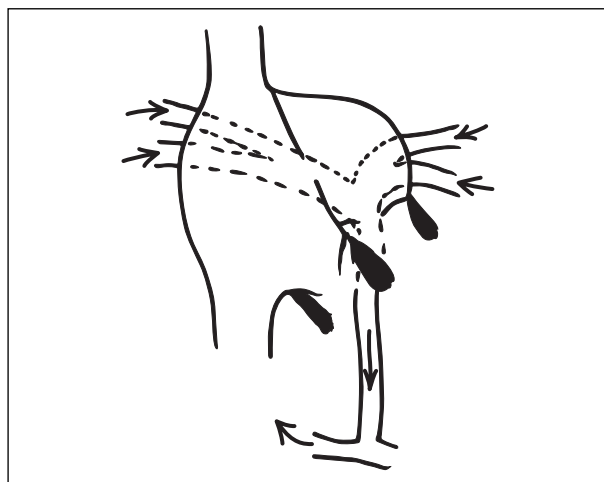


**FIGURE 13** *Infradiaphragmatic total anomalous pulmonary venous connection*

Even when the connection is obstructed, affected infants may, surprisingly, not present immediately after birth. Affected infants present with a combination of cyanosis and heart failure and may be very sick by the time the diagnosis is made.[28] In the series by Wren and colleagues, only 9% presented before the routine newborn examination and 86% remained undiagnosed at the time of discharge.[6]

### Management
The only surgical option is early primary repair, reconnecting the pulmonary veins to the left atrium.

### Outcome
The long-term outlook for survivors of surgery is very good although in some cases there is recurrent and fatal pulmonary vein stenosis. Perioperative mortality has fallen in recent years but is still significant. Operative survival must be related, in part, to preoperative condition but this is difficult to separate in published reports.[29] Medium-term mortality ranges from 8% to 35%.[6]

### Benefit of early diagnosis
Mortality with TAPVC is high and preoperative clinical condition is considered to be one of the main predictors of postoperative survival. Hence early diagnosis can potentially improve outcome by ensuring better preoperative status.

## Transposition of the great arteries (*Figure 14*)
### Description
This is the commonest type of cyanotic congenital heart disease presenting in newborn infants. In so-called 'simple' transposition the main abnormality is ventriculo-arterial discordance (the aorta arises
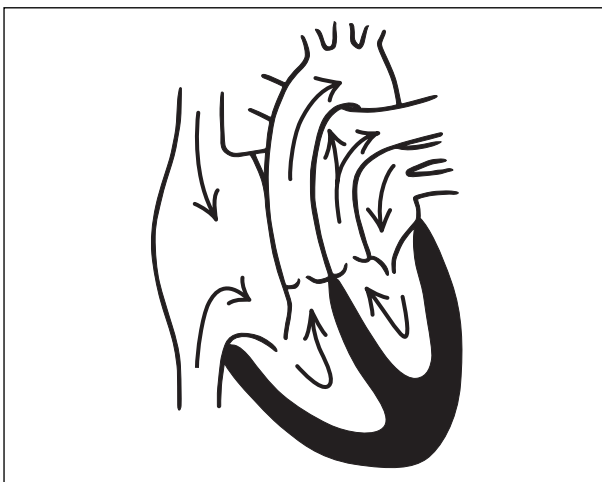


***FIGURE 14*** *Transposition of the great arteries*

from the right ventricle and the pulmonary artery from the left ventricle). The separate pulmonary and systemic circulations are incompatible with life. Early after birth some cross-flow between the circulations is maintained by patency of the duct and the foramen ovale.

### Prevalence at live birth
In Hoffman and Kaplan's review of 41 reports the prevalence was 30 per 100,000 live births (lower quartile 23, upper quartile 29).[11] In the North East series the prevalence was also 30 per 100,000 live births.[4]

### Natural history
Without treatment, most infants would die soon after birth and very few survive for a year.[27]

### Presentation
Infants present soon after birth with early cyanosis and a few die very early before diagnosis. In the North East series, 76% presented with cyanosis before the routine newborn examination but 17% went home with the problem unrecognised.[6] In the Paris series, mean age at postnatal diagnosis was 73 hours.[30]

### Management
On recognition of cyanosis, infants are started on prostaglandin infusion to maintain ductal patency. The situation is stabilised by a balloon atrial septostomy. The normal surgical strategy is primary early repair with an arterial switch operation.

### Outcome
In a report of experience from Paris in 1988–97 of infants diagnosed in a cardiac unit, the overall mortality was 11%.[30] The mortality in all infants in the North East in 1987–94 was 20%.[6] Six per cent of infants died before definitive surgery at Great Ormond Street from 1978 to 1998.[31] The surgical mortality for the switch operation in that report was 14%. In a recent series from Paris the surgical mortality was 6%.[32]

### Benefit of early diagnosis
Early diagnosis prevents the development of acidosis and circulatory failure secondary to hypoxaemia. Bonnet and colleagues, from Paris, showed an overall mortality of 11%, with no preoperative or postoperative deaths in infants diagnosed antenatally, and there was 6% preoperative mortality and 8.5% postoperative mortality in those diagnosed postnatally.[30] By contrast, in a similar report from Boston, there was no improvement in mortality after antenatal diagnosis.[23]

## Ventricular septal defect (*Figure 15*)
### Description
VSD is the umbrella term for holes in the interventricular septum. Occasionally the holes are multiple. In most common physiological circumstances, when the resistance to blood flow through the lungs is much lower than the resistance to flow through the body, blood flow through the ventricular septal defect is from left ventricle to right ventricle. This increases the volume with which the right ventricle and lung vasculature have to deal. Blood returns from the lungs to the left side of the heart, which dilates. The amount of flow through the hole depends largely on its size – a VSD is called 'restrictive' if it is small enough for a pressure differential to exist between its two sides. Flow also depends on the pressure and resistance differential between the pulmonary and systemic circulations.

Many other types of congenital heart disease are associated with VSD, for example, TGA or COA.

### Prevalence at birth
VSDs are by far the most common form of congenital heart defects. The prevalence figures will depend on the technology used to detect them – Doppler ultrasound will detect VSDs too small to produce an audible murmur, many of which are of no functional or clinical importance and will close spontaneously.[11] In some studies, performing echocardiograms on every newborn infant, huge numbers of tiny muscular VSDs were identified, affecting 2–5% of infants. Thus estimates of the prevalence of congenital heart defects generally may be greatly influenced by inclusion or exclusion of these small defects from the taxonomy and also by method of ascertainment.

### Natural history
This depends on the size and position of the defect. Most small holes tend to close spontaneously. Even larger holes near a tricuspid valve leaflet can became smaller over time. This is because part of the septal leaflet of the tricuspid valve hits the edge of the VSD as it opens (more than 100,000 times per day) and over time this forms an 'aneurysm', which reduces or can even close the VSD. However, in the meantime, blood flow through a large hole can be sufficient to render the lungs stiff and overload the left side of the heart to the extent of causing symptoms of breathlessness, sweating and failure to thrive. If these symptoms are not addressed and the hole does not close spontaneously, the pulmonary vascular resistance will rise progressively. In the short term this reduces the flow through the VSD and improves the symptoms. However, the pulmonary vascular resistance rises inexorably and when this exceeds the systemic resistance, as it will in advanced PVOD, flow reversal through the VSD occurs, blue blood passing from right to left ventricle and so the systemic circulation.

When the VSD is situated just under the aortic valve, occasionally aortic valve tissue can be sucked into the defect; the aortic valve mechanism then becomes leaky.

### Presentation
Because the pulmonary resistance falls only slowly from its high intrauterine levels during the first days of life, blood flow through a VSD – and the murmur that corresponds to it – is relatively small. In Wren and colleagues' study in the Northern Region, 83% of newborn infants eventually recognised as having VSDs had already left hospital before the diagnosis was made.

### Management
Children who exhibit symptoms due to a VSD need treatment. Some may be managed for a while with medical treatment in the hope that a useful amount of spontaneous closure will occur. For a few, the position in the ventricular septum makes them amenable to non-surgical closure with a device deployed transvenously, but most need an operation to close the hole. In the absence of complicating features, mortality is low.

### Outcome
Most small VSDs close spontaneously. Most patients with larger VSDs needing surgery do well.



**FIGURE 15** *Ventricular septal defect*

### Benefit of early diagnosis

There is no real benefit to early diagnosis of VSDs in infancy. A large number of defects detected in the newborn period will close spontaneously. A very small proportion of babies with large VSDs remain asymptomatic with no murmur because the pulmonary resistance does not fall and, if they are not recognised, they are at risk of developing irreversible PVOD in later childhood or adulthood. In some infants, knowing about the VSDs allows surgery to be planned for before the winter bronchiolitis season, as babies with large open VSDs are more susceptible to this lung infection and can die with it.

## Epidemiology of congenital heart defects

The frequency, distribution and outcome of congenital heart defects at the population level provide important information with which to assess the burden of disease associated with these malformations. Comparisons of disease frequency within and between countries can provide clues about putative causal factors, while trends in associated mortality and morbidity are helpful in assessing the quality of health service provision. This brief review of the epidemiology of congenital heart defects includes structural abnormalities of the heart and intrathoracic vessels that are of actual or potential functional importance but excludes congenital arrhythmias and cardiomyopathies.[11]

As will be apparent from the previous sections in this chapter, interpretation of the descriptive epidemiology of congenital heart defects needs to take into account the approach used to ascertain, define and group cases. In particular for rare defects, differences over time may reflect differences in case definition, completeness of ascertainment and methods used to confirm diagnoses.[33–35] Classification and coding systems are reviewed in greater depth in the section that follows. The size of any individual study will determine both the precision of any estimates of prevalence for congenital heart defects as a whole and also for individual defects, some of which may be relatively uncommon. Hence it may be difficult to interpret geographical variability, which may reflect sampling error, differences in ascertainment or true differences in frequency.[8]

The prevalence of congenital heart defects at live birth will depend on the extent of antenatal detection, the proportion of fetal diagnoses resulting in termination of pregnancy and methods used to ascertain cases. The authors of a UK-wide study of fetal diagnoses of serious congenital heart disease at term (defined as necessitating surgical intervention or causing death in the first year of life) reported that, in 1993–95, a fetal diagnosis was made in just under one-quarter of affected pregnancies, approximately half of which ended in termination.[8] These figures are likely to have increased in the last decade but studies based on population denominators rather than specialist centres are required for interpreting any epidemiological trends and these are not currently available.[7]

With these caveats, what is known about the epidemiology of congenital heart defects?

## Birth prevalence

In their review[11] of 62 studies published since 1955 and reporting the prevalence of congenital heart defects, Hoffman and Kaplan estimated the prevalence of moderate and severe forms of congenital heart defects to be 6 per 1000 live births and of severe forms to be 2.5 per 1000 live births (examples of moderate and severe defects are given in the section 'Severity', p. 56). Wren and O'Sullivan found that 74% of all congenital heart defects recognised in childhood were diagnosed by the first birthday, a further 18% between 1 and 4 years of age and a final 8% between the ages of 5 and 13 years.[12]

Hoffman and Kaplan's estimate increased more than 10-fold to 75 per 1000 live births if small muscular VSDs and other functionally unimportant anatomical abnormalities are included. Hoffman and Kaplan attributed this to increasing use of echocardiography and concluded that there was no evidence to conclude that the incidence of congenital heart defects had changed over the 50-year period encompassed in their review. Although it has been suggested that an increase over time is possible, as a result of the higher risk of congenital heart defects in the offspring of affected adult survivors, this may be tempered by trends in terminations of affected fetuses. Wren and colleagues were able to examine temporal variation in prevalence using data from a study based in the Northern Region of England.[4] The year by year prevalence of congenital heart defects according to whether complex, significant or minor is shown in *Figure 16*: a highly significant increase in minor defects, mainly small VSDs, was found. Roguin and colleagues reported a birth
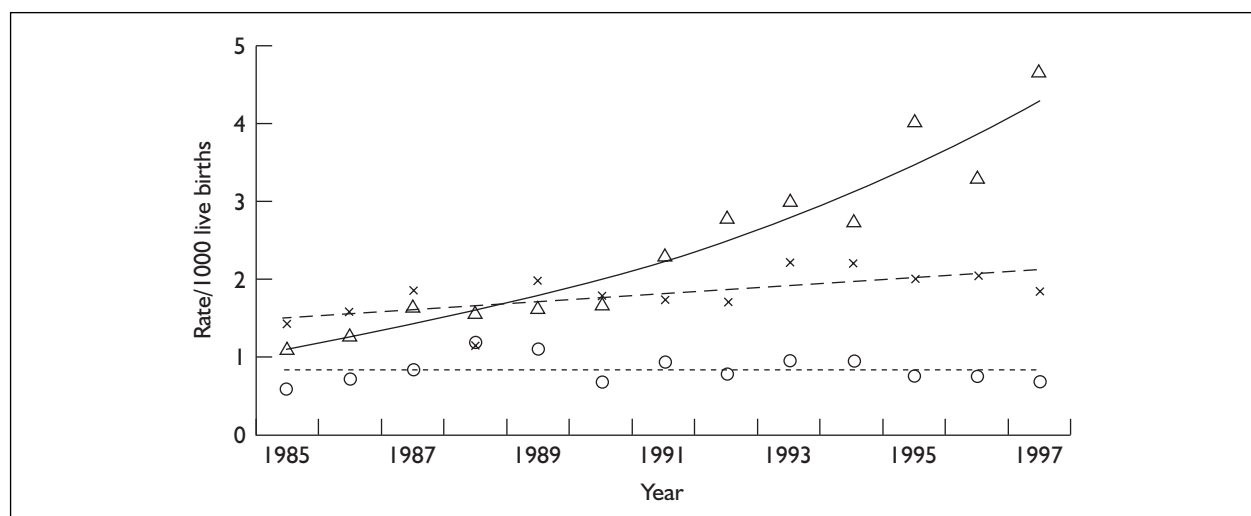
**FIGURE 16** *Trends in prevalence of congenital heart defects over a 13-year period. Year by year prevalence at live birth of 411 complex (open circles), 870 significant (crosses) and 1151 minor (open triangles) cardiovascular malformations. All cases (with the exception of persistent ductus arteriosus and isolated atrial septal defect) were classified as being 'complex', 'significant' or 'minor'. 'Complex' heart defects included all cases of heterotaxy or atrial isomerism and all cases characterised by atresia or severe hypoplasia of a valve or chamber. Hearts with a common inlet valve (CAVSD) or common outlet valve (truncus) were also included in this group. 'Significant' cardiovascular malformations were those in which four valves and four chambers were present but where intervention was or would be required. This group, for example, includes all cases of simple transposition, TOF, large VSD and COA of the aorta. 'Minor' malformations were those where intervention would not be required. These were mainly mild or moderate AS or PS and smaller VSDs. Reproduced from Wren C, Richmond S, Donaldson L. Temporal variability in birth prevalence of cardiovascular malformations. Heart 2000;**83**:414–19.*

prevalence of 53 per 1000 live births for muscular VSDs.[36]

In Hoffman and Kaplan's review, the seven most common defects were VSD [median prevalence per 1000 live births (interquartile range, IQR) 2.8 (1.8, 4.5)], PDA [0.57 (0.32, 0.78)], ASD [0.56 (0.37, 1.06)], ASD [0.34 (0.24, 0.40)], PS [0.53 (0.36, 0.84)], AS [0.26 (0.16, 0.39)] and COA [0.36 (0.29, 0.49)].[11] The last two are defects that may present acutely in early life.

Other defects presenting acutely in early life were less common. These included PA, HLH, TAPVC and TGA. The median prevalence (IQR) of these four defects was 0.08 (0.076, 0.15), 0.23 (0.15, 0.28), 0.09 (0.06, 0.12) and 0.3 (0.23, 0.39), respectively. Wren and colleagues were unable to find any temporal trends in these specific defects.[4]

## Variation in prevalence by sex, ethnic group and area

Neither Hoffman and Kaplan nor Wren and colleagues reported sex distribution in their studies. However, in a report from the New England Regional Infant Cardiac Program, girls were more likely to have lethal congenital heart defects than boys.[37]

Hoffman and Kaplan reported an excess of AS and COA in white compared with black or Hispanic populations.[11] Correa-Villasenor and colleagues reported an excess of white infants among cases with AS, PA, COA and D-TGA and a deficit of white infants among cases with PA.[38] Sadiq and colleagues reported an excess of complex congenital heart defects in Asian infants in Birmingham, and an excess of COA among non-Asian infants.[39] It has been suggested that consanguinity could have an impact on the prevalence of birth defects in some regions of the UK, but the evidence remains unclear. Furthermore, the national impact of consanguinity was felt to be adequately represented by the Northern Region population data. It is unclear whether there is a geographical variation in the birth prevalence of congenital heart defects. Bull reported geographical variability in the incidence of affected pregnancies in her national study of fetal diagnoses, but was unable to differentiate between extremes of case ascertainment and true variation.[8]

## Mortality

The 1-year mortality for infants with congenital heart defects born in the Northern Region in the decade 1985–94 was 18%.[12] Five-year mortality for

infants born between 1980 and 1997 and included on the Glasgow Register of Congenital Anomalies was reported to be 25%.[40] This compared with an estimated 1-year mortality of 25% reported from the Scottish Congenital Anomalies Register for the period 1988–94, but this may reflect differences in the spectrum of congenital heart defects included in these two registers.[41]

Cases resulting in death without diagnosis will lead to an underascertainment of mortality. Abu-Harb and colleagues reported 185 deaths among 1074 infants diagnosed in infancy, 56 (30%) of whom died without diagnosis.[14] Wren and O'Sullivan predicted the survival to 16 years for specific congenital heart defects from a combination of observed diagnoses in infancy adjusted for 1-year survival and predicted further survival to 16 years taken from the literature.[12] They reported that 74% of all congenital heart defects recognised in childhood are diagnosed in infancy and that, given survival to 1 year of age, the risk of death by 16 years of age is very low, with 96% of those surviving infancy going on to survive to 16.

Defect-specific mortality based on 1590 infants included in the Northern Region study was highest for HLH (45/45; 100%) and IAA (16/24 cases; 67%).[6] Between one-fifth and one-third of children with TGA, TAPVC, AS and PA did not survive to their first birthday.

### Aetiology
Genetic factors contribute significantly to the aetiology of congenital heart defects, as evidenced by the recurrence risks for future siblings and the offspring of affected individuals.[42] The most common chromosomal cause of significant congenital heart disease remains trisomy 21, and the second most common chromosomal cause is deletion in chromosome band 22q11.[43] Associations with lethal trisomies are well recognised.

Diminished birthweight is a recognised feature of some congenital heart defects, notably for infants with TOF, endocardial cushion defect, HLH syndrome, PS and VSD.[4]

Associations with maternal diabetes have been reported.[44,45] No significant diagnosis-specific associations were found with gestational diabetes. Wren and colleagues reported a fivefold increase in risk of cardiovascular malformations in infants of mothers with pre-existing diabetes, notably for TGA, truncus, and tricuspid atresia (TA).[45]

The association with paternal occupations has been evaluated in the Baltimore–Washington Infant Study, a population-based case–control investigation of congenital heart disease and environmental factors.[46] A range of associations with specific defects and occupations involving jewellery making, welding, lead soldering, ionising radiation and paint stripping were observed.

Hence evidence for any modifiable environmental factors which might be relevant to the primary prevention of congenital heart defects is at present lacking.

## Classification and coding systems for congenital heart defects

Many classifications and coding systems have been developed for grouping congenital heart defects but there is no system that is comprehensive and appropriate for use in all contexts. Most describe the structure of the heart but not the impact of individual defects on its overall function. This diversity of classification methodology has been highlighted as a major difficulty in comparing the results of different epidemiological and clinical studies of congenital heart defects.[35] Another practical problem is the enormous variety of conditions coming under the heading of congenital heart defects. It may take 25 codes to describe a complex cardiac malformation. The detail is very important; an example is DORV (double outlet right ventricle) which can, depending on the associated cardiac abnormalities and particularly the size and position of the VSD, describe a malformation fixed by a single low-risk operation or a heart which requires many palliative operations and has poor survival through childhood.

The main approaches to classifying congenital heart defects are summarised here. These include systems based on heart structure, embryological development, clinical features or surgical procedures.

### Heart structure
Descriptions of heart structure are the basis of diagnostic categories used in clinical practice. These descriptions may be of a recognised cluster of cardiac defects that occur frequently together and are given a combined diagnostic title, for example, TOF, they may represent individual anatomical features, for example, a stenotic valve, or they may comprise a list of separate defects that are present in a single heart. The presence or

absence of an additional defect can make an enormous difference to the overall clinical effect and yet these lists do not describe the severity or the relative functional importance of different structural abnormalities. Structure-based classifications have been assigned explicit hierarchies in some studies,[4,47] but not others.[11,48,49]

Sequential segmental analysis is a systematic method of describing congenital cardiac defects and was originally derived from post-mortem anatomical investigation.[50–53] A heart is described in terms of its atria, atrio-ventricular connections, ventriculo-arterial connections and additional cardiac anomalies. This system is particularly useful for describing complex cardiac malformations that do not fall easily into the usual coding or diagnostic categories. However, the function of the heart in life, for example, the direction of flow of blood and how well it is oxygenated, can only be inferred from the structural description.

The structural diagnosis is the basis for ICD 10 (International Classification of Diseases),[54] BPA (British Paediatric Association)[55] and Read coding systems[56], used by cardiologists and hospital administrative systems to record diagnosis and to relate this to care. ICD codes are recorded by trained non-medical coders as a hierarchical list but this is not always representative of the clinician's view of the functional importance of each structural defect. However, the ICD 10 system is used for coding routine hospital episode data, and so it is useful to be able to cross-map these to other codes and classifications as was undertaken for the Bristol Royal Infirmary Inquiry.[57]

## Developmental classification

Developmental classifications are often used in studies of antenatal diagnosis or factors predicting congenital heart defects.[58,59] However, such groupings are particularly variable, reflecting changes in the understanding of the embryological development of the heart.

## Clinical presentation

Clinically, one of the commonest practices is to group congenital heart defects by significant physiological elements, for example, cyanotic heart defects are those in which the systemic arterial blood is not fully saturated with oxygen, in contrast to non-cyanotic defects, in which the blood is fully oxygenated. Alternatively, congenital heart defects can be classified by the pulmonary blood flow, which may be high, normal or low. Although used often in clinical practice, these groupings have limited usefulness as, within each group, defects are heterogeneous in the underlying structural problem, timing of presentation, severity, natural history and surgical outcome.

## Surgical coding systems

The most commonly used system for coding surgical procedures in hospitals in the UK is the OPCS 4 (Office for Population Censuses and Surveys) Classification of Surgical Operations and Procedures, Fourth Revision.[60] This lists operative procedures by organ using a four-digit code. Other detailed coding systems are used by specialist registries.

As the Bristol Royal Infirmary Inquiry was concerned with surgical performance, congenital heart defects were grouped, and then ranked, according to the 'primary' operative procedure; this required considerable 'lumping' to bring sufficiently large groups of fairly comparable cases together in order to compare outcomes across centres. The surgical mortality for these groups was analysed. Data sources included national and local surgical registers, which had to be recoded using OPCS 4 before comparison with routine hospital data was possible.[61]

## Screening classification

There are no systems for classifying congenital heart defects from the perspective of natural history or the potential to alter outcome through earlier detection. An anatomical classification is likely to under-report the prevalence of PA, IAA and COA, which are often found in association with other defects. The study of trends in prevalence reported by Wren and colleagues[4] (*Figure 16*) used a hierarchical classification to take into account both the anatomical and physiological effects of specific defects occurring in the same heart. In Chapter 3, the natural history and outcomes of congenital heart defects in childhood are discussed and the evidence for better outcomes through earlier detection in the preoperative period is considered in more detail. In Chapter 5, a new classification for congenital heart defects is proposed which takes into account the potential for improving outcomes through earlier detection of specific congenital heart defects in infancy.

# Chapter 3
# Childhood outcomes of congenital heart defects

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**Chapter outline**

In this chapter, we report a structured review of the published literature concerning outcomes for children with congenital heart defects in order to inform outcomes used in a decision model of newborn screening for congenital heart defects. We searched for studies comparing childhood mortality and morbidity in screened and unscreened populations. We compared mortality and morbidity for different defects, focusing upon a range of health, social and educational outcomes.

**Key messages**

- There have been major improvements in survival and, nowadays, over 80% of children born with congenital heart defects survive to the age of 16 years.
- Most deaths from congenital heart defects occur in the first year of life and these are most likely to be related to extra-cardiac anomalies, cardiovascular collapse during the changes from fetal to newborn physiology, heart failure or surgical mortality.
- As length of survival increases, the quality of that survival and the long-term health, social and educational outcomes assume greater importance to children with congenital heart defects and their families.
- The long-term cardiac sequelae of congenital heart defects include cardiac arrhythmias, congestive heart failure, infective endocarditis, PVOD and valve insufficiency. As surgical management improves, these complications tend to occur later in life.
- High-quality long-term outcome studies addressing physical disability, neurodevelopmental, cognitive or psychosocial outcomes and the capacity to participate in normal childhood activities are lacking.
- Severe neurological deficits (cerebral palsy, epilepsy and global learning difficulties) appear to be uncommon (5–10%) in this patient group. Milder neurological problems (motor delay, speech disorders and visual defects) are more common and occur in up to one-quarter of children.
- Cognitive abilities of children with congenital heart defects are within the normal range but subtle difficulties may have a greater impact on academic performance as children get older.

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## Introduction

Over the last 40 years, advances in management have led to major improvements in the early survival of children with congenital heart defects. This is likely to continue. Mortality estimates are available for the UK for children reaching adulthood[12] but the survival experienced by today's young adults, who received surgery 20 years ago, may be very different to the actuarial outlook for today's infants. This reflects the rapid rate of change in cardiac procedures. Longer term outcomes for these recently introduced technologies are not available. Furthermore, the outcomes reported by a study may vary depending on its timing relative to the introduction of a new technique; mortality may be higher in the 'learning curve' when a unit first begins using a new surgical technique.[31,62]

As currently over 80% of children born with congenital heart defects survive to the age of 16 years, it is important to obtain more information about the quality of that survival. Submissions to the Bristol Royal Infirmary Inquiry highlighted the lack of information regarding later mortality after surgery[63] and also regarding the quality of life experienced by survivors.[64] In addition, long-term health, social and educational outcomes are most important to children with congenital heart defects and their families.[64–66]

Almost without exception, the definitive surgical intervention for specific congenital heart defects remains the same irrespective of how the diagnosis has been made. As discussed in this chapter, earlier detection through newborn screening might improve outcomes by allowing definitive management to be commenced either before death or before the acute onset of clinical deterioration experienced by individuals with some types of congenital heart defects. Prevention of preoperative collapse, through the timely commencement of effective clinical management, could improve both short-term outcomes (mortality and length of stay in hospital) and longer term outcomes (neurological status and educational attainment).

Different defects vary in their timing and causes of death, with some contributing significantly more to infant mortality because of their prevalence, how difficult they are to treat or their predisposition to collapse before definitive surgery. In the context of population-based programmes, it is also important to identify which heart defects should be the focus of newborn screening programmes.

In this chapter, we report a structured review of the published medical literature concerning outcomes for children with congenital heart defects. This was undertaken in order to inform the outcomes to be used in a decision model of newborn screening for congenital heart defects. In this review, we attempted to identify studies of childhood mortality and morbidity in which screened and unscreened populations were compared. Studies investigating the early predictors of outcomes in childhood were located and the role of screening in preventing collapse before diagnosis and subsequent adverse outcomes explored. We also explored mortality and morbidity for different congenital heart defects, focusing on a range of health, social and educational outcomes.

## The review process

A search strategy, for Ovid MEDLINE, was devised to identify published literature on health outcomes for children with congenital heart defects primarily up to 16 years of age, focusing on outcomes after screening (Appendix 1). As the management of congenital heart defects is rapidly changing, the search was limited to papers published in the past 15 years (1988–2003). Abstracts were included if they met pre-specified eligibility criteria (*Table 2*).

**TABLE 2** *Inclusion and exclusion criteria for the outcomes literature review*

*Inclusion criteria*
Congenital heart defects diagnosed in childhood
Management relevant to UK healthcare practices
Study types: randomised controlled trials, controlled
    trials, cohort, case–control, case series with >20 cases
Studies reporting actuarial survival with congenital heart
    defects in a child population (up to 16 years of age) or
    studies of neurological, developmental, psychosocial
    and cognitive outcomes of congenital heart defects
    between 1 and 16 years of age
Human
MEDLINE references from 1988 to 2003

*Exclusion criteria*
PDA
Papers reporting acquired heart disease or heart
    disorders in which the clinical diagnosis is not clear
Papers only reporting early mortality after surgery
Papers reporting congenital heart defects diagnosed in
    adulthood
Studies of cardiac transplantation
Papers reporting outcomes from countries in which the
    prevalence or management of congenital heart defects
    is not relevant to UK experience

Our search strategy identified 2143 abstracts, which were reviewed for eligibility. The most frequent reasons for excluding studies were (1) case series with <20 cases, (2) only surgical mortality reported, (3) adult population reported, (4) diagnoses were unclear, acquired heart disease or PDA and (5) studies of heart transplantation. With the addition of papers identified from reference lists, a total of 212 published papers were eligible for inclusion in this review. Of these, 22 reported late complications or causes of death, 104 actuarial survival, 54 exercise capacity, 20 neurodevelopmental outcomes, 14 cognitive outcomes, 13 behaviour and 36 early predictors of outcome. No randomised controlled trials were identified and the majority of studies were case series, which provide data that are difficult to combine.[63] Three large population-based cohort studies were identified, from the UK, Finland and the Czech Republic (see *Table 3*). However, more than half of the studies identified ($n = 123$) had sample sizes <100. Many smaller studies recruited subjects over long periods, often during which changes in management occurred, and follow-up times for individuals within studies varied.

Data extracted from all eligible studies included study type, country, study population, control group, defects studied, instruments used, length of follow-up, main outcome measures and main findings of relevance to this review. All papers included in this review are described in the detailed literature table presented in Appendix 2. Studies are subdivided into those reporting:

- **mortality** among those with congenital heart defects in childhood, including age and causes of death, and comparing actuarial survival for different malformations, and
- **health, social and educational outcomes among survivors**, including physical disability and exercise capacity, neurodevelopmental ability, cognitive ability, school performance, social and emotional competence up to 16 years of age.

The following narrative review describes current evidence concerning outcomes for children with congenital heart defects and is presented according to the outcomes that the studies reported. In addition, the literature reporting early (that is, perinatal and perioperative) predictors of outcome is reviewed.

### Methodological considerations in reporting mortality

In the most recently published national mortality data, from 2002, congenital heart defects were

responsible for 3% of all infant deaths and 46% of deaths due to congenital malformations in England and Wales.[67] Routine statistics from the Office for National Statistics provide an up-to-date record of death registrations by age, sex and cause of death, coded using ICD-10. However, as discussed previously, the coder's hierarchical list of ICD codes may not represent the clinician's view of the functional importance of each defect. Abu-Harb and colleagues also highlighted the problem of under-ascertainment of congenital heart defects in studies using routine data and the need to supplement these data with reports from other sources,[14] notably case series or population-based cohort studies from specialist centres.

Mortality rates reported for different cardiac malformations vary considerably between studies. However, as many papers reporting outcomes from congenital heart defects use different grouping and classification systems, as described previously, direct comparison of mortality is difficult. Discrepancies in reported mortality may be due to differences in the type and severity of defects included within a particular group. Examples of this are AS and TAPVC, which have a wide spectrum of severity and a wide range of reported survival rates, as detailed in Appendix 3.

Mortality is recognised as the preferred method for comparing screened and unscreened populations as it is not influenced by lead time bias (overestimation of survival time due to measuring from a starting point of early detection by screening procedures rather than from clinical symptoms and signs[1]). However, many published long-term follow-up studies of mortality with congenital heart defects report actuarial survival, reflecting the predominance of case series with no population denominator. Actuarial survival is not an ideal measure for outcomes after screening, but lead time bias may be less likely to occur with studies of congenital anomalies as the condition is present from birth and the interval between birth and confirmed diagnosis may be short.[68] In addition, studies of survival after cardiac surgery varied in their reporting of actuarial survival, with some excluding early surgical mortality. We have selected figures only from reports which include early surgical mortality for this review. We identified in searches 113 studies that reported actuarial survival, of which 15 were excluded for the following reasons: the population did not include children aged 1–16 years old (three papers), the study reported acquired heart disease only (one paper), <20 cases (two papers), operative mortality was excluded (five papers), data were

missing or inadequately reported (two papers) and duplicate publications (four papers). Four further studies were included from reference lists. Appendix 3 provides an overview of the 104 papers reporting actuarial survival which were included in the review. A further 22 papers reporting long-term mortality and causes of death, related to age or to specific congenital heart defects, were also included in the review and are listed in Appendix 3.

An additional consideration in comparing studies with respect to either mortality or survival is the rate of fetal diagnosis in each of the studies. A diagnosis of a congenital heart defect may be suspected or made antenatally: where the defect has a poor or difficult prognosis, this allows parents to prepare for the diagnosis, for delivery to be planned where treatment is available and for the option of termination of pregnancy or palliative care to be considered. In a national study of fetal diagnosis of serious congenital heart defects, a fetal diagnosis was made in 23% of affected pregnancies and, after terminations and stillbirths, in 12% of all affected live births.[8] Antenatal diagnosis influences the prevalence and pattern of congenital heart defects at term. 'Four-chamber defects' (affecting the architecture of the centre of the heart) are more likely to be detected on antenatal ultrasound than 'outlet defects' (affecting the architecture of the outlet of the heart).[69,70] Antenatal detection may decrease the prevalence at birth of the more severe and more easily detectable defects, if associated with a high uptake of termination of pregnancy.[71] As antenatal detection rates and termination of pregnancy rates vary geographically and over time, this will also contribute to geographic variation and temporal trends in prevalence.[8]

A further important issue is whether a study reporting mortality has good ascertainment of death. In the Northern Region study, 18% of all live-born infants in whom congenital heart defects were recognised in infancy died during the first year of life.[12] Half of these infant deaths occur in the first month of life.[72] Although comparable to the figure of 17% obtained from the Office of National Statistics data for 2002, the Northern Region study was also able to estimate the proportion of infants with congenital heart defects who die before a diagnosis is made and in whom the condition is not recognised until post-mortem examination. Abu-Harb and colleagues reported that ~30% of infants who die in the first year are first diagnosed at post-mortem, although only about one-quarter of these had lesions amenable to surgery.[18]

**TABLE 3** *Cohort studies of survival with congenital heart defects*

| Study | Type of study | Country, period, study population (*n*) | Period of follow-up | Main outcome measures |
|---|---|---|---|---|
| Wren and O'Sullivan[12] | Prospective regional cohort study | Northern Region (UK) Children born 1985–94 Confirmed congenital heart defects cases (*n* = 1942) | Up to 15 years of age | Death at any time up to 15 years old |
| Samanek and Voriskova[76] | Prospective regional cohort study | Bohemia, Czech Republic Children born 1980–90 Confirmed congenital heart defects cases (*n* = 5030) | Up to 15 years of age | Death at any time up to 15 years old |
| Nieminen *et al.*[77] | Historically defined national cohort study | Finland 1953–89 All operations for congenital heart defects (*n* = 6336) | Mean of 22 years after surgery (range 9–45 years) | Death at any time after surgery |

Mortality among those with congenital heart defects may not always be causally associated with the heart defect. Deaths during the first year of life amongst those who have congenital heart defects are significantly more likely to occur in infants who have associated extra-cardiac congenital anomalies.[73] Some extra-cardiac congenital anomalies are considered to be lethal, for example trisomy 13 and 18 (associated with VSDs and valve abnormalities). Other associated congenital anomalies, which are compatible with survival into adulthood, include Down's syndrome (associated with ASVD), Di George syndrome (associated with TOF, IAA, VSD and truncus),[74] and gastrointestinal malformations (associated with septal defects, TOF and COA).[75] Deaths in these infants may not be attributed to a cardiac cause in mortality studies and the contribution of congenital heart defects to infant mortality may therefore be underestimated.

Special studies with high ascertainment of cases can supplement routine data and allow adjustment for changes in prevalence at birth and underascertainment of cases not diagnosed before death. Studies varied in their methods of ascertaining cases of congenital heart defects but three cohort studies identified in this review had particularly good ascertainment of cases and outcomes (*Table 3*). The Northern Region study was a prospective regional cohort study with multiple sources of case ascertainment, whether diagnosed before death or at post-mortem, in infants born to mothers resident in the region. Survival until 16 years of age was calculated for the cohort and for each malformation group.[12] Samanek and Voriskova prospectively identified all children with suspected congenital heart defects in Bohemia between 1980 and 1990, who were referred to a single centre for echocardiography or were identified at post-mortem carried out for all children who died before 15 years of age.[76] They report malformation specific survival for different periods after birth but include both operated and unoperated cases so the actuarial survival cannot be combined with the results of other studies in Appendix 3. A Finnish cohort study identified a historical cohort of children operated for congenital heart defects between 1953 and 1989 and achieved 96% follow-up of these cases through linked data sources.[77] The follow-up time for individual cases ranged from 9 to 45 years, with a mean follow-up of 22 years, and was calculated from the time of first operation. The cases followed up therefore received surgery at different ages and at different periods so will have experienced both older and newer surgical techniques. The variation in methodology between these large population studies underlines the problems with combining data from mortality studies of congenital heart defects.

A systematic review of paediatric open-heart surgery prepared for the Bristol Royal Infirmary Inquiry[63] has also recently highlighted the difficulty with quantitatively combining longer-term outcomes for congenital heart defects. Vardulaki and colleagues concluded that the quality of reporting of longer term outcomes was so inconsistent that they limited their review to early surgical mortality only (deaths within 30 days of surgery) for pooled malformation and operation groups.[63]

## Operative mortality

The majority of children with significant congenital heart defects require a surgical procedure and this is usually performed in the first year of life. Of the large variety of cardiac

**TABLE 4** *Surgical mortality by malformation: a comparison of two studies*

| Malformation | Percentage who died within 30 days of surgery | |
| --- | --- | --- |
| | **Bristol review**[63] | **Finnish study, Nieminen et al.**[77] |
| UVH (single ventricle, complex congenital heart defect), including Fontan operations | 26 | – |
| Fontan operation (for complex defects, including UVHs) | – | 15 |
| TAPVC | 24 | – |
| Truncus | 23 | – |
| Complete ASD | 15 | – |
| TGA | 11 | 13 |
| TOF | – | 9 |
| VSD | – | 8 |
| COA | – | 4 |
| ASD | – | 1 |

defects for which surgery seems to offer a significant benefit, relatively few are anatomically 'correctable' and, for many lesions, surgery is electively staged, with several operations during childhood, e.g. HLH syndrome.[22,78,79] In the Finnish study, 16% of affected children had undergone more than one heart operation,[77] varying from 16% of those with COA to 33% of children with TGA, VSDs or TOF and 80% of univentricular hearts (UVHs).

Paediatric open-heart surgery involves cardiopulmonary bypass and, in complex cases, requires deep hypothermia and circulatory arrest. All congenital heart operations carry a mortality risk and, at all stages of childhood, the majority of deaths occur in temporal relation to surgery. Surgical mortality is generally reported in terms of early surgical mortality (death in the perioperative period, often defined as in-hospital mortality or death within 30 days of operation), or late surgical mortality (death >30 days after operation).

Early surgical mortality was 7% overall in the Finnish cohort study, with surgical mortality for individual malformations varying from 1% of ASD to 26% of UVHs (severe, complex malformations with only one functional ventricle).[77] In the systematic review undertaken for the Bristol Inquiry,[63] early surgical mortality was compared for the higher risk open-heart procedures in the period 1984–95: improvement over time was observed for each operation. The early surgical mortality estimates for these studies are summarised in *Table 4*. The mean age at operation for children in the Finnish study was older (5.1 years) than for children in the Bristol review

(3.5 years), but this may also reflect the type of operations that are reported by each study.

There is an extensive literature relating to the anatomical risk factors predictive of death after surgery for particular conditions. More generally, there is good evidence that poor clinical status at the time of operation for congenital heart defects increases the probability of death after surgery.[80–83] This is discussed in more detail later in this chapter. Some babies are diagnosed but die before undergoing definitive surgery, for example, TGA. These data suggest that screening can improve mortality for children with congenital heart defects by detecting them earlier and preventing significant clinical deterioration prior to surgery.

## Death during the first year of life from congenital heart defects

According to routine mortality data from the Office for National Statistics,[67] 30% of deaths due to congenital anomalies of the circulatory system occur between birth and 14 years of age with 17% of these deaths occurring in the first year of life (*Table 5*). Deaths in infants with congenital heart defects are most likely to be related to extra-cardiac conditions, surgical mortality, heart failure and the changes from fetal to newborn physiology. By contrast, among older children, sudden cardiac death and, rarely, heart failure, infections and lung disease are responsible (*Table 5*).

The contribution of specific defects to childhood mortality depends on prevalence and also early mortality and associated conditions. The

**TABLE 5** *Mortality from congenital heart defects at different ages*

| | Aged <1 year | Aged 1–14 years |
|---|---|---|
| Percentage of all deaths due to congenital heart defects that occur in this age group (Office of National Statistics, 2002)[67] | 17 | 13 |
| Causes of death | Extra-cardiac congenital anomalies (44%)[84] <br><br> Perioperative death[61,63] <br><br> Unoperated malformations[72,85] <br><br> Heart failure[18] | Perioperative deaths; sudden cardiac death[86] <br><br> Rarely: congestive heart failure; infective endocarditis; PVOD |
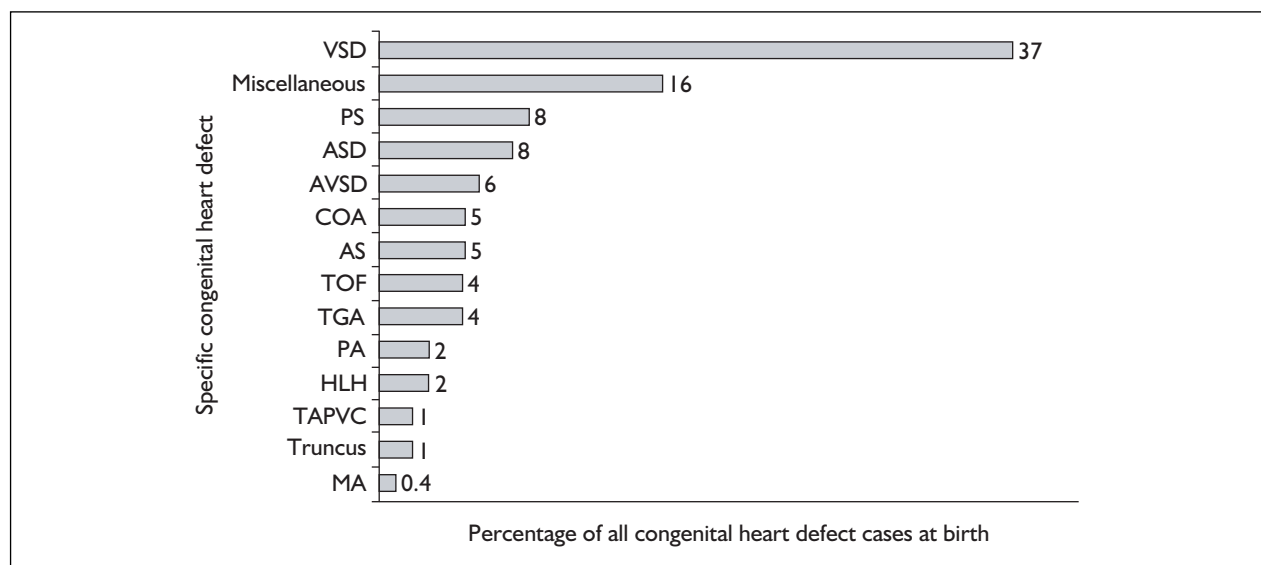


**FIGURE 17** *Birth prevalence by specific congenital heart defect (n = 1590). 'Miscellaneous' includes PDA (4% of all congenital heart defects) and a wide variety of rare and complex congenital heart defects, of which the most common are congenitally corrected TGA and UVHs. Reproduced from Wren C, O'Sullivan JJ. Survival with congenital heart disease and need for follow up in adult life.* Heart *2000;**84**:499–503.*

prevalence of specific malformations at birth, based on the Northern Region study,[12] is shown in *Figure 17*. These data exclude trisomies and document the most severe or primary defect. Hence they may include children in whom the named defect is not the sole cardiac defect and also those in whom other non-cardiac malformations may be present. The congenital heart defects most likely to present after infancy are VSDs, ASDs, AS and COA. Hence a proportion of the total prevalence shown here will not be recognised until after 1 year of age.[12] The most common single malformations are VSD, ASD and PS.

In *Figure 18*, deaths due to specific defects are shown as a proportion of all deaths due to congenital heart defects in the first year of life.[12] The specific defects which contribute most to

these deaths are VSD, HLH and atrioventricular septal defect (AVSD).

HLH has a relatively low prevalence at live birth but mortality in the first year of life is very high. It is therefore a leading cause of death from congenital heart defects in infancy. Earlier detection through screening is likely to improve outcome for this group of children by preventing preoperative clinical deterioration, which currently leads to worse outcomes after surgery.[22,23]

VSD and AVSD contribute most to infant mortality because these defects are common, the severe cases manifest in infancy and they are often associated with extracardiac congenital anomalies which may contribute to mortality (for example, trisomy). A study from Bohemia found a non-cardiac cause for death in all infants dying with

**FIGURE 18** *Percentage of all deaths due to congenital heart defects by specific defect: age 0–1 years (n = 1590). 'Miscellaneous' as in* Figure 17. *Reproduced from Wren C, O'Sullivan JJ. Survival with congenital heart disease and need for follow up in adult life.* Heart *2000;***84***:499–503.*

ASD, in 93% of infants dying with TOF, in 84% of infants dying with VSD and in 57% of infants dying with COA.[84] Most deaths from non-cardiac causes occurred on the first postnatal day.[84] Screening is unlikely to be beneficial in preventing deaths in this group of infants with extra-cardiac anomalies.

By contrast, deaths in children with TGA, truncus and PA are less common but more likely to be attributable to sudden clinical deterioration directly related to the cardiac defect. The congenital heart defect was considered directly responsible for death in 82% of infants with TGA, 79% of infants with HLH and 68% of infants with PA.[84]

Infants with COA and TAPVC cases presenting in the newborn period are usually more severely affected and more likely to die in infancy. Repair of TOF can often be electively delayed until after 1 year of age, so deaths in infancy are likely to be related to earlier surgery or to severe defects. A second mortality peak occurs in adulthood after the development of complications due to milder defects. ASDs are prevalent but a rare cause of infant death: many will close spontaneously in childhood[87] and most individuals with persisting mild defects have a normal life expectancy.[88]

Earlier detection of congenital heart defects offers a survival advantage because it can avert death or prevent deterioration of clinical status before definitive surgery and thus improve outcome after operation. The greatest impact from newborn screening will arise from the detection of hitherto unsuspected congenital heart defects in infants who could otherwise die before a diagnosis is made, die in the period between first suspecting a heart defect and definitive surgery or clinically deteriorate (collapse) before surgery. Specific defects falling into these categories include HLH, MA, TGA, AS, PA, IAA and COA.

## Death beyond infancy and occurring in childhood

For children with congenital heart defects who survive surgery and the first year of life, there is relatively good survival into the teenage years. Approximately 13% of deaths due to congenital heart defects occur in the period from 1 to 14 years old (Office of National Statistics, causes of death by age and selected causes, 2002[67]). In the Northern Region, mortality between 1 and 16 years of age has also been calculated for different malformations based on a comprehensive review of published studies:[12] overall 13.5% of the deaths due to congenital heart defects occurred in this age group, comparable to the estimate from routine data. These studies also demonstrate the wide variation in malformation-specific survival, and in the complications and causes of death. The contribution of specific malformations to deaths from congenital heart defects in children aged 1–16 years is shown in *Figure 19*.
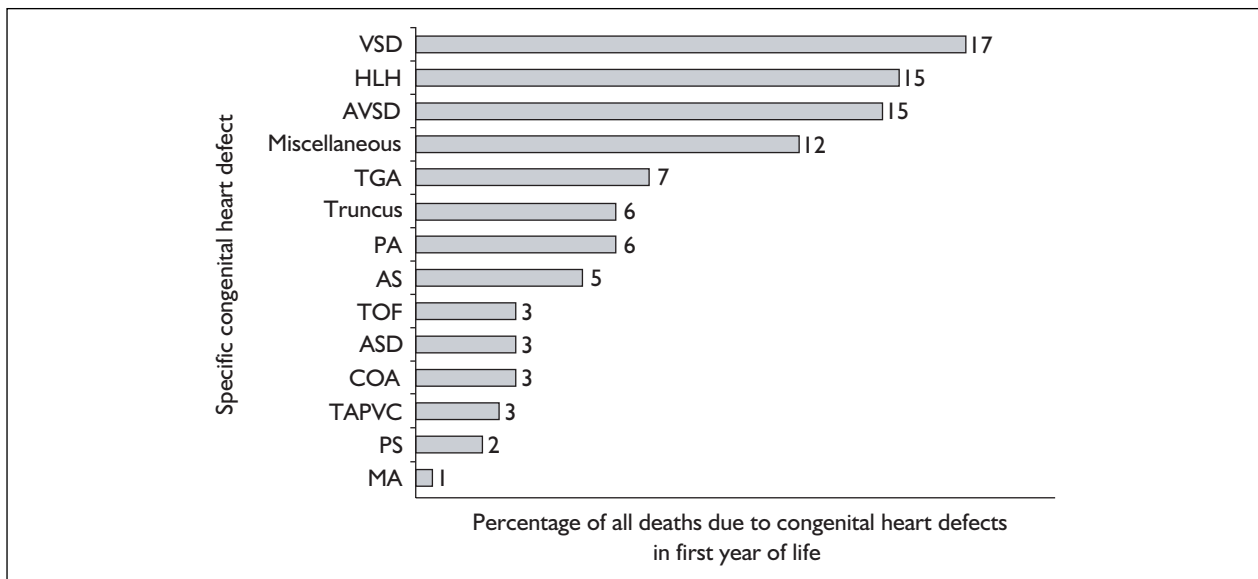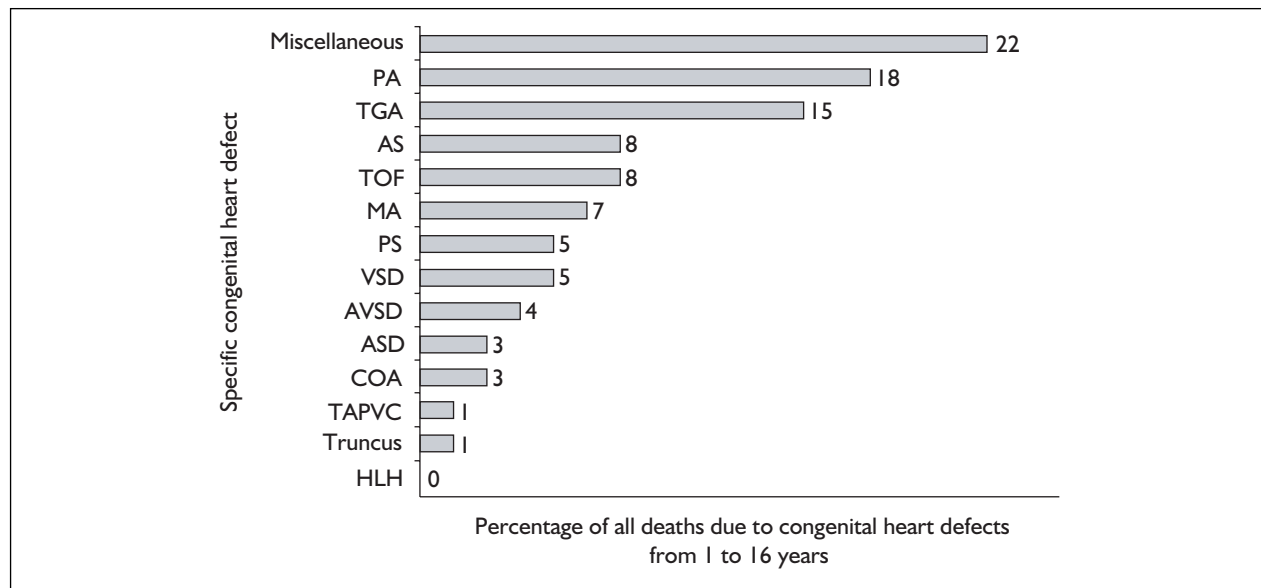
**FIGURE 19** *Percentage of all deaths due to congenital heart defects by specific heart defect: age 1–16 years (n = 1590). 'Miscellaneous' as in* Figure 17. *Reproduced from Wren C, O'Sullivan JJ. Survival with congenital heart disease and need for follow up in adult life.* Heart 2000;**84**:499–503.

Less prevalent but more severe congenital heart defects, such as PA, TGA, AS, TOF and MA, are most likely to contribute to mortality in this age group. The main causes of death in this age group are sudden cardiac death and deaths related to surgery.[86] Screening is unlikely to affect mortality in this age group.

Overall, improved survival is leading to a rapidly increasing population of adults who have been operated for congenital heart defects. It is estimated that in the UK each year 2500 children with these disorders currently reach adulthood.[12,89] The problems faced by teenagers with congenital heart defects must now be explored to inform the transition from paediatric to adult cardiological care and to ensure that services are appropriate to their needs.[90,91]

## Adults

Many cardiac malformations can only be palliated or incompletely repaired by surgery. The long-term sequelae of operated and unoperated congenital heart defects include cardiac arrhythmias, congestive heart failure, infective endocarditis, PVOD (otherwise called pulmonary hypertension or Eisenmenger's syndrome) and valve insufficiency. As surgical management improves, these complications tend to occur later in life. The table in Appendix 3 lists the main complications associated with different

malformations. Some longer term complications of congenital heart defects, such as arrhythmia, arise largely as a complication of clinical management and treatment. It is unlikely that newborn screening will prevent deaths occurring as a result of these longer term complications.

**Arrhythmias** are an increasingly important cause of mortality in older children and adults with congenital heart defects[86,89,92] and may be related to the primary malformation or to scarring and late complications after surgery. Treatment of arrhythmias may involve electrophysiological ablation, cardiac surgery, pacemaker insertion or intracardiac defibrillator implantation. Arrhythmias are a cause of sudden cardiac death in both children and adults with congenital heart defects.[86,93] Such deaths often occur more than 20 years after initial surgery. Sudden cardiac deaths are 25–100 times more likely in adults with congenital heart defects than in the unaffected population. The congenital malformations most often associated with fatal ventricular arrhythmias are TGA, TOF, AS, COA and PA.[94] Children and adults with PVOD are also at higher risk of arrhythmic death.[86,92,93]

**Heart failure** is a complication of congenital heart defects that is associated with chronic abnormalities in cardiac haemodynamics and is characterised by progressive ventricular dysfunction, exercise limitation and neurohormonal activation.[95–97] Surgery aimed at improving valvar function or

closing shunts can improve cardiac status but myocardial abnormalities persist. Pharmacological treatments, such as angiotensin-converting enzyme (ACE) inhibitors and beta-blockers, are used if there is congestive heart failure (fluid retention and symptoms of dyspnoea) in addition to exercise limitation.

**Infective endocarditis (or subacute bacterial endocarditis)** refers to a rare infection of the endocardial lining of the heart, usually on the valves or close to septal defects. Any abnormal structure of the heart that causes turbulent blood flow can predispose to infection, leading to cardiac damage and perhaps death. Infective endocarditis is rarely encountered in clinical practice. Congenital heart defects are the most common underlying cause of infective endocarditis in children; however, it is very unusual for a congenital heart defect to be diagnosed through presentation with infective endocarditis. Infective endocarditis is more common with AS, VSDs and palliated cyanotic heart disease[98–100] and it is rarely associated with ASDs or mild PS.[98] Death may occur in about 25% of those affected.[101] Children and adults with congenital heart defects are advised to take prophylactic antibiotic treatment at times of risk, such as surgery, dental treatment or childbirth,[89] although there is currently no good trial evidence that antibiotic prophylaxis is effective or that the risk of infective endocarditis is increased following invasive procedures.[102]

**Pulmonary vascular obstructive disease** (PVOD or Eisenmenger's syndrome) is caused by the abnormally high pulmonary pressure and blood flow associated with some congenital heart defects. It is a rare complication that develops in later childhood and adulthood. Individuals with unoperated atrioventricular septal defects, TGA, VSDs and ASDs are at greater risk of PVOD. Palliative medical treatment is available but rarely halts progression and lung transplantation is rarely indicated. Survival for patients with PVOD has not improved markedly over the last few decades and prevention, by radical repair of the cardiac defect, is the best approach. It is extremely unusual for a congenital heart defect to be diagnosed through presentation with PVOD.

Nieminen and colleagues reported 78% actuarial survival over 45 years for all congenital heart defects (with a mean follow-up period of 22 years) compared with 93% 45-year survival for the general population.[77] However, this study

summarised deaths over a long period during which surgical techniques changed considerably. The most common causes of death in adults with congenital heart defects are sudden cardiac death (arrhythmia), progressive heart failure and perioperative death.[92] The specific defects most commonly associated with death in young adulthood are TGA, PA and COA[92,103] and these deaths are likely to be associated with surgery.[104] One-quarter of all adults with congenital heart defects will have severe or complex malformations; all require lifelong follow-up and care[12,89] and the outlook into middle age of many newer treatments is inevitably unknown.

# Childhood outcomes with congenital heart defects

The wider health, social and educational outcomes of children with congenital heart defects are relevant to their ability to function and achieve independence in activities of daily life and self-care at the same rate as their peers. No studies identified by the search included comparisons of screened and unscreened populations. However, it was possible to review the expected functioning for children with congenital heart defects in several domains, including exercise capacity (occasionally related to daily activities), neurodevelopmental outcomes and cognitive functioning or school performance. This review therefore explored the contribution of diagnosis and severity to eventual morbidity outcomes and highlighted areas for further research into the factors preventing childhood disability as a consequence of congenital heart defects.

## Exercise capacity and daily functioning
Clinical follow-up of survivors with congenital heart defects may include monitoring of cardiac function using a number of different methods, for example, chest X-ray, electrocardiography, echocardiography, exercise testing, radionuclide tests, cardiac catheterisation and magnetic resonance imaging.[105] These methods do not directly measure exercise tolerance in daily activities.

The 54 studies reporting exercise capacity in children included three reviews, eight studies employing a control group of children without congenital heart defects and 43 non-randomised case series measuring exercise capacity after surgery. There were no randomised controlled trials. Thirty-eight studies reported exercise

**TABLE 6** *NYHA functional classification*

| Class | Definition |
|-------|------------|
| I | Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea or pain |
| II | Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea or anginal pain |
| III | Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnoea or anginal pain |
| IV | Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased |

Reproduced from The Criteria Committee of the New York Heart Association. *Nomenclature and criteria for diagnosis of diseases of the heart and great vessels*. 9th ed. Boston, MA: Little, Brown; 1994.

outcomes more than 5 years after surgery. Forty-nine studies looked at one type of congenital heart defect only. The majority (*n* = 26) of studies used unmodified New York Heart Association (NYHA) functional class as the only measure of exercise tolerance in daily activities.

Research studies of outcome among survivors of congenital heart surgery often report the NYHA functional class after operation as an indicator of a child's physical limitations and exercise capacity related to daily activities, ranging from I (best) to IV (worst) (*Table 6*). The system has broad categories based on subjective descriptions of daily physical activity, either by self-report or doctors' report. It was developed for use in adults with heart failure and has a strong association with mortality in such adults but the relevance in children is uncertain.

Child self-report or proxy report by parents or doctors must often be used when the system is applied in children. Objective tests of exercise performance and ventilatory anaerobic threshold demonstrate that children in NYHA Class I can still have a 25% reduction from normal exercise capacity.[107] Other tests, such as exercise testing (treadmill test) using the Bruce protocol, may be more successful at measuring children's exercise capacity in the future,[108] but they are not yet employed widely.

Child questionnaires, based on the NYHA classification system, have been developed to measure exercise tolerance related to daily activities in children. Children or parents complete these but none are used widely or well validated and they have only been tested in small populations with cyanotic congenital heart defects.[109–111] The results from these

questionnaires suggest that children, and their parents, often underestimate exercise tolerance and restrict exercise activities and school attendance when there is only mild functional limitation.[109,110,112] The responses to these exercise questionnaires reflect children's and families' experiences of living with congenital heart defects: the limitations that they report will be influenced by what they are **physically able** to do and also by what they **believe** that they can do.[113]

Most children with congenital heart defects seem to regain good exercise capacity after operation, although a minority will have complex disease or further complications, such as pulmonary hypertension or heart failure, which severely limit activity. Some manifestations of specific congenital heart defects, for example, cyanosis, are associated in general with greater limitations on exercise.[105] Even if corrective surgery does not benefit survival, there may still be a significant improvement in exercise capacity and in the ability to participate in normal daily activities.[105] *Table 7* compares NYHA Class and other exercise results for survivors with different congenital heart defects.

Although the NYHA functional classification is simple and widely employed, it is likely that this instrument underestimates the number of children who are limited in their exercise capacity with additional problems related to the use of a proxy respondent, such as a parent or health professional. Questionnaires for children permit a more detailed exploration of children's daily abilities but are not yet validated against a normal population or control group. It is clear that there is a need, in both clinical practice and research, to evaluate more widely the non-invasive methods for measuring exercise capacity in daily activities during childhood.

*TABLE 7 Exercise capacity for different malformations*

| Malformation | NYHA Class I (after surgery) | Additional outcomes |
|---|---|---|
| TGA | 84–87% Class I 12–18 years after Mustard repair[114,115]<br><br>87–98% in Class I 3–10 years after Senning/Switch repair[116–121] | Exercise tests: reported to be normal in 94% at 5 years after the arterial Switch repair[122]<br><br>Self-reported: mild limitations in exercise after 25 years (arterial Switch repair)[123]<br><br>35% of children report normal exercise 6–12 years after the Mustard operation[109] |
| AS | 88–97% in Class I after 15 years[99,124,125] | Aerobic tests: reduced exercise capacity in children[121]<br><br>Sports associated with sudden cardiac death[105] |
| TAPVC | 100% in Class I after 15 years[126] | No studies found |
| HLH | All survivors in Class I or II very soon after surgery[127] | Long-term exercise studies not found;<br><br>Self-reported: 'satisfactory' exercise capacity at 1–2 years postoperatively[128] |
| COA | No studies reporting NYHA identified | Oxygen consumption/exercise tests reported: normal in children after surgery[129,130]<br><br>Self-reported: limitations rarely noted in adults[131]<br><br>Exercise-induced hypertension reported in 17–80% of adults[132–142] |
| IAA | 85% Class I/II after surgery[82]<br>15% Class III/IV after surgery[82] | 97% in Class I 2 years after surgery but included a mixed group of subjects with AS and IAA[125] |
| PA | 97% Class I/II after 2–18 years[143] | Self-reported: few restrictions in employment or school attendance[143]<br><br>'Most' survivors (PA with intact ventricular septum) were in Class I after 12 years[144] |
| VSD | No studies reporting NYHA identified | Self-reported normal activity at 10 years[107]<br><br>Exercise capacity 92–100% of predicted in adults[107,145–147]<br><br>Exercise-induced hypertension reported in children[148] |
| TOF | 70–85% Class I, 15–25% Class II and 2–3% Class III at 10 years after surgery[149–152]<br>91% NYHA Class I at 20 years after surgery[153]<br>97% Class I at 5–7 years after surgery[154,155] | Most report no limitations at 20 years[156]<br><br>Better function if repaired in infancy reported in some studies[157] but not others[158]<br><br>50% participate regularly in sport[156] |
| Atrioventricular septal defect (AVSD) | 95–100% Class I up to 10 years[159,160]<br>70% in Class I at 12 years after surgery[161]<br>83% Class I, 11% Class II and 6% Class III at 4 years after surgery[162] | No studies found |
| ASD | 94% Class I up to 1 year after surgery[163] | Exercise-induced hypertension reported in some children[148]<br><br>Associated with sudden cardiac death[105] |

## Developmental and neurological outcomes

### Neurological outcomes

Research studies reporting the neurodevelopmental sequelae of congenital heart defects have used neurological examination, standardised developmental tests and standardised cognitive tests to measure outcomes. However, the tests used vary between studies and depend on the age of the children studied.[164–167] Hence it is difficult to compare different studies.

Severe neurological deficits (cerebral palsy, epilepsy and global learning difficulties) are uncommon and found in only 5–10% of all children who have undergone congenital heart surgery, whereas milder neurological problems are more common and occur in up to one-quarter of children.[105,164,166,168,169] Severe neurological complications are more common in children who have HLH[170–173] after surgery in younger infants (<3 months old),[171] in operations involving the aortic arch,[81] in surgery that is complicated by multiple organ failure[174] and possibly in acyanotic heart malformations.[175]

As children grow older, the frequency of diagnosis of neurodevelopmental problems increases, particularly of neurological deficits (nerve palsies, dyspraxias, seizures, etc.) and of speech and language disorders.[176] In addition, the presence of chronic illness can have an independent detrimental influence on development.[177]

Studies of congenital heart defects associated with chronic cyanosis report an association with impaired motor function and cognitive development.[105] A Canadian study of preschool functioning after surgery for congenital heart defects (excluding HLH), reported that only 21% of children had normal mobility, cognition and self-care skills for their age, whereas 37% were moderately disabled (primarily with mobility problems).[164] The long-term effects of operated HLH have not yet been fully explored as there are no large cohorts of long-term survivors, but preschool development has been reported to be slower in these children.[170,172,173,178,179]

### Motor delay

Motor deficits in children with congenital heart defects have been estimated to affect 20–50% of children depending on age and the cut-off points used.[164–167,180] Both fine and gross motor skills are affected.

### Sensory: hearing/vision

Visual palsies, visual field defects and squint have all been described in children with congenital heart defects following surgery but are infrequent neurological findings.[81,165,167]

### Speech and language delay

Mild speech and language delay occur after surgery for congenital heart defects.[169] Speech production disorders[165] and poorer vocabulary acquisition[166] are noted in preschool children but, at school age, both expressive and receptive language delay can be found in 40% of children who had repair of TGA as infants.[176]

### Cranial nerves

Cranial nerve abnormalities, most often affecting the facial nerves, are also infrequently found after cardiac surgery.[165,166,169,175]

## Cognitive outcomes and school performance

Standardised tests, such as WISC (Wechsler), have been used to give summary measures of IQ, which is generally reported to be in the low normal range for children with congenital heart defects.[105,165,181–183] Adjustment for socio-economic class is important as this has been shown to affect cognitive and language performance significantly.[165,167,184,185] Cognitive ability is poorer in children with cyanotic heart defects, even after surgery,[177,186] and operations involving circulatory arrest are associated with greater reductions in cognitive performance.[165,181] Possible explanations for the reduced cognitive ability in children with congenital heart defects are that early failure to thrive or cyanosis lead to poor brain development, that open heart surgery techniques damage the brain and/or that congenital syndromes associated with heart malformations are responsible.[105]

Children perform better at 5 years of age than in later childhood (8–14 years old) at tests of knowledge and acquired learning relative to test norms, suggesting that subtle cognitive difficulties have a more noticeable impact on academic performance as children get older.[176]

## Social and emotional functioning

The social functioning (family, peer and school relationships) and psychological functioning (behaviour, emotions and self-esteem) of children with chronic illness are as relevant to daily functioning as physical abilities. Standardised questionnaires and interviews have been used to obtain information from children, their parents

and teachers about the behavioural and emotional responses of children living with congenital heart defects.[187]

Behaviour problems are more likely to arise in children with heart malformations than in the normal population and may be more common in cyanotic heart defects, in children with greatest physical limitation and after cardiac arrest.[105,169,182,188–191] Socialisation skills were poor in >50% of preschool children who had had surgery for congenital heart defects.[164] Behavioural and socialisation problems, as reported by parents, are correlated with poorer school performance and self-reported quality of life in young people who have had repair of TGA in infancy.[190] A child's body image may alter with chronic illness[192] and children's understanding of their own illness is often poor.[193]

School-age children with congenital heart defects have been found to need more support from teachers in coping with their school absences, peer relationships and participation in educational activities.[194] Congenital heart defects can have significant stressful effects on parent–child relationships, encouraging more anxiety, restrictions imposed on activity and less independence.[105]

Other studies confirm that living with congenital heart defects can lead to wider disruption within the family network.[195] However, more recent studies have also suggested that children can adapt well to chronic cardiac illness[196] and that this is related to parental coping styles.[105,197]

## Early clinical predictors of outcome and the role of screening

Various studies have investigated antenatal, preoperative, intraoperative and postoperative factors that could predict long-term outcome for children with congenital heart defects but the critical time period and the relative importance of different predictive factors for functional outcomes are unclear. The impact of newborn screening is in the period between birth and definitive diagnosis, when presentation of the condition by a sudden deterioration in clinical status is possible and could require emergency treatment before surgery. This review identified 36 studies which analysed the contribution of early clinical predictors to outcome, including markers of preoperative collapse that are relevant to a screening model. The findings from these studies are summarised below.

### Antenatal and perinatal factors

The Baltimore–Washington Infant Study Group undertook an epidemiological investigation into both environmental and genetic risk factors in a cohort of children born with congenital cardiac defects.[198] Maternal and paternal exposures before and during pregnancy were associated with increased frequency of occurrence of specific malformations including paternal drug use and TGA, paternal anaesthesia and TOF, parental paint and pesticide exposures with septal defects[199] and maternal diabetes with double-outlet right ventricle and truncus.[44] Congenital cardiac defects also occur in association with congenital syndromes and extracardiac anomalies more frequently than would be expected by chance alone.[200,201] There is a higher frequency of cardiac defects in the relatives of children born with cardiac defects[202] and the recurrence risk in offspring of affected parents suggests both single and multiple gene inheritance is occurring, particularly for some lesions.[42] Certain factors are associated with worse outcomes from congenital heart defects, including the type and complexity of the malformation, associated extracardiac anomalies and congestive heart failure.[203–211]

Children born with congenital heart defects have a higher incidence of neurological abnormalities, including microcephaly, hypotonia, hypertonia, seizures, feeding difficulties and lethargy in the newborn period,[173,175] and these do not appear to be predicted by difficulties at birth, such as birth asphyxia.[164,166,212] Preoperative cerebral infarctions have been noted in 4% of children with congenital heart defects and are associated with subsequent abnormal neurological development.[105,213–215] Higher bilirubin levels and low birth weight may be associated with a higher rate of neurological complications postoperatively.[216] The abnormal neurology and growth deficits[217] identified in these newborns may either be due to the congenital heart defect or be the result of an earlier factor that has led to both the heart defect and other neurological sequelae, but as yet causal pathways are poorly elucidated.

### Preoperative collapse and other factors

The postnatal window in which affected children are presymptomatic is extremely variable between malformations (from minutes to years), but this is an important period, when early detection may be able to reduce clinical deterioration and prevent collapse, therefore allowing more timely surgery. Clinical deterioration, or collapse, before surgery has been linked to higher postoperative mortality for children with congenital heart defects[80] and a

longer intensive care unit stay.[218] Various measurements that serve as proxy for this clinical deterioration are incorporated in the risk adjustment scores used to compare management, including for cardiac admissions, in paediatric intensive care units.[219] Studies using these combined scores have demonstrated the significant detrimental impact of preoperative collapse on mortality. Other studies have used single markers of collapse, including preoperative hypoxia, acidosis, cardiac arrest and the need for inotropic support or assisted ventilation. Cyanosis prior to surgery is associated with a higher mortality than acyanotic heart defects[220] and complex malformations, which are also often cyanotic, are more likely to lead to worse postoperative mortality and functional outcomes than other congenital heart defects.[82,105,216] Many studies find that a younger age at surgery is associated with higher perioperative mortality, but the need for early surgery is often confounded with severity.[82] Other studies have found that a young age at surgery predicts better survival for malformations in which preoperative collapse is a feature, including TGA, truncus and PA.[204] Metabolic acidosis or the need for ventilatory support in the period before surgery is predictive of poorer operative survival[80–83,211,221] and increased incidence of neurodevelopmental (particularly speech and motor) sequelae in the long term.[164,176] Reduction in preoperative acidosis through antenatal screening has been demonstrated for several defects, including HLH and TGA.[22,222,223] These findings suggest that preoperative instability is predictive of worse mortality and neurological outcome, both postoperatively and in the longer term, and is preventable through earlier detection.

### Intraoperative factors

Comparisons have also been made between different intraoperative techniques, primarily between the use of low-flow cardiopulmonary bypass or deep hypothermic circulatory arrest. Circulatory arrest is associated with significantly greater neurological deficit and functional limitation postoperatively than low-flow cardiopulmonary bypass[105,164,180,224,225] for comparable cases and may also limit survival.[216,226] However, this may only occur after arrest times of 30 minutes to 1 hour.[167,214,225] Longer duration of cardiopulmonary bypass leads to an increased frequency of intraoperative seizures and also later neurological impairment.[79,81,166,167,180,204,227–229] including speech deficits.[176] These neurological deficits probably have multiple causes, including cerebral ischaemia during surgery.[171,230]

### Postoperative factors

Cardiopulmonary failure and the need for high levels of intensive care support after surgery indicate a poor short-term outcome, with early surgical mortality being especially high for infants who have organ failure on the first postoperative day,[231] and are associated with poor long-term outcomes.[185,232] Low cardiac output postoperatively, despite inotropic therapy,[176] is also associated with neurological and motor impairments in children of school age. Seizures during the operation or in the postoperative period are predictive of later neurodevelopmental problems or poorer cognitive outcomes.[81,172,180,227,233,234] Magnetic resonance imaging[215] and post-mortem studies have shown diffuse brain injury and areas of infarction after open-heart surgery and these may underlie the clinically apparent neurological deficits which develop later in children with congenital heart defects.[105]

## Implications of this review

This narrative review has summarised current knowledge regarding childhood mortality and morbidity in children with congenital heart defects. In this review, we hoped to compare these outcomes for screened and unscreened populations, and for children who have collapsed or been stable before cardiac surgery. No studies were available reporting survival following screening for congenital heart defects in the newborn period. Furthermore, the relative contribution of underlying congenital syndromes, the clinical effects of the specific heart malformation and the treatment process to overall mortality and morbidity in this group of children is still largely unclear.

Despite this, this review provided some evidence to suggest that preoperative collapse is associated with worse short-term outcome, higher postoperative mortality and later neurological sequelae, especially cognitive, speech and language and motor deficits. Malformations proven to present with preoperative collapse are TGA, PA, HLH, IAA, truncus and complex cyanotic defects.[80–83,105,216,221] These studies confirm that improved newborn screening may have a future role in improving outcomes of these specific congenital heart defects through earlier detection of heart defects and prevention of collapse and death before surgery.

However, there are insufficient studies providing data about the effects of screening or collapse on

other outcomes from which we could derive estimates relating to longer term outcomes for use in the decision model. In the absence of these data, we selected as an end-point of the model 'timely diagnosis': a diagnosis made preoperatively before collapse or death occurs. This concept assumes that effective management of a congenital heart defect, and prevention of preoperative collapse, begins at the point when a diagnosis is sufficiently confirmed to allow definitive management to be initiated; for example, treatment with prostaglandin infusion stabilises most babies with duct-dependent lesions prior to surgery. Newborn infants with a positive screening test and in whom a congenital heart defect has been confirmed by diagnostic echocardiogram before preoperative collapse will have received a 'timely diagnosis' and therefore potentially may have benefited from screening.

In addition, this review highlights the paucity of morbidity studies measuring outcomes that are relevant to the daily activities of children with congenital heart defects and their families. Most published studies focus on the immediate mortality or neurodevelopmental outcomes related to surgical interventions in specific malformation groups and rarely consider long-term outcomes or the preoperative predictors of these outcomes.[64,164] There are few high-quality long-term outcome studies looking at physical disability, neurodevelopmental, cognitive or psychosocial outcomes and the capacity to participate in normal childhood activities. As already emphasised in the report from the Bristol Royal Infirmary Inquiry, there is a notable lack of data to inform children, parents and clinicians about possible outcomes, despite their increasing participation in shared decision-making about future management or care.

# Chapter 4

# Newborn screening for congenital heart defects

**Chapter outline**

In this chapter, we review the rationale for screening for congenital heart defects in pregnancy and after birth. Current policy is reviewed and evidence about the effectiveness and cost-effectiveness of newborn screening is presented. Alternative newborn screening strategies are described and reviewed. Finally, the commissioning brief which formed the basis for this evaluation of newborn screening is presented together with comments about its interpretation.

**Key messages**

- The rationale for screening for congenital heart defects lies in its potential to influence natural history by early presymptomatic detection and intervention.
- Antenatal screening gives parents an opportunity for information and counselling with options for a planned delivery and intervention or termination of pregnancy.
- Newborn screening allows the presymptomatic identification of life-threatening congenital heart defects. This may lead to better postoperative and longer term outcomes.
- Newborn screening also allows other clinically important defects with later onset to be detected, that are associated with heart failure in infancy or pulmonary vascular disease in later life.
- Current relevant antenatal screening policy comprises a routine fetal 'anomaly scan' for all pregnant women at 18–20 weeks together with serum screening for Down's syndrome.
- Current newborn screening policy comprises a clinical examination at birth and at 6–8 weeks, with specific cardiac investigations for children with Down's syndrome.
- The effectiveness of current UK newborn screening policy is questionable, as it fails to detect more than half of babies with congenital heart defects undiagnosed by the time of routine neonatal examination, and more than one-third by 6 weeks. There is also evidence that screen-positive infants do not receive timely management.
- Trained midwives or advanced neonatal nurse practitioners appear to be as effective as junior doctors in newborn clinical screening for congenital heart defects.
- Pulse oximetry and echocardiography are potential alternative newborn screening strategies but their cost-effectiveness has not been adequately evaluated in a UK setting.

## Rationale and criteria for evaluating newborn screening programmes

Screening is defined as 'the systematic application of a test or enquiry, to identify individuals at sufficient risk to benefit from further investigation or direct preventive action, amongst persons who have not sought medical attention on account of symptoms of that disorder.'[235]

In the context of newborn programmes, screening is offered to apparently healthy infants and their parents with the objective of identifying those at high risk of a specific condition. It is anticipated that these individuals may benefit from further diagnostic investigation and early treatment. By definition, screening tests are not diagnostic tests and therefore cannot separate reliably those with a specific condition from those without. Hence infants with a negative screening result will include some affected infants, usually referred to as 'false-negatives'. Parents and health professionals may be falsely reassured by false-negative screening results. Conversely, those with a positive screening result will include unaffected infants, usually referred to as 'false-positives'. Parents and health professionals of infants with false positive screening results may be worried unnecessarily and their infants may be exposed to the risks of subsequent diagnostic tests. Therefore, decisions about what constitutes a positive test will be determined by balancing the goals of screening and the perceived disbenefits of missing affected individuals or falsely labelling healthy individuals.

However, screening programmes may also result in unintended information about infants who cannot then be simply characterised into either of these two categories. This unintended information may include information about the genetic carrier status of a newborn infant, for example, as occurs in newborn sickle cell screening programmes.[236] Alternatively, it may include the detection of milder variants of 'disease' which may have little functional implications for the individual concerned but which cannot be ignored by the parents or the health professional delivering screening.

Newborn screening is carried out at a potentially vulnerable time in the developing mother–child relationship. It is therefore especially important to consider the potential harms of newborn screening from the child and parents' perspective. A large

number of screening tests are offered to mothers during pregnancy and early childhood and the associated risks of a false-positive screening result are, for the most part, independent and additive. It has been estimated that as many as 2% of infants in the USA may have false-positive screening results arising from screening for four conditions based on the newborn dried blood spot.[237] In evaluating screening, it is therefore important that high-quality evidence regarding potential benefits and disbenefits of newborn screening is available to inform policy and, if a screening policy is introduced, to inform shared decision-making by parents and their health professionals.

In recognition that a whole screening programme and not just the screening test has to be acceptable, criteria have been proposed covering the condition, test, treatment and broader aspects of the programme. These provide a framework for appraising evidence in relation to current or proposed screening programmes, which in turn form the basis of policy recommendations. For a current programme, these may include recommendations to continue screening, perhaps with modifications, or to discontinue the programme. For a proposed programme, these may include advice either to implement or not to introduce.

# Rationale for screening for congenital heart defects

The epidemiological and clinical review presented in Chapter 2 highlights the significant burden of disease posed by congenital heart defects in terms of mortality and morbidity. As primary prevention is not possible for most congenital heart defects, the rationale for screening lies in its potential to influence this natural history by early presymptomatic detection and intervention. Screening can be offered antenatally or postnatally and the objectives of these linked but distinct programmes are discussed.

## Antenatal screening

Antenatal diagnosis of fetal heart defects using a four-chamber ultrasound view was introduced in the mid-1980s and by the early 1990s was extended to incorporate an outlet view.[238] Scanning is usually undertaken between 18–20 weeks gestation. Detection at this stage allows the parents an opportunity for information and counselling with options for a planned delivery and intervention or termination of pregnancy.

As discussed in Chapter 3, for some life-threatening defects, such as TGA, which require urgent intervention but which have a very short presymptomatic interval, a planned delivery in a unit with appropriate cardiological expertise can potentially make a large difference to the risk of death or collapse prior to definitive management.[16,30]

Since antenatal ultrasound identifies complex cardiac defects, one option available to parents is that of termination of the pregnancy. About half of the affected pregnancies detected antenatally in the UK end in termination.[8] Decisions will depend on information about natural history and longer term outcome for the specific defect, presence of associated major abnormalities and parental preference and choice.

Another option is to offer a scan at 18–20 weeks only to women with high-risk pregnancies. Wyllie and colleagues identify the following characteristics of a high-risk pregnancy: a family history of congenital heart defects, non-cardiac fetal abnormalities, maternal diabetes mellitus, fetal arrhythmias, non-immunological hydrops and exposure to teratogens.[239] However, they estimated that screening this subgroup of high-risk pregnancies would at best identify only 6% of all congenital heart defects.

In practice, however, and as discussed previously, the proportion of affected pregnancies or live births detected antenatally varies markedly in the UK, with an average detection rate of about 25%. This reflects a number of factors including those relevant to the specific defect (natural history, stage at booking, gestational age at scanning), the mother (obesity), the operator (skill and expertise at scanning) or the fetus/pregnancy (twins, oligohydramnios, polyhydramnios). Although it is unusual for life-threatening congenital heart defects to arise after 20 weeks gestation, other defects such as AS and PS may not be detectable at 18 weeks.[238,239] Hence for the foreseeable future it seems unlikely that fetal diagnosis will obviate the rationale for newborn screening.

## Newborn screening

The principal rationale for newborn screening lies in the presymptomatic identification of congenital heart defects that are either immediately life threatening or become so as a consequence of physiological changes occurring as the infant adapts to postnatal life. This allows definitive management to be initiated before death or cardiovascular collapse has occurred, which from

evidence presented in Chapter 3 may lead to better postoperative and longer term outcomes. Newborn screening may also detect other clinically important defects with later and more gradual symptomatic onset in infancy potentially averting the morbidity associated with heart failure and failure to thrive. Furthermore, some defects such as COA or those associated with high pulmonary blood flow may not present until adolescence or adult life, by which time irreversible physiological changes have occurred: early detection by newborn screening is likely to prevent these changes. However, direct evidence to support these last two objectives is lacking, specifically the frequency of these outcomes and the extent to which they may be prevented by newborn screening.

## Current UK screening policy

### Antenatal screening

Current guidance comes from a report published by the Royal College of Obstetricians and Gynaecologists (RCOG) in 1997 in which a routine 'anomaly scan' for all pregnant women at 18–20 weeks was recommended but not specified in any detail. This reinforced the advice of an earlier RCOG working party which met in 1984 but also stressed the importance of appropriate training and audit for sonographers.[7] Uncertainties about the role of newer tests (nuchal translucency) and the costs and cost-effectiveness of antenatal ultrasound were voiced.

More recently, two HTA reports attempting to fill some of these gaps have been published. The first presented an economic evaluation of antenatal ultrasound and suggested that in practice the detection rate for antenatal ultrasound was low.[7] It did not, however, evaluate first trimester screening based on evaluation of nuchal translucency. A second HTA report published in 2003 presented the findings of the Serum, Urine and Ultrasound Screening Study. This study aimed to identify the most effective, safe and cost-effective method of antenatal screening for Down's syndrome using nuchal translucency (NT), maternal serum and urine markers in the first and second trimesters of pregnancy.[240] It recommended that screening for Down's syndrome be based on the identification of increased NT combined with an integrated serum marker test. Although a policy of antenatal screening for Down's syndrome has been formally adopted in the UK, its predicted impact on the fetal diagnosis of congenital heart defects is likely to be small. Although there is general agreement that the

finding of increased NT warrants an expert fetal ultrasound assessment to exclude a cardiac defect, it is also clear that 'normal' NT does not rule out a congenital heart defect.[241] It has been suggested that antenatal screening for Down's syndrome would reduce live-born cases of Down's syndrome by 45%, live-born cases of congenital heart defects by 3.5% and cardiac surgery by 2.6% and hence have only a small effect on the requirements for paediatric cardiology services and paediatric cardiac surgery.[70,242]

### Newborn screening

It is difficult to identify clearly the time when clinical examination of the cardiovascular system was introduced into routine practice in the UK, but it is likely that this happened as an integral part of the clinical newborn examination which became more widespread in the 1950s with the rise in hospital deliveries. As with other newborn screening based on the routine newborn examination, the distinction between good clinical practice and screening can be a fine one. Current guidance published in *Health for all children* includes recommendations to examine the cardiovascular system of all infants shortly after birth and again at 6–8 weeks of age.[5] No specific guidance is given about the exact timing of the initial examination but it is emphasised that screening will not identify all infants with congenital heart defects. Some guidance is given about recognising infants who are at higher risk of a congenital heart defect, including Down's syndrome.

The Down's Syndrome Medical Interest Group publish explicit guidance about the cardiac assessment of affected infants.[243] The rationale for this is to avoid irreversible pulmonary vascular disease due to high pulmonary blood flow related to complete atrioventricular septal defects. About half of all babies with Down's syndrome will have congenital heart defects, and in around one-third of these this will comprise a complete atrioventricular septal defect. It is recommended that the cardiac status of all Down's syndrome children is established by 6 weeks of age, and that this must be achieved through clinical examination and echocardiogram in the newborn period or by clinical examination, electrocardiogram and chest X-ray in newborns and again at 6–8 weeks. Clinical examination alone is regarded as inadequate and the need for vigilance even if early tests are negative is stressed. Finally, it is recommended that parents and carers of all children with heart lesions should be given verbal and written information about infective

endocarditis preventive measures. It is unclear in what proportion of infants with Down's syndrome the diagnosis of a cardiac defect is made through earlier recognition of Down's syndrome, and in what proportion the diagnosis of Down's syndrome is first made through recognition of the cardiac defect either antenatally or postnatally.

## Effectiveness of current UK policy

Data to evaluate the performance of the current newborn screening programme are not routinely collected. Information from individual studies suggests that the detection rate of clinical screening is poor. A series of publications from the Northern Region study have addressed the effectiveness of screening.[6] This study covers practice over a period spanning from the mid-1980s to mid-1990s, and comprises a unique combined record of screening results, diagnosed cases and outcomes, including death, ascertained from multiple sources and based on a defined population. Although antenatal detection rates for congenital heart defects were lower than the national average in the Northern Region in the mid-1990s, the detection rate for life-threatening defects was similar to that achieved nationally.[8] It therefore presents an important window on the effectiveness of current UK policies. The key findings of this study relevant to the effectiveness of clinical screening are briefly summarised.

Over an 8-year period in this health region, one-third of babies presented before the routine newborn examination because of symptoms or non-cardiac abnormalities. When carried out, newborn screening failed to detect more than half of those affected, while examination at 6 weeks missed one-third. It was concluded that a normal heart examination did not rule out a congenital heart defect.[6] This report also noted failures of management arising through delay in seeking appropriate diagnostic investigations in those with a positive screening result. This was confirmed in a subsequent prospective study of 7204 infants: the newborn examination detected only 44% of cardiac defects, although the predictive value of a murmur at this age was found to be 54%.[244] Six babies per 1000 were found to have murmurs in this study compared with more than double that figure in a later study from South London.[245] In a further report from the Northern Region study, one baby in 100 was found to have a murmur at the 6–8-week check.[246] A congenital heart defect was confirmed in nearly half of those referred for diagnostic evaluation, and this led to the diagnosis of one-third of affected infants in the study population.

The performance of clinical screening in relation to life-threatening congenital heart defects has also been evaluated.[18] These defects included HLH, IAA, COA and AS, which have been shown to be the main causes of death from congenital heart disease after discharge from hospital and before diagnosis. Overall, only 31% of infants were picked up at the newborn examination. A high proportion of those not detected as newborns presented with symptoms before the 6-week examination. Notably, there was a failure to act upon the positive screening result in a timely manner and this led to death of at least one infant out of the 120 included in this study.

Hence current policy is associated with a low detection rate, especially for life-threatening defects. The newborn examination appears particularly crucial for such infants, most of whom will have presented with symptoms, collapse or death by the time of the second recommended screening examination at 6 weeks of age. Hence a negative clinical screening examination test does not rule out serious congenital heart defects. Of concern is the fact that infants with a positive screening result are not referred for a timely diagnostic evaluation and that a proportion of these develop symptoms or die before a diagnosis is confirmed and without definitive management having been initiated.

Some information is also available from the literature regarding the number of newborn examinations and the effectiveness of different health professionals as primary screeners.

In the past, newborn examinations were carried out twice before discharge, once within 24 hours of birth and again a few days later. However, earlier discharge from hospital following delivery means that the majority of infants receive only a single examination in hospital.[247] Does this matter in relation to the detection of congenital heart defects? The effectiveness of a single examination compared with two before discharge was compared in a randomised trial with respect to congenital conditions diagnosed in hospital and confirmed in outpatients.[248] Although overall more abnormalities were suspected in the infants receiving two examinations, there was no significant difference in the prevalence of those suspected of having a congenital heart defect or in the proportion of babies with a confirmed heart defect. Hence it was concluded that a single

examination was no worse than two examinations with respect to newborn detection of congenital heart defects. The trial was too small to examine this conclusion for individual defects.

A second issue relates to the training and competency of the person performing the examination. Advanced neonatal nurse practitioners (ANNPs) have recently been introduced into neonatal care in the UK and are being instructed in the newborn examination. In an observational study, ANNPs performed as well as junior doctors [senior house officers (SHOs)] in terms of their effectiveness at detecting cardiac abnormalities and in their positive predictive value. In another study, midwives specifically trained in the newborn examination were compared with SHOs given no specific training using video recordings to evaluate the quality of the newborn examination.[249] When rated by a consultant paediatrician masked to the identity of the examiner, a similar percentage of cardiac screening examinations performed by midwives and SHOs were rated as appropriately completed. When rated by a senior midwife, SHOs performed significantly worse than midwives. This trial was unable to disentangle the effects of training from professional grouping since SHOs were not offered the same formal training as midwives. In a related publication on maternal satisfaction,[250] mothers' perception that the quality of midwife examination was at least as satisfactory as that of SHOs was maintained to 3 months after delivery.

Hence midwives and ANNPs trained in the newborn examination appear able to deliver clinical screening to at least the standard provided by SHOs, who are usually 'informally' rather than explicitly trained. In addition, it is likely that the training curricula in newborn examination developed for midwives and ANNPs have broader relevance to junior doctors in training. However, none of these trials evaluating number of newborn examinations or training of the personnel carrying them out alter the conclusion that the current policy of newborn clinical screening alone appears an ineffective strategy for the detection of clinically important congenital heart defects.

## Alternative newborn screening strategies

### Pulse oximetry

The rationale for considering pulse oximetry as a screening test for congenital heart defects lies in the observation that infants with life-threatening defects are not detected by clinical screening and that many of these defects are associated with cyanosis but not an audible murmur.[18] Hence pulse oximetry which estimates arterial oxygen saturation by measuring the absorption of light in human tissue beds may preferentially detect infants whose cyanosis escapes clinical detection.[251] Normal values for pulse oximetry are generally assumed to be the same as those for arterial oxygen saturation in the newborn. These values may be influenced by altitude but in general, levels below 95% are considered to be abnormal. The precision of oximeter readings varies with the absolute value is generally cited as ±2% above 70% and ±4% below 70%. The accuracy and precision of these monitors have been studied in a range of populations, including newborn infants. Low peripheral perfusion (blood flow to the skin and limbs) or skin temperature, skin pigmentation and movement may all interfere with precision or introduce biased estimates of arterial saturation.

From our literature search, we identified four published studies reporting the use of pulse oximetry in asymptomatic newborn populations.[252–255]

In a preliminary study, Hoke and colleagues assessed the utility of arm and leg oxygen saturation as a candidate screening test for the early detection of ductal-dependent left heart obstructive disease in 2876 newborns admitted to well baby nurseries and 32 newborns with congenital heart defects.[254] Overall, 57 newborns in the well baby nurseries (0.02%) were found to have a leg saturation <92% in room air or a saturation 7% lower in the leg than in the arm and of these four were found to have 'critical' congenital heart defects, including one infant with COA. Of the 32 newborns with congenital heart defects, 11/13 (85%) with left heart obstructive disease had abnormal oxygen saturation tests, as did 15/19 (79%) with other forms of congenital heart defects.

Richmond and colleagues undertook a larger prospective study of 6166 infants born in a district general hospital in the North of England.[253] Oxygen saturation was measured over 2 minutes after the age of 2 hours and before discharge in one foot of all babies not admitted directly to the neonatal unit. Babies with fractional oxygen saturation <95% were examined by a midwife and the saturation repeated. Infants with an abnormal examination or a persistent low oxygen saturation were assessed by echocardiogram. Infants who did

not have low saturation still received the routine newborn and 6-week clinical screening examinations. Over the period of the study 98% of eligible infants were screened. An initial low oxygen saturation was found in 5% but persisted in only 1%. Congenital heart defects were found in 8.1 per 1000 infants, and in half this was an isolated VSD. Of the 24 infants with other malformations, a low arterial saturation was the first sign of any problem. An additional 13 babies with low arterial saturation were ill for non-cardiac reasons that benefited from medical intervention, including seven infants with transient tachypnoea of the newborn, two of whom later required ventilation, one with subclinical fits secondary to brain haemorrhage and the other with a spontaneous pneumothorax. This study demonstrated that pulse oximetry in the first 24 hours of life can result in timely recognition of serious cyanotic congenital heart defects and also other serious illnesses that require medical intervention. However, evidence from this and another study by the same authors suggests that the detection of COA may not be improved with this test.[18]

In a subsequent larger study, Koppel and colleagues assessed 11,281 asymptomatic newborns in the well infant nurseries of two hospitals in New York.[252] Diagnostic echocardiograms were performed in infants with oxygen saturations <95% within the first 24 hours of life. Three infants with 'critical' congenital heart defects were detected, two of whom had TAPVC and one truncus. A further nine infants from among 15 with fetal diagnoses of congenital heart defects were also positive. Six of the infants with critical congenital heart defects were symptomatic before screening. Two infants received false-negative diagnoses, one with COA and the other with hypoplastic left pulmonary artery. The authors calculated a detection rate of 60%, a false-positive rate of 0.05% and a positive predictive value of 75%.

Reich and colleagues assessed 2114 otherwise well newborns before discharge from the maternity unit.[255] A single pulse oximeter reading was performed before discharge and infants with saturation values <95% in whom this persisted on second reading were assessed by echocardiogram. Thus 88 (3.8%) of infants received an echocardiogram, which was abnormal in 43 (positive predictive value 49%). A similar percentage of 'control' infants who were not screened by pulse oximetry required echocardiograms, of which 39% were abnormal.

One child with TAPVC was not detected by pulse oximetry.

From this review, pulse oximetry shows promise as a newborn screening test. It is a relatively cheap technology, is portable and appears to be well validated in newborn infants. The screen-positive rate does not appear to result in a huge increase in infants being referred for echocardiograms and the positive predictive value of a low oxygen saturation seems high in all three studies. However, existing experience is based on too small a sample to define the detection rate overall and for specific defects, and infants with COA and TAPVC have been missed. Interestingly, an unintended benefit of this screening test is the detection of infants who are ill for non-cardiac reasons and who may also benefit from earlier recognition of their illness. A hyperoxia test, which monitors changes in the degree of cyanosis whilst oxygen is being administered, could help distinguish lung disease from cyanotic heart defects. However, this also has implications for the diagnostic assessment protocols as a negative echocardiogram may not necessarily be reassuring. It has been suggested that larger studies are required.[9]

## Screening echocardiography

Echocardiography is used postnatally in high-risk infants for the diagnosis or exclusion of congenital heart defects and for assessment of cardiovascular function. There is only limited experience in the literature of its use in low-risk populations as a screening test. However, the review of prevalence studies by Hoffman and Kaplan and also by Wren and colleagues discussed earlier has highlighted a rising prevalence of structural heart abnormalities such as muscular VSDs which are of no functional or clinical importance and which by and large only come to light as a consequence of echocardiography.

The only study reporting performance of screening echocardiography identified from our literature search was carried out in Northern Ireland.[256] Mothers were randomised before delivery to screening echocardiogram or routine clinical screening examination. A total of 9697 infants were eligible for the study and a further 1710 infants were excluded if they were at high risk of congenital heart defects and requiring diagnostic echocardiography. Risk factors included maternal diabetes, fetal congenital heart defects diagnosis, family history of congenital heart defects, Down's syndrome, admission to special care and postnatal signs or symptoms suggestive

of congenital heart defects. Screening was performed at 48 hours by a trained ultrasonographer in the maternity hospital. There were 4875 infants allocated to the scan group and 4822 assigned to clinical assessment alone. During the study, 124 scan-allocated infants and 50 controls were identified as having significant congenital heart defects before hospital discharge. This included infants with VSDs, PDA, PS and ASDs. No increase in the detection of life-threatening congenital heart defects was demonstrated.

With a minimum of 3 years of follow-up there were 27 additional late diagnoses – none of which were life threatening – in controls and one in scanned infants. The predictive value and the false-positive rate were not reported and it was not possible to determine from the data presented what proportion of infants had diagnoses of structural abnormalities of no functional importance.

## Cost-effectiveness of newborn screening

Through our literature searches and from reference lists of key articles, we looked for studies reporting cost-effectiveness of newborn screening that might be applicable to the UK setting.

Two studies reporting cost-effectiveness of different antenatal screening strategies were identified.[257,258] One study assessed the cost effectiveness of different strategies to evaluate heart murmurs in children.[259] We found one study reporting the cost-effectiveness of screening in child healthcare centres in The Netherlands.[260] This study did not evaluate newborn screening.

## Commissioning brief

The HTA commission brief identified the following question for the commissioned review:

> "What is the cost-effectiveness of auscultation and echocardiography in the detection of congenital heart disease in the newborn period and up to 1 year of life?"

The rationale for this was given as follows:

> "Up to six in every 1000 live-born infants have a cardiovascular malformation. Most of these are asymptomatic at birth. Early recognition is important because clinical presentation and deterioration may be sudden and some treatable causes may cause death

before diagnosis. Also, irreversible pulmonary vascular disease could be avoided by earlier ascertainment, and complications such as endocarditis reduced. Difficulties arise in the examination of the heart as the newborn period is a time of change for the cardiovascular system as adaptations continue to be made to extra uterine life."

The reviewers were asked to include the natural history of the condition, the properties of the tests used and evidence of their clinical impact, the effectiveness of different management options for children who test positive, and psychosocial effects on parents and families. They were asked to consider infants at high and low risk of cardiovascular abnormalities and also specific cardiovascular abnormalities in the newborn period and up to 1 year of age. The reviewers were, in addition, asked to consider – although not cover – the issue of antenatal diagnosis.

Cost-effectiveness modelling was specifically requested with assessment of the range of uncertainty associated with the results.

Following our initial literature review, we modified the research question posed in the commissioning brief by including pulse oximetry, evidence for which was published after the commissioning brief and tender had been issued. At an early stage in the review of outcomes we elected not to include the prevention of infective endocarditis as an outcome of newborn screening. For this to be plausible required that infective endocarditis would be the presenting feature in children or young adults with hitherto undiagnosed but not life-threatening or otherwise symptomatic congenital heart defects and that newborn screening would prevent this outcome by early presymptomatic detection. We could find no evidence in the literature or in discussion with cardiologists and other experts to suggest that this was a significant problem in the UK. Our research protocol is described below.

## Proposed study and interpretation of commissioning brief

### Study design
We proposed to conduct a systematic review with cost-effectiveness modelling together with two empirical studies: the first to determine parental and clinician utilities for different functional outcomes for children with congenital heart defects, and the second to explore parental perceptions of screening for congenital heart defects.

## Systematic review

We systematically reviewed published and unpublished literature to determine:

- the prevalence and natural history of the specific malformations that comprise congenital heart defects
- the predicted impact of antenatal screening for Down's syndrome and structural abnormalities of the fetus on birth prevalence of these malformations
- specific risk factors for these malformations which may be relevant to targeting high-risk groups within a screening programme
- the effectiveness of surgical and non-surgical treatment of these malformations in terms of survival to adult life
- the performance of clinical screening, pulse oximetry and echocardiography as screening tests for these disorders in the newborn period and later infancy
- the findings of previous economic analyses of screening for congenital heart defects
- the psychosocial effects on parents and families of congenital heart defects identified through screening or clinical presentation.

The review methods were based on those recommended for systematic reviews for health technology assessment.[261] The results of the reviews are presented in Chapters 2, 3, 4, 5 and 9 for the different parameters. The review was also used to identify probabilities for the parameters included in the decision model (Chapter 6).

## Developing a taxonomy for screening

We reviewed existing classification systems for congenital heart defects and their relevance for classification of defects according to the potential to benefit from newborn screening. We devised a screening classification for congenital heart defects and assessed it using data available from a large population-based register of congenital heart defects. This work is presented in Chapter 5.

## Developing a framework for decision-making

We assessed the effects, costs and cost-effectiveness of alternative newborn screening strategies by developing a probabilistic decision model. Specifically we characterised the screening strategies for evaluation, according to test, timing and target population, and developed defect-specific decision analytic models of management and treatment pathways. We identified and valued resource use and probability pathways to populate these decision analytic models and conducted incremental cost-effectiveness analyses of alternative screening strategies. We explored the effect of uncertainty in the values of the model parameters on the findings using a probabilistic decision analysis and examined the conclusions under a range of different scenarios. Finally, the value of further research to policy decisions was explored using expected value of information analysis. The methods and results of these analyses are presented in Chapters 6 and 7.

## Valuing quality of life in relation to congenital heart defects

Descriptions of the health states associated with each malformation considered in the model were derived in association with health professionals and from the literature review of outcomes. A convenience sample of health professionals caring for children with congenital heart defects and parents of a child with a congenital heart defect were asked to place a value on the health states using a visual analogue scale of the type used for the EuroQol EQ-5D. This is presented in Chapter 8.

## Incorporating parental perspectives

A systematic review of the literature relating to this aspect of screening was undertaken with emphasis on identifying parental perceptions in relation to different screening outcomes. A narrative review identified the main themes to emerge and any gaps in the literature. A focus group was arranged through Heartline allowing access to parents of affected infants who have and have not been diagnosed through screening. This was used to identify and explore issues of relevance to parents and their families. This is reported in Chapter 9.

# Chapter 5
# Defining the benefit of screening for specific congenital heart defects

**Chapter outline**

In this chapter, a method of grouping congenital heart defects with relevance to screening is developed, by considering the physiological and anatomical features of specific congenital heart defects and their associated predicted presymptomatic interval. This classification was evaluated with reference to a large population-based dataset and this confirmed the ability of the taxonomy to differentiate defects according to clinical features and timing of presentation. Taking into account clinical features, presymptomatic interval and prevalence, conditions were assigned to life-threatening, clinically significant or clinically non-significant categories. The potential benefits of newborn screening in each of these groups is described.

**Key messages**
- The heterogeneity of congenital heart defects presents particular problems for newborn screening as screening tests vary widely in their capacity to detect specific defects and no test can detect all defects equally well.
- Congenital heart defects can be classified by presymptomatic interval and natural history, allowing identification of defects with the greatest potential to benefit from newborn screening.
- **Life-threatening** congenital heart defects are structural cardiac malformations in which collapse is likely and this group comprises TGA, COA/IAA, AS, PA and HLH/MA.
- **Clinically significant** congenital heart defects are structural cardiac malformations which have effects on heart function but collapse is unlikely or the prevention of collapse is unlikely to be feasible. The most common defects in this group are VSD, CAVSD and ASD.
- **Clinically non-significant** defects are anatomically defined cardiac malformations which have no functional clinical significance and include the VSDs which are only detectable using echocardiography. These require no treatment.
- From this we propose the detection of **life-threatening** congenital heart defects with a view to preventing death and avoiding preoperative collapse as the primary objective of newborn screening for congenital heart defects.
- A secondary objective of newborn screening is the detection of **clinically significant** congenital heart defects.

## The objectives of newborn screening for congenital heart defects

In addressing the objectives of newborn screening for congenital heart defects, it is important to consider the recognised goals of screening: that there should be an effective treatment, an advantage (either increased survival or improved outcome) in giving the treatment earlier and a reliable screening test to detect the condition. Screening aims to identify early those infants who are at risk of adverse or irreversible outcomes as a consequence of congenital heart defects, whilst they are still presymptomatic, and then to manage or treat them in a way that prevents or reduces the complications of their condition. One of the first questions that arises, therefore, is whether there are specific structural heart defects that are of particular relevance to understanding how the maximum benefit from newborn population screening for congenital heart defects can be achieved.

Ideally, screening should comprise a single test that will detect the majority of defects. However, the heterogeneity of congenital heart defects presents particular problems for screening as currently known tests vary widely in their capacity to identify different individual defects and no test can identify all defects equally well.

A clinical examination, usually by a doctor, currently forms the basis of screening for congenital heart defects. This is a combination of four elements: inspection of an infant for cyanosis (blue colouring, particularly of the lips and digits), auscultation of the heart (listening for abnormal heart sounds or murmurs with a stethoscope), palpation of the femoral pulses (feeling the groin for decreased pulses) and checking an infant more generally for abnormalities that may indicate a clinical syndrome, such as Down's syndrome, which is commonly associated with congenital heart defects.

Although current practice is to screen for all congenital heart defects as a group using this routine newborn clinical examination, research from the Northern Region has shown that one-third of children become symptomatic before this is carried out.[6] Furthermore, the Northern Region study demonstrates that with routine screening, up to 65% of those with congenital heart defects are

not picked up and remain undiagnosed at 6–8 weeks. A series of different screening tests might in fact be indicated for the detection of some congenital heart defects.

In the specific context of screening for heart defects, it is also unlikely that there is a single time-point after birth that can be applied to screen for all defects. If screening took place in the delivery room, some problems would not be discernible because the ductus is still wide open, yet if the screening is scheduled for any time-point after this, a proportion of infants will already have become dangerously ill. The benefit of early detection in the more stable patient group is questionable, whereas for infants at risk of early clinical deterioration a well-timed screening test should be of particular benefit. There is therefore a group of infants with specific congenital heart defects that are likely to gain maximum benefit from newborn screening and it is important to define this group carefully.

## Development of a screening classification system for congenital heart defects

The purpose of developing a screening classification system for congenital heart defects is to highlight the individual defects for which the population benefit from newborn screening is potentially the greatest. These defects should be the primary target of a screening programme. The screening tests used and the timing of screening should reflect the presentation and natural history of these defects. Previous classification systems for congenital heart defects are outlined in Chapter 2 but none of these have been designed to inform newborn screening. A first task in this review was to develop a classification system for congenital heart defects from a screening perspective.

In developing this new classification system for screening, malformations were grouped according to two different criteria: the **physiological and anatomical features** of the malformation and the timing of presentation after birth (**presymptomatic interval**). This classification is useful in presenting the range of diagnoses by lead time (defined as "the time gained in treating or controlling a disease when detection is earlier than normal, for example, in the presymptomatic stage"[1]) and also by likely clinical presentation and complications.

After considering the wide variety of taxonomies currently in use, we included within our classification system the recognised diagnostic naming categories that are common in clinical practice and also mapped these on to the diagnostic and procedure-based coding systems used in the UK, for example, the ICD,[54] BPA,[55] OPCS[60] and Read coding systems.[56] It is important to be able to translate between different congenital heart defect taxonomies in order to compare data from different studies and to utilise routine data sources to inform clinical practice, as was demonstrated clearly by the Bristol Royal Infirmary Inquiry.[61,262]

### Physiological and anatomical features

In addition to focusing on presymptomatic interval, we proposed grouping defects into six groups (A–F) within this classification system. Each group corresponds to the major anatomical point at which the normal flow of blood through the heart, lungs and body has been disrupted and this is indicated on the diagram in *Figure 20*. The congenital heart defects in each of these groups share common symptoms and signs caused by the disruption in blood flow at this point. In Group A, the femoral pulses will be decreased or delayed once the ductus closes and a murmur or cyanosis will be found in some but not all cases. In Group B, the predominant sign is cyanosis, which may or may not be accompanied by a murmur. In Group C, low pulmonary blood flow will lead to cyanosis, or cyanotic spells in less severe defects, and a murmur may be audible in some cases. In Group D, cyanosis is present in the severe cases only, such as obstructed total anomalous pulmonary venous connection. A murmur may not be present, particularly in the less critical cases. In Group E, there is unrestricted mixing of oxygenated and deoxygenated blood but cyanosis will be mild and sometimes undetectable by the eye. Neither murmurs nor decreased pulses are found, but the hyperdynamic circulation eventually leads to breathlessness and sweating. In Group F, a murmur will be heard in the majority of cases arising from the shunting of blood from the left to right heart across a septal or similar defect. In all groups, a baby with a significant structural malformation resulting in cardiac failure will feed poorly and be breathless, but often not before an infant reaches several weeks of age.

### Rationale for differentiating by presymptomatic interval

Some malformations are likely to present with severe symptoms or collapse before a screening test can identify them, whereas others, with a longer presymptomatic interval, may be detected by screening before any clinical deterioration. This

**D**

**GROUP D**: Pulmonary venous hypertension – *High left atrial pressure.*

*Leads to:*
Poor feeding and breathlessness
Murmur
Pulmonary vascular obstructive disease

**LEFT ATRIUM**

**LEFT VENTRICLE**

**A**

**GROUP A**: Systemic ventricle outflow obstruction – *Obstruction to the flow of blood exiting the left ventricle into the aorta.*

*Common symptoms and signs:*
Poor feeding and breathlessness
Poor pulses
Congestive heart failure
Arrhythmias and sudden death
Infective endocarditis

**B**

**GROUP B**: Transposition streaming – *Cyanosis due to deoxygenated and oxygenated blood being pumped through the wrong circuits.*

*Leads to:*
Poor feeding
Cyanosis
Murmur
Pulmonary vascular obstructive disease

**E**

**GROUP E**: Mixing with unrestricted pulmonary blood flow – *Mild cyanosis and progressive breathlessness as pulmonary vascular resistance falls.*

*Leads to:*
Poor feeding and breathlessness
Failure to thrive
Cyanosis
Congestive heart failure
Pulmonary vascular obstructive disease

**F**

**GROUP F**: Left to right shunt – *Progressive breathlessness as pulmonary vascular resistance falls but no cyanosis.*

*Leads to:*
Poor feeding and breathlessness
Murmur
Congestive heart failure
Pulmonary vascular obstructive disease
Infective endocarditis
Chest infections
Failure to thrive

**LUNGS**

**BODY**

**RIGHT ATRIUM**

**RIGHT VENTRICLE**

**C**

**GROUP C**: Low pulmonary blood flow – *Obstruction of blood flow exiting the right ventricle into the pulmonary artery.*

*Leads to:*
Murmur
Mild cyanosis (spells)
Progressive cyanosis

*FIGURE 20  Screening classification for congenital heart defects*

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| | GROUP A | GROUP B | GROUP C | GROUP D | GROUP E | GROUP F |
|---|---|---|---|---|---|---|
| **PHYSIOLOGY** | Systemic ventricle outflow obstruction | Unfavourable streaming (transposition-streaming) | Low pulmonary blood flow | Pulmonary venous hypertension | Mixing with unrestricted pulmonary blood flow | Left to right shunt |
| **CONGENITAL HEART DEFECTS with SHORT PRESYMPTOMATIC INTERVALS** | Hypoplastic left heart syndrome<br>Critical aortic stenosis<br>Interrupted aortic arch<br>Tight coarctation of the aorta | Transposition of the great arteries (duct-dependent)<br>Transposition of the great arteries + small atrial septal defect<br>Transposition of the great arteries + ventricular septal defect<br>Double outlet right ventricle (transposition type) | Pulmonary atresia + intact ventricular septum<br>Pulmonary atresia + ventricular septal defect<br>Critical pulmonary stenosis<br>Severe tetralogy of Fallot<br>DORV + pulmonary stenosis<br>Univentricular heart + tricuspid atresia + pulmonary atresia<br>Severe Ebstein's anomaly<br>Congenitally corrected transposition of the great arteries + pulmonary stenosis/atresia + ventricular septal defect | Obstructed total anomalous pulmonary venous connection<br>Critical mitral stenosis<br>Severe cor triatriatum | Unlikely to present during this period | Unlikely to present during this period |
| **CONGENITAL HEART DEFECTS with MODERATE PRESYMPTOMATIC INTERVALS** | Coarctation of the aorta<br>Moderate aortic stenosis | Transposition of the great arteries with large ventricular septal defect<br>Double outlet right ventricle (Taussig–Bing type) | Tetralogy of Fallot<br>Severe pulmonary stenosis<br>Pulmonary infundibular stenosis+ ventricular septal defect<br>Absent pulmonary valve<br>Ebstein's anomaly<br>Congenitally corrected transposition of the great arteries + ventricular septal defect + pulmonary stenosis | Mild/moderate mitral stenosis<br>Mitral regurgitation<br>Cor triatriatum | Unobstructed total anomalous pulmonary venous connection<br>Univentricular heart with unrestricted pulmonary flow<br>Truncus arteriosus | Large ventricular septal defect<br>Double outlet right ventricle with subaortic ventricular septal defect<br>Atrioventricular septal defect or common atrium<br>Aortopulmonary window<br>Large patent ductus arteriosus<br>Congenitally corrected transposition of the great arteries + tricuspid regurgitation + ventricular septal defect |

*FIGURE 20 Screening classification for congenital heart defects (cont'd)*

| | GROUP A | GROUP B | GROUP C | GROUP D | GROUP E | GROUP F |
|---|---|---|---|---|---|---|
| CONGENITAL HEART DEFECTS which **OFTEN REMAIN ASYMPTOMATIC THROUGHOUT CHILDHOOD** | Moderate or mild aortic stenosis<br><br>Subvalvular aortic stenosis<br><br>Supravalvular aortic stenosis<br><br>Bicuspid aortic valve<br><br>Moderate or mild coarctation of the aorta | Unlikely to present during this period | Moderate pulmonary stenosis<br><br>Pulmonary valve insufficiency<br><br>Congenitally corrected transposition of the great arteries | Mitral valve disease | Unlikely to present during this period | Atrial septal defect<br><br>Small ventricular septal defect<br><br>Small patent ductus arteriosus<br><br>Patent foramen ovale<br><br>Partial anomalous pulmonary venous connection |

**FIGURE 20** *Screening classification for congenital heart defects (cont'd)*

classification system aims to differentiate between three categories of cardiac malformations with reference to the **presymptomatic interval**. A presymptomatic interval (often referred to as a 'detectable preclinical phase') is essential for screening: without this there is no opportunity to advance diagnosis, and hence management, through early detection. This initial classification serves to identify those defects which might be amenable to detection through screening after birth. We have grouped congenital heart defects into three categories defined by the duration of the presymptomatic interval:

- **Short presymptomatic interval**: congenital heart defects which have a short interval between birth and presentation, that is, these defects are likely to present with life-threatening symptoms or signs in the first week after birth (many are 'duct-dependent' lesions which present as the ductus arteriosus closes).
- **Moderate presymptomatic interval**: congenital heart defects which will present with symptoms or signs after a longer interval, that is, after the first week of life but within the first year of life.
- **Often remain asymptomatic during childhood**: congenital heart defects which may present with symptoms or signs between the ages of 1 and 16 years, but which more often remain asymptomatic throughout childhood (until about 16 years old) and present later with complications, that is, the presymptomatic interval is very long.

## Timing of the screening test

The natural history of specific heart defects depends on the spectrum of severity usually associated with that defect and varies from the more severe (e.g. tight COA or critical valve stenoses) which present early, to the less severe (e.g. mild COA or valve stenoses). The timing of the first test should allow the identification of infants who might become rapidly unwell before discharge from the maternity unit, that is, infants with defects associated with a short presymptomatic interval in Groups A–D.

Screening also has different objectives and considerations depending on the presymptomatic interval. Within the group of diagnoses with a short presymptomatic interval, a significant proportion of children are likely to present within the first week of life with life-threatening symptoms. Although they are likely to be small in actual numbers, they represent a group in which death or collapse may be avoided through earlier detection. This group can be further subdivided

into: (1) defects which **present so rapidly after birth (within 12–24 hours)** that a programme of newborn screening may not have any impact and (2) defects which **may not become symptomatic until after discharge** but which can cause collapse requiring readmission with **serious problems in the first week of life**. The role of antenatal screening should be considered for the former, whereas the latter are potentially amenable to detection by newborn screening before discharge from hospital.

The benefits of newborn screening for congenital heart defects with a **short presymptomatic interval** would be the:

- avoidance of collapse, shock or critical cyanosis, with associated risk of death or hypoxic insult, leading to longer term neurological or renal sequelae
- early diagnosis, to allow timely and prompt access to appropriate surgical or medical management
- reduction of perioperative morbidity and mortality through early identification of congenital heart defects before any clinical deterioration has occurred.

The moderate presymptomatic interval includes defects which usually present after the first week and up to the first year of life.

Within the group of diagnoses with a **moderate presymptomatic interval**, the benefits of screening would be the avoidance of:

- deaths due to congenital heart defects (about 30% of infants with cardiac malformations who die do so undiagnosed in the first year of life)[14]
- complications of heart defects, such as failure to thrive, feeding difficulties, breathlessness and repeated chest infections
- PVOD in adult life, in those defects with increased pulmonary blood flow or pulmonary venous hypertension
- admissions to intensive care units, for example, with bronchiolitis, by initiating definitive management earlier in children with congenital heart defects.

The timing of a screening test will be influenced by age at discharge from maternity hospital, as, in the UK, the majority of births take place in hospital. Department of Health statistics show that the average length of stay in hospital after delivery is <4 days for 75% of women.[263] More importantly, 10% of women leave hospital on the

same day as they give birth and 27% leave on the next day.

## Validation of the congenital heart defect classification system using Northern Region data

### Objective

In order to validate the assumptions made in assigning defects to groups by presymptomatic interval within this classification system, we examined with respect to a presymptomatic interval of specific defects a population dataset of children born with congenital heart defects in the Northern Region.

The Northern Region study population used for this validation was derived from the former Northern Health Region (Cumbria, Northumberland, Tyne and Wear, Durham and Cleveland), which has a population of ~3.1 million. All infants with suspected heart disease in 15 of the 16 districts are referred to a single centralised paediatric cardiology centre at Freeman Hospital, Newcastle upon Tyne. The dataset comprised 1590 children in the Northern Region Paediatric Cardiology database, who were born between 1987 and 1994. During this period, a routine newborn clinical examination was the only newborn screening method used for identifying congenital heart defects.

Information about children with congenital heart defects is collected in a comprehensive regional dataset, which is able to capture and to link all births and deaths with congenital heart defects in the region. It is derived from three main sources:

1. The **Paediatric Cardiology Database**, established in 1990 and held at Freeman Hospital, which prospectively registers all congenital heart defects. Children born between 1985 and 1989 were ascertained retrospectively but ascertainment is believed to be complete for all significant and complex heart disease. All diagnoses are confirmed by a paediatric cardiologist.
2. The **Northern Regional Survey of Perinatal, Late Neonatal and Infant Mortality** allowed infants with cardiovascular malformations, who die before a cardiological diagnosis is made, to be identified.
3. The **Northern Regional Congenital Abnormality Survey**, set up by local clinicians in 1985, is a register of all pregnancies to mothers resident in the Northern Region where

a significant physical abnormality is suspected before birth, and those where an abnormality is identified after birth.

Within the Northern Region, each child is given a primary diagnosis from a hierarchical list of congenital heart defects. They may also be assigned a secondary diagnosis when a second defect also exists. Each defect is also categorised by severity into complex (including atresia or severe hypoplasia of a heart chamber or valve, or a common inlet/outlet valve), significant (with four chambers and four valves but requiring intervention) or minor (not requiring intervention).[4] The classification system used in the Northern Region was mapped on to the screening classification described in this chapter.

### Methods

We calculated the age at diagnosis in weeks and compared the median and interquartile ranges with the grouping used in the new classification system.

The Paediatric Cardiology Database records the date of birth and the date on which the child was first examined, and the diagnosis of a congenital heart defect was confirmed by a paediatric cardiologist. However, symptoms may have been present clinically before this. For the period from 1987 to 1994 only, the database also recorded the date on which a heart defect was first suspected (this could be date of referral to a paediatric cardiologist or a reference in the case notes to a probable cardiac diagnosis).

We tested our assumption that age at diagnosis could be used as a proxy for age at presentation by comparing the interval between the date a heart defect was suspected and the date it was diagnosed for children who had both dates recorded. We found that this interval varied widely, from 0 to 362 days, with 16% having both the suspected heart defect and diagnosis recorded on the same day. However, the length of time between suspecting a heart defect and confirming diagnosis reflected the severity of the malformation, and was greater for milder defects; for example, the proportion of children with ASD, VSD and PDA who were diagnosed on the day of suspecting the defect was 4, 6 and 6%, respectively, compared with 46, 59 and 56% for PA, HLH and TGA.

This suggests that using the age at diagnosis to estimate the end of the presymptomatic interval is more accurate for severe congenital heart defects

with a short presymptomatic interval. For the purposes of this validation, we assumed that the time between presentation and diagnosis was short and could be discounted for defects in the short and moderate presymptomatic interval groups. Any overestimate of the length of the presymptomatic interval will be greater for defects that are not life threatening and present in later infancy or childhood.

## Results of the validation

*Table 8* shows the median age (and interquartile range) at diagnosis for 17 congenital heart defects.

Within the Northern Region dataset, the five diagnostic groups which present at the earliest age are TGA, pulmonary valve atresia (PVA) with IVS, HLH, PVA with VSD and IAA, which all have a median age at diagnosis within the first week of life. The majority of infants with TGA or PVA with IVS are diagnosed within 24 hours of birth and 75% of these cases are diagnosed within the first week after birth.

At least one-quarter of cases of truncus, UVH, TOF and COA of the aorta are diagnosed within the first week of life, but the median presymptomatic interval is longer, between 1 and 2 weeks, for these congenital heart defects.

The median presymptomatic interval is >4 weeks for the remaining heart malformations in *Table 8*. For certain malformations, such as TAPVC, CAVSD and AS, 25% of cases are diagnosed within the first 14 days of life, reflecting the wide range of severity found in these malformations.

Congenital heart defects that present in the first week of life have a short presymptomatic interval and should fall into Groups A–D in the classification. This is largely borne out by the data from the Northern Region, with the exception of truncus and CAVSD in Groups E and F, respectively, which can have a short presymptomatic interval although the median presymptomatic interval is >7 days after birth.

**TABLE 8** *Northern Region: median age at diagnosis*

| Predicted age at diagnosis | Group | Diagnosis | Number (%) | Actual median age at confirmed diagnosis | | Interquartile range (weeks) |
|---|---|---|---|---|---|---|
| | | | | **Weeks** | **Days** | |
| *Short presymptomatic interval* | | | | | | |
| Within 24 hours | B | TGA | 84 (5.3) | 0.1 | <1 | 0.00–0.35 |
| | C | PA + IVS | 24 (1.5) | 0.1 | <1 | 0.10–0.50 |
| From 1–7 days | A | HLH | 46 (2.9) | 0.3 | 2 | 0.10–0.60 |
| | C | PA + VSD | 48 (3.0) | 0.3 | 2 | 0.10–2.00 |
| | A | IAA | 24 (1.5) | 0.6 | 4 | 0.30–1.20 |
| *Moderate presymptomatic interval* | | | | | | |
| From 1 to 2 weeks | E | Truncus | 24 (1.5) | 1.1 | 8 | 0.40–5.50 |
| | C/D | UVH[a] | 31 (2.0) | 1.4 | 10 | 0.40–7.20 |
| | C | TOF | 98 (6.2) | 1.5 | 11 | 0.60–6.90 |
| | A | COA | 106 (6.7) | 2.0 | 14 | 1.00–7.40 |
| After 2 weeks | D/E | TAPVC | 27 (1.7) | 4.3 | – | 1.60–15.0 |
| | F | CAVSD | 81 (5.1) | 4.6 | – | 0.70–9.90 |
| | F | VSD | 590[b] (37.1) | 7.4 | – | 2.30–14.0 |
| | A | AS | 56 (3.5) | 8.0 | – | 0.50–16.0 |
| | C | PS | 126 (7.9) | 10.0 | – | 2.40–25.0 |
| | F | Secundum ASD | 54 (3.4) | 14.0 | – | 3.00–31.00 |
| | F | PDA | 82 (5.1) | 15.0 | – | 5.00–35.00 |
| | F | Primum ASD | 17 (1.1) | 20.0 | – | 5.30–27.00 |
| | | Other[c] | 72 (4.5) | – | – | – |
| | | Total | 1590 (100.0) | – | – | – |

[a] UVH includes MA, tricuspid atresia and single ventricle malformations.
[b] No data available for two children.
[c] Other = all other congenital heart defects.
Data taken from Northern Region database (*n* = 1590).[6]

Congenital heart defects in the moderate presymptomatic interval category have a median age at diagnosis ranging from 1 week to 6 months. For some congenital heart defects, the age at diagnosis is distributed widely across the first year of life and these defects appear in both the short presymptomatic interval and moderate presymptomatic interval categories of the taxonomy, indicating that there are both severe and milder forms of the malformation (e.g. AS, pulmonary valve stenosis (PS) and COA). Within Group F, the median time to diagnosis for most conditions is 7 weeks or more after birth (with the exception of CAVSD).

The graphs in *Figure 21* show the cumulative frequency of diagnosis by age at diagnosis over the first year of life for the defects in each group of the taxonomy (for additional graphs see Appendix 5). From these graphs, it is possible to consider the potential for detection by screening at different times after birth for each group of diagnoses.

## Prevalence of congenital heart defects in each group

In *Table 9* (extended table in Appendix 6), we also looked at the prevalence of conditions in each of the six groups of the screening classification in the Northern Region dataset and compared this with two other epidemiological studies of congenital heart defects at live birth. These are estimates only as some congenital heart defects cannot be mapped into the screening classification, particularly for Groups D and E.

In terms of UK prevalence, the most important group of diagnoses is Group F, including VSD, ASD, PDA (not preterm) and CAVSD, which make up around half of all cases of congenital heart disease per 1000 births. The largest diagnostic category is VSD, of which a proportion will be clinically insignificant or spontaneously resolving.

The results from the three studies are very similar, demonstrating that over half of all congenital heart defects are represented in Group F, the remainder being found predominantly in Groups A and C. As conditions from Groups A and C have a short presymptomatic interval and higher mortality, they contribute significantly to the burden of disease.

## Discussion

The findings of this comparison of our proposed congenital heart defects taxonomy with the Northern Region dataset suggest that the

classification system is robust with regard to presymptomatic interval and can be used as a basis for determining the timing for different types of screening tests in the newborn period. Although this dataset is from a 'screened' population who received a newborn examination, there are no comparable UK data on 'unscreened' populations and so this dataset provides us with the best available baseline from which to consider which congenital cardiac defects present early in infancy. We could not, with this validation, verify the assumptions made in assigning malformations to anatomical and physiological groups, nor did the data available allow us to investigate whether the majority of children within a specific diagnostic group would be detected by a single screening test or had similar presenting symptoms.

In this study, all the congenital heart defects which had a median age at diagnosis of <1 week could be found in those included in the short presymptomatic interval category of the proposed congenital heart defects screening taxonomy classification. It is notable that up to 25% of children with CAVSD in the Northern Region were diagnosed within the first week of life and this is likely to be due to its strong association with Down's syndrome. One-quarter of cases of truncus were also diagnosed within the first week of life. This is a much rarer defect and likely to be diagnosed owing to breathlessness or associated syndromes.

Certain diagnoses present throughout the first year of life, for example AS and TAPVC, reflecting the fact that these are a group of diagnoses of very variable physiological severity. Defects included in Group F have a median age of diagnosis of >6 weeks from birth. By 8 weeks after birth, 75% of the most clinically important diagnoses have been made in the Northern Region (TGA, PVA, HLH, IAA, truncus, UVH, TOF, COA). This suggests that the 6–8-week examination may identify diagnoses, such as the majority of those in Group F, that are not likely to collapse and may be stable.

## Prediction of potential for detection according to type of screening test

The newborn clinical examination, currently used to screen for congenital heart defects, is likely to detect some cases with murmurs in each of the Groups A, B, C, D and F, some cases of decreased femoral pulses in Group A and cases with more
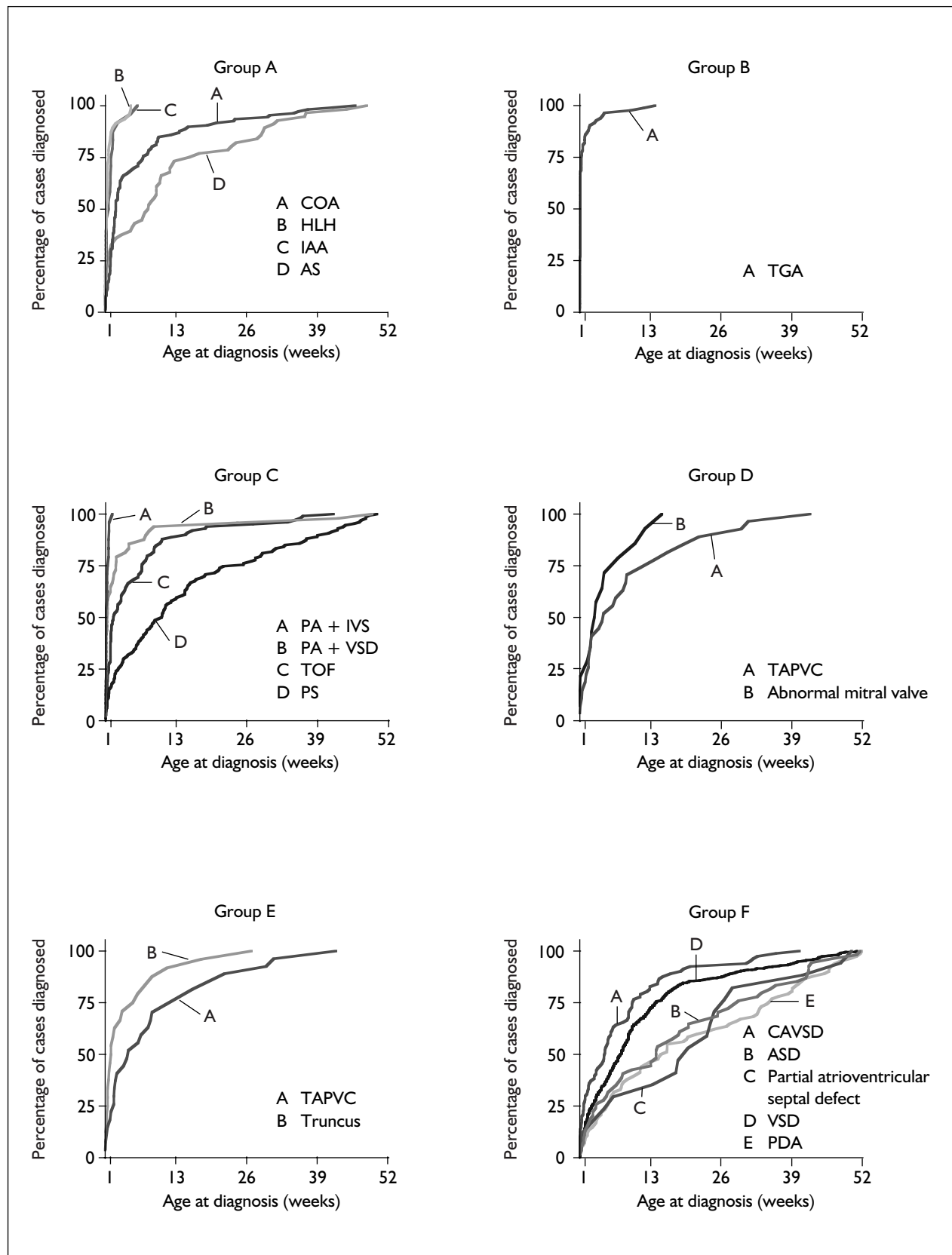
**FIGURE 21** *The cumulative proportion of each group of congenital heart defects with a confirmed diagnosis by age at diagnosis during the first year of life. TAPVC appears twice in these graphs as it cannot be attributed to a single group using the Northern Region diagnostic categories.*

**TABLE 9** *Prevalence of congenital heart defects: comparison of the six groups*

|  | Group A | Group B | Group C | Group D | Group E | Group F |
|---|---|---|---|---|---|---|
| Northern Region 1985–97[4]<br>4% unclassifiable | 0.58/1000<br>(10%) | 0.30/1000<br>(5%) | 1.19/1000<br>(21%) | 0.09/1000<br>(2%) | 0.09/1000<br>(2%) | 3.24/1000<br>(58%) |
| Merseyside 1979–88[264]<br>8% unclassifiable | 1/1000<br>(16%) | 0.3/1000<br>(5%) | 1.4/1000<br>(22%) | 0.2/1000<br>(3%) | 0.06/1000<br>(1%) | 3.4/1000<br>(53%) |
| Baltimore–Washington Infant Study 1981–82[265]<br>10% unclassifiable | 0.6/1000<br>(18%) | 0.2/1000<br>(6%) | 0.64/1000<br>(19%) | 0.1/1000<br>(3%) | 0.06/1000<br>(2%) | 1.7/1000<br>(51%) |

marked cyanosis in Groups A–D. Less severe defects may have very audible murmurs (for example, in Groups D and F) and so the clinical examination detects a mix of severe, life-threatening and milder, well-tolerated defects.

Pulse oximetry detects the presence of cyanosis, which may not always be apparent on clinical inspection. For cyanosis to be discerned by the unfamiliar eye, oxygen saturations have to be below about 80%; many cyanotic heart defects show levels above this at some stage in their course. Pulse oximetry may therefore detect the severe defects from Groups B, C and D and some severe cases in Group A, but conversely will not detect defects in Groups E or F.

A screening echocardiogram is likely to be performed by a technician, rather than an experienced cardiologist. If the pattern of detection of the corresponding antenatal echocardiography screening programme (at 18–20 weeks gestation) is reflected postnatally, we would expect that 'four chamber defects' (within the heart) are most likely to be detected, whereas some 'outlet defects' (defects in the blood vessels leaving the heart) are more likely to go undetected. Therefore we would expect newborn screening echocardiography to be effective at detecting HLH (Group A), UVH and TOF (Group C), MS and cor triatriatum (Group D). The septal defects in Group F, even if small, will be detected by Doppler flow technology used with echocardiography if there is blood flow across the defect. However, many of these septal defects, particularly VSDs, have no functional or clinical significance and will spontaneously resolve as discussed previously in Chapter 2. Cases involving outlet defects – TGA (Group B) and especially COA or IAA (Group A) – are less likely to be found on screening echocardiography and detection is also more dependent on the skill of the operator.[266,267]

The limitations of different screening strategies, regardless of presymptomatic interval, are related to the performance of currently available tests: clinical examination, pulse oximetry, and cardiac echocardiography.

- A test that identifies specific physiological characteristics (e.g. pulse oximetry for cyanosis) will not identify children with a heart defect unassociated with cyanosis. There is a risk of falsely reassuring parents that their child does not have a congenital heart defect. Furthermore, a test to identify cyanosis is not specific for congenital heart defects and will identify other causes of hypoxaemia, which has implications for further follow-up investigations for the children identified.
- A test which is targeted at an anatomical or structural diagnosis (e.g. echocardiography) will identify mild or clinically unimportant (e.g. spontaneously resolving) defects but long-term follow-up is still required for these 'false positives'.

Therefore, different screening tests will differentially identify congenital heart defects and will not always identify infants with the most severe and life-threatening defects. Our proposed classification system groups by symptoms and signs allowing the success of different screening tests in detecting specific malformations to be more easily predicted and assessed.

## Defining the benefit of newborn screening for specific congenital heart defects

In defining the specific congenital heart defects which might benefit from screening, we utilised our taxonomy to consider severity and prevalence, which reflect the burden of disease and also the

potential for detection and treatment in the
newborn period.

## Severity

The major benefit of earlier detection of
congenital heart defects lies in preventing death
or collapse before surgery. Therefore, the defects
that should be targeted by any screening strategy
are those that present with rapid, life-threatening
collapse within the first week of life. HLH, TGA,
PA and IAA were demonstrated to be the four
defects that presented rapidly in the first week of
life. In addition, there were six further defects for
which at least one-quarter of cases were diagnosed
in the first week of life: truncus, UVH, TOF, COA,
CAVSD and AS. Although all these malformations
have a short interval before presentation, few will
present with life-threatening collapse. TOF and
CAVSD can be tolerated in the majority of cases
without collapse and surgical correction can be
performed electively.

TAPVC is an additional congenital heart defect
which has an obstructed (severe) form that
presents early in newborn life with collapse.
However, in the Northern Region dataset all
TAPVC was grouped together and it was not
possible to identify this form separately. Similarly,
AS has a wide range of severity but the cut-off
between severe and moderate disease is difficult to
define prospectively so it is considered as a group.
Therefore, the following congenital heart defects
should be considered to have the greatest
potential for collapse in the newborn period:
HLH, TGA, PA, IAA, COA, AS and TAPVC.

## Prevalence

However, a further consideration for a population-
based screening programme is the prevalence of
specific congenital heart defects. The most
prevalent congenital heart defects with the
potential for early collapse are COA, TGA, PA, AS
and HLH. IAA can be considered to be within the
spectrum of COA and these defects may therefore
be combined. MA is a rare type of UVH and can
also be considered to be a severe form of HLH.
Owing to the very low prevalence MA, it was
considered along with HLH. Truncus is also rare
but is not clearly linked to any other major heart
defect, and it was therefore considered part of a
group of miscellaneous rare defects, some of which
can be severe, but which have low prevalence.

## Life-threatening congenital heart defects

Hence we defined six congenital heart defects
which were most likely to benefit from early

detection and therefore should be the focus of an
evaluation of newborn screening: COA/IAA, TGA,
PA, AS and HLH/MA. For the purposes of
screening, we have defined these six defects as
**'life-threatening congenital heart defects'**. These,
and the further groupings described below, are
defined in *Table 10*.

A significant proportion of these defects present
within the first week of life, so newborn screening
should be initiated within the first few days of life
and preferably before discharge from hospital.
These defects also fall within the Groups A–D in
our screening taxonomy, and so may be expected
to present with signs of cyanosis, murmur and
decreased femoral pulses, which would suggest
that screening strategies such as clinical
examination and pulse oximetry, and also
echocardiography, all of which have the potential
to detect these signs to a greater or lesser extent,
may be effective. We defined detection of life-
threatening congenital heart defects as the
primary outcome of screening in our model (see
Chapter 6).

## Clinically significant congenital heart defects

However, in addition to these life-threatening
congenital heart defects, there are other serious
congenital heart defects for which long-term
outcomes are unlikely to be improved by early
detection, either because collapse is unlikely, or its
prevention is not feasible because the screening
protocol may operate too late to avert the
collapse. For some, prevalence is such that the
population impact from screening would be
minimal. Early diagnosis of clinically significant
defects may be considered as desirable by some
health professionals and parent support groups.
Arguments for the benefit of earlier diagnosis
include earlier planning of clinical care and
management and reduction in the morbidity (for
example, failure to thrive, heart failure) associated
with some defects. We have defined these defects
as **'clinically significant congenital heart defects'**
in the model. They are found in the short and
moderate presymptomatic interval and
asymptomatic (in childhood) categories in our
screening taxonomy. We defined detection of
clinically significant congenital heart defects as a
secondary outcome in our model (See Chapter 6).

In *Figure 22*, the cumulative percentage diagnosed
by age at diagnosis is compared for these two
groups of congenital heart defects, life-threatening
defects and clinically significant defects, using the
data from the Northern region described earlier.

**TABLE 10** *Terms used to differentiate between types of congenital heart defects for screening*

| Term used | Description | Specific malformations | Screening classification category |
|---|---|---|---|
| Life-threatening congenital heart defects | Structural cardiac malformations in which collapse is likely. Prevention of collapse before definitive management (surgery) is thought to decrease the risk of mortality and long-term morbidity (e.g. disability) | E.g. TGA, COA/IAA, AS, HLH/MA, TAPVC, PVA | Short or moderate presymptomatic interval |
| Clinically significant congenital heart defects | Structural cardiac malformations in which collapse is unlikely or prevention of collapse before definitive management is either **not** thought to affect long-term morbidity (e.g. disability) or not considered to be feasible | E.g. TOF, CAVSD, VSD, ASD, PDA (not preterm) | Short or moderate presymptomatic interval or asymptomatic |
| Clinically non-significant congenital heart defects | Anatomically defined cardiac malformations which have no functional clinical significance and may resolve spontaneously. These require no treatment. Increased numbers of these are detected by echocardiography | E.g. spontaneously resolving or small VSDs and ASDs, PDA (not preterm), very mild PS | Asymptomatic |
| No congenital heart defect | No structural abnormality of the heart | None | Not included |
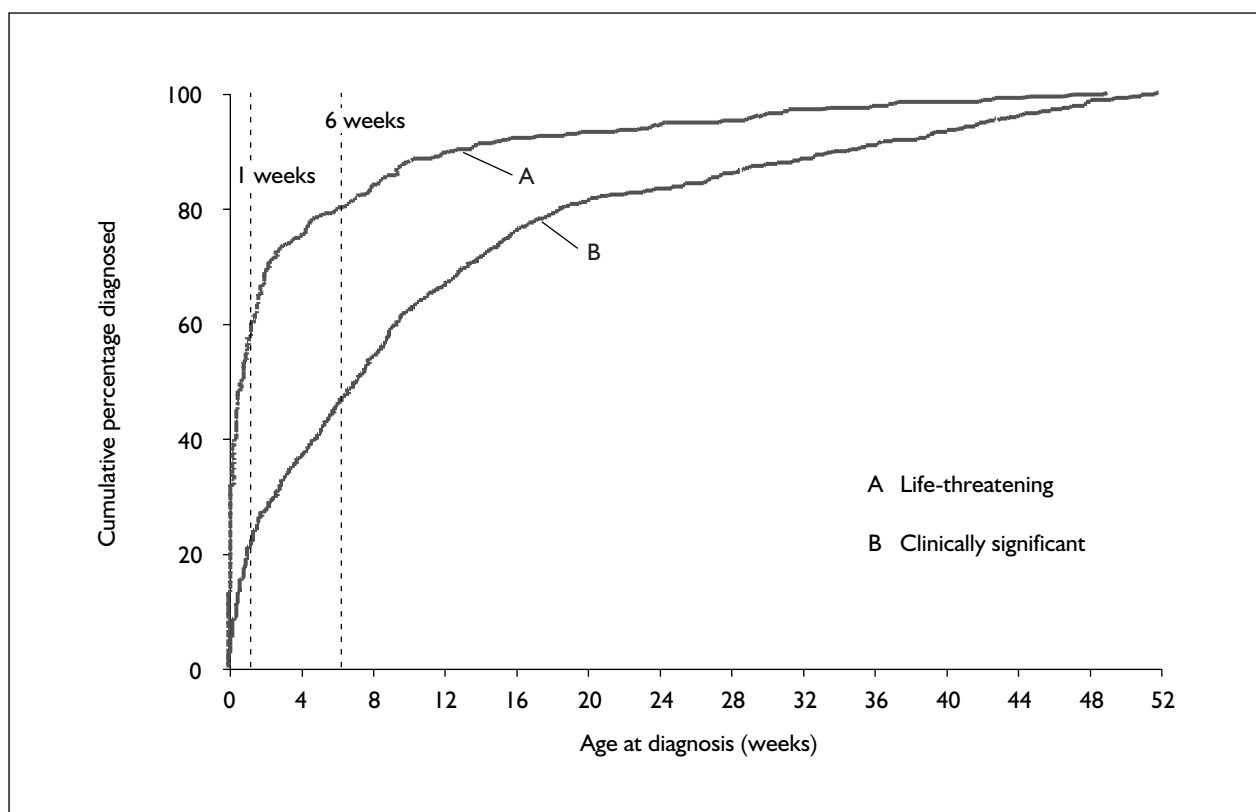


**FIGURE 22** *The proportion of life-threatening and clinically significant congenital heart defects with a confirmed diagnosis by age at diagnosis during the first year of life*

It can be seen that 50% of life-threatening defects are diagnosed in the first week of life, whereas only 20% of the clinically significant congenital heart defects are diagnosed by this age. By the time of the current 6-week clinical examination, only 20% of life-threatening congenital heart defects remain undiagnosed.

## Clinically non-significant congenital heart defects

There remain some congenital heart defects that are not covered in the above two categories but which are relatively prevalent. These include spontaneously resolving or small VSDs and ASDs, PDA (not preterm) and very mild PS, which have no functional effects but are anatomically present. These defects are observed if echocardiography is performed and would otherwise not be diagnosed or give rise to clinical manifestations at any age. These defects are called **'clinically non-significant congenital heart defects'** in the model and are only found in the 'often remain asymptomatic during childhood' category of our screening taxonomy. We did not consider detection of these defects to be an objective of newborn screening. However, they have 'costs' for parents and health professionals if they are detected, as current clinical practice is to undertake clinical tests and medical follow-up over a number of months or years to observe and confirm resolution of the heart defect. Although this practice is on the one hand reassuring to parents and clinicians, it may also lead to overprotection of the child whose heart is then considered to be mildly abnormal.

## No congenital heart defects

Infants with no anatomical heart abnormality, that is, with normal hearts, are included in the group defined as **'no congenital heart defect'** in the model. By definition, they are not included in the screening classification. These conditions are defined in *Table 10*.

# Chapter 6
# Developing a decision model

**Chapter outline**

In this chapter, we report the methods used to develop the decision model. The screening strategies and outcomes of the model are described together with the model structure. Deterministic and probabilistic analytic methods are described together with the model outputs of test performance, effectiveness, costs, cost-effectiveness ratios and cost-effectiveness acceptability curves. Model inputs are characterised and the search and review strategies used to identify relevant sources of data for the model are discussed. Parameter values for the prevalence of congenital heart defects, probabilities for the model and approaches to assigning distributions to the various probabilities are presented. The chapter concludes with a discussion of the methods used for the expected value of information analysis.

**Key messages**
- The three screening strategies compared in the model are clinical examination alone, pulse oximetry with clinical examination and screening echocardiography with clinical examination.
- The primary outcome of the model is 'timely diagnosis', that is, a diagnosis made preoperatively before collapse or death occurs, of six life-threatening congenital heart defects: COA/IAA, AS, TGA, HLH/MA, TAPVC and PA.
- The secondary outcome is the diagnosis of clinically significant congenital heart defects, including those defined in the primary outcome.
- The model was programmed so that, for each screening strategy, there was a pathway for infants with each type of life-threatening congenital heart defect or no heart defect.
- Probabilities for the model parameters were obtained from published literature, unpublished datasets and subjective probabilities derived from expert opinion.
- The model was based on 100,000 live-born infants entering the screening pathway. The base case analysis assumed that the antenatal detection rate for specific congenital heart defects from the Northern Region applied, that newborn screening was performed at 24 hours of age and that the primary outcome was used.
- Alternative screening scenarios explored in a sensitivity analysis were that the antenatal detection rate was double the national rate, the timing of the newborn screen was at birth or at 48 hours of age, echocardiography with clinical examination detected all congenital heart defects, no collapse occurred between the screening test and the start of treatment and the coverage of echocardiography with clinical examination was the same as for other screening strategies.

## Introduction

We developed a decision analytic model to assess the cost-effectiveness of alternative screening strategies for congenital heart defects relevant to the UK.

The following sections provide details on the structure of the model, the key assumptions and data sources used to populate the model.

## Screening strategies

Three newborn screening strategies were identified, as follows.

### Clinical examination
This involves looking for cyanosis (blue colouring, particularly of the lips and fingers), listening for abnormal heart sounds or murmurs with a stethoscope (auscultation) and feeling the pulses in the groin for decreased pulsation. This examination is usually carried out by a junior doctor responsible for the routine examination of all newborn infants before discharge from the maternity unit, although, increasingly in some areas, midwives are taking on this role. We defined a **presumptive positive result in this strategy** as the finding of cyanosis or murmurs or decreased pulses in the groin.

### Pulse oximetry with clinical examination
Pulse oximetry is a simple, non-invasive method of monitoring the percentage of haemoglobin which is saturated with oxygen. The pulse oximeter consists of a probe attached to the infant's finger, toe or edge of the foot, which is in turn linked to a computerised display of the percentage of haemoglobin saturated with oxygen and the heart rate. Light shines from the probe and is partly absorbed by haemoglobin. This information can be used to calculate the proportion of haemoglobin which is oxygenated. This examination can be performed by a junior doctor, midwife or other health professional. The equipment required is portable and can be used in the home and hospital.

An oximeter identifies hypoxaemia (low oxygen in the blood). The oximeter is dependent on a good peripheral circulation and so does not work reliably when a baby has a low blood pressure or is dehydrated, for example.

Although pulse oximetry may identify babies with congenital heart defects that result in cyanosis, it will not identify defects that are only associated with murmurs or delayed or absent pulses. Therefore, we assumed that screening with pulse oximetry would be carried out together with clinical examination.

Finally, pulse oximetry may also identify babies who are cyanosed for other (non-cardiac) reasons, including lung disease, and therefore a baby with a positive screening test result may require other investigations.

We defined a **presumptive positive result** in this strategy as the presence of hypoxaemia (arterial saturation <95% on two consecutive occasions[253]) and/or the finding of cyanosis or murmurs or delayed or absent pulses in the groin.

### Screening echocardiography with clinical examination

An echocardiogram is a scan of the heart using sound waves. It allows the four chambers, large blood vessels and the heart valves to be visualised while the heart is beating. With Doppler technology, it can also be used to assess the direction of blood flow. The examiner uses a small hand-held probe with gel over the end and moves it gently over the chest to locate the heart and examine its structures. Visualisation of the main chambers of the heart by this method is usually referred to as a four-chamber view, whereas visualisation of the main arteries leaving the heart to rule out, for example, TGA, is referred to as an outlet view. The outlet view can be more difficult to obtain. The examination may also reveal developmental structural abnormalities of the heart which are not considered clinically important and which may not have been recognised otherwise since they may not be associated with murmurs or other clinical signs or symptoms.

An echocardiogram may be used as a screening test for congenital heart defects in fetuses, newborn babies and older infants and children. Such screening examinations are usually carried out by a trained radiographer or echocardiographer. The equipment is not portable. A clinical examination is usually carried out as well, but by medical or midwifery staff.

We defined a **presumptive positive result** in this strategy as the finding of an abnormal heart structure on a four-chamber or outlet view and/or the finding of cyanosis or murmurs or decreased pulses in the groin on clinical examination. This includes developmental structural abnormalities which may have no clinical or functional significance.

Irrespective of the screening strategy, all infants with presumptive positive screening results need further evaluation by a more experienced examiner, who will usually undertake a longer and more detailed diagnostic echocardiogram and a clinical examination.

## Outcomes used in the decision model

### Timely diagnosis

We found some evidence from our review presented in Chapter 3 to support the assertion that preoperative collapse is likely to be associated with higher postoperative mortality and morbidity. In the longer term, this is likely to be associated with adverse neurological sequelae, especially cognitive, speech and language, and motor deficits.

In view of the lack of direct evidence on the effects of screening on longer term outcomes or collapse, we defined the end-point of the decision model as 'timely diagnosis', that is, a diagnosis made preoperatively before collapse or death occurs. As discussed previously, this concept assumes that effective management of a congenital heart defect, and prevention of preoperative collapse, begin at the point that diagnosis is sufficiently confirmed to initiate definitive management. Hence we assumed that newborn infants with a positive screening test and a confirmed diagnosis of a congenital heart defect by diagnostic echocardiogram, and in whom there has been no preoperative collapse, will have received a 'timely diagnosis' and will have benefited from screening.

### Primary outcome

As described in Chapter 5, congenital heart defects that may present with preoperative collapse include TGA, AS, PA, HLH (including MA), COA of the aorta (including IAA) and TAPVC.[22,80,82,83,105,204,211,221,227] For the purposes of the decision model, we assumed the primary outcome measure of newborn screening to be a timely diagnosis in these 'life-threatening' defects.

## Secondary outcome

We assumed the secondary outcome of newborn screening to be the detection of clinically significant but non-life-threatening defects in addition to the diagnosis of life-threatening defects. The secondary outcome therefore included children with a diagnosis of clinically significant VSD or other clinically significant non-life-threatening defects as listed in Chapter 5. These outcomes are summarised in *Box 1*.

## The model structure

The decision tree model was programmed for 100,000 live-born infants. The pathways were depicted up to the point of diagnosis and the model was characterised by two phases. The first part of the model consisted of an Excel spreadsheet programmed to determine the proportion of infants in whom there was no prior concern about their heart which would warrant a specialist opinion. In the second spreadsheet, we described the pathway probabilities for each of the screening strategies for those in whom there was no prior concern.

## Diagnosis prior to newborn screening

We assumed that the prevalence of unrecognised or unsuspected congenital heart defects at the point of screening would be affected by the following infants being recognised as requiring a diagnostic echocardiogram to detect or exclude

**BOX 1** *Definition of outcomes used in decision model*

| | |
|---|---|
| Primary outcome | Timely diagnosis of congenital heart defects listed below: a diagnosis of the following conditions made preoperatively before collapse or death occurs:<br>• TGA<br>• AS<br>• TAPVC<br>• HLH/MA<br>• COA/IAA<br>• PA |
| Secondary outcome | The diagnosis of clinically significant non-life-threatening defects **and** the timely diagnosis of the defects identified as primary outcome following a positive newborn screening test. Thus the outcome measure was extended to include:<br>• clinically significant VSD<br>• all other clinically significant non-life-threatening defects |

congenital heart defects before routine screening. These infants include those with (*Figure 23*):

1. a congenital heart defect diagnosed as a result of antenatal screening
2. readily recognisable extracardiac defects associated with congenital heart defects, such as
   (a) Down's syndrome
   (b) lethal trisomy (13 or 18)
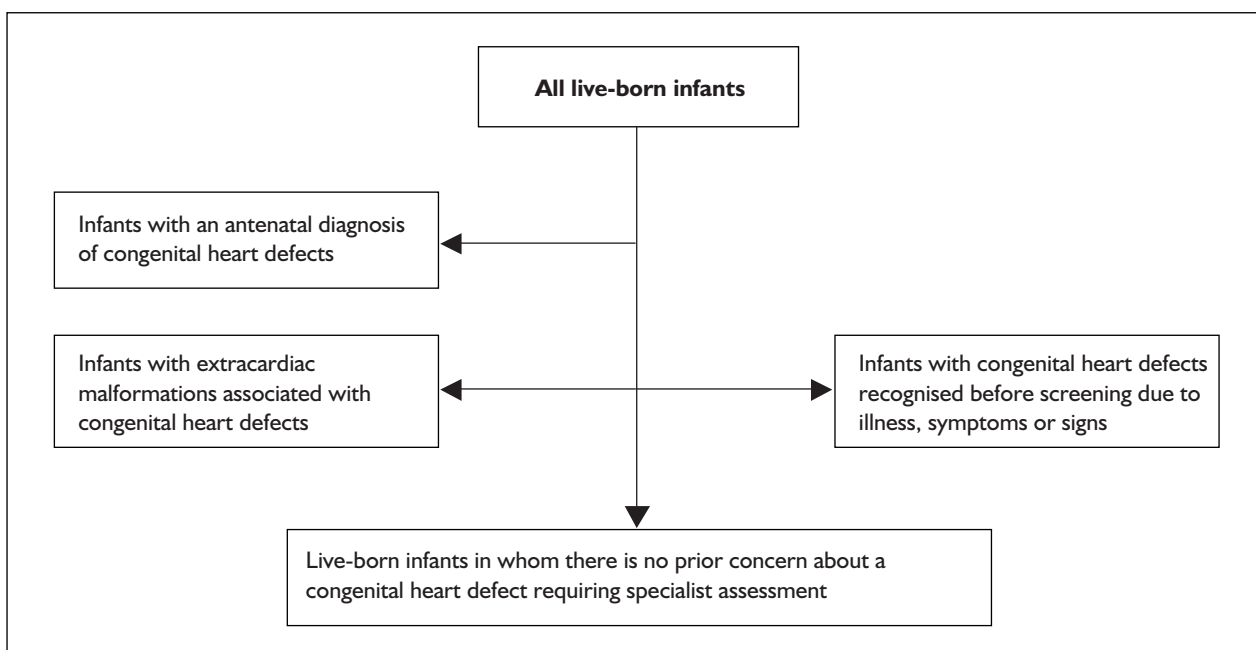   (c) gastroschisis or exomphalos (omphalocoele)



**FIGURE 23** *Eligibility for newborn screening*

3. newborns with congenital heart defects recognised before screening owing to illness, symptoms or signs.

We considered the remaining newborn infants to be 'eligible' for screening in our model in relation to the prevalence of congenital heart defects at the point of screening.

## The age at which screening is offered

The prevalence of congenital heart defects at the point of newborn screening also depends on the age at which screening takes place [see the sections 'Eligibility for newborn screening' (p. 68), 'Antenatal diagnosis of congenital heart defects' (p. 68), 'Newborns with extracardiac defects associated with congenital heart defects' (p. 68) and 'Congenital heart defects recognised before screening' (p. 69)]. Infants can become ill and collapse from congenital heart defects before newborn screening. These infants would no longer receive newborn screening, as they would be referred for urgent specialist investigation and management. This is particularly true for defects such as TGA. The later the age at which screening takes place, the greater is the proportion of infants with certain congenital heart defects who will have already presented owing to illness, symptoms or signs. We assumed that newborn screening would be offered around 24 hours of age in the base case and in sensitivity analyses investigated the effect of varying age at screening to birth and to 48 hours of age.

## Modelling the screening strategies

The overall structure of the model is depicted in *Figure 24*. We programmed the model such that, for each screening strategy, there was a probability that infants offered newborn screening had a particular type of congenital heart defect or that no congenital heart defect was present. As shown in *Figure 25*, the model subsequently depicted a probability that these infants were screened. Infants may not be screened, for example, owing to being discharged from the maternity ward before screening is carried out.

In practice, the test result (presumptive positive or negative) would be known before the diagnosis (type of defect). We did not, however, model the sequence of events chronologically. As defect-specific data were available on the positive and negative screening rates, we modelled the type of defect first followed by the probability of a positive or negative screening test. Modelling the test result first would have meant aggregating the data to give an estimate of the overall probability of a

positive screening result across all congenital hearts defects and also an overall probability of a negative screening result. Either ordering (test result first followed by defect and vice versa) is permissible and mathematically equivalent in terms of the expected values of the strategies being compared.[268,269]

*Figure 25* shows the decision tree pathways for infants with a specified congenital heart defect. The probabilities associated with the pathways are notated with letters, the meaning of which is described in *Box 2*. The model repeated these tree pathways for all defects, but each defect was populated with a different set of values for the probabilities as described in the tables in Appendix 9. We assumed that those with a specified congenital heart defect who are not screened have a probability of becoming acutely ill and of collapsing [C]. Following collapse, they have a probability of dying before diagnostic echocardiography can be performed [E]. Alternatively, if they do not collapse, we assumed their diagnosis would be suspected through other non-life-threatening signs or symptoms and confirmed with diagnostic echocardiography [F]. We modelled the probability of the diagnosis occurring before the child's first birthday since this reflected the emphasis of the commissioning brief and because most clinically significant congenital heart defects will have been diagnosed by 1 year.

We assumed that infants with congenital heart defects who were screened have a probability of a presumptive positive screening result (effectively, the sensitivity or detection rate of the test for that specific defect) [B]. All infants with a presumptive positive result have a true positive screening test. We assumed that infants with true positive screening tests have a probability of becoming acutely ill and collapsing before a diagnostic echocardiography [D]. Following collapse they have a probability of dying [G]. Alternatively, if they do not collapse before diagnostic echocardiography their diagnosis is considered 'timely'.

Those infants with specified congenital heart defects and in whom the screening result is presumed negative have false-negative screening tests. We assumed that infants with false-negative screening tests have a probability of becoming acutely ill and collapsing before a diagnostic echocardiogram [C] and a probability of dying following collapse [E]. Alternatively, if they do not collapse, their diagnosis may be suspected through other non-life-threatening signs or symptoms and
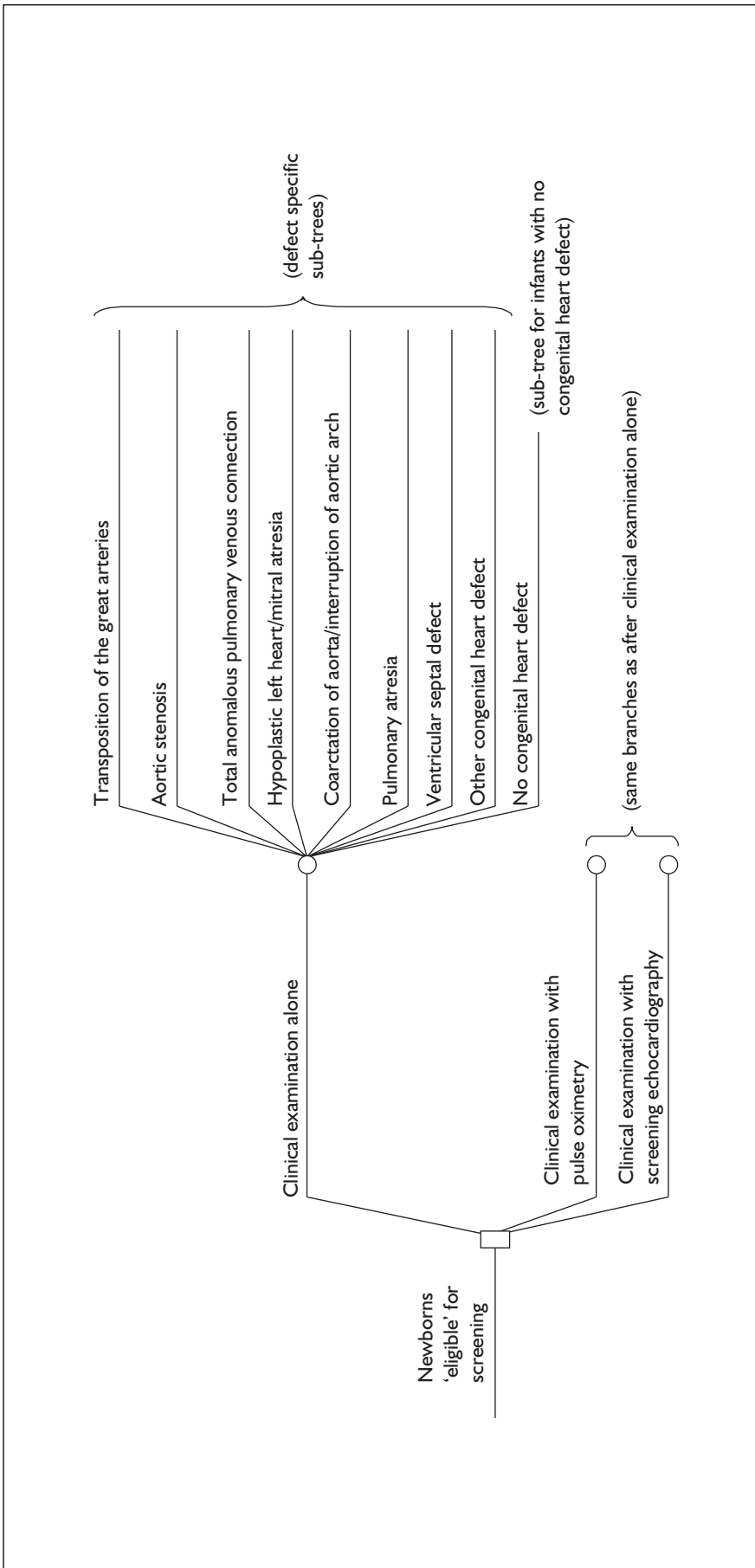
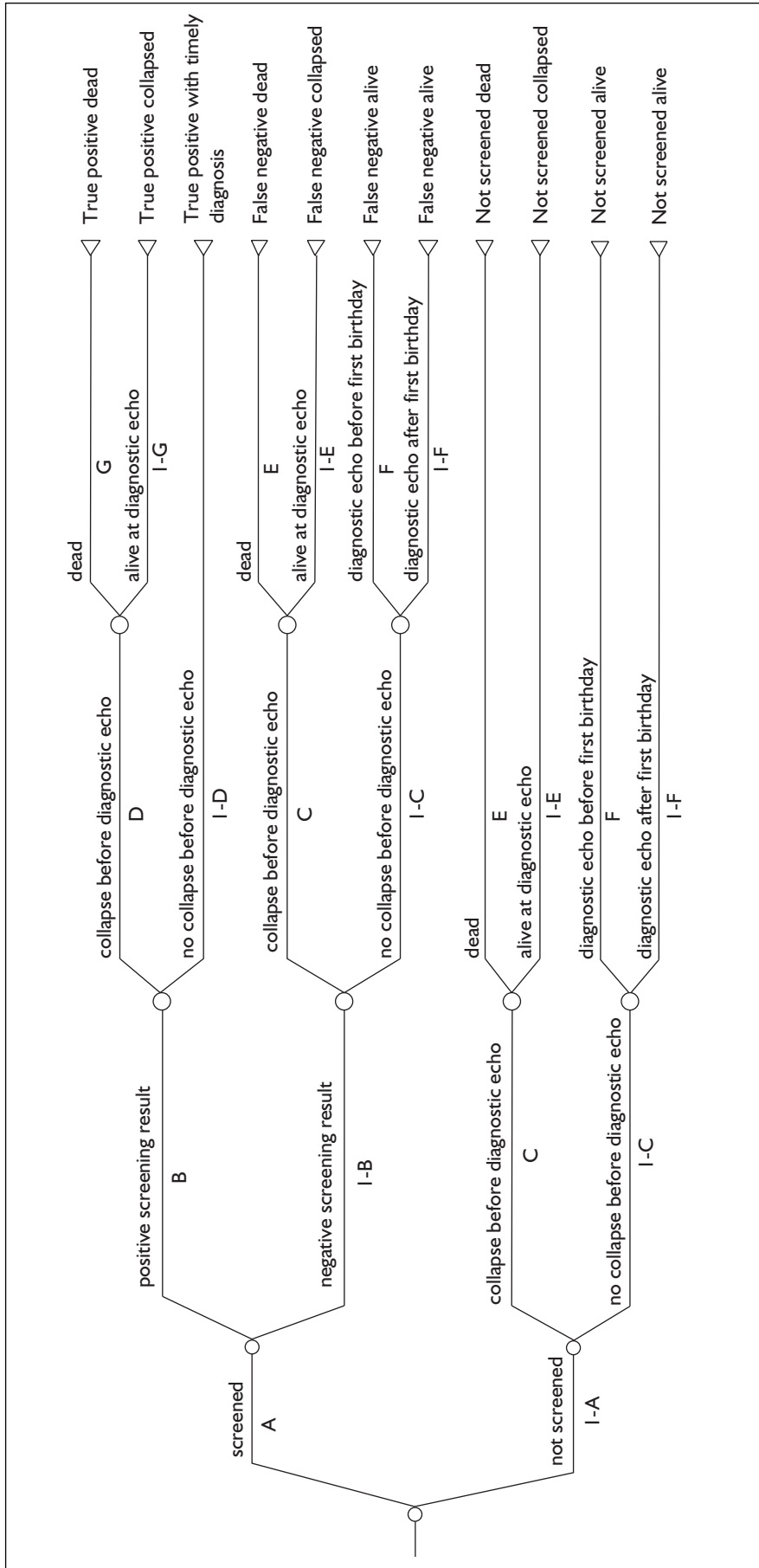**FIGURE 24** *Overall structure of the decision model*

**FIGURE 25** *Decision tree pathways for infants with specified congenital heart defect (diagnostic echo = diagnostic echocardiography)*

**BOX 2** *Specified probabilities used in decision tree pathways for infants with and without congenital heart defects*

| Name | Description |
|------|-------------|
| A | Probability of a newborn 'eligible' for screening being screened |
| B | Probability of an affected newborn having a positive screening test (i.e. test sensitivity or detection rate) |
| C | Probability of an affected newborn collapsing before diagnostic echocardiography following a negative screening test OR no screening test |
| D | Probability of collapse given positive screen and before diagnostic echocardiography |
| E | Probability of an affected newborn dying following collapse after a negative screening test OR no screening test |
| F | Probability of diagnosis without collapse given negative screen OR no screening in an affected newborn |
| G | Probability of an affected newborn dying following collapse after a positive screening test |
| H | Probability of an unaffected screened newborn having a negative screening test (i.e. test specificity) |
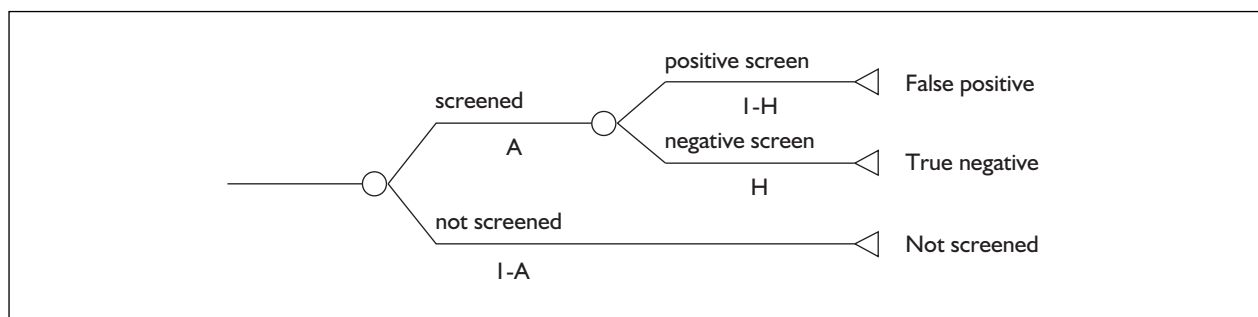


**FIGURE 26** *Decision tree pathways for infants with no congenital heart defects*

confirmed with diagnostic echocardiography. We modelled the probability of diagnosis occurring before the child's first birthday [F]. These probabilities are given letters in *Figure 25* and the specific probabilities relating to these letters are described in *Box 2*.

*Figure 26* displays the decision tree pathways for infants with no congenital heart defects. By definition, screened newborns with no congenital heart defects either have false-positive or true-negative screening test results. Again, the probabilities associated with the pathways are notated with letters, the meaning of which is described in *Box 2*.

## Screening test performance

In addition to the primary and secondary outcomes described above, we programmed the model to estimate, per 100,000 live births, the following outcomes for each screening strategy:

* detection rate
* number of infants with true- and false-positive screening results
* number of infants with true- and false-negative screening results

* the positive predictive value
* the false-positive rate.

## Economic analyses

### Deterministic analysis

We programmed the model to select the base-case values for the probability and cost parameters. The model estimated the expected total cost associated with each screening strategy for a population of 100,000 live births. The base-case analysis assumed that the antenatal detection rate for specific congenital heart defects from the Northern Region applied (see the section 'Antenatal diagnosis of congenital heart defects', p. 68) and that newborn screening was performed at 24 hours of age (see the section 'The age at which screening is offered', p. 62). The measure of effectiveness for the base case was primary outcome as discussed in the section 'Primary outcome', p. 60. The secondary outcome was considered in the sensitivity analyses. The results of the cost-effectiveness analysis were presented as incremental cost-effectiveness ratios,[270] such that the difference in cost for each strategy compared with the next most effective alternative is divided

by the difference in effectiveness to give the additional cost per additional timely diagnosis.

## Probabilistic analysis

We also programmed the model to run a probabilistic analysis of cost-effectiveness whereby the model parameters (probabilities and costs) were assigned a probability distribution. Monte Carlo simulation was used to sample from each of the parameter distributions in order to estimate the expected costs and expected number of cases detected with timely diagnosis associated with each run of the model. The model then plotted the results of 10,000 simulations in a cost-effectiveness plane with the expected costs on the *y*-axis and the expected number of cases with timely diagnosis on the *x*-axis.

The net-benefit framework[271] was used to express the output of all simulations in monetary terms (net monetary benefit, *NMB*):

$$NMB \ = \ Rc \times E - C$$

where *E* is the health outcome (in this analysis, the number of timely diagnoses), *C* the associated costs (in this case, the total expected cost of the screening strategy) and *Rc* the maximum value the health service is willing to pay for the health outcome.

The advantage of this framework is the straightforward interpretability of the results of the cost-effectiveness analysis when multiple mutually exclusive screening strategies are being compared.[268] If the net monetary benefit of one strategy exceeds the net benefits of its comparators, then this strategy is cost-effective relative to its comparators for the given ceiling ratio of society's willingness to pay for health outcome.

For each of the 10,000 iterations derived from the Monte Carlo simulation, we programmed the model to calculate the net monetary benefit associated with each strategy for a given maximum value of a timely diagnosis. The model used these data to estimate the probability of each strategy being cost-effective. For example, if 4000 of the 10,000 runs estimated the net monetary benefit to be greatest for clinical examination alone, 5000 runs estimated the net benefit to be greatest for pulse oximetry with clinical examination and 1000 runs estimated the net benefit of screening echocardiography with clinical examination to be the greatest, then the probability of clinical examination alone being cost-effective would be

0.4, the probability of pulse oximetry with clinical examination being cost-effective would be 0.5 and the probability of screening echocardiography with clinical examination being cost-effective would be 0.1. The probability of each strategy being cost-effective was estimated over a range of £0–150,000 for the maximum value assigned to a timely diagnosis. The results were summarised as a cost-effectiveness acceptability curve, whereby the probability of the strategy being cost-effective is plotted against the maximum value assigned to a timely diagnosis.[272]

# Model inputs

## Search for published data sources

In order to determine the prevalence of congenital heart defects and the value of the probabilities within the model, a literature search was carried out using the databases MEDLINE, EMBASE and CINAHL accessed through Ovid. The search strategy is given in Appendix 7 and employed four concepts:

1. congenital heart defects
2. newborns
3. screening
4. diagnostic tests for newborn screening.

Within each concept, all search terms were combined with OR, and then the intersection of these concepts was derived using AND.

The abstracts of papers identified by the search were reviewed independently by two reviewers (RK and CD) for their eligibility for inclusion.

### Inclusion criteria
- congenital heart defects
- screening tests and programmes relevant to UK
- prevalences relevant to UK
- study types: randomised controlled trials (RCTs), controlled trials, cohort, case–control, case series >20
- screening tests in first year of life: pulse oximetry, clinical examination, newborn echocardiography
- outcomes of congenital heart defects to 16 years of age
- cost-effectiveness papers of screening for congenital heart defects, outcomes, treatment to age 16 years
- human
- MEDLINE references from 1966 onwards; EMBASE from 1980 onwards; CINAHL from 1982 onwards.

Papers were excluded if the operative and screening techniques considered were now superseded owing to technological advances. Full papers were obtained for eligible abstracts. Where two reviewers did not agree on the eligibility of the abstract, the full paper was obtained and a further review performed. Where both reviewers could still not agree, a third reviewer (CB) was asked to adjudicate.

The number of papers deemed eligible by each reviewer after the initial and final abstract reviews is summarised in Appendix 7. Overall there were 34 papers out of 417 which were considered eligible to provide information for the decision model. A further 182 papers (44%) provided useful background material for the narrative component of the review but not for the decision model parameters.

## Unpublished data and grey literature

We identified in the published literature and through members of the British Paediatric Cardiac Association, two regional UK paediatric cardiology databases that were sources of unpublished data relating to screening or the identification of congenital heart defects in the newborn period. These were the Northern Region dataset (the original data for the published studies)[6] and surgical operation data (raw data) from the Merseyside Cardiac Database.

## Data extraction

Initially, we intended to use a proforma to extract the data for the pathway probabilities from the published papers, which was to be carried out by three reviewers (RK, CD and CB). This, however, required studies to report their data against a population denominator of live births and to follow up the study population long enough for any cases missed by screening to declare themselves clinically. Analysis of the eligible studies revealed that the majority identified groups of children with congenital heart defects and retrospectively investigated the diagnosis of their condition, comparing screening with clinical detection. Only 10 studies were based on a population denominator of live births and these were all regional or hospital based. Ascertainment of cases not identified in the first year of life was limited except for studies based in the Northern Region.[6,12,14,18] Two studies of screening echocardiography existed but these had high exclusion rates and did not provide population-based condition-specific parameter estimates that could be used in the model.[256,273] One study of pulse oximetry in newborns provided useful input data but was too small to provide estimates of condition-specific detection rates for life-threatening congenital heart defects.[253] The remaining studies investigated clinical examination (usually auscultation only) as a screening strategy. No studies compared the different screening strategies under review. Only one paper provided data on screening coverage[248] and four studies presented probabilities that could be extracted for the model.[6,12,253,256]

It was therefore decided that the parameters for the model should be based primarily upon the original coded Northern Region dataset,[6] as the source was related to a population denominator (live births), follow-up was over 15 years and the dataset included post-mortem diagnoses of congenital heart defects. The study data were collected over the period 1985–97. Moreover, the data were condition specific, using a previously well-described classification[4] that could be applied to the model.

## Prevalence data
### Sources of data
The primary source of prevalence data for the model was the original Northern Region dataset used by Wren and colleagues.[6] The data are summarised in *Table 11* and given in full in Appendix 8. From this paper it was possible to extract prevalence data for the individual defects of interest. It should be noted that the study only covers the Northern Region of England, with an average of 38,000–40,000 live births per year. UK figures presented by Bull[8] and the structured review of published sources of prevalence data provided by Hoffman and Kaplan,[11] nonetheless, suggest similar prevalence rates for the major congenital heart defects.

We assumed that the secondary outcome of newborn screening was the detection of clinically significant but non-life-threatening defects **and** the timely diagnosis of life-threatening defects following a positive screening test. Echocardiography has been shown to identify more VSDs and other clinically non-significant congenital heart defects than previously diagnosed.[11] This is because screening echocardiography detects many defects which spontaneously resolve in infancy, e.g. small VSDs,[36] or have no functional effects on the heart. On the basis of the published literature, we assumed that the prevalence of ventricular septal defect would increase by 95% with echocardiography in the newborn period[36,273] and the prevalence of PDA, ASD, and PS by 61%. The

*TABLE 11 Summary table of prevalence data*

| | All congenital heart defects | TGA | AS | TAPVC | HLH/MA | COA/IAA | PA | VSD | Clinically significant CHD (excluding VSD) | Clinically non-significant CHD (VSD detected with echocardiography) | Clinically non-significant CHD (PDA, PS, ASD with echocardiography) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Number per 100,000 live births | 623.7 | 26.7 | 31.7 | 8.5 | 12.1 | 51.3 | 22.3 | 236.3 | 226.5 | 4159.0 | 59.0 |
| Number eligible for screening at 24 hours, per 100,000 live births | 516.7 | 14.7 | 27.7 | 7.5 | 9.1 | 46.3 | 15.3 | 188.3 | 199.5 | 4159.0 | 59.0 |
| Number eligible for screening at 48 hours, per 100,000 live births | 414.7 | 6.7 | 23.7 | 4.5 | 4.1 | 36.3 | 8.3 | 167.3 | 155.5 | 4159.0 | 59.0 |

latter reflected the upper quartile of congenital heart defects detected by screening echocardiography as quoted by Hoffman and Kaplan.[11] The number of defects that would be detecting using echocardiography in 100,000 live-born infants is calculated and displayed in the three right-hand columns of the prevalence table in Appendix 8.

In the first year of life, additional deaths will occur that are unrelated to congenital heart defects and these have been estimated for 100,000 live births using published studies from the Northern Region.[14] Between the ages of 1 and 16 years, further cases of congenital heart defects were detected in the Northern Region study and adjusted for underascertainment.[12] The number of congenital heart defects detected between 1 and 16 years old has been estimated from the Northern Region data for a population of 100,000 live births (adjusted for infant deaths). These estimates are detailed in the prevalence table in Appendix 8 and a total prevalence at birth calculated for each congenital heart defect in the model.

### Eligibility for newborn screening
As discussed previously, we assumed that the prevalence of congenital heart defects in those eligible for screening would be affected by the following infants being offered a diagnostic echocardiogram to detect or exclude congenital heart defects prior to routine screening: newborns with a congenital heart defect diagnosed as a result of antenatal screening, newborns with the extracardiac defects associated with congenital heart defects and newborns with congenital heart defects recognised before screening owing to illness, symptoms or signs. We were able to supplement the information in the paper by Wren and colleagues[6] with access to the original coded dataset. The Northern Region dataset was therefore used to calculate the number of exclusions from routine screening amongst children with congenital heart defects and these are described here and detailed in the prevalence table in Appendix 8.

### Antenatal diagnosis of congenital heart defects
The dataset from the Northern Region study was used to provide information about the number of newborn infants with congenital heart defects who had been diagnosed as a result of antenatal screening.[6] This enabled us to calculate rates per 100,000 live births used in our base-case analysis. The study by Bull provided data on antenatal diagnosis for the whole of the UK but used a

different classification to that in the Northern Region study and reported antenatal diagnosis for only four out of the six life-threatening defects included in the model.[8] The figures for single defects reported by both studies were largely comparable but a higher overall detection rate was reported by Bull, which was related to the higher number of non-life-threatening defects identified antenatally. We therefore used the Northern Region dataset in the base-case analysis. The implications of the UK antenatal detection rates for newborn screening performance were examined in sensitivity analyses. To examine the implications of possible future improvements in the performance of fetal ultrasound, we doubled the rates derived from the UK study and applied these in an additional sensitivity analysis.

Subsequent to a presentation of the model to a workshop involving the National Screening Committee Child Health and Antenatal Subgroups in January 2004, we undertook a further analysis to determine the outcomes, costs and incremental cost-effectiveness ratios across a wider range of antenatal detection rates from 0 to 100% (assumed to be constant across all congenital heart defects). This analysis is described in greater detail in the section 'Scenarios explored within the model' (p. 74).

### Newborns with extracardiac defects associated with congenital heart defects
As described earlier, we estimated the number of newborns with extracardiac defects associated with congenital heart defects. These extracardiac defects included Down's syndrome, lethal trisomies (13 or 18) and gastroschisis or exomphalos (omphalocoele).

The Northern Region study excluded infants with certain conditions which would warrant further specialist assessment of their hearts. These included infants with Down's syndrome, lethal trisomy, extracardiac defects and conditions requiring urgent surgery and premature infants (<35 weeks gestation). For our model, the range of exclusions was based on a prospective view of screening coverage. Therefore, we assumed that infants who were not identified as having a condition warranting special investigation within a few hours of birth would undergo routine newborn screening for congenital heart defects. In addition, we expected premature infants to have a routine newborn examination as for term infants.

We were able to identify from the Northern Region study dataset the number of infants excluded from

screening for each exclusion criterion and to apply this number per defect within a population of 100,000 infants with congenital heart defects. The Baltimore–Washington Infant Study identified the extracardiac malformations most commonly associated with congenital heart defects (gastrointestinal, genitourinary and ophthalmic), but if these were unlikely to be identified on the first day of life, they were not considered to be reasons for exclusion from screening.[200] We used data from a UK study of cardiac defects associated with gastrointestinal defects at birth to determine which gastrointestinal defects should be used as criteria for exclusion from routine cardiac screening.[75] We further contacted specialists in the field to enquire about current practice in investigating the cardiac status of children with gastrointestinal defects and to what extent these were identifiable on the first day of life (Spitz L, Institute of Child Health and Great Ormond Street Hospital, London: personal communication, 2002). We also used data from the UK National Down's Syndrome Register[274] to inform exclusion rates for Down's syndrome, which was felt to be largely identifiable before hospital discharge (Alberman E, Mutton DE, National Down Syndrome Cytogenetic Register: personal communication, 2003).

We calculated the prevalence of specific extracardiac defects using the Eurocat surveillance data.[275] The figures are given in Appendix 8.

### Congenital heart defects recognised before screening

As discussed above in the section 'The age at which screening is offered' (p. 62), it was also recognised that some infants become ill and collapse from congenital heart defects before routine screening can take place, which affects the prevalence of congenital heart defects that can be detected at the point of screening. The later screening takes place, the more defects will have presented clinically.

We used the original coded dataset for the Northern Region in the study by Wren and colleagues to identify when infants were suspected to have congenital heart defects.[6] The number of infants with signs and symptoms of a congenital heart defect by the time of the newborn screening examination was estimated by enumerating those diagnosed with a congenital heart defect after clinical presentation to a paediatric cardiologist and those referred after antenatal screening. Three cut-off times were used, birth, 24 hours and 48 hours, and the number of infants with

congenital heart defects remaining to be detected (i.e. not yet having presented clinically to a paediatric cardiologist or through antenatal screening) was calculated at these time-points.

## Probability data
### Data sources
Probability estimates for the input parameters in the model were taken from published literature sources, the Northern Region dataset used in the study by Wren and colleagues[6] and subjective probabilities from clinical experts.

The base-case value of the probabilities labelled B–G in *Figure 25* and *Box 2* are given in *Tables 38–45* in Appendix 9. The probabilities vary according to the type of congenital heart defect. For purposes of the probabilistic analysis of cost-effectiveness, the probabilities were assigned beta distributions. The beta distribution has been suggested by others as being the most appropriate for probabilities as it is bounded by 0 and 1. The distribution parameters ($\alpha$, $\beta$) represent the number of two possible complementary events such as success/failure, positive/negative test result, collapse/no collapse or life/death.[276,277] Further details are given in Appendix 9.

### Subjective probabilities
Where no database or published data were available, experts provided estimates. Typically the data required for the model were a series of conditional probabilities for a particular context. There is an extensive literature around the various options for eliciting subjective judgements and the number of experts used in our research was typical of case studies documented in the literature. We used the strategy that Clemen and Winkler[278] call 'behavioural' (i.e. using a face-to-face situation to generate a 'group' probability distribution by consensus) rather than a 'mathematical approach' (using one of a variety of algorithms to combine independently elicited estimates). Neither 'behavioural' nor 'mathematical' approaches have been demonstrated to be generically superior and they may be used in combination. The 'behavioural' approach was appropriate to this model as the probabilities to be estimated were very tight with a low level of disagreement between individual's estimates.

For each estimate required, between two and five paediatric cardiologists independently provided a point estimate and range (with probabilities expressed as percentages).[279] From these a single estimate and range were negotiated and the range was transformed into a beta distribution for use in

the model. In this way, the clinicians' ranges are translated into implicit fractions of patients that underlie their experience; thus more precise assessments (narrower subjective ranges) are obtained in a larger implicit sample size. An example would be the sensitivity of echocardiography to detect TGA. Experts estimated that 90% of this condition would be detected at routine newborn screening by a radiographer performing a screening echocardiogram, but that this may be as low as 85% or as high as 95%. The probability estimate used in the model for the detection of TGA using a screening echocardiogram would therefore be 0.9 (range 0.85–0.95).

### Probability of being screened [A]

The probability of a newborn being screened given that there was no prior indication for specialist cardiac assessment was estimated as 93% for clinical examination. based on the single screen strategy reported by Glazener and colleagues,[248] 93% for pulse oximetry with clinical examination based on the study by Richmond and colleagues[253] and 91% for screening echocardiography with clinical examination based on the study by Sands and colleagues.[256] The value used for screening echocardiography with clinical examination is consistent with that reported for newborn hearing screening, which reported coverage before discharge from maternity hospital of 91% (Davis A, MRC Hearing and Communication Group, University of Manchester: personal communication, 2002).

### Detection rate: probability of an affected newborn having a positive test [B]

We used the database for the Northern Region study to derive, for each congenital heart defect of interest, the probability of an affected newborn having a positive screening test by clinical examination alone.

There were limited data on the test sensitivity of pulse oximetry with clinical examination in newborn screening. The study by Richmond and colleagues only provided probabilities for ventricular septal defects and the other clinically significant congenital heart defects combined.[253] Hence expert opinion was used to provide estimates of the probabilities and ranges.

Probabilities for echocardiography with clinical examination were based solely on expert opinion and it was assumed that clinical radiographers rather than paediatric cardiologists would perform the screening test.

### Probability of collapse in affected infant given negative screening test or no screening [C]

Eligible infants with congenital heart defects who miss screening were assumed to have the same risk of collapse and death as infants with congenital heart defects with a negative screening result. The probability of collapse varied by condition.

### Probability of collapse in affected infant given positive screen and no diagnostic echocardiography [D]

Subjective probabilities were obtained for the probability of collapse in affected infants after a positive screen but before a diagnostic echocardiogram, confirming the diagnosis, had been performed by a cardiologist. These varied by condition but were the same for each screening strategy. The probability of an infant collapsing between the time of screening and the time of beginning definitive management (on confirmation of the diagnosis by diagnostic echocardiography) is related to the effectiveness of clinical management of a presumptive positive screening test. In a sensitivity analysis in the model, an alternative scenario was proposed in which collapse between a positive screening test and confirmed diagnosis never occurred, i.e. that all positive screening results were managed appropriately to prevent collapse.

### Probability of death in affected infant given negative screening test or no screening [E]

Subjective probabilities were obtained for the probability of collapse in affected infants after a negative screen, so assuming that the screening test result had been normal and the infant had collapsed and died later and before a diagnostic echocardiogram had been performed. These infants have false-negative screening results.

### Probability of diagnosis without collapse in affected infant given negative screen or no screening [F]

A study of survival outcomes for all serious congenital heart defects was performed and reported in the Northern Region in 2001, and included a review of all published studies providing data on outcomes of congenital heart defects between 1 and 16 years of age.[12] The three published papers, which were most relevant to UK experience, had the largest study population and were most recently updated, were identified for each malformation. In total, the review reported the results of 33 papers. We attempted to update this review from January 2001 until July 2002 by looking for more recent papers, beginning with those citing the original review, but found no

**TABLE 12** *Probability of negative screening test in an unaffected screened infant [H]*

| Screening strategy | Base-case value | Range of subjective probabilities | Probability distribution | Source |
|---|---|---|---|---|
| Clinical examination | 0.997 | N/A | Beta (4777.0, 14.0) | Ref. 248 |
| Pulse oximetry in addition to clinical examination | 0.990 | N/A | Beta (5520.0, 54.0) | Ref. 253 |
| Screening echocardiography in addition to clinical examination | 0.990 | 0.985–0.995 | Beta (391.1, 3.9) | Expert |

**TABLE 13** *Unit costs (£) per activity (2000–1 prices)*

| Unit costs | | Clinical examination alone | Pulse oximetry with clinical examination | Screening echocardiography with clinical examination |
|---|---|---|---|---|
| Screening tests | Staff | 1.17 | 2.34 | 7.7 |
| | Equipment | – | 0.48 | 23.97 |
| | Total | 1.17 | 2.82 | 31.67 |
| Diagnostic assessment | Staff | 60.20 | 60.20 | 60.20 |
| | Equipment | 23.97 | 23.97 | 23.97 |
| | Total | 84.17 | 84.17 | 84.17 |
| Management of collapsed infants | Treatment | 3215 | 3215 | 3215 |
| | Ambulance | 237 | 237 | 237 |
| | Post-mortem examination | 942 | 942 | 942 |

papers contributing new data to change the findings of this review. This review therefore provided the detection rates and survival data, for children with congenital heart defects from 1 to 16 years old, in the model.

***Probability of death of affected infant given collapse after positive screen [G]***
The probability of an affected infant, who has had a positive screening test and then collapsed, subsequently dying after the collapse, was estimated for each condition using subjective probabilities. These probabilities do not differ across screening strategies.

***Probability of negative screening test in an unaffected screened infant (test specificity) [H]***
The probability of a negative screening test being obtained from an unaffected screened infant was taken from published data in a population-based study of newborn screening using clinical examination in Aberdeen[248] and from a regional study of newborn screening using pulse oximetry.[253] The probability of a negative screening test using screening echocardiography was estimated using subjective probabilities. *Table 12* shows the probabilities used.

## Screening programme costs
We estimated the health service costs associated with the screening strategies up to the point of diagnosis. We estimated the unit costs associated with each screening test, a detailed diagnostic examination and the management of a collapsed infant. The staff, overheads, equipment and consumable items were considered.[280] All costs were adjusted to 2000–1 prices.[281] The unit cost estimates for the base case are summarised in *Table 13*.

***Costs associated with screening tests***
**Staff**
As described in the section 'Screening strategies' (p. 59), each of the three screening strategies comprises a clinical examination, within the routine newborn screening check, which is usually carried out in the hospital maternity ward before discharge. In the absence of any published data, we estimated the cost associated with the cardiovascular component of the routine newborn screening check by timing how long it took to carry out the examination. A total of 12 examinations performed by three junior doctors, with differing levels of clinical experience, were observed at University College London Hospitals

*TABLE 14  Distributions for resource use parameter (staff time)*

| Parameter | Base-case value (minutes) | Probability distribution[a] |
|---|---|---|
| Duration of clinical examination | 2.0 | Gamma (12.84, 0.16) |
| Duration of pulse oximetry | 2.0 | Gamma (12.84, 0.16) |
| Duration of echocardiography | 10.0 | Gamma (12.76, 0.78) |
| Duration of diagnostic echo | 30.0 | Gamma (12.76, 2.35) |

[a] Parameters for gamma distributions: $(\alpha, \beta)$.

*TABLE 15  Distribution for resource use parameter (equipment and management costs)*

| Parameter | Base-case value (£) | Probability distribution[a] |
|---|---|---|
| Pulse oximetry machine costs | 0.48 | Uniform (0.31, 0.64) |
| Echocardiography machine costs | 23.97 | Uniform (13.85, 34.09) |
| Cost for treating collapsed infants | 3215 | Uniform (1429, 7438) |
| Cost of post-mortem examination | 942 | Uniform (471, 1413) |
| Cost of ambulance transport | 238 | Uniform (119, 357) |

[a] Parameters for uniform distributions: (minimum, maximum).

NHS Trust. For costing purposes, we assumed that a senior house officer would carry out the examination and used figures based on salary plus oncosts provide by Netten and colleagues to value their time.[281] Costs were uprated by 40% to take account of overheads.

We assumed that pulse oximetry would also be carried out by a senior house officer and take as long as the clinical examination. Infants with an initial positive test (postductal fractional oxygen saturation <95%) were assumed to require a second confirmatory saturation measurement.

We assumed that a senior radiographer would perform the screening echocardiography. The time required to perform a screening echocardiogram was estimated in consultation with clinicians and radiography staff plus the observation of the murmur clinic at Great Ormond Street Hospital for Sick Children, London. The time costs of a senior radiographer were valued using figures based on the salary plus oncosts provide by Netten and colleagues to value their time.[281] Costs were uprated by 40% to take account of overheads.

As shown in *Table 14*, for purposes of the probabilistic analysis of cost-effectiveness, a gamma distribution was used to model the time required to perform the screening tests. Details are given in Appendix 9.

**Equipment costs**
The equipment costs apportioned to each screen were estimated as the annuitised capital costs plus the annual consumables and maintenance costs divided by the number of screening tests per annum.

We used market prices provided by Nellcor and Siemens to estimate the capital cost of the equipment for pulse oximetry and the newborn cardiology imaging equipment required for screening echocardiography. Two prices, £1232 and £1703 (2000–1 prices), were provided for a pulse oximeter (including VAT), depending on the type of machine. We assumed that one pulse oximeter would be used per hospital. Two prices, £94,000 and £152,750 (2000–1 prices), were also provided (including VAT) for a fully configured paediatric echocardiography unit. These cost figures were annuitised by assuming a life span of 5 years and a discount factor of 6%.[280]

The consumable items for pulse oximetry are the sensors. Given advice from clinical experts that the risk of cross-infection is considered negligible, we estimated two reusable pulse oximeter sensors would be required per annum at a cost of £250 each (Richmond S, City Hospitals Sunderland NHS Trust: personal communication, 2003, and manufacturer's information obtained from Nellcor). The costs of consumable items and the

annual cost of a maintenance contract for an echocardiography unit were obtained from the chief echocardiography technician at Great Ormond Street Hospital, London. The annual cost of a maintenance contract per machine was given as £10,354 (2000–1 prices) and the cost of consumables as £0.80 per screen.

In 2000–1, 549,566 hospital deliveries were undertaken in 197 NHS hospitals in England (Hospital Episode Statistics; source: Department of Health). The average annual number of deliveries per hospital was 2790 (median, 2815; interquartile range, 1980–3594). We assumed that the number of screening tests performed would be equivalent to the number of deliveries per hospital.

To take account of the uncertainty surrounding these costs and the uncertainty surrounding the annual number of newborn infants screened per setting, we calculated a low and a high cost estimate. The low cost estimate assumed a high delivery rate (75th percentile of the national number of deliveries per hospital) and used the lower figure for the capital costs. The high cost estimate assumed a low delivery rate (25th percentile of the national number of deliveries per hospital) and the highest equipment cost. The midpoint of the resulting range was used in the base-case analysis.

As shown in *Table 15*, for purposes of the probabilistic analysis of cost-effectiveness a uniform distribution was assumed for the equipment costs which reflected an equal chance of the unit cost estimated falling within the range of the low and high cost estimates described above.[281]

### Costs associated with diagnostic assessment

We assumed that for all screening strategies infants with a presumptive positive screening result would be referred to a paediatric cardiologist for a detailed examination including an echocardiogram in order to make the final diagnosis. We assumed such an examination would take 30 minutes.[282]

For costing purposes, we used figures based on the salary plus oncosts provided by Netten and colleagues to value the consultant's time.[281] Costs were uprated by 40% to take account of overheads.

As shown in *Table 14*, for purposes of the probabilistic analysis of cost-effectiveness, a gamma distribution was used to model the time required to perform the diagnostic examination. Details are given in Appendix 9.

### Costs associated with the management of collapsed infants

The unit cost of the additional clinical management for collapsed newborn infants was based on the median costs of treating newborns with severe respiratory failure using conventional management as reported by Roberts[283] uprated to 2000–1 prices.

As shown in *Table 15*, for purposes of the probabilistic analysis of cost-effectiveness a uniform distribution was assumed for the unit cost of collapse which reflected an equal chance of the unit cost estimated falling within the inter-quartile range of the cost figures presented by Roberts.[283]

We assumed that infants who collapsed having missed screening or discharge with a false-negative screening result would also require transport by ambulance to the hospital. For infants dying as a consequence of collapse, the cost of a post-mortem examination was added. The costs of ambulance transport and a post-mortem examination were based on figures reported by Bewley and colleagues.[284]

As shown in *Table 15*, for purposes of the probabilistic analysis of cost-effectiveness a uniform distribution was assumed for the unit cost of ambulance transport and unit cost of death which reflected an equal chance of the unit cost estimated falling within the range of varying the costs by a factor of 0.5 and 1.5.

## Scenarios explored within the model

We investigated the performance of the alternative screening strategies under a number of different assumptions defined in terms of the choice of antenatal detection rate and timing of screening. We programmed the model such that the following parameters had to be specified in order to run the model: antenatal detection rate based on either the Northern Region detection rate or the national rate or twice the national rate (to determine the effect of a hypothetically more effective antenatal screening programme overall in the UK); timing of screening at birth or 24 or 48 hours of age. Hence, any combination of these antenatal detection rates and timings of screening could be investigated. For reasons described in the section 'Antenatal diagnosis of congenital heart defects' (p. 68), we assumed an antenatal detection rate based on data from the Northern Region in the base case and assumed newborn screening took place at 24 hours.

We also programmed the model to investigate the effect of instant access to diagnostic echocardiography for infants with presumptive positive screening test results. This implies that the probability of an affected newborn collapsing after a positive screening test is zero. Although this scenario did not discriminate between screening strategies, it was investigated as a way of demonstrating the potential effect of initial diagnosis and management on the outcome of life-threatening congenital heart defects.

We also programmed the model to investigate some aspects of the screening echocardiography strategy. The following mutually exclusive assumptions regarding screening echocardiography were analysed with any combination of the antenatal detection rate and timing of screening options, and also the scenario that the probability of an affected newborn collapsing after a positive screening test was zero. Aspects of interest included variation in the coverage of screening echocardiography (93% compared with 91% in the base-case model) and improving the detection rate for screening echocardiography to 100%. These scenarios examined a better performance in terms of coverage and detection rate for screening echocardiography than assumed in the base case. In this way it was possible to examine the cost-effectiveness of screening echocardiography (the most expensive screening test in absolute terms) under the most favourable conditions.

### Extended sensitivity analysis for antenatal screening
Separately from the model but based on the data within it, we undertook an additional sensitivity analysis to consider explicitly the scenario of a very high antenatal detection rate and calculated the outcomes, costs and incremental cost-effectiveness ratios for the primary and secondary outcome measures across a wider range of antenatal detection rates from 0 to 100% (assumed to be constant across all congenital heart defects). Newborn screening was assumed to take place at 24 hours of age in this analysis. The results are presented in the section 'Extended sensitivity analysis for antenatal screening' (p. 85).

# Expected value of information analysis

We used the expected value of information (EVI) approach to analyse the impact of existing uncertainty on the comparison of alternative screening strategies in the probabilistic decision

model. The EVI approach has been highlighted recently as a potential aid for setting research priorities in the context of health technology assessment,[276,285–287] but applications of this approach to HTA projects are still few.[285] The EVI approach includes estimating the expected value of perfect information (EVPI).

The EVI approach quantifies the costs of current uncertainty. In a model with 10,000 simulations there will be 10,000 sets of results, each set corresponding to a run whereby the value for each parameter in the model is chosen at random from its defined distribution. The probability of a strategy being cost-effective is based on the proportion of runs where the strategy has the greatest net benefit (as described in the section 'Probabilistic analysis', p. 66) compared with the alternative strategies. A baseline decision to implement the strategy with the greatest probability of being cost-effective implies there is also a probability of making a 'wrong' decision, i.e. in a proportion of runs the greatest net benefit will be associated with an alternative strategy to the baseline decision. The opportunity cost of making a wrong decision can be estimated as the foregone net benefit associated with a wrong decision. Hence for each simulation where the net benefit is greatest for the alternative strategy (to the baseline), the opportunity cost is estimated as the net benefit of the optimal strategy minus the net benefit of the baseline strategy. The mean value of the opportunity cost is then estimated over all the simulations. This is known as the EVPI and will differ depending on the value assigned to maximum value of a timely diagnosis.

We estimated the EVPI over a range of £0–150,000 for the maximum value of a timely diagnosis using the base case assumption of the model [see the sections 'Deterministic analysis' (p. 65) and 'Base case' (p. 77)] for both the primary and secondary outcomes. The EVPI was then applied to a population of newborns. We assumed an effective lifetime of the screening technology to be 5 years, with the number of newborns (549,566) per year over this 5-year period based on the number of hospital deliveries in England during the year 2000–1. A discount rate of 6% was applied. The population EVPI is the potential value of further research to eliminate uncertainty or value of (further) information.

The EVPI for a single parameter or sets of parameters is known as 'partial EVPI'. Thereby a parameter or groups of parameters can be identified for which further data collection would

be most worthwhile in the sense that more precise estimates would reduce the uncertainty of the cost-effectiveness. Associated parameters such as test sensitivities of alternative screening strategies were analysed as single parameter groups. We estimated this by allowing uncertainty in the specified parameter(s) and fixing the other parameters at their prior mean (method 2 reported by Chilcott and colleagues[285]). This method is simpler than the more general two-level Monte Carlo method and is applicable when a linear relationship between model input parameters and the net benefit is a reasonable assumption. This assumption applies to most standard decision tree models where parameters occur only once on any path from the origin to the terminal node.[288,289]

Given that the maximum value for a timely diagnosis is unknown, we used a range of values for the maximum value of a timely diagnosis to estimate the EVPI. We assumed that the maximum value of a timely diagnosis ranged from £0 to £150,000. In this screening model, EVPI estimation was based on a population of 100,000 newborn infants. A technical discussion of EVI and the methodology used in estimating EVPI for the model is described in more detail in Appendix 10.

# Chapter 7
# Results of the decision model

**Chapter outline**

In this chapter, we present the key findings of the decision model. Screening strategies are compared with respect to predicted test performance, effectiveness, costs and cost-effectiveness under base-case assumptions for the primary and secondary outcomes. The robustness of these findings is examined using probabilistic sensitivity analyses. Analyses are presented relevant to different scenarios, including variations in effectiveness of antenatal screening, in delivery of newborn screening and in timely access to specialist cardiac services for those with positive newborn screening results. The results of the EVI analysis are presented. The conclusions of the model are discussed.

**Key messages**

- In a population of 100,000 live-born infants, an estimated 82 (68%) and 83 (69%) infants with life-threatening congenital heart defects are detected by pulse oximetry with clinical examination and screening echocardiography with clinical examination respectively, but only 39 (32%) by clinical examination alone.
- Of these, 71, 71 and 34, respectively, receive a timely diagnosis, reflecting the fact that a proportion of infants will collapse in the interval between screening and diagnosis.
- For the same population, the estimated number of false-positive screening diagnoses per 100,000 infants screened was 460 (0.5%) for clinical examination, 1168 (1.3%) for pulse oximetry with clinical examination and 4857 (5.4%) for screening echocardiography with clinical examination. The last value reflects the detection of infants with structural cardiac abnormalities with no clinical or functional significance.
- The estimated total screening programme costs per 100,000 live-born infants were £300,000 for clinical examination, £480,000 for pulse oximetry with clinical examination and £3.54 million for screening echocardiography with clinical examination.
- This results in an additional cost per additional timely diagnosis ranging from £4,900 for pulse oximetry with clinical examination to £4.5 million for screening echocardiography with clinical examination.
- For the secondary outcome, the additional cost per additional diagnosis was £1500 for pulse oximetry with clinical examination and £36,000 for screening echocardiography with clinical examination. These conclusions are sensitive to assumptions about the detection rates for screening echocardiography.
- Uncertainty analysis suggests that the probability of screening echocardiography with clinical examination having a cost-effectiveness of <£150,000 per timely diagnosis is <20%.
- Sensitivity analyses suggest that if societal willingness to pay is £50,000 per timely diagnosis then pulse oximetry is likely to be cost-effective until antenatal detection is >90%, whereas screening echocardiography is unlikely to be cost-effective unless societal willingness to pay is at least £10,000,000 per timely diagnosis.
- The key determinants for cost-effectiveness are the detection rates for pulse oximetry and screening echocardiography and screening test costs.

## Test performance

### Base case

In a population of 100,000 live-born infants, the model predicts 167 infants with life-threatening congenital heart defects, of whom 121 remain undiagnosed or unrecognised at newborn screening (*Table 16*). A further 543 infants have clinically significant congenital heart defects, of whom 425 remain undiagnosed or unrecognised at newborn screening.

The estimated percentage of live-born infants with a positive screening result varies from 5.4% for screening echocardiography with clinical examination to 1.3% for pulse oximetry with clinical examination and 0.5% for clinical examination alone. All these infants will require further clinical assessment and diagnostic echocardiography.

From the model, an estimated 82 (68%) and 83 (69%) infants with life-threatening congenital heart defects undetected at screening (*n* = 121) are detected by pulse oximetry with clinical examination and screening echocardiography with clinical examination, respectively, but only 39 (32%) by clinical examination alone. Of these, 71, 71 and 34, respectively, receive a timely diagnosis, reflecting the fact that a proportion of infants will collapse in the interval between screening and diagnosis. Taking all clinically significant and life-threatening congenital heart defects combined, the equivalent detection rates are 50, 62 and 32%

**TABLE 16** *Estimated performance of alternative screening strategies: base-case analysis (numbers per 100,000 live births, rounded to nearest whole number, unless stated otherwise)*

| | Strategy | | |
|---|---|---|---|
| | **Clinical examination (CE) alone** | **Pulse oximetry with clinical examination (PO)** | **Screening echocardiography with clinical examination (SE)** |
| Expected number of life-threatening congenital heart defects at birth (*n*) | 167 | 167 | 167 |
| Expected number of other congenital heart defects at birth (*n*) | 543 | 543 | 543 |
| Congenital heart defects only detected by echo (*n*) | N/A | N/A | 4218 |
| Number screened[a] | 92728 | 92728 | 90734 |
| Expected prevalence of life-threatening CHD at screen | 121 | 121 | 121 |
| Positive screening result: *n* (as % of number screened) | 499 (0.5%) | 1250 (1.3%) | 4940 (5.4%) |
|     True positives | 39 | 82 | 83 |
|     False positives | 460 | 1168 | 4857 |
| Negative screening result | 92230 | 91478 | 85794 |
|     False negatives | 73 | 30 | 27 |
|     True negatives | 92156 | 91448 | 85767 |
| Number of cases with timely diagnosis due to newborn screen[b] | 34 | 71 | 71 |
| Detection rate (%) | 32.3 | 67.9 | 68.5 |
| Positive predictive value (%) | 7.8 | 6.6 | 1.7 |
| False-positive rate (%) | 0.5 | 1.3 | 5.4 |

[a] This is the number actually screened per 100,000 live-born infants and takes into account exclusions and coverage (CE 93%, PO 93% or SE 91%), therefore = 100,000 minus [number of all congenital heart defect cases detected antenatally + number of all congenital heart defect cases recognised after birth but before screening + number of cases with Down's syndrome, lethal trisomy, gastrointestinal malformations not associated with congenital heart defect (128)] × (CE 93%, PO 93% or SE 91%) (= 119 for CE and PO and 116 for SE).
[b] Timely diagnosis = diagnosis before collapse or death occurs.

for pulse oximetry with clinical examination, screening echocardiography with clinical examination and clinical examination, respectively.

Overall, 5.4% (4857) of infants will receive a false-positive screening result with screening echocardiography with clinical examination and this includes 3644 infants with minor structural heart defects that are of no clinical or functional significance. These values are substantially lower for clinical examination alone (0.5%, 460 infants) and pulse oximetry with clinical examination (1.3%, 1168 infants). Hence the predictive value of a positive screening test for life-threatening congenital heart defects is 7.8% for clinical examination alone, 6.6% for pulse oximetry with clinical examination and 1.7% for screening echocardiography with clinical examination.

A summary of these findings for specific congenital heart defects is given in Appendix 11, *Table 47*. The most common conditions prevalent at the point of screening are COA, PA and HLH, which together account for 58% of all life-threatening congenital heart defects undiagnosed or unrecognised at this point. Clinical examination alone is always the least effective strategy in terms of detection rate for individual congenital heart defects. Screening echocardiography with clinical examination identifies the highest proportion of infants with aortic stenosis (82%). Pulse oximetry with clinical examination and screening echocardiography with clinical examination detect an approximately similar proportion of infants with HLH, TGA, PA and COA/IAA, but pulse oximetry detects a higher proportion of infants with TAPVC. Hence with the exception of AS, the model predicts that pulse

**TABLE 17** *Results of the economic analyses per 100,000 live births for the base case using the primary outcome (2000–1 prices)*

| Strategy | Total costs (£) | Timely diagnoses | Incremental cost-effectiveness ratio (£) |
|---|---|---|---|
| Clinical examination alone | 296,891 | 34.0 | – |
| Pulse oximetry with clinical examination | 476,193 | 70.6 | 4,894 |
| Screening echocardiography with clinical examination | 3,540,388 | 71.3 | 4,496,666 |

oximetry with clinical examination and screening echocardiography with clinical examination perform equally well for the most prevalent life-threatening congenital heart defects under assumptions made in the base case. When clinically significant but not life-threatening congenital heart defects are considered, screening echocardiography with clinical examination identifies a higher proportion of VSDs and other defects than any other strategy.

## Varying age at screening

The influence of varying age at screening was explored by estimating test performance should screening be performed immediately after birth or at 48 hours of age instead of at 24 hours of age as modelled in the base-case analysis. Test performances under these circumstances are summarised in Appendix 11, *Tables 48–51*. At birth the prevalence of life-threatening congenital heart defects is 153 per 100,000 live births, higher than at 24 hours in the base case (*Table 48*). Similarly, at 48 hours the prevalence of life-threatening congenital heart defects is 84 per 100,000 live births, lower than at 24 hours (*Table 49*). Hence varying age at screening has a considerable impact on the frequency of congenital heart defects to be detected. However, absolute figures for sensitivity, false-positive screening results and positive predictive values for each screening strategy are similar to those reported for the base case, as is the ordering of the strategies in terms of detection rates and false-positive screening diagnosis. Hence varying age at screening alters the absolute effectiveness of all the screening strategies by altering the prevalence of congenital heart defects to be detected but it does not alter conclusions about their relative effectiveness. This is also true when detection rates for specific defects are considered (*Tables 50* and *51*).

## Economic analyses

### The base case using the primary outcome

The total cost, effects in terms of the number of timely diagnoses and the incremental cost-effectiveness ratios are shown for the base case in *Table 17*. The total cost was lowest for clinical examination alone at £296,891 per 100,000 live births. The total cost of pulse oximetry with clinical examination was £476,193 per 100,000 live births compared with £3,540,388 for screening echocardiography with clinical examination. Clinical examination alone was estimated to result in 34.0 timely diagnoses per 100,000 live births. The addition of pulse oximetry was more than twice as effective as clinical examination alone. Screening echocardiography with clinical examination was only marginally more effective than pulse oximetry with clinical examination with 71.3 timely diagnoses per 100,000 live births compared with 70.6 for pulse oximetry.

The cost per additional timely diagnosis, as indicated by the incremental cost-effectiveness ratios, was £4894 for pulse oximetry with clinical examination compared with clinical examination alone. As indicated above, the cost of screening echocardiography is substantially higher than pulse oximetry, but it is only marginally more effective, hence the additional cost per additional timely diagnosis with screening echocardiography with clinical examination compared with pulse oximetry with clinical examination was £4,496,666.

*Figure 27* presents the results of the 10,000 Monte Carlo simulations in a cost-effectiveness plane for the base case where the primary outcome measure is used. It shows, for all 10,000 runs of the model, that screening echocardiography with clinical examination is more costly than the two alternative strategies, but that the effectiveness of pulse oximetry with clinical examination and screening echocardiography with clinical examination is poorly differentiated, with the plots for the two strategies covering a similar range of effectiveness.

The probabilistic analysis used in the decision model takes account of joint uncertainties in the probability and cost values. For each of the 10,000 iterations derived from the Monte Carlo
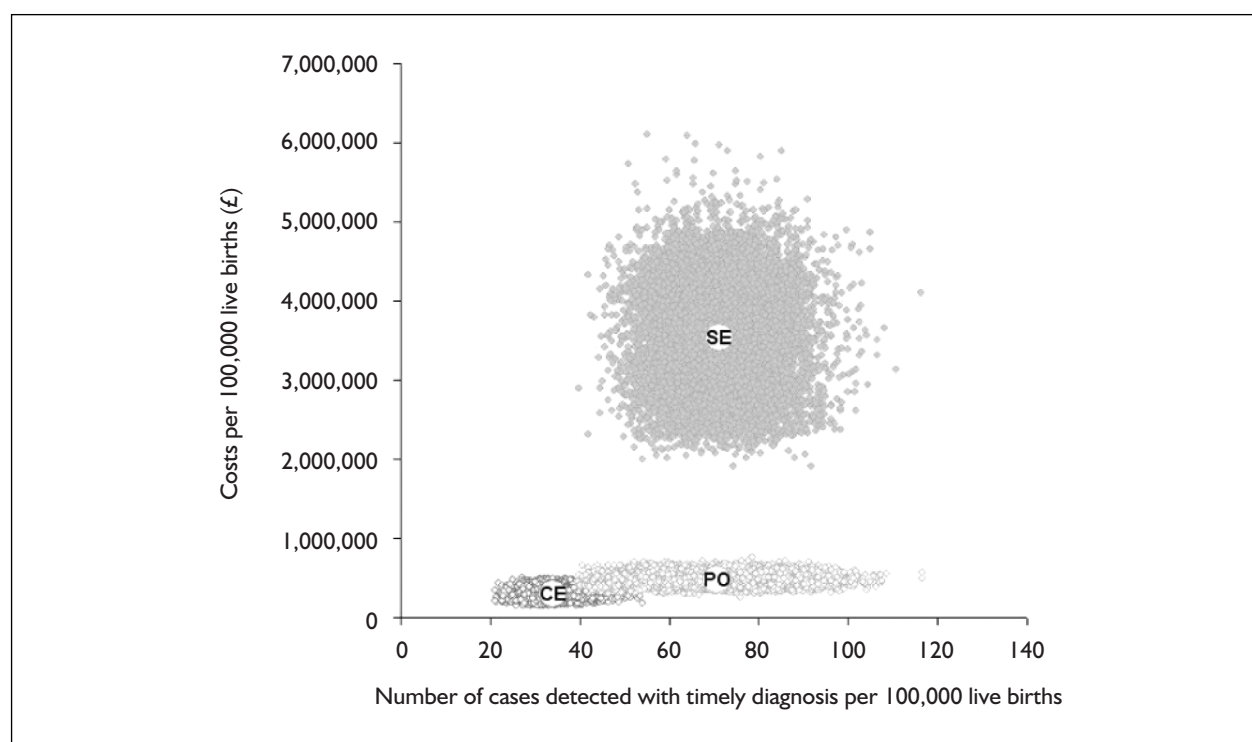
**FIGURE 27** *Results of 10,000 Monte Carlo simulations for the base case using the primary outcome measure (CE = clinical examination alone; PO = pulse oximetry with clinical examination; SE = screening echocardiography with clinical examination)*

**TABLE 18** *The probability of each screening strategy being cost-effective given a maximum value for a timely diagnosis (base case; primary outcome)*

| Strategy | Probability of each screening strategy being cost-effective for the following maximum values for a timely diagnosis | | | | | |
|---|---|---|---|---|---|---|
| | £0 | £2000 | £5000 | £10,000 | £50,000 | £150,000 |
| Clinical examination alone | 1 | 0.99 | 0.47 | 0.08 | 0 | 0 |
| Pulse oximetry with clinical examination | 0 | 0.01 | 0.53 | 0.92 | 1 | 0.91 |
| Screening echocardiography with clinical examination | 0 | 0 | 0 | 0 | 0 | 0.09 |

simulation, the net monetary benefit was estimated within the model for each strategy over a range of £0–150,000 for the maximum value assigned to a timely diagnosis. The model then used these data to estimate the probability of each strategy being cost-effective for a given maximum value assigned to a timely diagnosis. *Table 18* gives, for each screening strategy, the probability of being cost-effective for a given maximum value for a timely diagnosis between £0 and £150,000. For example, if the maximum value society places on a timely diagnosis is £5000 then the probability of pulse oximetry with clinical examination being cost-effective is 0.53, for clinical examination alone it is 0.47, with zero probability of screening

echocardiography with clinical examination being cost-effective. However, if the maximum society value society places on a timely diagnosis increases to £150,000, the probability of pulse oximetry with clinical examination being cost-effective increases to 0.91, the probability of clinical examination alone being cost-effective is zero and the probability of screening echocardiography with clinical examination being cost-effective is 0.09.

The results are also summarised in *Figure 28* as a cost-effectiveness acceptability curve, where the probability of the strategy being cost-effective is plotted against the maximum value society is willing to pay for a timely diagnosis. The
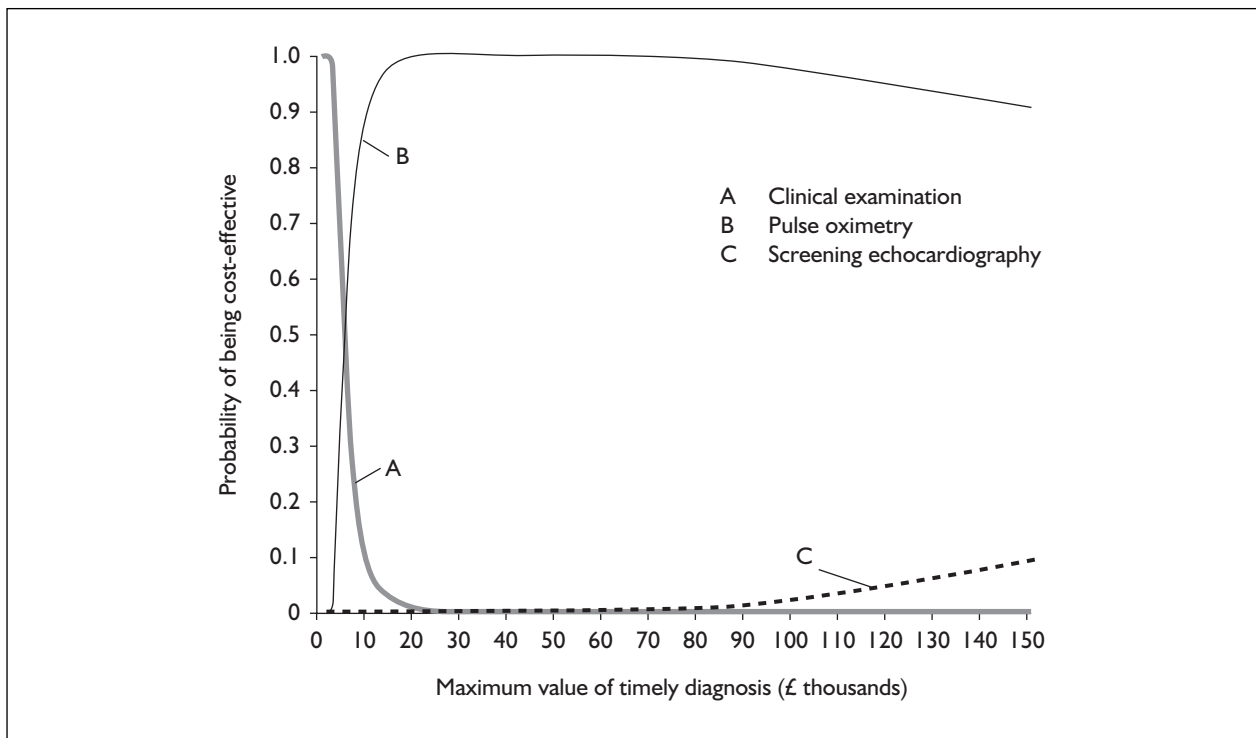
**FIGURE 28** *Cost-effectiveness acceptability curves for base-case analysis (primary outcome)*

**TABLE 19** *Results of the economic analyses per 100,000 live births for the base case using the secondary outcome (2000–1 prices)*

| Strategy | Total costs (£) | Diagnoses of secondary outcome | Incremental cost-effectiveness ratio (£) |
|---|---|---|---|
| Clinical examination alone | 297,627 | 222.4 | – |
| Pulse oximetry with clinical examination | 476,016 | 342.2 | 1,489 |
| Screening echocardiography with clinical examination | 3,457,233 | 427.4 | 36,013 |

maximum value society is willing to pay for a timely diagnosis at the point where the curves cross is equivalent to the mean incremental cost-effectiveness ratio presented in *Table 17*. The curves for pulse oximetry with clinical examination and screening echocardiography with clinical examination shown in *Figure 28* would therefore go on to cross at the point where the maximum value that society is willing to pay for a timely diagnosis is £4.5 million.

## The base case using the secondary outcome

As described in the section Secondary outcome (p. 61), we assumed the detection of clinically significant defects combined with the timely diagnosis of life-threatening defects, following a positive screening test, was the secondary outcome of newborn screening.

The total cost, the number of diagnoses as defined for the secondary outcome per 100,000 live births and the incremental cost-effectiveness ratios are shown for the base-case values in *Table 19*. The total costs are very similar to the base-case analysis using the primary outcome, but clinical examination alone now produces an estimated 222.4 diagnoses per 100,000 live births, compared with 342.2 for pulse oximetry with clinical examination and 427.4 for screening echocardiography with clinical examination.

As indicated by the incremental cost-effectiveness ratio, when the secondary outcome measure is used, the cost per additional timely diagnosis for pulse oximetry with clinical examination compared with clinical examination alone becomes £1489 as opposed to £4894 when the primary outcome measure is used. The addition of screening
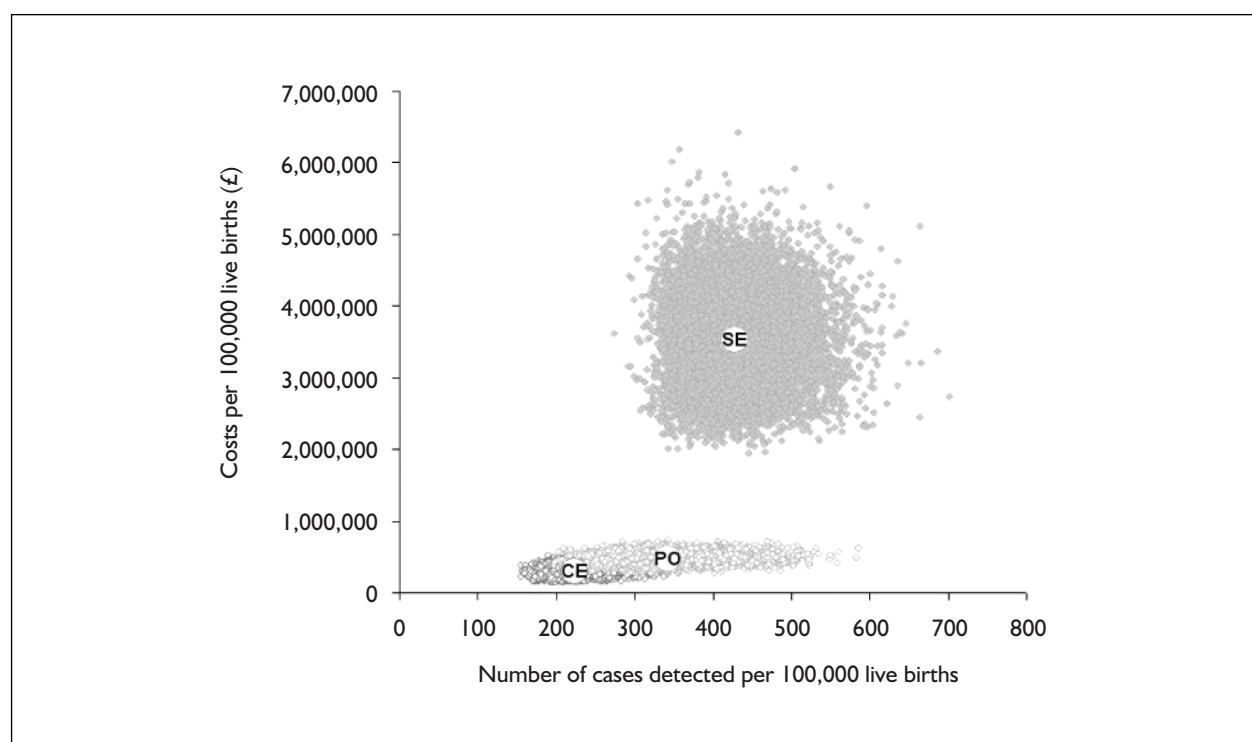
**FIGURE 29** *Results of 10,000 Monte Carlo simulations for the base case using the secondary primary outcome measure*

**TABLE 20** *The probability of being cost-effective given a maximum value for a secondary outcome diagnosis for each screening strategy (base case; secondary outcome)*

| Strategy | Probability of each screening strategy being cost-effective for the following maximum values for a secondary outcome diagnosis | | | | | |
|---|---|---|---|---|---|---|
| | £0 | £2000 | £5000 | £10,000 | £50,000 | £150,000 |
| Clinical examination alone | 1 | 0.23 | 0.02 | <0.01 | 0 | 0 |
| Pulse oximetry with clinical examination | 0 | 0.77 | 0.99 | 0.996 | 0.29 | 0.04 |
| Screening echocardiography with clinical examination | 0 | 0 | 0 | 0 | 0.71 | 0.96 |

echocardiography is now more effective than pulse oximetry, hence the additional cost per additional timely diagnosis with screening echocardiography with clinical examination compared with pulse oximetry with clinical examination becomes £36,013 as opposed to the cost of £4,496,666 observed when the primary outcome measure is used in the cost-effectiveness analysis.

The results of the 10,000 Monte Carlo simulations are presented in the cost-effectiveness plane for the base case, using the secondary outcome measure, in *Figure 29*. As for the primary outcome, this analysis shows that screening echocardiography is more costly than the two alternative strategies for all 10,000 runs of the model. The effectiveness of pulse oximetry with clinical examination and echocardiography with

clinical examination shows greater differentiation when the secondary outcome measure is used, with echocardiography overlapping only at the higher estimates of effectiveness for pulse oximetry.

In *Table 20* the probability of being cost-effective when the secondary outcome measure is used is summarised by screening strategy with maximum values for a timely diagnosis ranging between £0–£150,000. For example, if the maximum value society places on a timely diagnosis is £5000 then the probability of being cost-effective is 0.99 for pulse oximetry with clinical examination, 0.02 for clinical examination alone and zero for screening echocardiography with clinical examination. However, if the maximum value society places on a timely diagnosis increases to £150,000, the probability of pulse oximetry with clinical
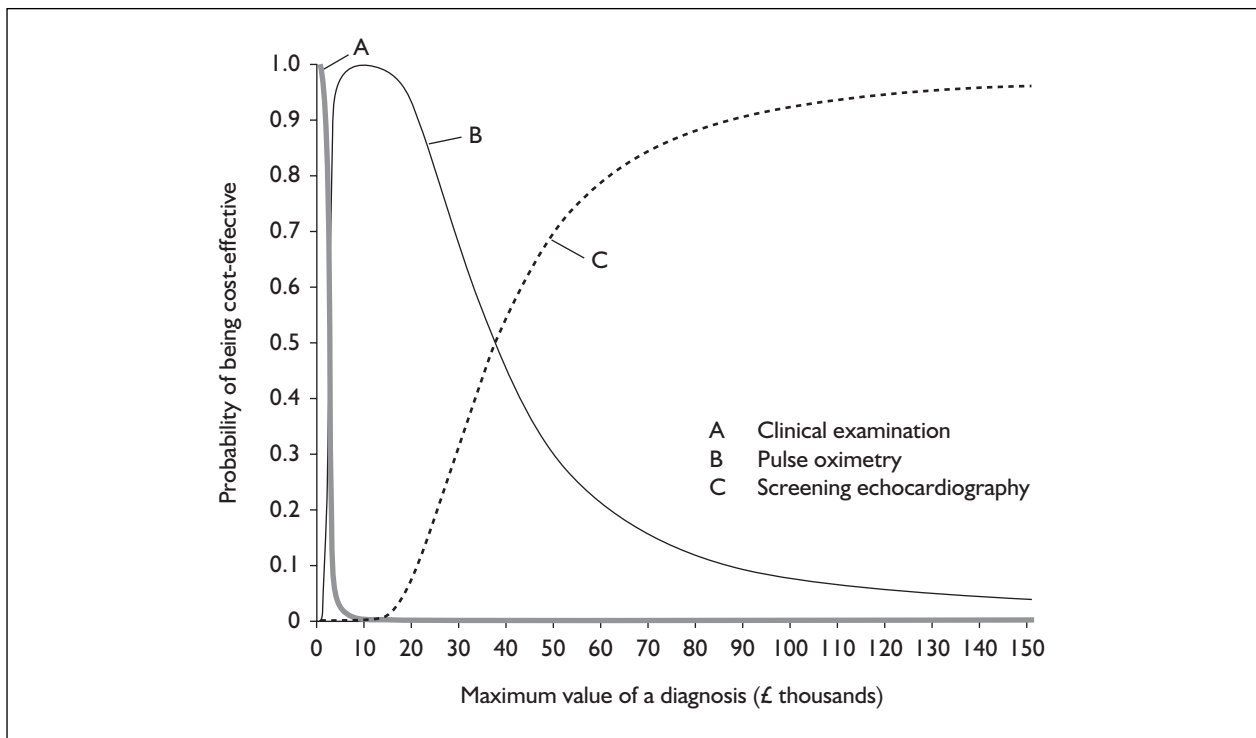
**FIGURE 30** *Cost-effectiveness acceptability curves for base-case analysis (secondary outcome)*

**TABLE 21** *Results of the economic analyses per 100,000 live births assuming screening takes place at birth and using the primary outcome (2000–1 prices)*

| Strategy | Total costs (£) | Timely diagnosis | Incremental cost-effectiveness ratios (£) |
|---|---|---|---|
| Clinical examination alone | 340,909 | 43.9 | – |
| Pulse oximetry with clinical examination | 506,290 | 92.4 | 3406 |
| Screening echocardiography with clinical examination | 3,578,532 | 92.4 | 'Dominated' |

examination being cost-effective is 0.04, that of clinical examination alone zero and that of screening echocardiography with clinical examination 0.96.

The results are also summarised in *Figure 30* as a cost-effectiveness acceptability curve, where the probability of the strategy being cost-effective is plotted against the maximum value society is willing to pay for a diagnosis.

## Scenarios explored within the model
The base-case analyses assume an antenatal detection rate based on Northern Region data and that screening took place at 24 hours. Implementing the national antenatal detection rates[8] and keeping all other parameters in the model at their base-case values resulted in slightly

higher incremental cost-effectiveness ratios for pulse oximetry with clinical examination and slightly lower incremental cost-effectiveness ratios for screening echocardiography with clinical examination, but the overall findings remained similar. Details are given in *Table 52* in Appendix 11. The results of the extended sensitivity analysis, to determine the effects of antenatal screening over a wide range of antenatal detection rates, are presented in the section 'Extended sensitivity analysis for antenatal screening' (p. 85).

*Tables 21* and *22* show the impact of implementing newborn screening at birth rather than 24 hours, keeping all other parameters in the model at their base-case values. Screening echocardiography becomes 'dominated' by pulse oximetry with clinical examination, meaning that pulse oximetry

**TABLE 22** *Probability of being cost-effective given a maximum value for a timely diagnosis for each screening strategy (screening at birth; primary outcome)*

| Strategy | Probability of each screening strategy being cost-effective for the following maximum values for a timely diagnosis: | | | | | |
|---|---|---|---|---|---|---|
| | £0 | £2000 | £5000 | £10,000 | £50,000 | £150,000 |
| Clinical examination alone | 1 | 0.92 | 0.18 | 0.01 | 0 | 0 |
| Pulse oximetry with clinical examination | 0 | 0.09 | 0.82 | 0.99 | 0.995 | 0.90 |
| Screening echocardiography with clinical examination | 0 | 0 | 0 | 0 | <0.01 | 0.11 |

**TABLE 23** *Results of the economic analyses per 100,000 live births assuming screening takes place at 48 hours and using the primary outcome (2000–1 prices)*

| Strategy | Total costs (£) | Timely diagnosis | Incremental cost-effectiveness ratio (£) |
|---|---|---|---|
| Clinical examination alone | 243,986 | 23.7 | – |
| Pulse oximetry with clinical examination | 436,249 | 47.1 | 8,195 |
| Screening echocardiography with clinical examination | 3,513,094 | 48.7 | 1,928,151 |

**TABLE 24** *Probability of being cost-effective given a maximum value for a timely diagnosis for each screening strategy (screening at 48 hours; primary outcome)*

| Strategy | Probability of each screening strategy being cost-effective for the following maximum values for a timely diagnosis | | | | | |
|---|---|---|---|---|---|---|
| | £0 | £2000 | £5000 | £10,000 | £50,000 | £150,000 |
| Clinical examination alone | 1 | 1 | 0.90 | 0.35 | 0.01 | <0.01 |
| Pulse oximetry with clinical examination | 0 | 0 | 0.10 | 0.66 | 0.99 | 0.94 |
| Screening echocardiography with clinical examination | 0 | 0 | 0 | 0 | 0 | 0.06 |

with clinical examination is marginally more effective and is less costly in relation to cost per timely diagnosis. This is reflected in the probabilistic analysis, which takes account of joint uncertainties in the model's probability and cost values, and suggests that even if the maximum value society is willing to pay for timely diagnosis is £150,000, the probability of screening echocardiography with clinical examination being cost-effective is 0.11 (*Table 22*).

*Tables 23* and *24* demonstrate the impact should newborn screening take place at 48 hours, keeping all other parameters in the model at their base-case values. The results presented in *Table 23* show that screening later leads to fewer timely diagnoses and a marginal decrease in screening programme costs for all strategies. In this scenario, the additional cost per additional timely diagnosis for pulse oximetry with clinical examination is £8195 compared with £4894 as in

the base case and £1,928,151 for screening echocardiography with clinical examination compared with £4,496,666 in the base case.

The results of the probabilistic analysis presented in *Table 24*, however, still suggest that even if the maximum value society is willing to pay for an additional case detected with timely diagnosis is £150,000, the probability of screening echocardiography with clinical examination being cost-effective is only 0.06.

The above analyses were repeated using the secondary outcome measure, whereby we assumed a secondary outcome of newborn screening was the detection of clinically significant defects plus a timely diagnosis of life-threatening defects following a positive screening test. Although the absolute value of the incremental cost-effectiveness ratios was altered, the overall findings were robust and not changed by using the national antenatal

detection rate or by changing the timing of screening, with all other parameters in the model remaining at their base case values. Details are given in *Table 53* in Appendix 11.

We investigated the effect of eliminating failures of management of infants with positive screening results by assuming instant access to diagnostic echocardiography. This was modelled by assuming zero probability of an affected newborn collapsing after a positive screening test in all of the screening strategies. Although the incremental cost-effectiveness ratio for screening echocardiography with clinical examination was reduced slightly, the overall findings remained the same. Details are given in *Tables 52* and *53* in Appendix 11.

We also investigated assumptions about different parameters for screening echocardiography with clinical examination. The incremental cost-effectiveness ratio for screening echocardiography with clinical examination was most sensitive to assumptions about the detection rate of screening echocardiography: if this is assumed to be 100%, the incremental cost-effectiveness ratio becomes £126,606 for the primary outcome and £22,291 for the secondary outcome measure (*Tables 52* and *53* in Appendix 11).

Finally, we investigated the scenario which most favoured screening echocardiography with clinical examination. This assumed that screening took place at birth and used the following probabilities: the Northern Region antenatal detection rate, zero probability of collapse after a positive screen, 93% coverage and 100% detection rate for screening echocardiography. For the primary outcome, this resulted in a predicted incremental cost-effectiveness ratio for pulse oximetry with clinical examination of £2224 compared with £4894 in the base case and for screening echocardiography with clinical examination of £88,103 compared with £4,496,666 in the base case. For the secondary outcome, the predicted incremental cost-effectiveness ratio for pulse oximetry with clinical examination was £863 (£1489 in the base case) and for screening echocardiography with clinical examination £17,755 (£36,013 in the base case).

### Extended sensitivity analysis for antenatal screening

This additional analysis demonstrated that, as the proportion of congenital heart defects detected antenatally increased, the number of cases remaining to be detected by newborn screening also fell. However, even with antenatal detection rates of 90% overall in the UK, 10 cases of life-threatening congenital heart defects and a further 40 cases of clinically significant congenital heart defects (per 100,000 live births) were predicted to be detected through newborn screening with pulse oximetry or screening echocardiography used in addition to clinical examination. A full description of the analysis and results are presented in Appendix 12.

The incremental cost-effectiveness ratio for the detection of additional cases of life-threatening congenital heart defects through newborn screening rises more steeply once the antenatal detection rate increases above 80%. *Figure 31* shows that the incremental cost-effectiveness ratio for pulse oximetry with clinical examination, compared with clinical examination alone, rises sharply if >70% of life-threatening cases are detected antenatally. The incremental cost-effectiveness ratio for each additional case of a life-threatening congenital heart defect detected by pulse oximetry, once an antenatal detection rate of 80% is reached, is about £30,000 and with an antenatal detection rate of 90%, the incremental cost-effectiveness ratio is around £50,000. Similarly, for additional cases detected by screening echocardiography, the cost per timely diagnosis rises sharply after a 70% antenatal detection rate is reached (*Figure 32*).

The societal willingness to pay per additional diagnosis made with newborn screening will determine the cut-off levels for cost-effectiveness but pulse oximetry is likely to be cost-effective, even with antenatal detection rates of 80–90%, if societal willingness to pay is £10,000 per timely diagnosis or additional case detected.

If willingness to pay for each additional timely diagnosis is about £10,000, then pulse oximetry with clinical examination ceases to be cost-effective once the antenatal detection rate for life-threatening congenital heart defects rises above 60%, but if willingness to pay is £50,000 then pulse oximetry with clinical examination is likely to be cost-effective until antenatal detection is >90%. Screening echocardiography with clinical examination is unlikely to be cost-effective if societal willingness to pay is <£10,000,000 per timely diagnosis.

## Expected value of information analysis

The cost-effectiveness acceptability curves presented in *Figures 28* and *30* suggest that with
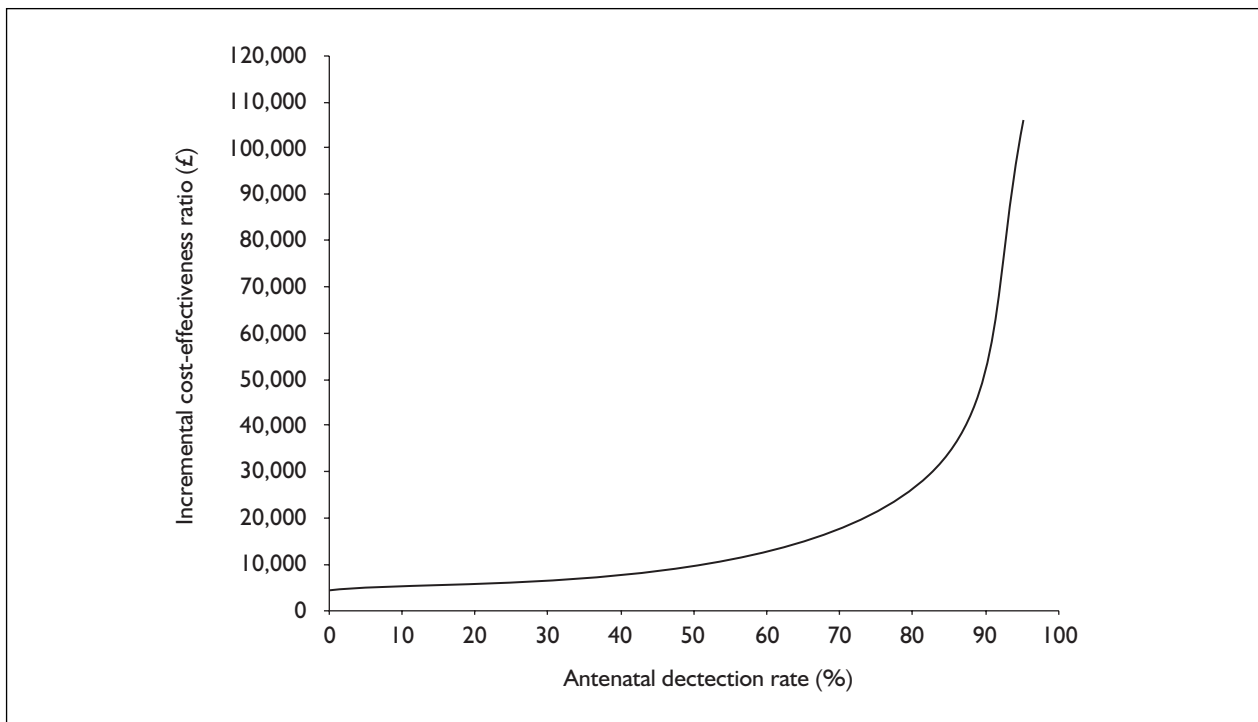
**FIGURE 31** *Incremental cost-effectiveness ratio for pulse oximetry (pulse oximetry with clinical examination relative to clinical examination alone) and antenatal detection rate – primary outcome*
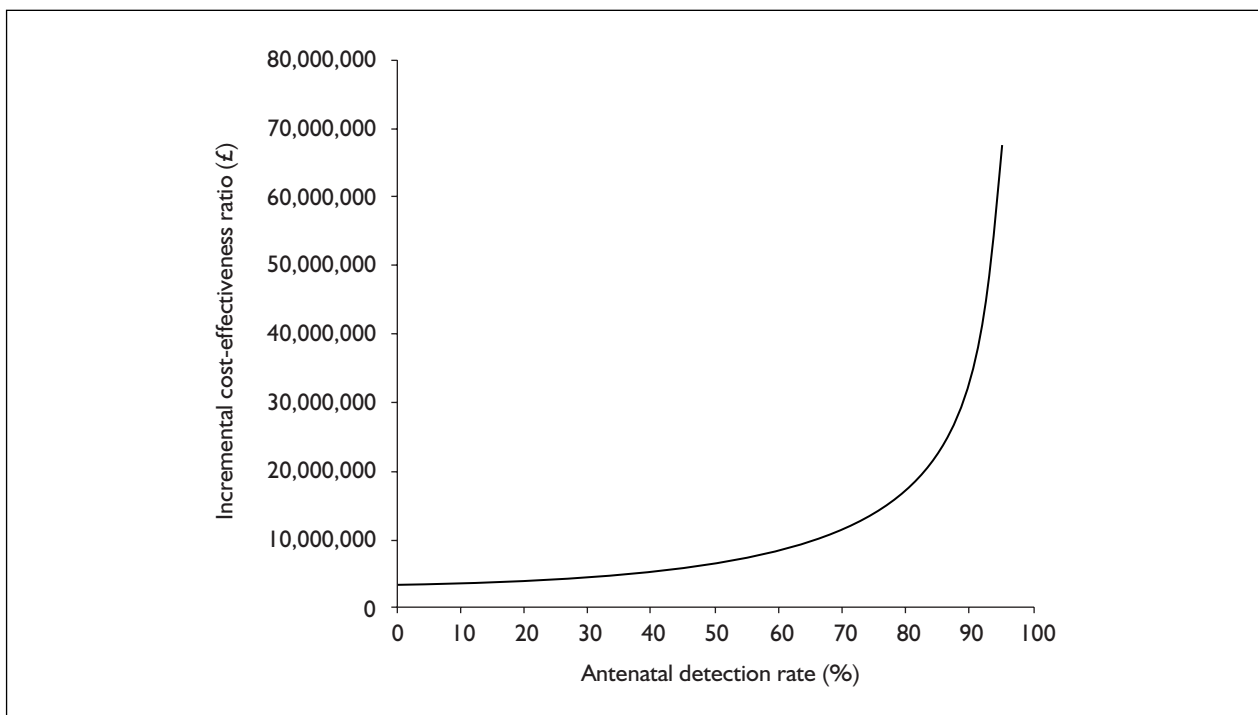


**FIGURE 32** *Incremental cost-effectiveness ratio for screening echocardiography (screening echocardiography relative to pulse oximetry) and antenatal detection rate – primary outcome*

current uncertainty there is a probability that the wrong decision may be made in terms of cost-effectiveness. For example, in the base case using the primary outcome, if the maximum value society is willing to pay for a timely diagnosis is £5000, the baseline decision will be to implement pulse oximetry as 53% of the simulations estimate pulse oximetry with clinical examination as having the greatest net benefit. There is, however, a probability of 0.47 that the decision to implement
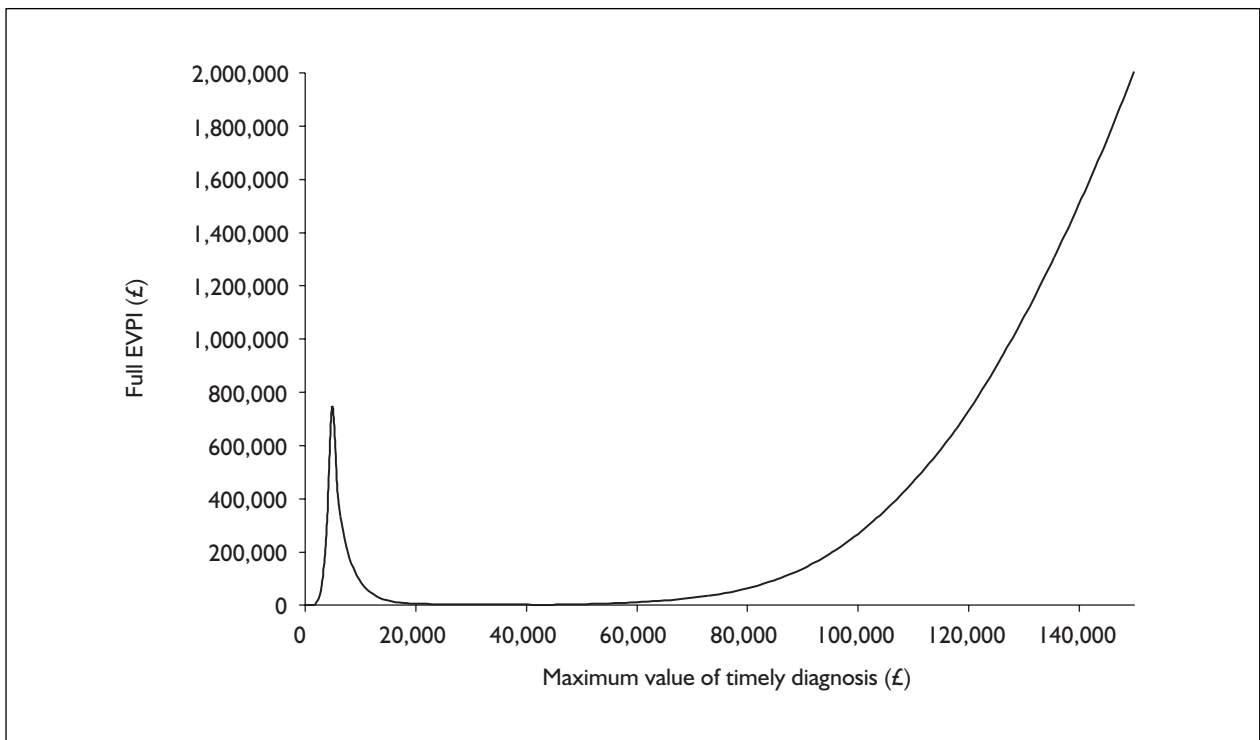
**FIGURE 33** *Population expected value of perfect information: full model, base case, primary outcome*

pulse oximetry with clinical examination is the wrong decision, as 47% of the simulations estimate clinical examination alone to have the greatest net benefit. Where this is the case, the opportunity cost, or forgone net benefit, is the net benefit of clinical examination minus the net benefit of the baseline strategy (pulse oximetry with clinical examination). The mean opportunity cost over all the simulations was estimated over a range of £0–150,000 for the maximum value of a timely diagnosis. This was then applied to a population of 546,566 based on the number of hospital deliveries in England (see the section 'Expected value of information analysis', p. 75).

**Expected value of perfect information: base case, primary outcome**
*Figure 33* illustrates the population EVPI for the full model where the maximum value of a timely diagnosis is between £0 and £150,000. The results suggest that the EVPI peaks around £750,000, where the maximum value of a timely diagnosis is around £5000. This directly corresponds to the crossing over of the cost-effectiveness acceptability curves of clinical examination alone and pulse oximetry with clinical examination illustrated in *Figure 28* and is the point of greatest uncertainty. The potential value of future research to reduce uncertainty is £750,000.

The data presented in *Figure 33* also suggest that EVPI is positive for values beyond £80,000 per timely diagnosis. Following the previous logic, the EVPI will also peak where the maximum willingness to pay for timely diagnosis is around £4.5 million, where the cost-effectiveness acceptability curves for pulse oximetry and echocardiography would cross (see *Table 17*). The population EVPI at this point equates to ~£577 million.

Although the true maximum value for a timely diagnosis is unknown, we considered it unlikely to be greater than £80,000. Therefore, we present the expected value of partial information analysis for parameter groups for a range of £0–14,000 per timely diagnosis in *Figure 34*, reflecting the peak in *Figure 33*. *Table 25* presents the maximum EVPI for the parameter groups. This is the point of greatest uncertainty, where the maximum value of a timely diagnosis is £5000.

EVPI was found to be greatest for the following parameters: detection rate for pulse oximetry, screening costs and the detection rate for clinical examination (*Table 25*). These can be interpreted as the key areas of uncertainty in the model. Further research to reduce the uncertainty around these specific parameter groups would be most valuable and potentially cost-effective provided
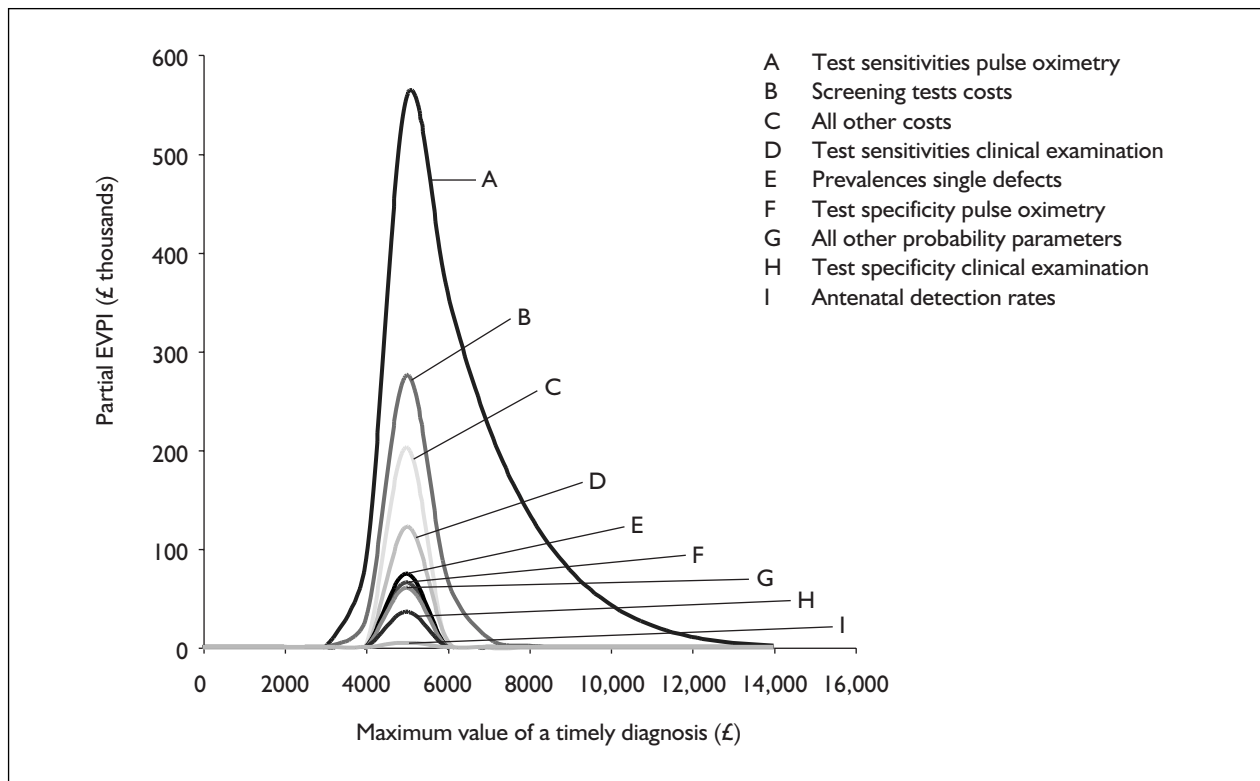
87

**FIGURE 34** *Population expected value of perfect information for parameter groups using the primary outcome*

**TABLE 25** *Expected value of perfect information using the primary outcome (at £5000 per timely diagnosis)*

|  | **Expected value of perfect information (£)** |
|---|---|
| Full model | 744,000 |
| *Parameter groups* | |
| Prevalences of single congenital heart defects | 66,000 |
| Antenatal detection rates | 4,000 |
| Test sensitivities clinical examination | 123,000 |
| Test sensitivities pulse oximetry | 557,000 |
| Test sensitivities screening echocardiography | 0 |
| Test specificity clinical examination | 36,000 |
| Test specificity pulse oximetry | 75,000 |
| Test specificity screening echocardiography | 0 |
| All other probability parameters | 60,000 |
| Screening tests costs | 275,000 |
| All other costs | 202,000 |

that the research budget remains within the sums presented in *Table 25*.

## Expected value of perfect information: base case, secondary outcome

The population EVPI using the secondary outcome is shown in *Figure 35* for the full model over a range of £0–150,000 per diagnosis. The results suggest that the EVPI peaks around £14.5 million, where the maximum value of a diagnosis is around £36,000. This directly corresponds to

the crossing over of the cost-effectiveness acceptability curves of pulse oximetry with clinical examination and screening echocardiography with clinical examination, illustrated in *Figure 30*, at the point of greatest uncertainty: £14.5 million is the potential value of future research to reduce uncertainty.

*Table 26* presents a detailed account of the maximum EVPI at £36,000 per diagnosis. The figures in *Table 26* reflect the peaks shown in
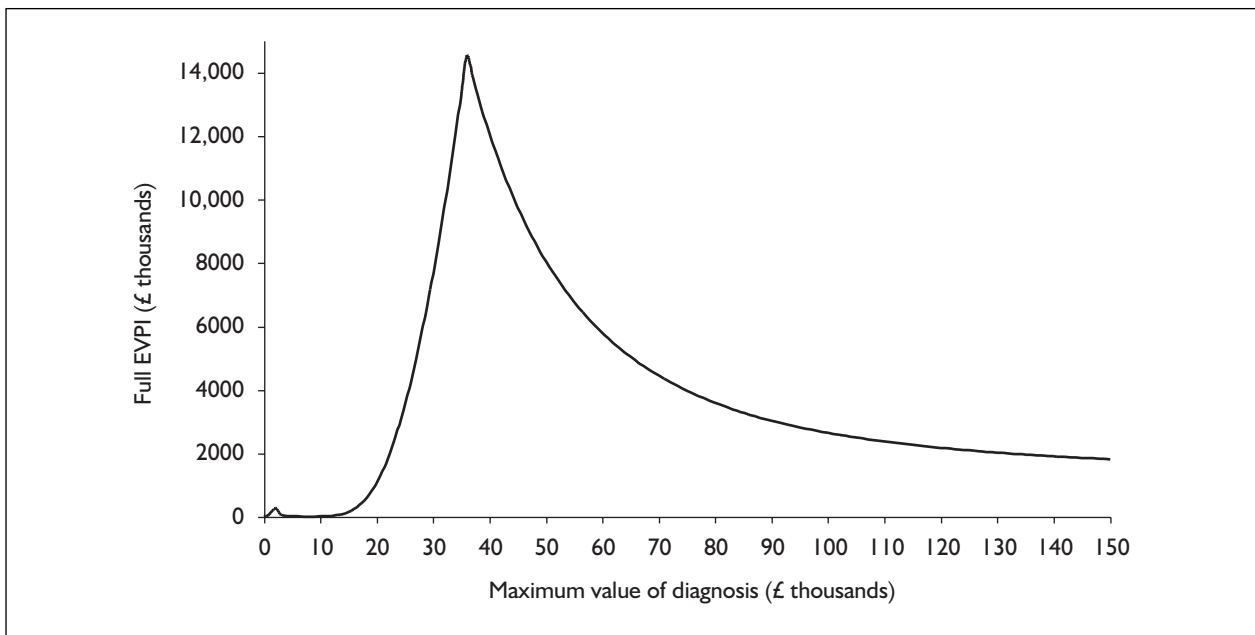
**FIGURE 35** *Population expected value of perfect information for the full model using the secondary outcome*

**TABLE 26** *Expected value of perfect information using the secondary outcome (at £36,000 per diagnosis)*

|  | Expected value of perfect information (£) |
|---|---|
| Full model | 14,450,000 |
| | |
| *Parameter groups* | |
| Prevalences of single CHDs | 323,000 |
| Antenatal detection rates | 1,000 |
| Test sensitivities clinical examination | 0 |
| Test sensitivities pulse oximetry | 11,320,000 |
| Test sensitivities screening echocardiography | 4,958,000 |
| Test specificity clinical examination | 0 |
| Test specificity pulse oximetry | 1,000 |
| Test specificity screening echocardiography | 158,000 |
| All other probability parameters | 411,000 |
| Screening tests costs | 5,285,000 |
| All other costs | 810,000 |

*Figure 36*. The results suggest that further research on the test sensitivities for pulse oximetry with clinical examination and screening echocardiography with clinical examination and screening costs provides most value and would be potentially cost-effective provided that the research budgets remain within the figures presented.

# Discussion

## Review and interpretation of main findings

We have developed a decision analytic model to predict test performance, effects in terms of the primary outcome (timely diagnoses of life-threatening congenital heart defects) and the secondary outcome (clinically significant congenital heart defects and primary outcome combined), costs and cost-effectiveness for three different newborn screening strategies and to allow their comparison. Uncertainties in the data have been explored using three related methods: probabilistic analyses, cost-effectiveness acceptability curves and EVI analyses. As data sources have relied on expert opinion for a range of critical parameters, the evaluation of uncertainties is of great importance to decision-makers, allowing the evidence base for current and alternative screening policies to be better characterised and the value of investing in
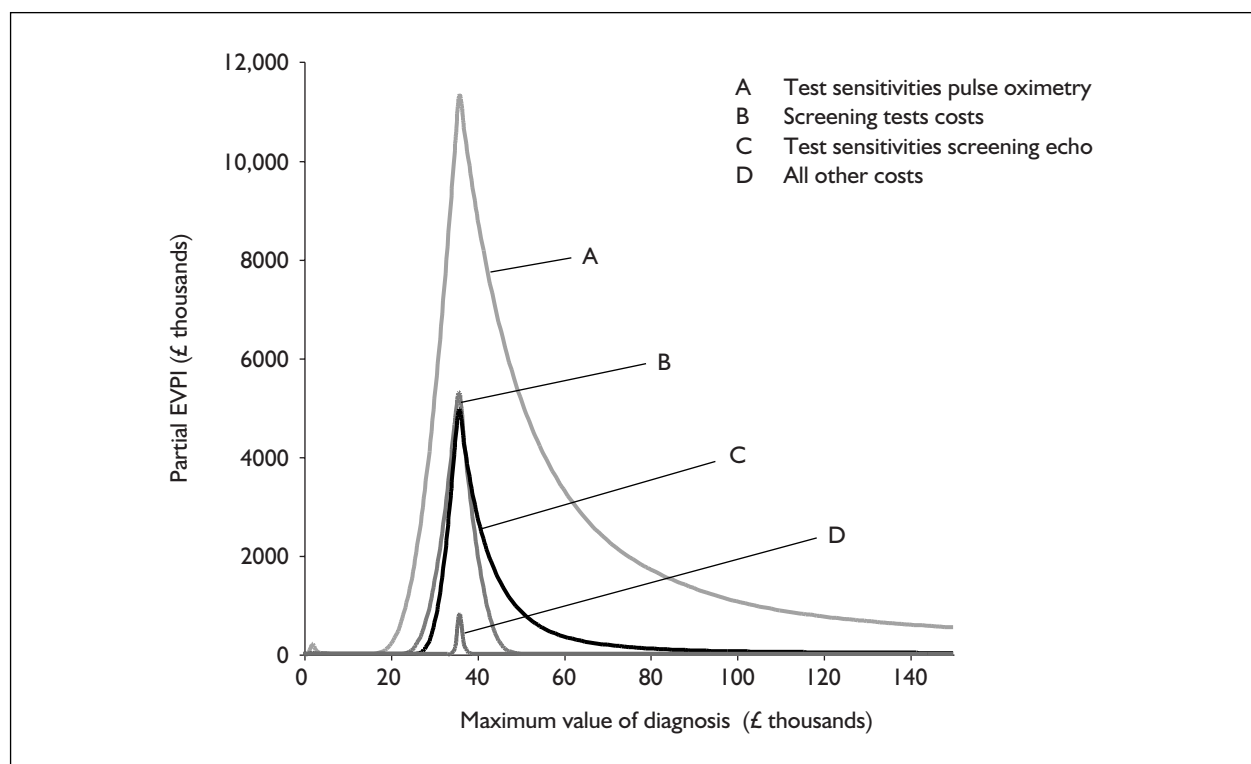
**FIGURE 36** *Population expected value of perfect information for parameter groups using the secondary outcome*

different potential research questions to future policy to be estimated.

The model predicts that screening echocardiography with clinical examination and pulse oximetry with clinical examination will detect a similar proportion of life-threatening congenital heart defects and timely diagnoses of these as defined in the primary outcome. It also predicts that these proportions are much greater than predicted for the current UK policy of clinical examination alone. However, probabilistic analyses demonstrate that there is uncertainty in these predictions reflecting the limited data available for either strategy and that defect-specific detection rates were based largely on expert opinion.

When all clinically significant congenital heart defects are considered in combination with the timely diagnoses of the primary outcome, screening echocardiography with clinical examination and pulse oximetry with clinical examination become more differentiated in terms of detection rates. Although the model has distinguished these outcomes conceptually, in practice a screening programme employing any of the strategies considered will inevitably be based on the secondary outcomes since it would not be ethical or appropriate to disregard information

about clinically significant heart defects. This suggests that careful scrutiny of the broader consequences of these strategies is required, notably in relation to the false-positive rates and their consequences.

The values predicted for false-positive rates in the model suggest that these are very high (5.4%) for the screening echocardiography strategy. This reflects the detection of transient structural abnormalities which are of no clinical or functional importance and which are included in the model as false-positive diagnoses. Although the model includes the costs of follow-up and diagnosis of these false-positive diagnoses, one limitation is its failure to capture the non-economic consequences and potential disbenefits for parents and infants of false-positive diagnoses in screening. Since screening for congenital heart defects needs to be considered in conjunction with the total antenatal and newborn screening experience of mothers and their infants, the additive effects of false positive diagnoses become highly relevant.[237]

If the objective of newborn screening is to detect life-threatening defects, as represented by the primary outcome, the economic results suggest that pulse oximetry with clinical examination is cost-effective relative to clinical examination alone, provided that society considers the value of a

timely diagnosis to be worth at least £4894. Screening echocardiography with clinical examination, on the other hand, is unlikely to be cost-effective since it was shown to cost more and its effectiveness is poorly differentiated from that of pulse oximetry with clinical examination. Moreover, the incremental cost-effectiveness ratio for screening echocardiography suggests that society would have to place a value of £4.5 million or more for a timely diagnosis for screening echocardiography with clinical examination to be considered cost-effective.

## Sensitivity and scenario analyses

The results were sensitive to the outcome measure used (Appendix 11, *Tables 52* and *53*). If the secondary outcome is used, where the detection of clinically significant congenital heart defects as well as the primary outcome is thought to be beneficial, then the effectiveness of screening echocardiography with clinical examination becomes more differentiated from pulse oximetry with clinical examination. The incremental cost-effectiveness ratio suggests that screening echocardiography with clinical examination is cost-effective if society considers the value of a timely diagnosis to be worth at least £36,013 and the secondary outcome is used.

Joint uncertainties in the probability and cost values used in the model were taken into account in the probabilistic analysis and the scenarios explored within the model investigated the robustness of the findings to uncertainties in the antenatal detection rate, to age at screening, to access to diagnostic echocardiography, to the coverage and to the detection rate of screening echocardiography (Appendix 11, *Tables 52* and *53*).

The overall results were robust to the scenarios explored with the exception of the detection rate of screening echocardiography. If the detection rate for screening echocardiography were really to be 100%, then our model suggests that screening echocardiography with clinical examination would be cost-effective. This is, of course, highly dependent on the value assigned to a timely diagnosis and the extent to which society is averse to false-positive diagnoses in newborn screening. Taken narrowly, in the context of the primary outcome, societal values would need to be at least £126,606 for a timely diagnosis and £22,291 for a diagnosis of the secondary outcome for screening echocardiography to be the strategy of choice.

It is worth noting that varying the antenatal screening detection rate across a range of

plausible values for the UK in the model, and across a wider range of values in the extended sensitivity analysis, did not discriminate between newborn screening strategies. Clearly, for some of the defects included in our primary outcome (notably TGA) antenatal screening is an optimal strategy, since it enables delivery in a centre with access to definitive and life-saving management to be planned. For specific defects, such as COA, telemedicine may facilitate timely diagnosis. However, access to urgent surgical treatment or balloon septostomy still involves delay if transport to a specialist centre is required. Antenatal diagnosis would allow delivery in a specialist centre and prompt surgical care, and the role of improved antenatal detection of these defects merits further consideration. Although our brief did not include an evaluation of antenatal screening, it is clear that further work on this aspect of national screening policy for congenital heart defects is warranted. The model presented here could be adapted to examine antenatal detection and its influence on newborn screening policies. This model could also accommodate further adaptation to include population-based antenatal screening data should this become available. Clearly, approaches to the early detection of congenital heart defects, through screening, require an integrated approach across antenatal and newborn screening programmes.

## Limitations of the model

Our model (and its analysis) does have limitations. As described in Chapter 3, data are lacking on the long-term outcomes relating to preoperative collapse. Therefore, we used alternative definitions of a timely diagnosis as the outcome measure for the cost-effectiveness analysis. These outcome measures do not, however, allow cost-effectiveness comparisons with other healthcare programmes to guide decisions on allocative efficiency. In order to do this we would need a broader outcome measure such as quality-adjusted life-years (QALYs) gained. The difficulties in obtaining such a measure are discussed in Chapters 3 and 8. A further limitation of the outcome used is that it does not take account of the health effects of screening beyond 16 years of age.

Our analysis was also limited by the paucity of data on the pathway probabilities included in the model. In addition, the data available were derived from observational studies rather than randomised trials. We were therefore required to rely on expert opinion and subjective probabilities. While the evolution of treatment for congenital

heart defects precludes confident estimates of the outcomes of new technologies,[31] nonetheless the evidence base for the longer term outcomes of existing screening and management policy is very poor, as highlighted in our systematic review as well as in the findings of the Bristol Enquiry.[57,61,262,290] Whatever the screening strategy policy adopted, data systems to collect information on process measures (coverage, timeliness of diagnosis and management) and on longer term outcomes are required for performance management and quality assurance.

A further issue relates to the dependence of covariates in the model. For example, when investigating the age at screening our model allowed the prevalence of defects at screening to alter with the time of screening, but assumed that the mean detection rate and its associated uncertainty for each strategy remained the same. We found no papers examining whether test performance depends on age at screening. Were this to be the case, and in view of the sensitivity of screening echocardiography to detection rate, then better information about the consequences of different ages at screening is important.

Given that data on the costs associated with screening, diagnosis and collapse were also lacking, we estimated the costs of screening and diagnosis from a variety of sources including our own observations. Our model did not, however, take account of the costs of the training required for pulse oximetry or screening echocardiography. We derived the cost of treating a collapsed infant from an economic evaluation of term infants participating in a randomised trial. Although these babies probably need similar intensive care treatment, the extent to which they are a good proxy for infants that have collapsed with congenital heart defects is unknown. Finally, the costs of quality assurance were not included.

## Expected value of information

There is considerable uncertainty surrounding the decision of whether the current policy of clinical examination should be supplemented by either pulse oximetry or screening echocardiography. The objective of the EVI analysis was to estimate the potential value of further research to reduce these uncertainties and to identify those parameters (or sets of parameters) for which more precise estimates would be most valuable. These can be seen as the key areas of uncertainty in the model.

As discussed previously, the EVPI for the full model and for the specified sets of parameters

depends on the definition of health outcome (here primary and secondary outcome) and the monetary valuation of that outcome. The true value that society places on a timely diagnosis of a congenital heart defect is, however, unknown. The issue of whether the detection of all clinically significant and/or only life-threatening heart defects is considered to be beneficial is a matter of judgement. Even though policy decisions may be predicated on the primary outcome, it is likely that the secondary outcome scenario will be enacted as it is not possible to ignore information about other clinically significant congenital heart defects in the course of screening for life-threatening defects. As our analysis has shown, this judgement will inevitably determine the potential value of further research.

The advantage of the EVI analysis is that it highlights which uncertainties are important and quantifies them in absolute terms.[285] As mentioned previously, there was a lack of evidence from good-quality RCTs or observational studies for a number of model parameters. Instead, experts were asked to provide their conservative estimate of these parameters. It was therefore important to assess the impact of these uncertainties on the model outcomes, that is, net benefits of alternative screening strategies. The most important model input variables were the detection rates for pulse oximetry, detection rates for screening echocardiography and screening test costs. Future research concerned with the implementation of screening modalities for congenital heart defects should attempt to reduce uncertainty in the estimation of these parameters. We assumed that all newborn babies would be affected by the screening implementation decision. The choice of 5 years as the effective life expectancy of the screening technology was, however, arbitrary. A longer lifetime would, of course, imply a higher value of perfect information.

Future work is needed to establish the value of the reduction in uncertainty that is achievable through research.[291] Formal methods for the estimation of the expected value of sample information (EVSI), that is, the value of uncertainty through collection of data from an additional finite sample and the estimation of expected net benefit of sampling, have, however, only recently been established.[288] The latter analysis is aimed at determining whether future research is potentially cost-effective and, if so, estimating the optimal sample size taking into account the EVSI and the cost of sampling.

The EVI analysis of the newborn screening model for congenital heart defects suggests that further research to reduce the uncertainty of the model is potentially valuable. Overall, the most important model parameters to be subject to further research scrutiny are the detection rate of pulse oximetry and screening costs. If the detection of all clinically significant congenital heart defects including life-threatening defects as defined by the secondary outcome are thought to be beneficial, then further research might also focus on the detection rate for screening echocardiography.

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# Chapter 8

# Valuing quality of life in children with congenital heart defects

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**Chapter outline**

In this chapter, we review outcome measures available to evaluate quality of life in children. We then describe a study exploring the perspectives of parents and health professionals towards the quality of life of children with congenital heart defects. We developed eight health state descriptions of degrees of cardiac and neurological disability resulting from congenital heart defects. We presented these with a self-administered anonymous questionnaire to two groups of respondents: parents of a child with a congenital heart defect and the health professionals who care for them. Respondents were asked to rank and then score these health states on a visual analogue scale; they then marked the state 'death' on the scale. The views of health professionals and parents about the quality of life of children with congenital heart defects, as represented by these typical health states, were compared.

**Key messages**

* Emphasis is now being placed on the inclusion of patients, or parents of young patients, in shared clinical decision-making with health professionals, taking into account patients' preferences, their perception of their own health, and the impact of treatment on them.
* This study has shown that it is possible to develop condition-specific health state descriptions for children with chronic health problems that reflect their preschool development and abilities at school age in health, social and educational dimensions.
* Parents and health professionals placed similar values on the quality of life outcomes of hypothetical children with congenital heart defects.
* Both parents and health professionals seemed more averse to neurological than to cardiac disability.
* Health professionals were no more likely than parents to score a health state worse than death.
* Further exploration of the values assigned by children and adults with congenital heart defects is required to inform joint clinical decision-making, while investigation of the values assigned by the general public would inform the allocation of healthcare resources.

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## Introduction

In Chapter 3, published studies of longer term morbidity outcomes for children with congenital heart defects were appraised. Increasingly, as new health technologies extend the lives of patients with chronic illnesses, the quality of survival becomes as important as quantity. Knowledge about the longer term outcomes that matter to patients provides an important basis for shared clinical decision-making between patients and health professionals. Through this review, we have demonstrated that there is remarkably little research into the social and educational outcomes that contribute to the quality of life of children and adolescents living with heart malformations. Importantly, there is insufficient evidence to describe the outcomes experienced by survivors throughout childhood, for the purposes of comparing screening outcomes in a decision analysis model. Even less is known about patient evaluations of outcomes (patient-based outcomes) or the preferences of children or parents for different outcomes. Parents and health professionals may differ on the relative importance of specific outcome measures. This was underlined by the views expressed by one mother giving evidence to the Bristol Royal Infirmary Inquiry,

> "My Sophie is still classed as a success, even though she cannot walk, see, talk, move, she can't do anything for herself, but under their criteria, because she lived for 30 days after her operation, she is still counted as one of their successes, and I think that is a travesty."[292]

This chapter will explore the measurement of patient-based outcomes, quality of life and preference-based measures in relation to children, and the implications of these outcome measures for individual and societal decisions about clinical management and healthcare. The aim of newborn screening for congenital heart defects is to improve both survival and long-term health, social and educational outcomes of children with congenital heart malformations. Further work to evaluate the impact of congenital heart defects on the quality of life of children and their families is important to understanding the role of screening in preventing adverse long-term outcomes. Furthermore, we will present a study comparing parents' and health professionals' preferences for health outcomes in children with congenital heart defects.

## Patient-based outcome measures for children

Patient-based outcome measures are increasingly being employed as end-points in clinical trials and wider health services research to "assess health, illness and benefits of health interventions from the patient's perspective."[293,294] Patient-based outcome measures can contribute to the evaluation of the quality of health care and the performance of health professionals[295] play a role in consumer involvement in the wider health services research agenda.[296] Generic instruments for measuring patient-based outcomes can be divided into those that are not preference-based (quality of life, health profiles or health status measures) and preference-based measures (including utilities).[293]

Health-related quality of life (HRQoL) "refers specifically to the impact of health and illness on the individual's … quality of life".[297] This draws on many different concepts of well-being, including material wealth, relationships with others, subjective emotions (self-esteem, fulfilment, happiness) and the ability to participate actively in daily life. HRQoL instruments are classified into disease-specific measures and generic measures.[297–299]

Most quality of life instruments are designed for use in adults and these instruments are often inappropriate for measuring quality of life in children.[300] The independence and abilities of children are related to their developmental age and will change with time, just as a child's concept of quality of life and adaptation to chronic illness may vary with age.[299] Family functioning is an important component of quality of life in children and therefore impacts on the family might be expected to influence the child also.[297] Therefore, instruments to measure health status must reflect a range of domains that are relevant to a child's overall functioning, including physical functioning (sensory impairments, restrictions on daily activities, disability), social functioning (family, peer, school relationships) and psychological functioning (behaviour, emotions, self-esteem). Although work is in progress to develop instruments for use in children with congenital heart defects,[301] currently there is no validated condition-specific instrument.

Children may be unable to respond to standardised quality of life instruments and so often proxy respondents (usually parents or health professionals) answer on their behalf. However, there are discrepancies between child and parent ratings, particularly when evaluating subjective states.[297,299]

It is generally agreed that adults will accept the possibility of ill-health in the distant future if they can maximise health now, but this may not be true for children or for the parents or health professionals making decisions for them.[268] Health professionals appear to value life-years in the distant future in preference to life-years in the immediate future when selecting treatment options for children.[302] However, this aspect of quality of life has not yet been fully explored and there is a real necessity for further studies to involve parents.

## Preference-based measures

The principle of preference-based measures of HRQoL is to assess the preferences or values individuals assign to particular states of health. Respondents are asked to consider both positive and negative aspects of a health state and combine these into a single score.[303] In contrast to psychometric measures, where respondents score each independent dimension (which can be aggregated into a single overall score), preference-based measures require individuals to value health on a single scale.[304] Preference-based measures result in a score on a scale with absolute reference points: usually 0 representing death and 1 representing excellent or perfect health. The exercise can be set up to allow negative scores for health states considered worse than death by the respondent.

There are three main techniques to elicit the preferences of individuals for health states: the standard gamble (SG), the visual analogue scale (VAS) and the time trade-off (TTO).[305] Preferences measured by the TTO and VAS methods are usually referred to as value scores, whereas preferences measured by the SG are utilities.[280] Although all three instruments have been widely employed to assess preferences for health, there has been a longstanding debate on which instrument is the most appropriate for this use[305] as health states can either be elicited directly, by asking respondents to value their own state of health, or indirectly using specific description or multi-attribute classification instruments, such as the EQ-5D or the Health Utility Index (HUI). All three approaches have been used in the context of child and adolescent health.[306–310]

The issue of which approach to use will depend partly on the purpose of the study. For example, there appears to be a growing consensus among health economists that multi-attribute classification systems that include a pre-existing set of preferences as provided by the general

public should be used to inform resource allocation decisions.[311] On the other hand, it has been suggested that value judgements embedded in clinical guidelines should reflect the preferences of the population served by the guideline.[268] These preferences could be elicited by asking affected patients themselves or by using specific written descriptions of health states that respondents may or may not have experienced.

There has been a recent growth in the number of empirical studies attempting to assess preferences for paediatric health states.[306,308,309,312] The most comprehensive appraisal of adolescents', parents' and health professionals' preferences was undertaken by Saigal and colleagues in a series of studies of extremely low birth weight survivors.[313–316] They reported that specialist neonatology doctors and nurses tended to assign lower utility values to childhood health outcomes than did adolescent survivors of newborn intensive care and their parents.

## Shared clinical decision-making

Clinicians are increasingly inviting patients to participate in making decisions about their medical and surgical treatment.[308,317] Emphasis is now being placed on the preferences of patients, their perception of their own health and the impact of treatment.[295] Shared decisions, usually made in the context of one individual child, may be made at times of medical emergency, after receiving a screening result or to decide the appropriate timing of elective surgery. There may be no clear discussion of the differences that might exist between parent and professional values at the time of decision-making. Individual decisions are based on probabilities of risk and benefits and we need to know how these are valued by parents and health professionals[318] and how they influence the decision-making process. The relative importance of different aspects of quality of life to children, their families and health professionals must be understood as the implicit basis for shared decision-making. Whether an individual parent or child participates actively in decision-making in the consultation or relies on advice from the health professional, an analysis of the risk and benefits can help ensure that the decision made is in keeping with their underlying values.[268]

In order to be able to take responsibility for their adult health and to share in decisions about treatment, children and their families need to have information about the prognosis of their condition in terms of activities that will be pertinent to their daily lives. Counsellors of parents whose children have congenital heart defects have found that parents are not concerned by detailed management strategies but by long-term survival and the ability of their child to lead a normal life in the future.[319] A lack of knowledge about long-term outcomes limits parents' ability to make choices[320] and this is particularly pertinent when parents are faced by an unexpected positive screening result and must make choices on behalf of their newborn child. When different management options are being compared for their effectiveness in optimising the quality of life of children with congenital heart defects, the outcome measures used should describe children's competencies in relation to their peers and participation in normal childhood activities. Parents need to be informed about the outcomes that they regard as important so that they can participate effectively in making decisions.

## Aim

Our study builds on previous work comparing preferences of health professionals and parents and explores whether these differences also exist in the context of congenital heart defects. Specifically, we wished to elicit preferences for health outcomes of children with congenital heart defects from the perspective of cardiologists, nurses and other professionals working in paediatric cardiology. We also wished to compare their preferences with those obtained from parents of children with congenital heart defects. We focused on the profile of abilities of preschool and early school age children.

## Methods

### Study sample
*Health professionals*
Doctors, nurses and other health professionals working in paediatric cardiology were recruited for this study at the conference 'Cardiology in the Young', which took place on 2–5 April 2002 at the Institute for Child Health at Great Ormond Street Hospital, London. An anonymous self-administered questionnaire and coloured cards with health state descriptions were included in the conference pack handed out to each delegate. CD presented the study objective and design to the participants at the beginning of the conference and asked the delegates to take part. Completed questionnaires were returned to us by the end of the conference. To provide an incentive to take

part, we arranged a prize raffle (price value £30) at the end of the conference for all those who returned a questionnaire.

### Parents

Parents of children with congenital heart defects were consecutively recruited between July and October 2002 in the Cardiothoracic Outpatient Clinic or Cardiac Ward at Great Ormond Street Hospital for Children, London. One or two researchers approached parents on the ward (CB) or in the waiting area of the outpatient clinic (IG, JB, CD, CB and RK) and explained the study and the self-administered questionnaire. All parents whose child was attending the clinic or ward with a congenital heart defect and who were able to understand the English questionnaire were eligible to take part in the study. If both parents were present in the outpatient clinic or on the ward, we requested that one parent alone completed the questionnaire. We asked parents to complete the questionnaire by giving their own personal views and not to try to imagine themselves as a child, or to consider the health state description as specifically relating to their own child. Parents were given the opportunity to complete the questionnaire at home and return it in a stamped, addressed envelope. The time taken to complete questionnaires was therefore not recorded. Questionnaires were completed and returned anonymously. We obtained written consent to participation from all parents who took a questionnaire.

### Pilot testing

The time taken to complete the questionnaire was piloted on a group of colleagues who took an average of 20 minutes (range 12–45 minutes) to complete it.

### Ethics approval

The study was approved by the Local Research Ethics Committee of the Institute for Child Health at Great Ormond Street Hospital Trust.

## Health state descriptions

To develop health state descriptions, we undertook a review of existing developmental scales and quality of life measures for children. We identified eleven important dimensions of HRQoL for this age group: feeding/eating, independent living, gross motor mobility, fine motor ability, cognitive/school performance, vision, hearing, speech and language, social interaction, emotional understanding and healthcare needs.[297,315,321,322]

In addition, we reviewed descriptions of the experiences of children with congenital heart defects published by patients and their parents on the web pages of support groups [http://www.tchin.org maintained by Congenital Heart Information Network (CHIN) and http://www.guch.demon.co.uk/index.htm maintained by Grown-up Congenital Heart Patients Association (GUCH), assessed March 2002]. Drawing also on our clinical experience in paediatric medicine and paediatric cardiology, we (RK, CB) developed eight hypothetical health state descriptions, which emphasised a child's abilities in one or more dimensions. The draft health state descriptions were reviewed by a second paediatric cardiologist (CW), a clinical paediatric epidemiologist (CD) and a health economist (JB) until consensus was reached.

For the purpose of our study we decided to develop a template that could be used for describing any congenital heart defects rather than attempting to describe health states for specific malformations. The outcomes matrix is shown in *Figure 37*, with health states categorised according to different degrees of cardiac and neurological disability (none, some, severe). In the last column, two levels of cardiac disability (some/severe) were merged as the differentiation between these, against a background of severe neurological disability, was minimal. The descriptions of the health states of children at school age were written in the format of the HUI II[323] but included some aspects of development relative to peers in earlier childhood. They can be understood as an extended snapshot of a child's health at school age. All health state descriptions were written on coloured cards and coded according to the colour. Examples of these are given in Appendix 13.

## Rating exercise

We used a VAS, similar to that used in the EuroQoL EQ-5D questionnaire,[324] and sometimes referred as the 'thermometer rating scale', to assess preferences for all eight hypothetical health states in a self-administered questionnaire. The EuroQol thermometer is widely accepted as the most feasible and acceptable method to elicit preferences using a questionnaire format.[305] The VAS is presented as a 20-cm vertical scale, with worst imaginable health at the bottom and best imaginable health at the top. Prior to the valuation task, respondents were first asked to rank all eight health states from worst to best and to write this order in eight boxes on the

**FIGURE 37** *Outcomes matrix*

questionnaire. They were subsequently asked to indicate the position of the health states on the scale by drawing a line straight across the thermometer rating scale and writing the colour of the health state card on this line. In addition, we asked raters to draw a line across the thermometer scale to mark the value of death relative to the other health states in their opinion. Values on the original or raw scale were rescaled to 0 (dead) and 1 (best imaginable health) first by dividing by 100 and then using the equation $V_i = (x_i - d)/(1 - d)$, where $V_i$ is the value of the health state, $d$ is the value to death on the raw scale and $x_i$ is the value of the health state on the raw scale.[280] In circumstances where respondents did not indicate death on the VAS, missing data were imputed as 0. In a sensitivity analysis, both adjusted group means (with and without imputing) were compared for their equivalence.

Questionnaires were excluded from the analysis of the VAS scores if respondents did not value all health states or their valuation of the health states contradicted their prior ordering, for example, a respondent ranked a health state as best but valued it on the scale only at third best.

We also obtained additional information regarding the age and gender of the respondents, the number of children they had and whether they perceived any of their children to be disabled. Conference delegates were also asked to state broadly their profession (doctor, nurse, other) and to indicate whether paediatric cardiology was their main area of work.

## Statistics

Data were entered into Excel 2000 (Microsoft) and analysed using Stata 7. We used the variance ratio test for testing equality of variance among groups. Differences in mean values on the VAS between parents and health professionals were tested using unpaired *t*-tests for equal variances. Additional non-parametric tests (two-sample Wilcoxon rank test) were performed to assess the robustness of the results obtained from the parametric tests when data appeared to be skewed. Differences in proportions were tested using the $\chi^2$ test. Relationships between demographic variables and VAS scores were compared using multivariate regression.

### Power calculation
A minimum important difference of 0.1 unit on the 0 to 1 VAS was considered to be a clinically important difference between the two groups of respondents in the power analysis. Based on the variability of previous studies that estimated

standard deviations between 0.2 and 0.3 (midpoint 0.25),[325] a study sample of 98 health professionals and 98 parents provides a >80% power to detect this difference using a two-tailed statistical test at a 5% level of statistical significance.

## Results

A total of 180 questionnaires were given out to health professionals and 106 completed questionnaires were returned by the end of the conference, giving a response rate of 59%. All health professionals completed the ranking exercise and were included in the analysis. Seven health professionals' questionnaires were excluded from the analysis of the VAS scores: four respondents did not value all health states, two respondents did not perform the valuation task and the VAS scores could not be read in one case.

A total of 193 parents consented to take part in this study and 109 returned the questionnaire, giving a response rate of 57%. All parents completed the ranking exercise. Ten parent questionnaires were excluded from the analysis of the VAS scores: three respondents valued some or all health states the same, the VAS scores of five respondents contradicted their prior ordering of the health states and two respondents did not complete the valuation. Thus ranking data are available for 109 parent and 109 health

professional respondents and rating data are available for 99 respondents in each group.

Sociodemographic characteristics of all respondents are displayed in *Table 27*. The ages of the 106 health professionals ranged from 22 to 68 years, 30 (28%) were male and the median age was 38 years. The majority of health professionals (88%) identified paediatric cardiology as their main area of work: 52 (53%) were doctors, 39 (40%) nurses and seven participants worked in other health-related professions. Fifty-three (50%) health professionals were parents themselves, with an average of two children, and one health professional reported having a child with a disability. However, in the following text, 'parents' is used to refer to parents of children with congenital heart defects only and not to health professionals who are parents.

Parents were slightly younger than health professionals (median age 37 years, range from 18 to 60 years) and 20 (18%) respondents were male. The average family size was two and 29 parents considered at least one of their children to have a disability.

### Ranking exercise

All respondents in both groups were included in an analysis of the ranking exercise. Results are shown in *Table 28*; the best health state is ranked as 1 and the worst is ranked as 8.

**TABLE 27** *Sociodemographic characteristics of participants*

|  | Health care professionals (*n* = 106) | Parents (*n* = 109) |
| --- | --- | --- |
| *Age* | | |
| Mean (SD) (years) | 39.3 (8.9) | 37.0 (7.3) |
| Median (years) | 38 | 37 |
| IQR (years) | 33–45 | 22–50 |
| Min. max. (years) | 22, 68 | 18, 60 |
| *Sex* | | |
| Male, *n* (%) | 30 (28.3) | 20 (18.5) |
| *Working in paediatric cardiology* | | |
| Yes, *n* (%) | 88 (83.0) | N/A |
| *Health profession* | | |
| Doctor, *n* (%) | 52 (53.1) | |
| Nurse, *n* (%) | 39 (39.8) | N/A |
| Other, *n* (%) | 7 (7.1) | |
| *Have children* | | |
| Yes, *n* (%) | 53 (50.5) | 109 (100) |
| No. of children, mean (SD) | 2.1 (0.9) | 2.2 (1.1) |
| *Child with disability* | | |
| Yes, *n* (%) | 1 (1.0) | 29 (29.6) |

TABLE 28 *Ranking exercise: comparison of rankings between healthcare professionals (n = 106) and parents (n = 109)*

| Hypothetical health state | Disability | | Group | Rank, n (%) | | | | | | | | Median rank | IQR | Mean | SD |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cardiac | Neurological | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | | | | |
| Pink | None | None | HPs | 106 (100) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 | 1–1 | 1 | 0 |
| | | | Parents | 106 (97.2) | 1 (0.9) | 0 (0) | 0 (0) | 1 (0.9) | 0 (0) | 0 (0) | 1 (0.9) | 1 | 1–1 | 1.1 | 0.78 |
| Purple | Some | None | HPs | 0 (0) | 76 (71.7) | 21 (19.8) | 5 (4.7) | 2 (1.9) | 2 (1.9) | 0 (0) | 0 (0) | 2 | 2–3 | 2.4 | 0.83 |
| | | | Parents | 2 (1.8) | 79 (72.5) | 19 (17.4) | 7 (6.4) | 2 (1.8) | 0 (0) | 0 (0) | 0 (0) | 2 | 2–3 | 2.3 | 0.71 |
| Orange | None | Some | HPs | 0 (0) | 28 (26.4) | 46 (43.4) | 25 (23.6) | 4 (3.8) | 1 (0.9) | 2 (1.9) | 0 (0) | 3 | 2–4 | 3.2 | 1.01 |
| | | | Parents | 0 (0) | 24 (22.0) | 43 (39.4) | 32 (29.4) | 8 (7.3) | 1 (0.9) | 1 (0.9) | 0 (0) | 3 | 3–4 | 3.3 | 0.98 |
| Yellow | Severe | None | HPs | 0 (0) | 1 (0.9) | 29 (27.4) | 42 (39.6) | 29 (27.4) | 3 (2.8) | 2 (1.9) | 0 (0) | 4 | 3–5 | 4.1 | 0.93 |
| | | | Parents | 1 (0.9) | 2 (1.8) | 37 (33.9) | 33 (30.3) | 30 (27.5) | 5 (4.6) | 1 (0.9) | 0 (0) | 4 | 3–5 | 4.0 | 1.02 |
| Turquoise | Some | Some | HPs | 0 (0) | 0 (0) | 7 (6.6) | 32 (30.2) | 63 (59.4) | 3 (2.8) | 1 (0.9) | 0 (0) | 5 | 4–5 | 4.6 | 0.70 |
| | | | Parents | 0 (0) | 3 (2.8) | 10 (9.2) | 32 (29.4) | 58 (53.2) | 5 (4.6) | 0 (0) | 1 (0.9) | 5 | 4–5 | 4.5 | 0.9 |
| Red | Severe | Some | HPs | 0 (0) | 0 (0) | 3 (2.8) | 1 (0.9) | 6 (5.7) | 92 (86.8) | 3 (2.8) | 1 (0.9) | 6 | 6–6 | 5.9 | 0.64 |
| | | | Parents | 0 (0) | 0 (0) | 0 (0) | 5 (4.6) | 9 (8.2) | 86 (78.9) | 6 (5.5) | 3 (2.8) | 6 | 6–6 | 5.9 | 0.66 |
| Green | None | Severe | HPs | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (0.9) | 3 (2.8) | 69 (65.1) | 33 (31.1) | 7 | 7–8 | 7.3 | 0.56 |
| | | | Parents | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 3 (2.8) | 77 (70.6) | 29 (26.6) | 7 | 7–8 | 7.2 | 0.49 |
| Blue | Severe | Severe | HPs | 0 (0) | 1 (0.9) | 0 (0) | 1 (0.9) | 1 (0.9) | 2 (1.9) | 29 (27.4) | 72 (67.9) | 8 | 7–8 | 7.6 | 0.86 |
| | | | Parents | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (0.9) | 9 (8.3) | 24 (22.0) | 75 (68.8) | 8 | 7–8 | 7.6 | 0.68 |

HPs, healthcare professionals.

Health professionals and parents ranked all health states in the same order as shown by median ranks (*Figure 38*). The health state with no cardiac and no neurological disability was ranked as best by all health professionals and almost all (97%) parents. The health state with severe cardiac and severe neurological disability was ranked as worst by 68% of health professionals and 69% of parents.

There was less agreement about health states ranked as third, fourth and fifth compared with the health states rated as best and worst. This trend was apparent to a similar degree for both parents and health professionals. IQRs for all ratings were the same across both groups, with the exception of the health state with no cardiac and some neurological disability, which had an IQR of 2–4 for health professionals and 3–4 for parents.

## Visual analogue scale values

Descriptive statistics of adjusted VAS scores of 99 healthcare professionals and 99 parents for all eight hypothetical health state descriptions are presented in *Table 29*. Overall, healthcare professionals rated all health states lower on the VAS than did parents. Differences for mean scores between health professionals and parents were not statistically significant with the exception of the health state with some cardiac and some neurological disability. Similar findings were

obtained using non-parametric tests. The variability of VAS scores in both the health professional and parent groups was highest for the two health states describing the most severe cardiac and neurological disability and showed least variability in the best-ranked health state (no cardiac and no neurological disability).

A comparison of VAS scores of health professionals is shown on *Figure 39*.

Parents of children with congenital heart defects differed in their valuations depending on the number of children they had. Parents with only one child rated all health states higher than parents with more than one child, suggesting the hypothesis that parents' values change with their experience of having other children. This interesting finding, based on secondary analysis, should be interpreted with caution and might be the subject of future studies.

Death was not marked on the VAS by 18 health professionals (18.2%) and 14 parents (14.1%). We imputed these missing values as 0 and compared scores with the scores obtained from the sample that rated death. Again, the findings were not influenced by the exclusion of those with imputed values for death. There was no difference in the VAS score assigned to death by health
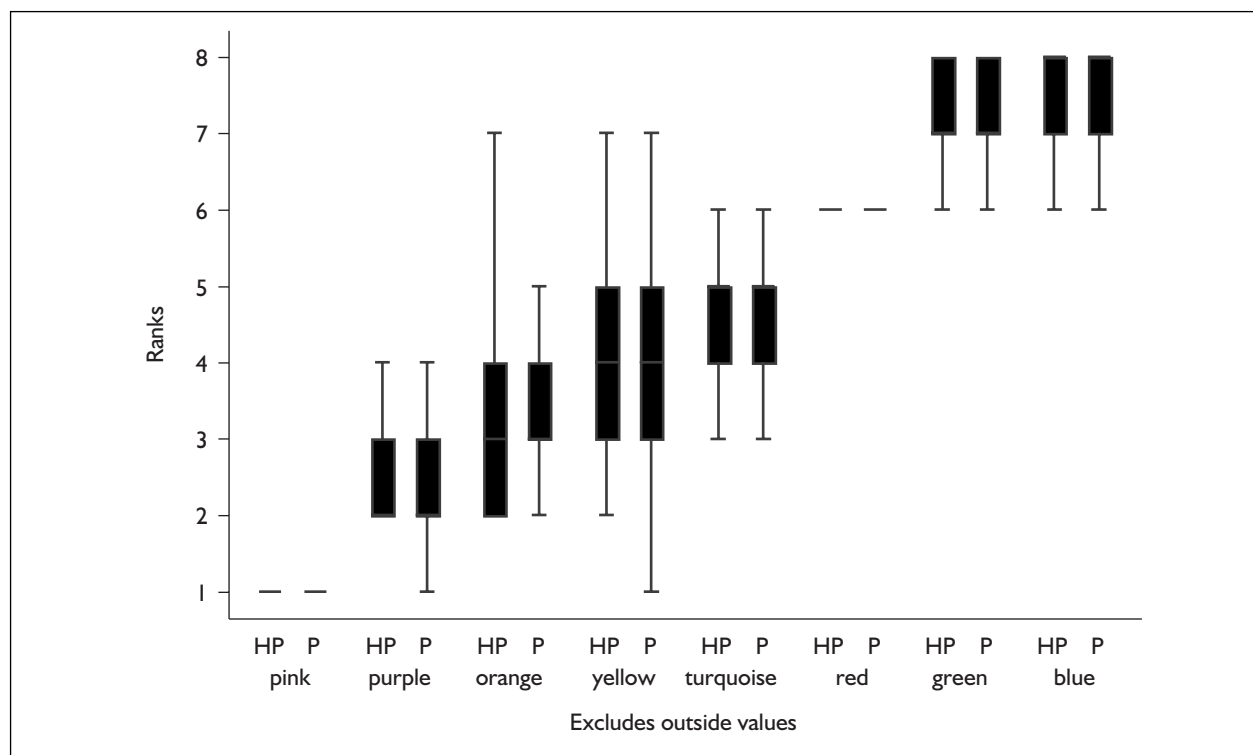


**FIGURE 38** *Ranks of health states (HP, health professionals; P, parents)*

**TABLE 29** *Comparison of healthcare professionals (n = 99) and parents (n = 99): adjusted VAS scores[a]*

| Hypothetical health state | Disability | | | Healthcare professionals | | | | | | | Parents | | | | | | | Mean difference | 95% CI of the difference | | p-Value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cardiac | Neurological | | Mean (SD) | Median | 25th | 75th | Min. | Max. | | Mean (SD) | Median | 25th | 75th | Min. | Max. | | | Lower | Upper | |
| Pink | None | None | | 0.94 (0.07) | 0.95 | 0.91 | 0.98 | 0.7 | 1 | | 0.95 (0.05) | 0.97 | 0.94 | 1 | 0.79 | 1 | | −0.01 | −0.03 | 0.0003 | 0.055 |
| Purple | Some | None | | 0.79 (0.14) | 0.8 | 0.7 | 0.89 | 0.25 | 1 | | 0.81 (0.15) | 0.85 | 0.76 | 0.9 | −0.12 | 0.97 | | −0.03 | −0.07 | 0.01 | 0.16 |
| Orange | None | Some | | 0.70 (0.18) | 0.74 | 0.58 | 0.85 | 0.12 | 0.97 | | 0.73 (0.15) | 0.75 | 0.63 | 0.85 | 0.29 | 0.98 | | −0.03 | −0.07 | 0.02 | 0.24 |
| Yellow | Severe | None | | 0.62 (0.17) | 0.64 | 0.5 | 0.75 | 0.1 | 0.97 | | 0.65 (0.17) | 0.69 | 0.5 | 0.79 | 0.18 | 0.92 | | −0.03 | −0.08 | 0.02 | 0.18 |
| Turquoise | Some | Some | | 0.56 (0.17) | 0.56 | 0.43 | 0.68 | 0.17 | 0.92 | | 0.62 (0.15) | 0.63 | 0.5 | 0.73 | 0.18 | 0.88 | | −0.06 | −0.11 | −0.02 | 0.01 |
| Red | Severe | Some | | 0.44 (0.17) | 0.43 | 0.33 | 0.55 | 0.04 | 0.9 | | 0.48 (0.19) | 0.47 | 0.35 | 0.65 | −0.05 | 0.88 | | −0.04 | −0.09 | 0.008 | 0.10 |
| Green | None | Severe | | 0.27 (0.20) | 0.26 | 0.12 | 0.39 | −0.22 | 0.87 | | 0.33 (0.22) | 0.31 | 0.19 | 0.5 | −0.2 | 0.82 | | −0.06 | −0.11 | 0.0001 | 0.051 |
| Blue | Severe | Severe | | 0.25 (0.22) | 0.22 | 0.09 | 0.37 | −0.24 | 0.87 | | 0.29 (0.23) | 0.26 | 0.15 | 0.47 | −0.3 | 0.8 | | −0.04 | −0.10 | 0.02 | 0.21 |

[a] Differences represent differences in VAS scores between healthcare professionals and parents, with 95% confidence interval (CI) of the difference; negative differences indicate that HPs provided lower scores than parents.
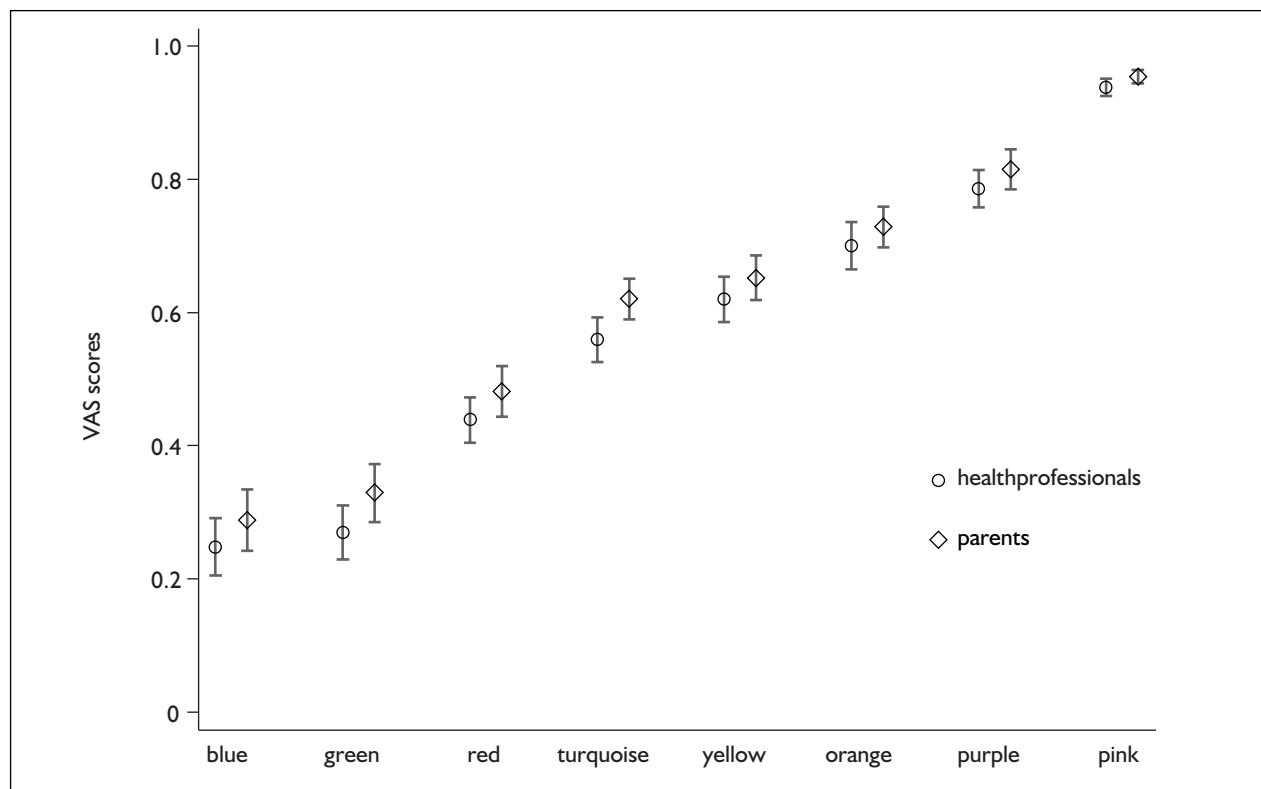
**FIGURE 39** *Comparison of VAS scores of health professionals and parents*

professionals or parents (mean score: health professionals 0.09, parents 0.07; $p = 0.18$).

One or more health states were considered worse than death by 17 respondents. Four health states were rated worse than death, two of which represented the most severe neurological status ($n = 17$, $n = 15$) and one represented the most severe cardiac status ($n = 1$). Details of the respondents who rated some health states worse than death, compared with all other respondents, are presented in *Table 30*. Respondents who rated one or more health states worse than death were significantly more likely to have children compared with all other respondents ($p = 0.03$).

## Discussion

### Discussion of results
Relatively little is known regarding how parents of children with congenital heart defects and the health professionals caring for them value different aspects of quality of life in childhood. As new technologies are emerging that dramatically increase the likelihood of survival for a number of severe heart defects into adulthood, quality of life aspects become more important. To our knowledge, this is the first study that has

attempted to elicit preferences for paediatric health states involving congenital heart defects.

We have shown that parents of children who have congenital heart defects and the health professionals who care for them value typical health states of these children in a similar manner. Both groups assigned the lowest values on the VAS to the health state descriptions with severe neurological disability and valued the health state descriptions with severe cardiac disability higher than this, suggesting that in general both groups have a greater aversion to neurological disability. However, even worse cardiac disability could be explored. Health professionals were no more likely than parents to score a health state worse than death. However, amongst all respondents, those who had children were more likely to assign values worse than death to some health states. To our knowledge, this has not been previously examined and we know of no other studies reporting this finding.

This study has shown that it is possible to develop condition-specific health state descriptions for children with chronic health problems that reflect their preschool development and abilities at school age in health, social and educational dimensions. Parents and health professionals were

**TABLE 30** *Respondents who ranked one or more health states worse than death*

| | Respondents who ranked health states worse than death (*n* = 17) | Respondents who did not rank health states worse than death (*n* = 181) | *p*-Value |
|---|---|---|---|
| **Age** | | | |
| Mean (SD) (years) | 34.9 (7.6) | 38.7 (8.3) | |
| Median (years) | 36 | 38 | 0.07 |
| IQR (years) | 20–48 | 18–68 | |
| **Sex** | | | |
| Male, *n* (%) | 3 (17.6) | 43 (23.9) | 0.56 |
| Female, *n* (%) | 14 (82.4) | 137 (76.1) | |
| **Respondent group** | | | |
| Healthcare professional, *n* (%) | 10 (58.8) | 89 (49.2) | 0.45 |
| Parents, *n* (%) | 7 (41.2) | 92 (50.8) | |
| **Have children** | | | |
| Yes, *n* (%) | 9 (52.9) | 41 (22.9) | 0.03 |
| No, *n* (%) | 8 (47.1) | 138 (77.1) | |
| **Child with disability** | | | |
| Yes, *n* (%) | 1 (6.7) | 23 (15.1) | 0.37 |
| No, *n* (%) | 14 (93.3) | 146 (84.9) | |

able both to rank and to value the health states for congenital heart defects on a VAS, according to their own individual views. We have also shown that it is possible to undertake this valuation exercise using a short written questionnaire.

### Findings from previous research
Our study adds to the relatively small body of research into preference elicitation for health states in children. Only a few studies have compared preferences of health professionals and parents. Previously, Saigal and colleagues used health state descriptions for extremely low birth weight survivors, based on HUI methodology, and used these to show that neonatologists and newborn nurses differ from parents and adolescents in their values for health states of extremely low birth weight survivors.[315] In this study, the SG was used as the main method of valuation and respondents were asked to imagine themselves to be 8 years of age living in each of the health states for the next 60 years. Possible explanations for the discrepancies between this study and our own findings are that valuations for paediatric health states depend on the specific clinical context. In addition, preference scores obtained from neonatologists, who seldom undertake longer term care of their patients, may not accord with those of paediatric cardiologists, who do care for children with heart defects at least until adolescence.

Another related issue is whether health professionals and parents differ in their preferences regarding short- and long-term risks. In the context of acute fever in children, Kramer and colleagues demonstrated differences between parents and health professionals in their preferences regarding clinical care.[318] Parents were concerned to avoid investigations and procedures in the immediate and short-term and willing to accept the very low risk of later illness that might result from incomplete investigation. In contrast, Bennett and colleagues, studying meningitis with differing degrees of disability as a result of occult bacteraemia, found agreement between health professionals and parents.[326] Both groups were willing to accept transient, painful investigations for children if this decreased the chance of severe disability later in life. The findings from these studies may differ because of the different methodologies used, the nature of the outcomes being considered, the age of the children or the particular paediatric contexts in which they were undertaken (secondary as opposed to primary care).

### Discussion of methods
We wished in our study to begin by exploring differences between the values of parents and health professionals as they are most often involved in shared decision-making, particularly for infants with congenital heart defects. There are, however, issues about the methods used, which have some limitations and raise questions for further research. These include the use of the VAS, the perspective of respondents when completing the exercise, the repeatability and stability of the exercise, the use of condition-

specific health state descriptions and the use of parents as proxy respondents.

In our study, we used a VAS because most commentators would not recommend the use of the SG or TTO methods with a self-administered questionnaire format.[305] Health economists usually prefer choice-based techniques such as the SG or TTO because they are based on a notion of sacrifice and opportunity cost[305] and from this perspective the VAS is regarded as theoretically inferior. Recent recommendations, however, emphasise the need to take a considered approach to the selection of the valuation technique. Each of the three methods asks different questions and measures different but related concepts,[268,304,305] and the most appropriate choice might therefore be dependent on the specific situation. The SG may be more appropriate in situations where the risk attitude of respondents is an important consideration and the TTO is thought to be better suited to the valuation of chronic health states. On the other hand, when perceptions of overall severity are being compared, the VAS is probably the preferred instrument.[304]

The response rates of 59% for health professionals and 57% for parents are comparable to those in previous studies, as is the proportion of respondents who returned the questionnaire but did not complete the VAS,[305] and this probably reflects the burden of the task. Although all parents were approached personally by one of the investigators of the study and gave consent after the study objectives had been explained to them, a substantial proportion of ~40% did not return the questionnaire. Future studies should possibly use the interview format to elicit preferences.

A related issue is the choice of technique for assessing preferences in a paediatric population. Although empirical studies of adolescents' preferences have begun to emerge in the literature,[309,327,328] it is not clear to what extent younger children have well-defined preferences over a range of alternative choices. They might lack the cognitive and linguistic skills to complete instruments such as the SG, TTO and VAS. Only one study has investigated lower age limits for completing the SG and the VAS, and this suggested that the minimum age was 8 years for completing the VAS and 12 years for the SG instrument.[307,329]

In our study, we chose to ask parents to value health state descriptions according to their own views and independent of any consideration about the health status of their own child. However, we identified inconsistencies in the perspectives taken in previous research, particularly when parents have been asked to value health states experienced by children using choice-based techniques. For example, in several studies parents were asked to imagine themselves to be 10 years of age and living in a particular health state for the rest of their lives.[315,330] In contrast, Kuppermann and colleagues used the TTO method to ask parents how much time off their life expectancy they would be willing to trade to avoid their child experiencing particular outcomes after different childhood vaccinations.[312] Other researchers do not explicitly state the perspective taken,[303,306,331] but appear to assume they are measuring an adult (parent or other) perspective on children's health outcomes. We could not identify any comparative study that investigated the relative importance of different perspectives.

We were not able to assess test–retest reliability because respondents in our study were given an anonymous questionnaire to complete. However, the test–retest correlation coefficients for the VAS have been found to be acceptable in previous studies ($r = 0.61$–$0.95$).[305] As other researchers have rightly pointed out, there is also a need to investigate whether preferences are stable over time.[308,332] To our knowledge, only one longitudinal study to date has assessed stability of preferences in the context of child health and, more specifically in the antenatal and perinatal periods. Saigal and co-workers found that maternal preferences for disabling health states appear to be stable during the first year of life.[308] We were not able, in this study, to test the stability of our results over a longer period. In addition, it was not possible to incorporate a time-based preference in our study, but this would also be interesting to explore in future work.

The health state descriptions that we developed for this study were condition specific, relating primarily to children with varying severity of congenital heart defects. However, the health, social and educational dimensions explored by our health state descriptions are common to all children of school age and this instrument could be readily adapted for use in other groups of children with chronic illnesses, such as cystic fibrosis or Down's syndrome. Furthermore, we included a description of preschool development into the health state that was appropriate in the context of the congenital anomalies described: this was included as a comparison of development in motor, self-care and educational skills with peers

of the same age. Some attempts have been made to adjust for development in health status instruments and, for example, the HUI ask respondents to consider what is normal for the age of the child being assessed. There are, however, concerns about whether the same set of dimensions can be used to describe the functional, cognitive and behavioural characteristics of children from early infancy to late adolescence. Recent recommendations are for the development of age-specific modules in HRQoL and health status instruments.[333]

Another issue arising from this research is the use of parents as proxies rather than obtaining preferences from the children themselves. We did not include children among the respondent groups in this initial study but previous work has demonstrated that this is possible.[307,314,315,329] A few studies have investigated whether preferences for health states among parents and their children differ.[332] Saigal and colleagues compared adolescents' and parents' ratings, using the SG method and VASs, in a series of studies using a cohort of extremely low birth weight adolescents and a control group of healthy adolescents.[327] Both groups of teenagers rated their own health state and four hypothetical health state descriptions lower than their parents, indicating that both groups of parents were more generous than their children in assessing preference scores.[334] As lower ratings by teenagers were apparent not only in the patient group, but also in the control group, this suggests that there is a developmental influence on how adolescents view quality of life.[334] Teenage girls and their mothers have also been found to differ in their valuations of various health states.[335]

We found heterogeneity of response within the groups of parents and health professionals, reflecting the fact that different views are possible at an individual level. However, our study was not designed *a priori* to explore the values of different subgroups of respondents, although age and sex did not appear to be determining factors in the multivariate regression analysis.

## Conclusions

We conclude from this study that, in general, parents of children with congenital heart defects and the health professionals caring for them do not differ in their values for the quality of life of children with congenital heart defects. This suggests that parents and professionals involved in shared decision-making are working together from a similar set of preferences for long-term outcomes.

However, it has recently been suggested that preferences for future health states (outcomes) and for treatments may differ.[336] Patients might not prefer the treatments that maximise their chances of achieving their preferred health state. This might be particularly true for treatments with a high risk of adverse outcomes as is seen in paediatric cardiology. The findings of our study suggest a reassuring concordance in preferences for health outcomes between health professionals and parents, and also that both groups are similar in their aversion to treatments that might result in neurological disability as compared with cardiac disability, but future work needs to confirm these findings. Further studies are also needed to understand whether young people share the preferences of the adult respondents in our study.

Although there has been a recent growth in the number of empirical studies that attempt to elicit preferences for paediatric health states, the application of preference-based measures in child health needs further methodological development.[333,337] The methodology used in this study could be further developed by exploring the impact of comparing results using the VAS and SG methods, by including preschool development in the health state description, and by asking children to complete the exercise. There is a need to elicit preferences for paediatric health states from the general population if these are to inform clinical guidelines or resource allocation through the development of QALYs. At present, there is no consensus regarding the methodology for developing QALYs for children.

The variation in responses from individuals, demonstrated by this study, indicates that group values alone cannot inform clinical decisions about management for individual children. This study emphasises the need for all participants in shared decision-making to explore their values for outcomes in different health, social and educational dimensions, and their individual preferences for cardiac or neurological disability, in order to understand fully future management options. In individual consultations, the health state descriptions developed here might also be a tool for explicitly assessing the risks and benefits of different management options or the critical values that underlie the rejection of certain treatment options.[268] In the context of newborn screening, when parents must consider the

possible long-term outcomes for their infants, the presentation of health state vignettes can facilitate a discussion of values for different outcomes between health professionals and parents and are an important component of clinical decision aids.[338,339] Further research into the preferences of health professionals and parents, and eventually older children, for the longer-term health, social and educational outcomes after newborn screening is important as a basis for involving parents in the decision-making process after a positive screening test result.

# Chapter 9

# What matters to parents and families?

**Chapter outline**

In this chapter, we describe a structured review of the medical literature regarding parental experiences of newborn screening with relevance to screening for congenital heart defects. We link findings from the literature review with those from a focus group involving parents of children with congenital heart defects, which was set up to discuss experiences of screening methods and diagnosis of congenital heart defects in the newborn period.

**Key messages**

- Parents support newborn screening for heart defects, believing that this will prevent the sudden collapse and death of their baby, and this is true even for parents who have direct experience of a failure of screening.
- Parents prefer screening methods that are simple, accurate and do not cause discomfort to babies, and they also prefer screening to be done as early as possible.
- The worst psychosocial effects of screening are focused around poor management of the screening process and false test results.
- Parents experiencing a 'missed' or delayed diagnosis tend to show less confidence and trust in health professionals thereafter, particularly if the delay is due to poor management of a positive screening result.
- False-positive results can lead to anxiety in the period between the screening test and diagnostic test, but this anxiety is mostly short-lived.
- The detection of clinically non-significant heart defects has significant implications for screening technologies in which this is more likely, such as echocardiography, but the effect on parents is likely to depend upon management and has not yet been adequately explored.
- The focus group contributed specific information about the issues that lead to parental distress and limit parent–professional partnership in the care of children with congenital heart defects. The parents emphasise the need for universal screening standards, as well as knowledgeable and sympathetic health professionals to discuss screening outcomes with parents.

Parents who are offered screening for congenital heart defects in their newborn infants must consider the benefits and drawbacks of a screening process that has implications for their own lives, in addition to those of their infants and wider family. Parents' expectations of screening will be related to their level of knowledge, about both screening and congenital disorders, and to previous experience of these. Their understanding of screening may not concur with the views of professionals, not necessarily because they are uninformed about screening, but simply because they interpret the information in terms of personal circumstances.

It is important to examine the impact on individuals of a population-based screening policy, in order really to understand the wider value for society. This has often been seen as exploring the psychological and social, or psychosocial, aspects of screening and has been reviewed in a number of adult, newborn and antenatal screening programmes in a variety of ways. This chapter is therefore concerned with the psychosocial effects of routine newborn screening for congenital heart defects on parents and children.

## Aims

The aims of this review were to describe and consider the range of possible newborn cardiac screening outcomes from the perspective of parents, through

1. a review of published studies, which have explored the psychological and social impacts of newborn screening upon parents and families, and
2. a focus group involving parents of children with congenital heart defects that would directly explore and record parents' views.

## Introduction

Screening is most simply evaluated in terms of the clinical benefits that it offers, such as the reduction in premature deaths and disease, but attention has also been drawn to the need to evaluate the psychological effects of screening programmes.

## Background

This review considered the psychosocial effects on families of screening newborn infants for congenital heart defects of varying severity and clinical significance. The direct psychological

effects on parents, such as anxiety, and the implications for family relationships, were explored through parent views expressed in published research and a local focus group. Previous HTA studies of screening were the starting point to investigate further parents' perceptions of the screening process, screening outcomes and the communication of a diagnosis of a congenital heart defect.

The importance of parents' views, and the impact of congenital heart defects within families, are highlighted in the Bristol Royal Infirmary Inquiry.[10] The care of children with congenital heart defects relies upon a partnership of care between families and clinicians. Clinicians involved in antenatal and newborn screening should be aware of parents' expectations of screening and their need for information and support throughout the process. Screening has an important role to play in the diagnosis and early management of congenital heart defects.

Newborn screening for congenital heart defects has similarities with other newborn screening programmes in its focus on the newborn clinical examination. However, at the severe end of the spectrum, having a congenital heart defect can be a life-threatening condition and early detection is potentially life-saving. This differentiates congenital heart defects screening from other disorders in which chronic disability is the preventable outcome. The heterogeneity of congenital heart defects means that, in addition, many children are offered follow-up for clinically mild or non-significant disease without requiring any definitive medical treatment.

Screening technologies for detecting congenital heart defects range from clinical examination, which has most often been the subject of screening research, to pulse oximetry and echocardiography. Screening using non-invasive and imaging technology, for example fetal ultrasound for congenital anomalies or newborn hearing screening, have been explored from the parental perspective and the findings from these studies are probably also applicable to screening for congenital heart defects, whereas parental experiences of invasive techniques, such as blood sampling, are less likely to be relevant.

Specific questions addressed by this review were:

- What were the benefits and drawbacks of the screening process for parents and families, including their understanding and responses to the use of non-invasive technologies such as pulse oximetry and echocardiography?
- What were parents' responses to different screening outcomes: true positive (diagnosis), false positive, false negative and true negative?
- How does detection through screening compare with parents' experiences of clinical presentation of congenital heart defects?
- How might a future newborn screening programme for congenital heart defects take these psychosocial effects into account?

## Methods

### Literature review

We were interested in exploring the experiences of both parents in the context of other newborn screening examinations, which were seen as relevant to screening for congenital heart defects. Research into parents' views of antenatal and genetic screening, offering 'informed choice' regarding termination of pregnancy, often addressed issues that were not applicable to newborn screening. However, studies of screening at different ages were included in the review if they provided relevant information from the parents' perspective.

#### *Summary of previous structured reviews*

We performed a review of published reviews addressing parental experiences of newborn screening, taking as our starting point the Cochrane Library (including HTA reviews, Cochrane systematic reviews and protocols, NHS Centre for Reviews and Dissemination and the National Research Register). Three relevant Cochrane reviews[339–341] and nine HTA reports addressing the psychosocial effects of screening were identified. The HTA reports are summarised briefly in *Table 31*.

Pollitt and colleagues considered four areas which apply generally to newborn screening: (1) parental support for screening, (2) a comparison of diagnosis through screening with clinical diagnosis, (3) the results of screening (including errors) and (4) the effects on reproductive decision-making.[342] Research evidence showed that parents supported newborn bloodspot screening and valued earlier diagnosis, even of untreatable conditions such as Duchenne muscular dystrophy, because this allowed them more time to prepare practically and they also felt that they had a right to be informed early about their child's condition. Parents appreciated the value of screening to increase reproductive choice but it

*TABLE 31 Previous HTA screening reports reviewing psychosocial effects*

| HTA title | Reference | Description |
|---|---|---|
| Newborn screening for inborn errors of metabolism: cost, yield and outcome: a review | Pollitt *et al*. (1997),[342] Chapter 11 | Systematic literature review of psychosocial effects of newborn screening focused on the bloodspot test for inborn errors of metabolism |
| A critical review of the role of newborn hearing screening in the detection of congenital hearing impairment | Davis *et al*. (1997),[343] Chapter 6 | Focus group discussions to assess parental support included in a review of universal newborn hearing screening |
| Antenatal screening for Down's syndrome: a review | Wald *et al*. (1998),[344] Chapter 10 | A review of the psychosocial effects of screening, especially anxiety and uncertainty, included within a wider review of serum screening for Down's syndrome |
| Cystic fibrosis screening | Murray *et al*. (1999),[345] Chapter 13 | A review of screening research, including studies looking at parental responses to screening results, the implications of carrier status and support for screening |
| Antenatal and newborn haemoglobinopathy screening in the UK: review and economic analysis | Zeuner *et al*. (1999)[346] | A review of screening methods, benefits and problems of screening, including modelling of outcomes. Primarily concerned with effectiveness and cost-effectiveness. Also noted that identification of carrier status may affect reproductive choice |
| Screening for sickle cell disease and thalassaemia: a systematic review with supplementary research | Davies *et al*. (2000),[347] Chapter 4 | Concluded that antenatal screening is cost-effective and acceptable within high-prevalence populations who perceive a risk and have knowledge of the severity of the condition |
| False-negative results in screening programmes: systematic review of impact and implications | Petticrew *et al*. (2000)[348] | Psychological consequences of false-negative result in all types of screening. Concluded that limitation of these effects will depend upon increasing understanding of screening |
| Ultrasound screening in pregnancy: a systematic review of the clinical effectiveness, cost-effectiveness and women's views | Bricker, *et al*. (2000),[7] Chapter 6 | A wider review which included a structured review of qualitative literature concerning women's views of fetal ultrasound during pregnancy |

was unclear if this was reflected in their actions. Pollitt and colleagues found that parental responses to a diagnosis were similar whether the diagnosis was made through screening or clinically. False-negative results in screening were found to lead to false reassurance of medical staff and consequently delayed diagnosis. False-positive results appeared to increase anxiety in the short term, but there was no evidence that this persisted in the long term, especially after a diagnostic test excluded the condition. Petticrew and colleagues' broad review of the effects of false-negative results in all types of screening programmes concluded that false reassurance does not usually lead to detrimental health effects.[348] In general, parents are supportive of newborn screening and anxiety around the test result is short-lived.

A review of women's views of antenatal ultrasound discovered that women found this test attractive because it visually confirmed the health of the baby. Women expressed little anxiety about the ultrasound technology in more recent research. Women whose scans are abnormal or inconclusive appeared to have higher anxiety levels throughout the pregnancy.[7] Antenatal testing may also influence reproductive choices, but these are also strongly influenced by parents' understanding and knowledge of the disease for which the baby is being screened.[342,343,345–347]

An additional effect of some screening programmes is the identification of unaffected carriers, either parents or children through screening, for example for cystic fibrosis[345] or haemoglobinopathies.[346,347] The implications of this are not straightforward and will not be addressed in detail in this review.

### Current review
These issues were then explored further in a critical review of the published literature on

newborn screening. The methodologies of the reviews by Pollitt and colleagues[342] and Bricker and colleagues[7] influenced the approach taken in this report. As most studies were qualitative, information could not be synthesised using classical systematic review techniques.

### Search strategy

A search strategy based upon Bricker and colleagues' structured review of qualitative studies[7] was therefore employed using the concepts age at screening, population screening, outcomes of screening, people affected and cardiac disease. The keywords developed from these are described in Appendix 14. The databases searched were MEDLINE, EMBASE, CINAHL and PsycINFO. The period of the search was from 1966 to 2003 for MEDLINE and from 1980 to 2003 for the other databases as the date of commencement of screening for congenital heart defects is not known. Only studies which directly measured parent experiences or views are included in the evidence tables, but other studies identified during the review have contributed significantly to the context for interpreting these studies.

### Inclusion and exclusion criteria for abstracts

The inclusion criteria were:

- studies which reported any views obtained directly from parents, families or children
- qualitative and quantitative studies or reviews
- any language
- abstract available
- publication year: 1966–2003 (MEDLINE); 1980–2003 (EMBASE, CINAHL, PsycINFO).

The exclusion criteria were:

- study involving screening only after 1 year of age (with no relevance to newborn screening)

- implications for UK screening programmes and practice unclear owing to cultural differences.

Papers were selected from the initial search results by applying these criteria to the abstracts. Unpublished studies were not excluded but none were eligible for inclusion in the review. Papers were then read by one researcher and included either in the review or contributed to the background information. A summary of the research results is given in *Table 32*.

### Classifying studies

Studies that reported directly on parent experiences or views were categorised into nine themes, which emerged from the abstract review and the focus groups. These papers are listed in the literature tables in Appendix 15 along with a brief summary of details of each study. Studies and reviews that provided additional relevant information relating to each of these themes are referenced in the results section but not included in the tables. As the conclusions of many studies were only partially relevant to newborn screening or to congenital heart defects, no coherent grading system for quality could be usefully applied. Studies of quantitative and qualitative methodologies were valued equally within the context of this review.

### Themes identified by research

Research findings are grouped and discussed under the themes identified below. Additional information from the focus group study is included within the discussion of each of these themes.

Themes:
*Process of screening*
- anxiety and uncertainty
- communication of information
- technologies of screening
- parents' support for screening

**TABLE 32** *Summary of search results*[a]

| Database | Search results: No. of abstracts found by search | Eligible abstracts: No. of abstracts meeting criteria | Papers included the review |
|---|---|---|---|
| MEDLINE | 529 | 66 | – |
| EMBASE (+ *duplicates*) | 85 | 17 (+6) | – |
| CINAHL (+ *duplicates*) | 119 | 6 (+14) | – |
| PsycINFO (+ *duplicates*) | 17 | 4 (+5) | – |
| Reference lists | – | 18 | – |
| Cochrane Reviews | – | 3 | – |
| Total number | – | 114 | 58 |

*a* Total number given for MEDLINE and numbers of new references given for each additional database.

*Outcomes of screening*
- diagnosis of disease: true-positive screening results or 'delayed' clinical diagnosis
- false-negative results
- false-positive results
- diagnosis of 'non-disease'
- true-negative results.

## Focus group

In addition to a literature review, we organised a focus group with parents of children with congenital heart defects and recorded their views about newborn screening. Only one exploratory focus group was possible within the scope of this HTA but this contributed to highlighting areas for further exploration in the literature review or screening studies. The focus group involved parents of children with congenital heart defects and was not representative of general population views. However, this was an appropriate sample with which to explore a wide range of experiences relating specifically to congenital heart defects and screening, especially as this was an area in which the research literature was lacking.

Focus group participants were contacted through an advertisement placed in the newsletter of a national support group for families of children with congenital heart disease, Heartline (www.heartline.org.uk). Parents were invited to take part in a focus group to discuss their experiences of having their child screened for heart defects. It was planned that the group should consist of parents, both men and women,

who had a child with a congenital heart defect. It was to include parents of children identified through antenatal ultrasound scan, pulse oximetry, echocardiography and clinical examination. It was also planned to include parents whose child was not identified through these methods, but who became ill owing to their congenital heart condition, and also some parents whose child had a normal heart.[349]

It was, however, difficult to recruit a group of parents who satisfied all the above criteria and the final group was comprised of parents who mostly had young children with more severe malformations. There were three men in the group and the ethnic mix of the group was predominantly white. A summary of parents is given in *Table 33*.

## Organisation of the focus group

We employed a facilitator with experience of focus groups who also prepared her own report.[349] Two researchers organised the focus group recruitment and venue, and the facilitator and one researcher were present at the focus group.

The facilitator planned the questions to guide the focus group after discussion with the wider research team. Questions were designed to be open to allow participants to decide how they wished to respond, to encourage discussion, and to allow participants to change their opinions after talking to others.[349] Three scenarios – descriptions of children with possible screening pathways,

*TABLE 33 Focus group participants*

| A | Mother | Girl 5 months old; gestational diabetes during pregnancy so transferred to special care baby unit; low oxygen saturation measurements on pulse oximetry, which were investigated and led to a diagnosis of TGA with VSD. Has had a definitive operation this year |
|---|--------|---|
| B | Mother | 5-year-old son discovered to have a ventricular septal defect at 2 days old while in hospital. Had several antenatal ultrasounds at which no abnormality was found. Had an operation at 12 weeks old. She now feels he is well and he has no ongoing treatment |
| C | Father | 16-month-old girl with TGA discovered through clinical symptoms soon after birth. Switch operation performed at 7 days old. Well since operation |
| D | Father | Son discovered to have a heart defect clinically and received an operation at 18 months of age. Special needs |
| E | Father | 18-month-old girl who collapsed at home at 2–3 weeks old. Diagnosed as TGA. Well since operation |
| F | Mother | Preschool child with truncus discovered in hospital on the first day of life due to clinical symptoms. Two operations at 5 weeks and 1 year old |
| G | Mother | Child 18 months of age. Found to have VSD at 3 weeks old, having been sent home. Detailed scans during pregnancy and normal newborn examination. Had operation at 8 weeks and well since |
| H | Mother | 4-year-old boy discovered to have HLH on antenatal ultrasound. Three big operations |
| J | Mother | 6-year-old boy who was normal at newborn check but mother realised something was wrong by 3 months old. A heart condition was diagnosed and operated on within the week. He has been well since the operation |

relating to false-positive and false-negative newborn screening results – were devised and used to elicit responses to situations that the focus group participants had not directly experienced. Appendix 16 outlines the focus group questions.

The focus group was tape-recorded and transcribed by the facilitator, and a member of the research team made contemporaneous notes of the discussion, which were typed up within 24 hours of the focus group. The themes discussed at the focus group were developed from a preliminary literature review and informed further literature search strategies. The process of this review was therefore dynamic, as has been described previously in a structured review.[7]

The researchers discussed and compared the key themes identified in the transcript and notes and these were ranked according to the number of times they were discussed.[349]

## Results

There were 66 papers included in the review. These articles referred to studies. Most studies were qualitative and based on written questionnaires administered postally or at interview. Many used standardised psychological instruments to measure anxiety, depression, parenting stress and total stress. Many psychological studies were undertaken as part of a wider evaluation of a national, regional or pilot screening programme. A few studies used semi-structured interview or 'free' interview methodologies to explore issues with a small group of parents in more depth and these provided useful new insights into the meaning of the screening process for parents. The results are discussed under the themes described previously.

### Anxiety and screening: risk and uncertainty
*Literature review*
Many studies of parent experiences focused on the anxiety aroused by screening. Some studies additionally examined the knowledge of parents at different points in the screening process and a few studies asked about perceptions of health after carrier screening.[350–352] These studies most often drew comparisons between two groups who had different experiences of screening or before and after the confirmation of the diagnosis, and a wide variety of standardised and non-standardised questionnaires were employed to measure anxiety. Although many studies noted an increase in

anxiety after testing, few consider that the offer of screening itself might be a major precipitator of uncertainty and anxiety, despite references to this in more general screening literature.[344,352,353] As Wald and colleagues state, "anxiety is a necessary cost of realising that there is an increased risk of a serious disease".[344] It has also been emphasised, with particular regard to antenatal testing, that the offer of screening conveys to parents the underlying message that a defect is sufficiently serious to justify termination of pregnancy.[354]

Prior to antenatal screening, the anxiety levels of pregnant women who choose to be tested appear to be the same as for women who choose not to be tested.[355] Increased anxiety within a newborn screening programme has also been related to being given too little information about the screening process, rather than about test results,[356] and mothers report that separation from their baby during a screening test is the trigger for their anxiety.[357] In a study of newborn hearing screening, the critical anxiety points in the screening pathway were identified as the repeat screening test, when anxiety increased significantly, and receiving a definite answer as to whether the child was affected or not, when anxiety subsided.[358] This reduction of anxiety on confirming a diagnosis has also been found elsewhere.[359] Although a single repeat test may not increase anxiety,[360] further repetition of tests has a definite impact in raising psychological distress.[361–363] Perception of screening results as uncertain or inaccurate can lead to continued attendance for unnecessary medical follow-up.[364] These studies appear to confirm the view that certainty about a test result is a major factor in minimising the psychological effects of screening.[353,365]

One of the major potential risks of population screening in children is that, at every antenatal or newborn screening opportunity, parents have to consider the fact that their apparently healthy child may not be healthy, "a normal child is made abnormal".[366]

> "At the same time as a woman's pregnancy is confirmed, she is offered a series of tests that she must successfully negotiate in order to maintain the normality of her pregnancy"(translated from French).[367]

Children in whom the possibility of disease has been signalled by a positive screening result enter a liminal phase from which they may exit as a healthy, normal child (a false-positive case) or which may begin the transition towards a defined defect (a true positive case), "Screening makes

uncertainty explicit."[344] Where children need repeat testing because of borderline results, they enter a prolonged period of uncertainty, which can have long-lasting effects on parents and requires especially careful handling by professionals.[368] For other newborns, in whom a positive screening result is later discovered to be false, parental anxiety may also last well into the preschool years.[369] Although children may successfully regain normality after surgery, it is more likely that long periods of follow-up will define them as unwell for a large part of childhood. In addition, all future pregnancies in the family are within doubt. Parents are unlikely at any time to be ready for an abnormal screening result, however well they understand the limitations of screening, and uncertainty about the future will precipitate anxiety.

In only one study did parents describe a preference to live with uncertainty. This was when the choice was between avoiding the certainty of knowing that their child had a terminal degenerative disease (Duchenne muscular dystrophy) and the uncertainty of hoping that they might have a milder form of muscular dystrophy. These parents refused the final steps in diagnosis, preferring "to live in…hope".[370] This attitude may also provide a clue to people's 'misunderstanding' carrier status or genetic predisposition to a disease. 'Misunderstanding' a result may allow people to regain some certainty about their future and minimise the anxiety of knowing this result. Adults who test positive for familial hypercholesterolaemia prefer to believe that this is a dietary, and therefore controllable, problem rather than a genetic, uncontrollable condition.[371] The degree to which uncertainty must be tamed will vary with individuals and perhaps with gender: fathers of children with congenital heart disease demonstrate a strong need to maintain control in the face of their female partner's emotion and anxiety.[372] It may therefore be important to view parents' understanding of screening test results, and the actions that they subsequently take, in terms of a discourse between certainty and uncertainty rather than as a function of inadequate information provision.

### Focus group

Within the focus group, uncertainty and anxiety about screening were not explicitly discussed. However, parents related their first doubts about their child's health and 'normality' to medical investigations during the antenatal period:

> "I had detailed scans during pregnancy … They were monitoring her but I don't know why. I think they

knew … I think they had a good idea [*that something was wrong*]. I think it would have been better to know" [*B, mother*].

> "One trainee [*ultra*]sonographer was not as experienced, she called another and another one. They asked us to come back in two weeks to see the consultant. He said maybe there was a problem, maybe not … He didn't really put the wind up us … we were laid back, I remember. We hadn't been worried" [*J, mother*].

Some fathers described taking steps to establish control over the situation after their baby was born and a diagnosis of congenital heart defect confirmed:

> "Did anyone find out the cause? We did … We went to a genetic counsellor and it was good … I'm glad we had genetic counselling because we can decide. Next time around, they say it is up to us, we are so well informed now. We know what to expect" [*D, father*].

> "We took shifts in the end, especially when he got moved to HDU [*high dependency unit*]. We hadn't seen a nurse in 12 hours" [*C, father*].

> "You have to take control … check it's all been done" [*D, father*].

Parents' concern about the quality of screening and equitable standards of care[349] also appeared to be an attempt to decrease the uncertainty of the whole process, described as 'very hit and miss'. They wanted screening to be more systematic, beginning with increased training for technicians doing ultrasound scans in pregnancy or postnatally:

> "Our consultant says it is possible to get all [*ultra*]sonographers to the level of looking for all defects" [*E, father*].

> "They tell me [*it*] can be detected, they should be training more people" [*A, mother*].

and better standards of service throughout antenatal and postnatal care:

> "Surgery was fantastic, but it was the detection in the first place. There are grounds for improvement at maternity level" [*E, father*].

> "A universal standard which everybody has to follow" [*C, father*].

### Summary

The anxiety experienced by parents during the newborn screening process is likely to be a manifestation of the uncertainty that is generated about a child's 'normality'. In these circumstances, people take steps to gain control and reduce uncertainty by different means. This may be

reflected in the way people deal with information about screening and test results, and may account for them 'misunderstanding' health professionals or acting against their recommendations. However, parents do not attempt to tame uncertainty in every situation, as the example of parents of children with Duchenne muscular dystrophy indicates. For the parents of children with congenital heart defects who attended the focus group, establishing universal standards across the whole country was an important measure for reducing the risk of screening failures and improving the path towards diagnostic certainty.

## Communication with parents about screening

### Literature review

Parents like to know what to expect from a screening programme. Clear information and a greater understanding of the screening process reduce anxiety in parents.[356,373] Parents are particularly anxious about new screening tests if they feel they have not been fully informed when they are added to established programmes and this leads to further difficulty when communicating abnormal results.[374] Greater knowledge about tests has been found to make parents more positive towards screening and more accepting of false-positive results.[375] Even during the wait for repeat tests, health professionals can reduce anxiety with appropriate information and reassurance.[368] Informed consent procedures[376] and decision aids are effective methods of increasing knowledge about screening options[339] and can also reduce the likelihood of parents regretting a decision to participate in screening.[359] However, whilst women are interested in receiving more detailed information about screening benefits, disbenefits and options, health professionals seem more resistant to providing such information.[377]

Parents appear to be prepared to wait a considerable time for the results of some screening tests on the principle that "no news is good news",[378] but when they do receive results, they want to discuss these.[368] Parents' recommendations about the communication of screening results by health professionals included being given information as early as possible and being given diagnostic information at a specially arranged appointment. The health professional should be well-informed and able to answer questions,[374,379] but also "prepared to deal with the emotional ramifications of the news they deliver".[379]

Communication with parents about screening failure rates has been highlighted as a difficulty in

some screening programmes.[345,363] There is additionally some professional concern that mothers do not understand anatomical descriptions of their child's diagnosis, but it is not clear that it has any effect on parents' care or relationship with their child.[380,381]

### Focus group

Parents in the focus group talked about a need for more information during the screening, diagnostic and care pathway of their child.[349] This was described as a need not for written information, but to spend time discussing the diagnosis with a health professional who was both knowledgeable and supportive.

Parents talked about how the initial consultation about the diagnosis was too short:

> "That was it; all they gave us was a … leaflet to read about it. That was it" [*B, mother*].

> "We went back to speak to this specialist nurse … that was the only contact we had about this big decision we had to make. That was the only failing of the whole thing is that you are given this information and we were trying to take as much in as we could as well as what had actually happened and there was no, you know follow-up" [*H, mother*].

> "The communication [*was a problem*]. Sent home, not explained how to do things …" [*F, mother*].

Some parents even attempted to extend the consultation:

> "We stayed in the waiting room and bombarded the consultant with questions when he came out of the next scan" [*B, mother*].

One parent complained about a lack of compassion shown by doctors:

> "They see it as a weakness to be emotive … No empathy" [*C, father*].

Professionals with the ability to answer questions informatively were valued highly by parents, particularly if they were able to combine empathy and knowledge:

> "Even with the time pressure, the doctor drew us a diagram and gave us a very good explanation. The professionalism was amazing" [*E, father*].

> "We had a community paediatric nurse who visited. She had a particular interest in cardiology. She was invaluable because she could follow up when we were discharged home. Fantastic depth of knowledge because of a personal interest" [*H, mother*].

Simple procedures were applauded or suggested by parents to improve communication:

> "We were lucky. We got a letter after the consultation and it was very detailed (about the consultation). Our liaison nurse phoned us afterwards" [*G, mother*].

> "We would have liked someone else present during the consultation, then to be allowed to digest the information for half an hour and to go back and talk to a counsellor" [*H, mother*].

> "I'd like it [*information*] at the time of diagnosis and not one week later from the cardiac nurse" [*G, mother*].

All the parents in the focus group expressed some reservations about the information they had received and their communication with professionals. They do not describe a decision-making partnership with clinicians:

> "Doctor said there was a hole. I said 'can I just leave it?' and they said, 'no, it's too big' and he was really curt" [*B, mother*].

> "They treat you like an idiot" [*G, mother*].

> "The consultant came in smiling next and we thought it was OK, I suppose for them it is. Then we found out what it was and she left us for about three hours. It was a shock" [*C, father*].

One mother described what many parents had also done, which was to write letters complaining about information provision, but never to send them for fear of jeopardising a child's care:

> "I wrote so many letters, but never sent them off … You're relying on them and you don't want to rock the boat" [*J, mother*].

It is perhaps significant that the Bristol Royal Infirmary Inquiry, which involved parents with many doubts about their child's care, was initiated by a 'whistleblower' who was a health professional.

Parents within the focus group also valued being able to speak with other parents whose child had a congenital heart defect, and this was a strong motivator for attending the focus group.[349]

### Summary
The type of information provided to parents whose child is undergoing screening is crucial to minimising anxiety. Parents need to know about the actual process of screening, the steps in investigation and the confirmation of a diagnosis. It is sometimes health professionals themselves who are resistant to providing more detailed information, believing erroneously that it will increase anxiety. Parents also value being given information about results at the time of the test or soon after. Parents would like to receive information during a face-to-face consultation with a knowledgeable and sympathetic health professional. Currently, they do not often feel that they are treated as a partner in the decision-making process. Parents also seek the mutual support of other parents who have children with a similar health problem.

## Technologies for screening for congenital heart disease
### Literature review
Parents' views on the technologies involved in screening children for congenital heart defects were sought from other literature and from the focus group. Parents approve of screening tests that are quick, simple, involve no discomfort for the baby and can be done in young infants.[361] One important factor that is unclear regarding the newborn clinical examination is parents' awareness of the possible implications of the examination, which may appear routine. Parents do not appear to have a preference for certain types of examiners, for example midwives or junior doctors, but do wish to discuss healthcare issues of concern to them during the examination.[382] It is not known whether parents whose children have abnormal screening results vary in their views about newborn clinical examination.

Suspicion of a congenital heart defect is most often raised by the finding of a heart murmur on examination, and a murmur may indicate a structural heart malformation or may be 'innocent' (unrelated to any structural heart abnormality). Infants with a murmur are often referred to a hospital clinic where a diagnostic echocardiogram is performed by a paediatric cardiologist. Two studies have specifically explored the experiences of those referred to a cardiologist for investigation of a heart murmur, but neither involved a newborn population.[381,383] In a Canadian study, the majority of parents whose children were referred to a cardiologist, did not understand the medical concept of 'heart murmur' although doctors believed that they had explained this.[381] This resulted in lasting concerns in parents whose children were subsequently found to have normal hearts. In a UK study of adults referred for further tests, after a murmur was found during a routine medical examination, only three patients were found to have any heart abnormality and most were reassured by negative investigations. However, there was residual anxiety 1 year after a normal result in a significant proportion.[383] These findings suggest that a critical consideration with the

newborn clinical examination is communication about the finding of a heart murmur. False-positive results generate anxiety that may be long-term.

Women's views of ultrasound screening in pregnancy have been reviewed recently by Garcia and colleagues,[384] as part of a wider review.[7] Although many of the views expressed by women relate specifically to antenatal ultrasound, which is attractive to women because it allows them to visualise their unborn baby, some findings are likely to apply also to the use of ultrasound technologies elsewhere, such as echocardiography. Knowing what the scan is intended for and understanding the limitations of the scan are important to women's satisfaction with the outcomes of the scan. Whether this knowledge influences uptake of the scan is unclear. Most women expect a scan to reassure them that their baby is healthy, so they are often unprepared for inconclusive or abnormal results from a scan. A scan operator who is unable to discuss abnormal scan findings at the time, perhaps because they are not trained to interpret scans at this level, is also a source of anxiety for women.[384]

The views of parents towards newborn screening using pulse oximetry have not yet been explored in any published studies.

### Focus group
Parents in the focus group were critical of the newborn clinical examination, describing it as 'outdated' and 'pre-War'. Some were unclear as to whether their baby had received a routine examination. In general, they felt that the examination was performed too rapidly and by inexperienced staff:

> "Junior [*doctor examined each baby*] in 60–70 seconds, all the infants on the ward in 20 minutes, I don't think that is uncommon" [*E, father*].

> "Checks when the baby is born, it's 'yep, that's alright!'" [*E, father*].

They also believed that staff did not 'act on warning signs'.

A few parents were aware of pulse oximetry (oxygen saturation) as a possible screening test and believed it would be both useful and easy to apply:

> "Saturation tests on birth. That would reveal a problem" [*E, father*].

> "A saturation test can be done by anybody" [*B, mother*].

There was also much support for 'a routine scan before leaving hospital' (universal echocardiography), but some recognition that it may not be feasible to provide this, for example, in outlying areas or if there were insufficient trained professionals. Parents drew upon their experiences of a detailed diagnostic echo performed by a cardiologist, which is the 'gold standard' for detecting heart defects and they had no comparative experience of routinely performed newborn screening echo.

### Summary
Although the literature review demonstrated that parents are generally supportive of newborn clinical examination, the focus group participants described scepticism about its ability to detect heart disease. They predominantly had experienced their child's condition being missed by this method of screening. The clinical finding of a heart murmur may often be misunderstood by parents, raising unnecessary concerns about their child's health. Care should be taken with appropriate communication and management of further investigations.

Within the focus group, there was significant support for pulse oximetry as a method of screening, because it appeared to be simple and effective, and for universal echocardiography, because it was considered to be extremely accurate. They were unable to make a distinction between a technician-performed echocardiogram and that by an expert cardiologist as they had only experienced the latter. Parents prefer a technology that can be applied as soon as possible after birth and with little delay between screening and definitive diagnosis.

## The importance of 'knowing': parents' support for screening
### Literature review
Across the range of newborn screening programmes explored in the literature review, parents expressed support for screening irrespective of the level of treatment benefit it offered to their child.[358,359,370,385–387] Parents were also very accepting of new screening programmes.[388,389] Parents and prospective parents say they feel reassured by newborn screening[387] and expect it to lead to better care, allow time to prepare for the future of an affected child and to influence their future reproductive choices.[359,385,390] Although support for screening tends to be higher if there is an effective treatment,[391] parents still value screening for conditions for which there is no cure because they

find out earlier and do not have to experience distressing symptoms or unnecessary investigations before their child's diagnosis.[392–394]

As screening for congenital heart defects also occurs with the detailed ultrasound scan in pregnancy, it is relevant to consider support for this here also. Antenatal screening offers parents 'reproductive choice'; in effect, it allows them the option of termination if an unborn baby is severely affected. The difficulties for women of making such a choice, while coping with growing attachment to their unborn baby, and wider social views about disability have also been emphasised.[395] Informed choice is also a controversial area for professionals, and obstetricians' views of which conditions are serious enough to merit termination may not concur with women's views: 14% of obstetricians would never recommend termination for cystic fibrosis and 13% would not recommend late terminations for Down's syndrome.[396] Parents of children with metabolic disorders, asked if they would consider screening for future pregnancies, only wished to do so in 56% of cases, but 41% had acted to prevent further affected pregnancies.[397] Only one-quarter of parents of children with cystic fibrosis actually used antenatal testing in a subsequent pregnancy. Women were more likely to accept antenatal screening for cystic fibrosis if they considered themselves to be at risk of having a child with the condition, regarded cystic fibrosis as serious and were willing to terminate a pregnancy if the fetus had cystic fibrosis.[398]

Anxiety during the screening process or experience of a false positive result does not decrease a parent's willingness to undertake screening of subsequent children.[357,358,363,368,369,373,375] However, lower support for screening is shown by parents who have experienced delay between screening and final diagnosis on a previous occasion,[385] who do not feel they were fully informed about the screening process[370,374] or whose children have been found to have a minor problems for which no intervention is needed.[358] Screening is less likely to be declined when it is offered in person or as an adjunct to routine care.[399]

### Focus group
Parents described the difficulty of caring for a 'heart child', which added to the importance for them of effective screening and diagnosis. Within the focus group, parents expressed support for newborn screening but were more in favour of earlier detection through antenatal screening:

> "Ideally, they should pick it up in pregnancy" [*E, father*].

Interestingly, parents expressed this support although the majority had experience of their child's heart problem being missed by antenatal screening and the mother whose child's heart problem had been detected antenatally had mixed feelings about the benefit of knowing so early:

> "I would have liked to have time to think, liked to have been able to prepare leading up to the birth, to have control. During the pregnancy, I felt the baby was safe inside me at least" [*H, mother*].

Parents were critical of current antenatal and newborn screening services, as they exist in the UK, feeling that a lack of trained personnel and underfunding limits access to these services:

> "It's available, our next child could get [*an antenatal*] scan. Second time around, you can get it, it was all there" [*C, father*].

They felt that all hospitals should have access to a paediatric cardiologist who could check a newborn baby within 24 hours if there were concerns, perhaps via a video-link.[349]

### Summary
Parents support screening because it offers an early diagnosis, which they believe offers the benefits of early intervention, time to prepare for a child's needs and for screening in future pregnancies. In discussion, they regard antenatal and newborn screening as a continuum and want screening both for reassurance about their child's health and to be informed early if a disorder is present. Less support for screening is shown by parents who have experienced a lack of information about the screening process, the diagnosis of minor or non-significant conditions or delay in receiving a final diagnosis. Parents of children with congenital heart defects prefer antenatal screening because it offers information at an early stage, but their own experiences of this suggest that it causes a mixture of benefit and distress because it presents a difficult choice between continuation or termination of the pregnancy. Parents appear to be concerned that current screening services are suboptimal because they lack specialist personnel and do not make full use of newer technologies.

## True-positive results at screening compared with 'delayed' clinical diagnosis
### Literature review
Comparisons have been made between the psychosocial effects of an earlier diagnosis, due to screening, and a delayed diagnosis, made

through clinical signs and symptoms, in the context of many newborn screening programmes.[342,359,385,392–394,400–403] The evidence does not suggest that the emotional impact of the diagnosis or the influence on parent–child relationships is any different when made through screening or based on clinical manifestations.[342] The shock of the diagnosis itself is the greatest precipitator of parental distress.

There are some particular differences in parents' experiences, however, as parents whose children were screened described having more time to prepare emotionally and practically for the worsening of their child's condition[193] whilst those diagnosed clinically expressed "regret about misunderstanding their son's early symptoms".[359] Most distress and frustration are caused by a delay in confirming a diagnosis, once the possibility of a congenital disorder has been raised by symptoms or by screening.[370,385] One mother described rejection of her baby in the period between screening and diagnostic testing:

> "It destroyed the bond and natural feelings that I had at first and I had to start building a new relationship all over again."[385]

During this period, parents can experience difficulties with their children and poor relationships with health professionals, which may persist even after the diagnosis is confirmed. Whereas parents who experience an early diagnosis express greater confidence in the medical profession,[400] parents of children diagnosed late complain that health professionals do not take their early concerns seriously and are even 'dismissive' of them. This leads to a general preference amongst parents for diagnosis through screening.[403–405]

Parenting stress and psychological distress amongst parents of children with congenital heart defects are similar to those in parents of children with Down's syndrome and higher than in parents of children with cleft palate or no disability. Greater fear may be attached to the uncertainty about survival and hospital admission. A termination of pregnancy after antenatal detection of a congenital heart defect can result in persistent distress up to 10 months later.[406] After diagnosis of congenital heart disease in one child, women are less likely to have further children if the infant survives but more likely to conceive again if their baby dies.[407]

Postnatal depression occurs in 10% of mothers[408] and fathers[409] and is likely to be associated with

concerns about the normality of their child.[410] It is exacerbated by perception of the baby as 'difficult';[411,412] it influences mother–infant interaction,[413] with a longer term impact on the emotional and cognitive development of children.[408,414,415]

Mothers are more likely to report psychological distress than fathers[416] but a small study, involving in-depth interviews, identified similar emotional distress amongst fathers of children with congenital heart defects.[372] Fathers expressed joy at the birth tempered by "intense distress over the loss of the expected normal child" and fears about the outcome of surgery. Fathers tried to maintain control, often through work, and to provide support to their partners, "I didn't want my girlfriend to see me crying … to try to be strong for her."

Parents of children with congenital heart defects experience conflicting emotions of attachment and loss, and often value contact and support from other parents whose children have a similar disability.[379]

### Focus group
Parents in the focus group described the first diagnosis of their child's congenital heart defect as an enormous 'shock', whether the diagnosis was made antenatally or after birth, by screening or not. They also described confusion and difficulty in taking in the information:[349]

> "I was bewildered, I didn't know what was happening. One midwife said 'I think there is something wrong with the infant's heart'. That was it. Oh! It was terrible, really awful" [B, *mother*].

> "[The consultant] said 'your baby has a very serious heart defect'. It was a shock. I remember leaving and my husband had to support me back to the car … and I could hardly walk. I was absolutely devastated at this piece of news" [H, *mother*].

> "You just lose it. I thought, 'Oh gosh, she's not going to make it!'" [A, *mother*].

Parents have a real fear of their child dying, which is compounded, in many cases, by sudden separation from their baby and emergency treatment:

> "For us the nearest centre is 180 miles away. She had to travel by air–sea rescue helicopter … she wouldn't have got there fast enough otherwise. We had to follow by car … they took our mobile numbers. They phoned to say she'd arrived … I knew they wouldn't phone us to say she had died" [C, *father*].

"We couldn't go in the ambulance. My husband followed behind on the motorbike" [*F, mother*].

"They were taking him away, we went home without a baby" [*D, father*].

Often parents were given little opportunity to discuss the diagnosis before surgery, but this was appreciated where it was offered.

Most parents had experienced a late clinical diagnosis and they perceived this delay as life threatening. Parents were concerned that congenital heart defects should be detected in a timely manner, to prevent the 'horror' of a child collapsing and requiring emergency care:[349]

"When (our baby) was born he had a check-up, he had a bath and turned blue in the bath twice. We told the midwife. She said 'no that's perfectly OK, that's perfectly normal'. We trusted them. It was our first child. We got him home; he collapsed two weeks later" [*E, father*].

"He wasn't feeding, more problems, floppy, trachea pulling in, recession. I even mentioned it to the midwife, but she said it was nothing, that 'infants often breathe like someone who is dying'. There were so many symptoms, projectile vomiting. I didn't want to be a neurotic mother. One day he went floppy. I thought he was going to die. I took him to the local on-call GP service … and they said it was probably 'just a large poo'. They were dismissive all the time, 'maybe asthma' … I asked for him to be looked over … [*then*] He was rushed in [*to the hospital*] and they operated the next day" [*J, mother*].

"A trainee GP was the only one there … He did the usual – take a picture and take her away … The team from Bristol came, it was a different level of expertise … But we lost a lot of time" [*C, father*].

After these and similar experiences of delay in recognising their child's condition, parents showed less trust in health professionals and doubted information that they were given by them:

"I looked in her notes and found she had to be given resus[citation] after they tried to take a blood test in the night and they never mentioned it to us" [*C, father*],

or they expressed anger at perceived lack of respect from health professionals:

"They treat you like an idiot until you prove otherwise … But the number of times I've been treated like a complete moron until they realise that I'm not as thick as two short planks and will give drugs at the right time" [*G, mother*].

### Summary
Newborn screening includes many conditions of varying severity, which means that direct comparisons cannot be made between detection by screening or a later clinical diagnosis across all programmes. In the case of life-threatening congenital heart defects, a delayed diagnosis represents a time during which a child is at real risk of collapse and subsequent death or neurological disability. Timely implementation of surgery can prevent this. The literature review has therefore important messages for delayed diagnosis of congenital heart defects but the focus group adds greatly to this information. Whether the initial detection is through screening or clinically, there does not appear to be any difference in levels of parenting stress or in the way parents bond with their infants. The key influence of a delayed clinical diagnosis appears to be on parents' relationships with health professionals, whom they have consulted about their child's health problems on several occasions before the diagnosis is finally made. If parents feel their concerns were not taken seriously at this time, then this can result in longer term lack of confidence in health professionals that may affect a child's care.

In the case of a diagnosis of congenital heart disease, the lasting memory for parents is one of shock, irrespective of the child's condition, the time since birth or whether the diagnosis is made through screening or not. The impact of the diagnosis itself, and the potential threat to the life of a child, override other considerations. The experience is often made worse by separation from the baby very soon after diagnosis in order to allow urgent treatment, and by a lack of information at this time from health professionals. The management of the diagnosis is crucial to parents' ability to cope at this time.

## Congenital heart defect present: false-negative test result
### Literature review
Parents who receive a false-negative result on screening are initially reassured that their child is unaffected but later discover that their child is unwell. False-negative screening results may lead to a delayed diagnosis and possibly the loss of an opportunity to give counselling to parents at the appropriate time.[340] Relationships between parents and health professionals may be disturbed if professionals are falsely reassured by the test results and perhaps dismissive of continuing parental concerns. A review of the effects of false-negative screening results concluded that these did not appear to affect parent–child relationships in

newborn screening, but, in antenatal Downs' syndrome screening, false-negative results have been shown to lead to decreased parental acceptance of their child.[348]

Parents with children who had false-negative results with antenatal screening for Down's syndrome were followed up at 4 years and compared with a control group of parents whose children with Down's syndrome were never screened antenatally. Parents who had received a false-negative diagnosis had higher parenting stress and were more likely to blame others, such as medical staff, for this result. The poorer adjustment of these parents to their child's syndrome was also reflected in higher levels of anxiety in mothers.[417]

Clinical levels of depression and anxiety were found to be higher in women whose baby's congenital heart defect was diagnosed after a false-negative antenatal screen result, compared with those correctly identified through antenatal screening.[406] False negatives in screening for congenital heart defects are common but the impact of this 'false reassurance' is unclear.

*Focus group*
A false-negative result, at antenatal or newborn screening was experienced by the majority of parents in the focus group. In some cases, this does appear to have led to false reassurance amongst professionals and perhaps a delay in recognising that the child was ill:

> "I'm surprised that none of them picked it up. By the time it was, he was extremely grey, but no one noticed" [*C, father*].

> "The Health Visitor had seen him naked on the scales 10 times, I counted in his book, he'd put no weight on and he grunted all the time" [*J, mother*].

> "What I don't understand is if all the family knew something was wrong, why didn't the professionals know?" [*J, mother*].

After such experiences, parents were more likely to describe further encounters with the medical profession in terms of further conflict:

> "He was having routine follow-up because of his breathing. Then they said it was serious, he needs an operation. Then there was the battle to find the surgeon to do it" [*D, father*].

> "They were trying to get a blood sample. I went in and … found them trying to suck blood out with a straw … I blew, I lost it" [*C, father*].

*Summary*
A false-negative result on screening has been described in the literature as leading to poorer parental adjustment to their child. Parents in the focus group, and in the congenital heart disease literature, do not describe such effects on parent–child bonding. However, a false-negative result at screening, followed not long after by the diagnosis of a life-threatening congenital heart defect, does appear to lead to both false reassurance of professionals and delayed diagnosis and to blame directed at the medical profession by parents.

## No congenital heart defect: true-negative test result
*Literature review*
A true-negative test result is assumed when a newborn infant with a negative screening result does not later present clinically with a congenital heart defect. For these parents, the outcome of screening is that desired by all parents: reassurance and confirmation that their child is normal and healthy. A negative screening result is associated with a significant drop in anxiety and, in some cases, with a gradual decrease in knowledge about the condition and even about the results of the screen.[351] Communication about the possibility of failure in screening, false-positive or false-negative results, is often not satisfactorily conveyed in population screening programmes from which most participants expect to gain reassurance that there is no apparent disease.[345,387,418]

*Focus group*
The parents in the focus group had affected children and were not asked about a true-negative diagnosis.

*Summary*
If the outcome of screening is a true-negative result, this will only be confirmed in retrospect by the later absence of disease. Therefore, a negative screening result is reassuring but may be later reversed if disease develops. This risk of screening failure is difficult to communicate to parents who are looking for an unambiguous result from screening.

## No congenital heart defect: false-positive test result
*Literature review*
Over 50 false-positive results are generated for every true-positive result in newborn blood spot screening in the USA.[237] Parents appear to misinterpret information about possible failures of screening[351] and are often unprepared for a

positive screening result. Even when a positive screening result is later followed by a normal diagnostic test, they can feel that this distressing experience is too rapidly dismissed.[419] Parents have strong shock reactions to a first positive result in newborn bloodspot screening and fears about their child's general health persist even if this is a false-positive result.[342,420,421] A high proportion of parents who experience false-positive results on screening report significant anxiety because of the need for further investigation or hospitalisation[368,369,422] but only a small proportion report anxiety lasting long term.[368,369] These distress reactions have not been associated with poorer parent–child bonding.[342]

Parents whose children were found to have an innocent murmur were mostly reassured and less likely to perceive their child as having a serious health problem after the diagnostic test. However, 10% of parents continued to believe their child had a heart problem, even after proof that there was no malformation present.[381] Antenatal screening for congenital heart defects leads to slightly higher than normal levels of anxiety in false-positive cases (women referred for further investigation but whose baby is found to be normal), but less anxiety than if the diagnosis of congenital heart defect is confirmed.[406]

It is not only the women who are ill-equipped to cope with an abnormal result, but also health professionals, as one woman describes: "I've learnt a lot about how totally unprepared the medical services are … for the abnormal result; they are lulled into a sense of security that the tests will give comfort."[419] Post-test counselling is offered much less often to parents of children who have false-positive results than true-positive results.[423]

### Focus group
Participants within the focus group were offered a scenario involving a child who had been diagnosed as positive at a newborn clinical examination, then proven to have a healthy heart at further investigation 4 days later, and asked to comment on this. Their main concerns were the delay between the screening test and diagnostic follow-up:

> "Why wait four days for a scan – that is a very worrying time" [*G, mother*],

and the persistence of doubt even after a normal test result:

> "There will always be a niggling doubt after" [*J, mother*].

There was also some recognition that they, as a group, might have different views to parents of healthy children, however:

> "But the views of parents with normal children, about taking the child home [*may be different*]. Why put the wind up them. It's getting the right balance" [*H, mother*].

### Summary
A false-positive result is a worrying screening test result for parents beginning a period of uncertainty until further investigation proves the child to be healthy. The initial positive result elicits a shock response similar to that of a true diagnosis, and there is some evidence that there is lasting psychological distress amongst parents who have experienced this. Parents in our focus group expressed the same concerns as those described in the literature.

## Identifying minor abnormalities: true or false positives?
### Literature review
The diagnosis of 'innocent' heart murmurs has been linked to physical restrictions and disturbed psychological development in some children.[424] As echocardiography in newborn infants increases the number of infants in whom a minor VSD (of which up to 95% may spontaneously close) is found, this is a significant effect of echocardiographic screening. The effect on quality of life of infants with minor congenital cardiac diagnoses has been explored in a questionnaire with Swedish parents. Parent–child bonding and child quality of life (at 5 years old) appeared unaffected, but there was lower satisfaction with relationships in the wider family networks, suggesting that there is some overall effect related to this diagnosis.[424]

In the case of other minor abnormalities detected by screening, such as dilatation of the urinary tract detected at antenatal ultrasound scanning, the follow-up of infants may exacerbate parental concerns unnecessarily.[425] Women in whose infants a minor abnormality is found on antenatal screening have persistent anxiety post-partum and this can lead to decreased bonding.[426] Almost one-fifth of parents of children with a non-life threatening diagnosis, hearing loss, did not want to find out this diagnosis at birth as it disrupted normal attachment processes: "we could get started on what we needed to do, but I missed having the bonding time."[379]

One outcome of certain newborn screening programmes involving genetic testing is the

identification of 'mild' disease or of unaffected carriers who may pass a gene defect on to children who manifest the disease. Labelling of children with 'mild' disease may expose them to unnecessary treatments and investigations[340] and carriers of cystic fibrosis genes appear to have a poorer view of their own health.[427] The disclosure of carrier status in cystic fibrosis and sickle cell disease has an important emotional impact and wider social implications for affected families,[345] implications for future reproductive choice and the exposure of non-paternity. In addition, screening may not offer certainty about carrier status and the benefits of early treatment are still debatable.[341]

### Focus group
Parents were not asked to comment on this.

### Summary
In the context of congenital heart defects, the diagnosis of minor anatomical heart anomalies, which often spontaneously resolve and have no effect on health, is very pertinent. It is reassuring that Laane and colleagues[424] find minimal lasting effects from such diagnoses in children with congenital heart defects, but this may be an effect of good communication, and follow-up practices that do not emphasise the problem. In mild hearing loss, detection has led to more distress and effects on bonding. The experience of carriers for genetic disorders has been more widely studied revealing that, although anxiety appears to be short term, perceptions of health may be altered and there are wider social effects.

## Conclusions

The very process of screening will always generate some anxiety simply because it proposes to healthy individuals that they might be at risk of a disease or disorder. Parents of children with congenital heart defects emphasise the need for universal screening standards across the whole country as an important measure for improving their experience of the path towards diagnostic certainty and reducing the anxiety associated with screening.

Communication about the screening process, test results and final diagnosis and management is often poorly done, but parents have offered some simple recommendations for improving communication, which could be applied across a range of screening programmes, including the need to make time to talk and for a knowledgeable and sympathetic health professional to discuss

outcomes with parents. Parents often need to be put in contact with other parents in a similar situation for mutual support. When communication is carried out well, there are lasting beneficial effects on parent–professional care partnerships.

Parents have a preference for methods of screening which are simple, accurate and do not cause discomfort. The newborn clinical examination is generally accepted in the literature but the focus group participants were critical of it as a screening test for congenital heart disease. Parents would like screening to be done as early as possible and the antenatal scan is strongly supported for this reason. However, parents liked echocardiography, although their understanding of it was based on its use by expert cardiologists rather than in routine screening, and they responded very favourably to the potential use of pulse oximetry in screening.

Parents are supportive of newborn screening for congenital heart defects overall, believing that this will prevent the sudden collapse and death of their baby. This support does not appear to lessen even where parents have direct experience of a failure of newborn or antenatal screening.

A diagnosis of a congenital heart defect causes a terrible shock to parents, whether it comes after screening or after clinical symptoms and signs. The devastating emotional impact is often compounded by sudden separation from the baby who is rushed away for surgery or urgent medical care. Parents experiencing a delayed diagnosis tend to show less confidence and trust in health professionals thereafter, particularly if the delay is due to poor management of a positive screening result.

False-negative results on screening can lead to a delayed diagnosis because they give false reassurance to health professionals, who are then more dismissive of parental concerns. Professionals may need to receive more information about failure rates and detection of heart failure in infancy to address this. False-positive results can lead to anxiety in the period between screening test and diagnostic test, but for most newborn screening programmes, this anxiety appears to be short-lived and fades over time. Sometimes a minor, clinically insignificant heart abnormality is discovered by screening, and this has significant implications for some screening technologies, such as echocardiography, in which this is more likely. The effect of such diagnoses on parents is likely to depend upon management and follow-up but has not yet been adequately explored in long-term

studies. Negative screening test results are reassuring to parents but have failure rates, which must also be conveyed. This review of the evidence suggests that the worst parental experiences of screening are focused around poor management of the screening process and false test results. The focus group has contributed some specific information about the issues which lead to parental distress and limit parent–professional partnership in the care of children with congenital heart defects. However, further exploration of the psychosocial effects of screening results in the general population is still needed with specific regard to newborn screening for congenital heart defects.

# Chapter 10
## Discussion and synthesis

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**Chapter outline**
In this chapter, we present a synthesis of the findings of the systematic review, cost-effectiveness analysis and qualitative research to evaluate newborn screening for congenital heart defects. We discuss the implications of these findings for policy and research.

**Key findings**
- Early detection through newborn screening can potentially improve outcome of congenital heart defects.
- Evidence from individual centres suggests that the current screening programme performs poorly; data to evaluate performance and longer term outcomes nationally are unavailable.
- Pulse oximetry with clinical examination appears to be a promising alternative newborn screening strategy but further evaluation of detection rates and diagnostic follow-up is needed.
- Although screening echocardiography with clinical examination is associated with the highest detection rate, it is the most costly strategy and is associated with a 5% false-positive rate.
- Improving antenatal detection of fetal congenital heart defects reduces the birth prevalence but does not alter the relative effectiveness of different newborn screening strategies.
- Timely management of screen positive infants is essential irrespective of screening strategy if outcomes are to improve.

**Implications for healthcare**
- Based on the evidence presented, the addition of pulse oximetry to clinical examination in the first day of life should be considered, subject to further evaluation.
- Adequate diagnostic and treatment services are essential to ensure good outcome.
- Routine data systems, currently lacking, are needed for audit, quality assurance and to assess longer term follow-up. This would require clearly defined process and outcome measures.
- Information for parents about screening for congenital heart defects should be combined for antenatal and newborn screening.

**Recommendations for research**
- Research of an observational design is required to refine the detection rate and other aspects of pulse oximetry. This would be a worthwhile investment to reduce uncertainty in policy decisions. This evaluation should address the detection rate for life-threatening congenital heart defects, role of the hyperoxia test in improving specificity, the detection of other non-cardiac disease and its management and the value of a repeat examination after the first day of life.
- Research to evaluate antenatal screening strategies more directly should be considered.
- Further investigation of the psychosocial effects of newborn screening for congenital heart defects is needed.

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We have presented the findings of a systematic review, cost-effectiveness analysis and qualitative research to evaluate newborn screening for congenital heart defects. While focusing on clinical effectiveness, we have used literature reviews, a focus group and an exploration of parent preferences to identify processes and outcomes relevant to children and their families. In this chapter we synthesise and discuss these findings and explore the implications for policy and for research.

Our findings suggest that broadly, newborn screening for congenital heart defects meets the accepted criteria for a screening programme but that there is a strong case for modifying the current policy of clinical screening of the newborn and 6-week-old infant to include other more effective tests. The review and the decision analysis suggest that pulse oximetry in addition to clinical examination is a strong candidate for screening. There is, however, significant uncertainty about the detection rate of pulse oximetry, which requires further evaluation. As discussed previously, the model parameters for pulse oximetry with clinical examination and screening echocardiography with clinical examination are informed largely by subjective probabilities and expert opinion rather than published research studies. However, the sensitivity analyses combined with the findings of the expected value of information analysis suggest that there is a high

probability that pulse oximetry with clinical examination is a cost-effective screening strategy and one meriting an investment in further research.

The justification for this is based on analyses relevant to the timely diagnosis of life-threatening congenital heart defects alone, and also to the combined secondary outcome, which includes diagnoses of clinically significant congenital heart defects. In practice, a screening programme detects the latter, that is life-threatening and clinically significant defects, and it is the costs and incremental cost-effectiveness ratios for this secondary outcome that will be relevant to the health service and society. However, in appraising the current policy and its alternatives, we elected to distinguish between congenital heart defects by severity in order to reflect the different priorities attached to these two outcomes. In fact, the model suggests that there is little differentiation in detection rate for the primary and secondary outcomes with current screening policy (32% for both), but greater differentiation for pulse oximetry with clinical examination, which has a higher detection rate for life-threatening congenital heart defects (68%) than for the combined congenital heart defects outcome (50%). By contrast, screening echocardiography with clinical examination is the strategy that achieves the optimal detection rate for both life-threatening congenital heart defects (69%) and the combined congenital heart defects outcome (62%).

The choice of screening policy will depend on the value placed by society on a timely diagnosis of life-threatening congenital heart defects and also on the diagnosis of other clinically significant congenital heart defects. We were unable – because of the paucity of appropriate outcome data – to develop an outcome that allowed assessment of QALYs gained. However, using our surrogate outcome – timely diagnoses of life-threatening congenital heart defects – our analyses suggest that pulse oximetry with clinical examination is likely to be a cost-effective strategy across a range of assumptions, with incremental cost-effectiveness ratios ranging from £2000 to £8000 for the primary outcome and from £900 to £2200 for the combined secondary outcome. This compares with equivalent estimates for screening echocardiography of £126,000 to £5 million for the primary outcome and from £18,000 to £46,000 for the combined secondary outcome. **It is now important to evaluate further newborn screening with pulse oximetry in clinical practice through observational studies.**

One limitation of our cost-effectiveness analysis is that it does not incorporate values for the different outcomes and hence cannot weight the issue of false-positive diagnoses in other than monetary terms. The estimated 5.4% false-positive rate for screening echocardiography has significant implications for the parents of healthy infants and is one that both the literature and our preliminary qualitative research suggest merits closer attention. For pulse oximetry, positive screening results due to non-cardiac reasons were counted as false-positive results; however, these will include cases of serious lung disease which could benefit from earlier detection. **The hyperoxia test – in which the the partial pressure of arterial oxygen (PaO$_2$) is measured when an infant is receiving 100% oxygen – should be investigated for its ability to discriminate between cardiac and non-cardiac disease after a positive screening test.** Although the false-positive rate did not emerge as a key driver in our uncertainty analyses, future research to explore the clinical investigation and management **of positive screening** results, and also importantly parental and health professional values for these outcomes, would certainly be indicated. **Observational studies of pulse oximetry should therefore also evaluate management protocols for positive screening results and the management of non-cardiac disease. It is also unclear from previous studies, such as those undertaken in the Northern Region, that a repeat examination at 6 weeks of age is valuable in detecting congenital heart defects not identified at birth as many life-threatening defects are likely to present clinically in the interval between these screening tests. Further research into the use of pulse oximetry at birth might also evaluate the continuation of screening at 6 weeks of age or the existence of an additional screening opportunity after discharge from hospital**.

Our review has highlighted some issues that are generic for any newborn screening strategy for congenital heart defects. These include antenatal detection, information for parents, routine data and timely management of infants with life-threatening congenital heart defects.

Our model incorporated scenarios about antenatal screening but we were not given a brief in this project to consider directly the effectiveness of antenatal screening. Our conclusions about newborn screening are robust across a range of average antenatal detection rates for the UK but

did not explicitly consider the scenario of a very high antenatal detection rate. We undertook a separate additional sensitivity analysis of antenatal detection rates from 0 to 100% following discussions with the antenatal and child health subgroups of the National Screening Committee. The results of this analysis suggest that, even if antenatal detection rates were 90% overall in the UK, there would remain 10 cases of life-threatening congenital heart defects and 40 cases of clinically significant congenital heart defects per 100,000 live births which could be detected by newborn screening. The challenges in improving antenatal screening are considerable, as recently demonstrated in an HTA report,[7] and so unlikely to be relevant to immediate policy decisions about newborn screening.

In our focus group, parents indicated the importance of good information. They experience antenatal and newborn screening for congenital heart defects as a continuum and information for parents needs to reflect this. This is in line with other developments in maternal and child health screening programmes, notably for sickle cell and thalassaemia. **It is now important to evaluate the psychosocial effects of screening results and determine the best methods of communicating information about screening test results to parents**.

Our review has highlighted the lack of any reliable evidence for screening available from routine data. The Northern Region study is a landmark study internationally and has given an important window into the current programme. There is now an urgent need to develop data systems relevant to antenatal and newborn screening for congenital heart defects which can provide information about process and also longer term outcomes. A linked data system is essential as information on antenatal detection and termination rates is crucial for the interpretation of newborn screening between centres and over time.

Finally, our review illustrates the importance of timely management of infants with suspected life-threatening congenital heart defects. This is a factor that is relevant to all screening strategies and one that was highlighted by parents in our focus group as crucial. Although it does not differentiate the strategies, it is a crucial consideration when considering the continuation of a screening programme. It might be argued that it would not be ethical to continue newborn screening or extend it to any degree unless this is in place. Clearly this poses logistical challenges for infants born in units without easy access to paediatric cardiological expertise. For some defects, telemedicine may provide an important solution and this technology is the subject of an evaluation in Scotland. However, for defects such as TGA, it is unclear whether timely access to balloon septostomy can be widely achieved following diagnosis in the newborn period and, for this reason, further evaluation of antenatal screening for congenital heart defects should be considered. We believe that our model provides a conceptually useful framework from which this might be developed.

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# Acknowledgements

## Contribution of authors

All the authors were involved in the development of the decision analysis model and in regular discussion and planning meetings of project team. They all contributed to the writing, proof-reading and editing of the final report.

Rachel Knowles (MRC Health of the Public Research Fellow) undertook the review of classification and coding systems (Chapter 2), the systematic review of childhood outcomes (Chapter 3) and the systematic review of parent views (Chapter 9). With Catherine Bull (Consultant and Medical Adviser – Family Policy), she undertook development and validation of the CHD classification for screening (Chapter 5). Rachel Knowles and Catherine Bull also organised the parent focus group and compiled the report of parent views (Chapter 9). Rachel Knowles performed the systematic review for model parameters and, jointly with Catherine Bull and Carol Dezateux (Professor of Paediatric Epidemiology), undertook data extraction for the model parameters (Chapter 6).

Ingolf Griebsch (Health Economist) undertook the review of cost parameters and, with Jacqueline Brown developed the decision analysis model and the expected value of information analysis (Chapters 6 and 7).

Carol Dezateux was the Principal Investigator and developed the original project proposal with Catherine Bull and Rachel Knowles. She undertook a review of the epidemiology of CHDs (Chapter 2), was involved in data extraction for the model (Chapter 6), contributed to Chapter 2, and wrote Chapters 4, Chapter 10 and Appendix 10.

Jacqueline Brown (Senior Scientist – Health Economics) developed the decision analysis model and expected value of information analysis with Ingolf Griebsch (Chapters 6 and 7).

Catherine Bull contributed to writing Chapter 2 and developed the subjective probabilities for the model (Chapter 6). With Rachel Knowles, she constructed the CHD classification and validation (Chapter 5), developed health states for the quality of life study (Chapter 8), and organised the focus group (Chapter 9). She participated in data extraction for model parameters with Rachel Knowles and Carol Dezateux.

Christopher Wren (Consultant Paediatric Cardiologist). wrote the review of congenital heart defects (Chapter 2), assisted in the validation of the CHD classification (Chapter 5), contributed to the subjective probabilities (Chapter 6), and provided and analysed data from the Northern Region dataset for use in the model.

All authors participated in questionnaire administration for the quality of life study (Chapter 8).

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*We look forward to hearing from you.*