Screening for Congenital Heart Defects

External review against programme appraisal criteria for the UK NSC

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Introduction

Congenital heart defects (CHDs) are among the most common types of congenital malformations, affecting between 4 and 10 per 1000 live born infants. They are responsible for up to 40% of all deaths from congenital anomalies and account for 3.0–7.5% of all infant deaths. Serious CHDs are often only recognised when an infant develops life-threatening symptoms of cardiovascular collapse. The management of serious CHDs almost invariably involves surgical or catheter intervention with the aim of 'correcting' the cardiac defect and approximating normal anatomy. The type of intervention is unlikely to change with screening, however early detection in the fetal or newborn period is essential to provide anticipatory care at delivery or soon after birth and to prevent death before definitive management can be initiated, or the morbidity consequent on cardiovascular collapse.[1-5]

A review of screening for CHDs presents several challenges as "congenital heart defects" is a term which includes many different structural heart malformations with varying prevalence, clinical features, natural history, interventions and likely benefit from screening. Moreover some CHDs, for example some muscular ventricular septal defects (VSDs) are of no functional or clinical consequence and may resolve spontaneously in early childhood. In determining optimal screening strategies for CHDs, it is vital to consider the precise objectives of screening.

In the UK, current screening programmes may detect CHDs through referral for investigation of increased nuchal translucency at 11-13 weeks gestation (as part of Down's syndrome screening), due to abnormal cardiac findings on the fetal anomaly scan at 18-20 weeks gestation, or abnormal results at the newborn and infant examination. Although antenatal screening has the potential to detect CHDs, a UK-wide study found that a fetal diagnosis was made in only 23% of affected pregnancies and 12% of affected live births.[6] The cardiovascular component of the routine newborn clinical examination comprises observation for cyanosis, auscultation of the heart, and palpation of the femoral pulses, however there is evidence from a large, prospective UK study to suggest that under half of all CHDs present at birth are detected at the newborn examination.[7]

The current screening pathway for CHDs is complex and sequential screening strategies are not integrated across fetal and neonatal life nor is the impact of antenatal screening on newborn screening well-described. Technological developments have led to further potential screening tests for CHDs, in particular routine pulse oximetry performed in the newborn period, and review of the evidence supporting the introduction of these alternative tests into current clinical practice is warranted.

The objective of this review is to evaluate the current evidence against NSC screening criteria in order to

(1) clarify the objectives of screening for CHDs pre- and postnatally,
(2) summarise the evidence concerning screening for CHDs, particularly in relation to first trimester nuchal translucency measurement and second trimester fetal anomaly scan, and evaluate the impact of antenatal detection on newborn screening,
(3) appraise the evidence relating to proposed additional screening tests for CHDs, in particular routine pulse oximetry in the newborn period, including screening performance and referral for further investigations
(4) determine the gaps in evidence and the impact these may have on future decisions about screening.

In addition to an appraisal of the current published literature, this review is informed by an updated version of the clinical and cost-effectiveness model of newborn screening strategies[2] (by R Hunter & R Knowles; Annex 2) , which takes into account additional evidence published since 2005 relating to pulse oximetry and antenatal screening.

Appraisal against UK NSC Criteria

These criteria are available online at http://www.screening.nhs.uk/criteria.

1. The condition should be an important health problem

Prevalence and incidence

Congenital heart defects are among the most common types of congenital malformations, affecting between 4 and 10 per 1000 live born infants.[8-11] This prevalence estimate increases at least ten-fold with the inclusion of structural cardiac defects which are detectable largely only by echocardiography and have no functional significance, such as small muscular ventricular septal defects.[8 12] Apparent increases in the prevalence of CHDs are therefore likely to be due to increased detection of these minor defects as echocardiography is more frequently used for cardiac investigation.[8 13] The most serious CHDs are those requiring intervention or resulting in death within the first year of life[3 9], and those presenting within the first month of life can be considered 'life-threatening'. Life–threatening CHDs include hypoplastic left heart (HLH), interrupted aortic arch (IAA), transposition of the great arteries (TGA), obstructed total anomalous pulmonary venous connection (TAPVC), coarctation of the aorta (COA), critical aortic stenosis (AS) and pulmonary atresia (PA).

Evidence from one UK region with good capture of new CHD diagnoses and mortality over 20 years, estimated the prevalence at live birth of all CHDS as 6.4 per 1000 live births during this time, of which 15% were 'life-threatening' CHD subtypes. [9] There was no increase in the prevalence life-threatening CHDs over this period. In the last five years of the study, prenatal diagnosis comprised about 20% of CHDs with variation by CHD subtype, while post-mortem diagnoses decreased to 0. In around one quarter of newborns with CHDs the diagnosis was not made until after discharge home from hospital.

The most prevalent life-threatening defects at live birth are coarctation of the aorta (COA) and critical aortic stenosis (AS); ventricular septal defect is the most prevalent CHD but unlikely to lead to collapse or death.[2] A summary of CHDs and their prevalence is provided in Table 1.

The prevalence of congenital heart defects at live birth will also depend on the extent of fetal detection and the proportion of fetal diagnoses resulting in termination of pregnancy.[14 15] Less than half of all CHDs are detected prenatally.[16] Data from national surgical audit (NICOR Congenital[1], formerly CCAD) demonstrated that 35% of CHDs undergoing intervention were detected prenatally in 2010[17] and in the Pulse Ox Study 36% of major CHDs were detected prenatally.[3] In a UK wide study of fetal diagnoses of serious CHDs in term infants, a fetal diagnosis was made in just under one quarter of affected pregnancies, approximately half of which ended in termination.[6] Annually, around 100-150 pregnancy terminations in the UK are associated with CHDs.[18]

[1] NICOR is the National Institute for Cardiovascular Outcomes Research at University College London. NICOR Congenital comprises the congenital heart defects audit component of the Central Cardiac Audit Database (CCAD), which was established in 2001 to monitor paediatric cardiac surgical outcomes in all UK centres.

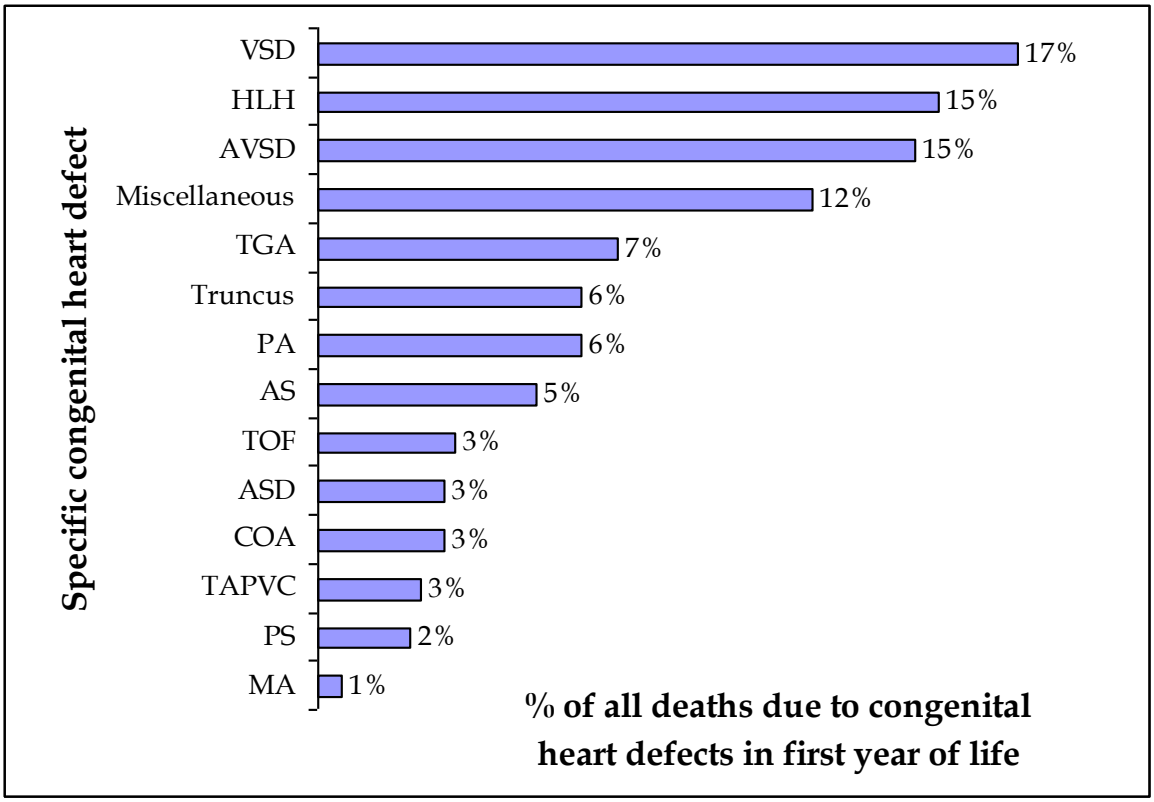
Table 1: Summary of congenital heart defects and their prevalence (adapted from Knowles, et al.[2])

Name of congenital heart defect	**Description**	**Median prevalence per 100,000 live births *(lower quartile, upper quartile)*[8]**	**Prevalence per 100,000 live births**[8 19 20]
Aortic (valve) stenosis	Narrowed aortic valve.	**26** *(16,39)*	**20**
Atrial septal defect	Hole in atrial septum allowing blood flow from left to right atrium.	**56** *(37, 106)*	**28**
Coarctation of the aorta	Narrowing of the distal aortic arch.	**36** *(29, 49)*	**35**
Complete atrioventricular septal defect	Lower atrial septum, inlet ventricular septum and atrioventricular valves are all malformed.	**34** *(24, 40)*	**27**
Hypoplastic left heart syndrome	Aortic valve atresia, possible mitral atresia and small left ventricle.	**23** *(15, 28)*	**14**
Interruption of the aortic arch	Part of the aorta fails to develop. Always associated with another major heart defect.	**Not cited**	**8**
Persistent (patent) ductus arteriosus	Fetal connection between pulmonary artery and aorta persisting after 6-12 weeks of age.	**57** *(32, 78)*	**50**
Pulmonary atresia	Pulmonary valve is closed. May have ventricular septal defect or intact ventricular septum.	**8** *(8, 15)*	**21** *(5 with intact ventricular septum; 10 with ventricular septal defect; 7 complex pulmonary atresia)*
Pulmonary stenosis	Narrow malformed pulmonary valve.	**53** *(35, 84)*	**65**
Tetralogy of Fallot	Subaortic VSD with anterior displacement of aorta and right ventricular outflow obstruction.	**35** *(29, 58)*	**31**
Total anomalous pulmonary venous connection	Pulmonary veins do not connect with left atrium and blood flows directly into systemic circulation.	**9** *(6, 12)*	**9**
Transposition of the great arteries	Pulmonary artery arises from left ventricle and aorta from right ventricle.	**30** *(23, 29)*	**30**
Ventricular septal defect	Hole(s) in the interventricular septum. Often associated with other heart defects.	**Over 4000** *(including studies involving routine echocardiography at birth)*	**197** *(echocardiography not used to screen)*

Associated mortality and morbidity

CHDs are responsible for up to 40% of all deaths from congenital anomalies[2 3] and 3.0–7.5% of infant deaths.[2 3 18 21] Examples of serious CHDs with high first-year mortality are provided in Figure 1 (data from the Northern region), and include hypoplastic left heart (HLH), transposition of the great arteries (TGA), truncus arteriosus, pulmonary atresia (PA) and critical aortic stenosis (AS).[19 22] Although these defects are individually rare, as a group they contribute significantly to death in infancy from CHDs. Atrioventricular septal defect (AVSD) and ventricular septal defect (VSD) are also prevalent and have high mortality, however these are likely to be due in part to the syndromes and co-morbidities that are often found in association with these defects.

Figure 1: Percentage of all deaths due to congenital heart defects between birth and one year of age by specific defect (n=1590) *Adapted from Wren*[14 2]



Key: PA=pulmonary atresia, TGA=transposition of the great arteries, AS=aortic stenosis, TOF=Tetralogy of Fallot, MA=mitral atresia, PS=pulmonary stenosis, VSD=ventricular septal defect, AVSD=atrioventricular septal defect, ASD=atrial septal defect, COA=coarctation of the aorta, TAPVC=total anomalous pulmonary venous connection, Truncus=truncus arteriosus, HLH=hypoplastic left heart, Miscellaneous=includes patent ductus arteriosus (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 transposition of the great arteries and univentricular hearts.

Most infants born with CHDs in the UK are diagnosed before one year of age, although around 25% of infants born with CHDs are not diagnosed before discharge and up to 15% of CHDs may remain undiagnosed at death.[23]

The type of intervention is unlikely to change with screening, however early detection in the fetal or newborn period is essential to provide anticipatory care at delivery or soon after birth and to prevent death before definitive management can be initiated, or the morbidity consequent on cardiovascular collapse. Children with CHDs classified as 'duct-dependent' are particularly likely to experience cardiovascular collapse during the first few days of life as the fetal circulation is replaced

by the neonatal circulation and the arterial duct (ductus arteriosus) closes. Cardiovascular collapse, characterised by severe hypoxaemia, shock and acidosis, can have significant long-term effects as a consequence of significant multi-organ insults, including hypoxic-ischaemic brain injury.[3 5] Poor clinical status at the time of intervention increases interventional mortality and has an adverse effect on outcome.[1]

It is estimated that around 80% of babies born with CHDs now survive to 16 years of age.[19] In the longer-term, children surviving with CHDs have a higher risk of cognitive and motor deficits, emotional and behavioural problems and these can have a significant negative impact on their educational outcomes and quality of life.[24 25]

Quality Adjusted Life Years (QALYs)

QALYs are a combined measure of morbidity and mortality, morbidity measured using utility scores derived from generic measures of health related quality of life. A utility score of 1 represents perfect health and a utility of 0 death; negative values, representing states worse than death, are possible. The utility score is multiplied by the amount of time spent with that utility score to calculate QALYs, hence 1 year in perfect health is equal to 1 QALY and 6 months in perfect health is equal to 0.5 of a QALY. QALYs are the recommended outcome for use in economic evaluations in the UK as they are a common unit that allow for comparable decisions about resource allocation across different diseases. Decision making bodies tend to use the threshold values of £20,000-£30,000 per QALY gained as an upper limit, with values below this being deemed as cost-effective.

There is limited information published on QALYs and screening for CHDs. Cost-effectiveness analyses of technologies used to screen for CHDs tend to use the outcome "cost per case detected"[26 27], with the disadvantage that it is not clear what an acceptable threshold for cost per case detected is for a technology to be deemed cost-effective. Some studies have started to calculate the life-time QALYs attributable to CHDs using epidemiological data to calculate mortality and collecting health utility scores from a randomly selected population that have had paediatric cardiac surgery for a CHD.[28 29] Using a Great Ormond Street cohort, Hunter et al.[29] estimated that over 55 years a repair of Tetralogy of Fallot results in an additional 35 QALYs (20.16 discounted) compared to the natural progression of the disease. The benefit of detecting and repairing other CHDs is currently unknown.

Management

Most newborns with a CHD can be stabilised with prostaglandin infusion and treated with surgery or catheter intervention. The aim of surgical or catheter intervention is to approximate normal anatomy and function, however palliative repair (e.g. a Fontan repair) is the outcome for some complex CHDs. The type of surgical repair or catheter intervention is rarely influenced by the timing of detection or diagnosis, however outcomes after surgery are likely to be improved if an infant undergoes a procedure prior to clinical deterioration.[1]

Prior to the development of paediatric cardiac surgery, most infants born with CHDs died during childhood but advances in intensive care and neonatal cardiac interventions introduced over recent decades have resulted in marked improvements in survival.[18] Nevertheless, if life-threatening CHDs are not detected sufficiently early then cardiovascular collapse, neurological sequelae or death remain potential outcomes.

Data on all paediatric cardiac interventions undertaken for CHDs in the 11 UK specialist centres are collected into a single national database at NICOR Congenital. Key data for infants operated for CHDs from the NHS National Audit of CHD, 2009[30] indicates that:

- Between April 2000 and March 2007, 52,342 procedures were performed for CHDs, including 31,112 surgical procedures and 21,230 therapeutic cardiac catheterisations
- 30 day survival after procedures for CHDs was 98.6% - this was 97.7% for surgery and 99.4% for catheterisation

- At 1 year after a procedure, survival was 93.7% - this was 91.0% for surgery and 97.5% for catheterisation.

Summary: Criterion 1

CHDs are important congenital disorders and convey the highest risk of infant mortality of any single group of congenital disorders. CHDs affect 4-10 per 1,000 live-born infants in England and Wales, with serious CHDs affecting around 1-2 per 1000 live-born infants. Around 95% of these infants will survive to surgical or catheter intervention, and around 80% will survive to 16 years of age.

Mortality has declined in recent decades due largely to advances in intensive medical care and surgical technologies, nevertheless prevention of clinical deterioration prior to intervention is likely to be the key to future improvements in survival, neurocognitive outcomes and quality of life in childhood and adulthood.

Although QALYs are the preferred method for estimating the cost-effectiveness of a health intervention, there is limited published information on QALYs and screening for CHDs. Cost-effectiveness analyses mainly calculate cost per case detected as the outcome but it is not clear at what threshold screening should be considered cost-effective.

2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage

Associated conditions

The aetiology of CHDs is multifactorial. Some conditions associated with higher CHD risk are diagnosed before or at birth and may indicate the need for referral for specialist cardiac investigation. Specific CHDs, such as complete atrioventricular spetal defect (CAVSD) are more likely to be associated with non-cardiac anomalies or syndromes than others, e.g. transposition of the great arteries (TGA) or hypoplastic left heart (HLH). Examples of common associated conditions are trisomy 21, or Down's syndrome, lethal trisomy (13 or 18), or non-cardiac congenital anomalies, which have been associated with a higher risk of CHDs (e.g. exomphalos, gastroschisis). Where such defects are evident or diagnosed at birth, specific investigations for CHDs are indicated and infants may be excluded from routine newborn screening.[31] Using Northern region and European Surveillance of Congenital Anomalies (Eurocat) data sources[2], it has been estimated that the number of exclusions from screening would be 195 per 100,000 live births, including 67 infants with CHDs.[2]

Rationale for antenatal screening

Antenatal screening offers women and their partners an opportunity for information and counselling that may help them better prepare for the birth of their child, the option of delivery in a setting that will permit rapid access to specialist surgical or medical care, or the possibility of considering pregnancy termination or palliative care in the newborn period.[32] Wald and Kennard[33] have proposed six categories of abnormality which might be detected prenatally; CHDs in the following three categories (derived from Wald and Kennard and the Royal College of Obstetricians and Gynaecologists[34]) would benefit from prenatal diagnosis:

1. CHD that is not satisfactorily reparable and can lead to serious disability, and for which termination of pregnancy would be offered.

[2] Sources: in the Northern region, in 1,590 live births affected by CHD, there were 73 non-cardiac anomalies, 21 lethal trisomies, and 107 children with trisomy 21; Eurocat data suggested that an additional 128 per 100,000 infants without CHD would have been excluded for these same indications.

2. CHD that is not satisfactorily reparable after birth, for which intra-uterine treatment reduces morbidity.
3. CHD that, if diagnosed prenatally, would lead to altered management or outcome postnatally.

With regard to these categories, there is some evidence from population-based studies of transposition of the great arteries (TGA) carried out in France to suggest that babies with antenatally diagnosed TGA experience reduced mortality[35] and improved neurocognitive outcomes[5] compared with those diagnosed after birth. Although intra-uterine interventions are increasingly being attempted, few CHDs are suited to this approach as yet.

Current practice is to offer all pregnant women a fetal anomaly scan between 18 weeks 0 days and 20 weeks 6 days. The fetal anomaly scan aims to visualize the four chambers of the heart and, ideally also the outlet tracts (great vessels), in order to identify structural abnormalities in cardiac anatomy. Doppler ultrasound may detect abnormal blood flow, for example across heart valves. In the first trimester, nuchal translucency is routinely measured as part of Down's syndrome screening. Increased fetal nuchal translucency is associated with increased risk of CHDs, however it is not currently used as a screening test.

Some CHDs are not detectable in early pregnancy due to their natural history of development, for example hypoplastic left heart syndrome (HLH) may begin as stenosis of the left outflow tract with hypoplasia of the left ventricle manifesting subsequently. Other CHDs, such as patent ductus arteriosus or foramen ovale, are normal during fetal life and can only be termed CHDs if they are persistent or have detrimental effects on physiological function in neonatal life.

Rationale for newborn screening

The rationale for newborn screening for CHD lies in its potential to influence natural history by early presymptomatic detection and intervention prior to cardiovascular collapse.[2] Infants with a life-threatening or critical CHD at risk of sudden cardiovascular collapse and/or death may only be diagnosed when these occur. There is evidence to suggest that recognition and treatment of these infants prior to cardiovascular collapse positively influences outcomes after surgery.[1]

Defining the targets of newborn screening for CHDs

CHDs are a heterogeneous group and have been classified in different ways for different purposes. A screening classification for CHDs to highlight the individual defects for which the population benefit from newborn screening is potentially the greatest and therefore the target of screening, has been proposed.[2] In this system, CHDs are grouped by preclinical period, clinical presentation and complications (Annex 1). The classification aims to identify *prospectively* a primary group of CHDs to be targeted by newborn screening (i.e. prevention of life-threatening collapse), and a secondary target group where parents and clinicians will have timely knowledge of the diagnosis although there is no evidence that this will alter management or outcome. For CHDs with no functional effects, screening offers no benefit.

Description of a screening classification to define target defects

CHDs can be grouped (A-F) corresponding to the main anatomical point at which the normal flow of blood through the heart, lungs and body is disrupted (Figure 2). CHDs in each group share common symptoms and signs caused by the disruption in blood flow. The relationship between the common signs in each group and newborn screening tests is shown in Table 2.

Table 2: Screening 'markers' of CHDs [adapted from the Screening Classification[2]]

Group	*Auscultation*	*Palpation*	*Observation/Pulse Oximetry*
A	Murmur (less likely)	Femoral pulses decreased or delayed	Cyanosis (some cases)
B	Murmur (some cases)	No effect	Cyanosis (predominant sign)
C	Murmur (some cases)	No effect	Cyanosis, or cyanotic spells (low pulmonary blood flow)
D	Murmur (less likely)	No effect	Cyanosis (severe cases only)
E	No murmur	No effect	Mild cyanosis; sweating/ breathless (later onset symptoms)
F	Murmur (predominant sign)	No effect	No

Clinical examination – Auscultation: CHDs which are likely to be associated with a murmur are often found in Group F and none of this group are likely to result in cardiovascular collapse in the first week of life. Murmurs may be detected in some life-threatening CHDs in Group A (aortic stenosis), Group B (TGA) and Group C (pulmonary valve abnormalities) and Group D (TAPVC).

Clinical examination – Palpation: CHDs which are likely to be associated with delayed or absent femoral pulses are found in Group A. Life-threatening CHDs within this group include interrupted aortic arch and coarctation of the aorta.

Clinical examination/Pulse oximetry – Cyanosis: Life-threatening CHDs which are likely to be associated with cyanosis are most often those in Group B (TGA), Group C (pulmonary valve abnormalities), and also in Group A (HLH, interrupted aortic arch) and Group D (obstructed TAPVC). Some CHDs in Group A (e.g. coarctation of the aorta and aortic stenosis) are less likely to be detected due to cyanosis.

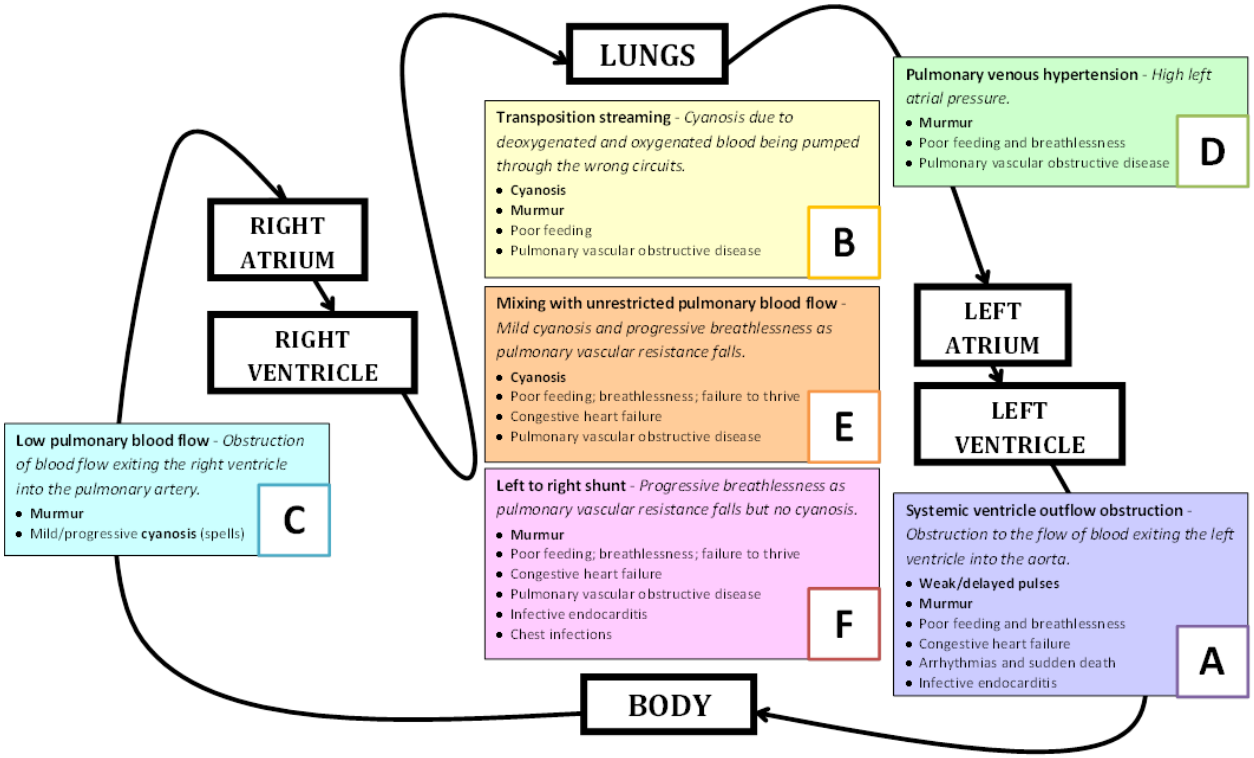
Timing of newborn screening and the natural history of CHDs

The timing of screening should reflect the natural history and clinical presentation. CHDs in the 'screening classification' are therefore also grouped according to two different criteria: the *physiological and anatomical features* and the timing of presentation after birth (*presymptomatic interval*). The use of clinically recognised diagnostic names allows mapping between different classifications, such as those used by Ewer[3 36], de Wahl Granelli[37], Wennerholm[38] and Prudhoe[31] (see Table 3). Nonetheless many pulse oximetry studies have used different classifications leading to significant heterogeneity in meta-analyses.[39]

The classification differentiates between three categories of CHD with reference to the presymptomatic interval (i.e. detectable preclinical phase, lead time or latent period):

- ***short presymptomatic interval:*** short interval between birth and presentation, i.e. these CHDs are likely to present with life threatening symptoms or signs in the first week after birth (many are 'duct-dependent' and present as the ductus arteriosus closes),
- ***moderate presymptomatic interval:*** present with symptoms or signs after a longer interval, i.e. after the first week of life but within the first year of life,
- ***often remain asymptomatic during childhood:*** may present with symptoms or signs after age 1 year but more often remain asymptomatic throughout childhood and present with late complications.

Figure 2: A Screening Classification for CHDs [taken from reference[2]– see Annex 1]



The natural history of each specific CHDs depends on the severity of the defect, thus it can vary from more severe (e.g. *tight* coarctation or *critical* valve stenoses) which present early, to less severe (e.g. *mild* coarctation or stenoses).

CHDs with a **short** presymptomatic interval can be considered life-threatening and the benefits of newborn screening include 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 management.
- Reduction of perioperative morbidity and mortality through early identification before clinical deterioration.

CHDS that are likely to result in collapse early in the newborn period include HLH, IAA, TGA, TAPVC and PA.

For CHDs with a **moderate** presymptomatic interval, the benefits of screening include avoidance of:

- Deaths due to CHDs
- Complications in childhood, such as failure to thrive, feeding difficulties, breathlessness and repeated chest infections (with possible intensive care admission)
- Pulmonary vascular obstructive disease in adult life (for some defects only).

CHDs 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. These could be considered a secondary target of screening as there is potential for offering timely knowledge of the diagnosis to parents and clinicians.

The different definitions used in key recent UK studies investigating newborn screening are compared in Table 3.

Table 3: CHDs targeted by newborn screening

Primary target of screening		
LIFE-THREATENING CHDs Knowles, et al. 2005[2]	**CRITICAL CHD** Ewer, et al. 2012[3]	**CRITICAL CHD** Prudhoe, et al. 2012[31]
Structural cardiac malformations in which collapse is likely: ▪ transposition of the great arteries (TGA) ▪ coarctation/interrupted aortic arch (IAA) ▪ aortic stenosis, ▪ total anomalous pulmonary venous connection (TAPVC) ▪ pulmonary atresia (PA) ▪ hypoplastic left heart (HLH)/mitral atresia.	▪ HLH ▪ PA with intact ventricular septum ▪ TGA ▪ IAA AND infants dying/needing surgery within 28 days of birth with ▪ coarctation ▪ aortic stenosis ▪ tetralogy of Fallot ▪ PA with ventricular septal defect (VSD) ▪ total anomalous pulmonary venous connection. ▪ pulmonary stenosis.	▪ HLH ▪ PA with intact ventricular septum ▪ TGA ▪ IAA AND infants dying/needing surgery within 28 days of birth with ▪ coarctation ▪ aortic stenosis ▪ tetralogy of Fallot ▪ PA with ventricular septal defect (VSD) ▪ total anomalous pulmonary venous connection. ***(NB excluding pulmonary stenosis.)***
	SERIOUS CHD Ewer, et al. 2012[3]	**SERIOUS CHD** Prudhoe, et al. 2012[31]
	Any CHD that is NOT defined as critical BUT requires intervention or results in death between 1 month and 1 year of age.	Any CHD that is NOT defined as critical BUT requires intervention or results in death between 1 month and 1 year of age.
Secondary target of screening		
(CLINICALLY) SIGNIFICANT CHDs Knowles, et al. 2005[2]	**SIGNIFICANT CHD** Ewer, et al. 2012[3]	
Structural cardiac malformations which have effects on heart function but collapse is unlikely or the prevention of collapse is unlikely to be feasible, e.g. ▪ VSD ▪ complete atrioventricular septal defect (CAVSD) ▪ atrial septal defect (ASD) ▪ tetralogy of Fallot.	Present at birth and persisting beyond 6 months of age of: ▪ small patent/persistent ductus arteriosus (PDA) ▪ small patent foramen ovale (PFO) ▪ small muscular VSD ▪ mild abnormal turbulence in branch pulmonary artery ▪ any non-major CHD requiring regular monitoring or drug treatment beyond 6 mths old.	
Not a target of screening		
(CLINICALLY) NON-SIGNIFICANT CHDs Knowles, et al. 2005[2]	**NON-SIGNIFICANT CHD** Ewer, et al. 2012[3]	**EXCLUDED CHD** Prudhoe, et al. 2012[31]
Anatomically defined cardiac malformations with no functional clinical significance, including VSDs only detectable using echo. These require no treatment.	Present at birth but not persisting beyond 6 months of age of: ▪ small PDA ▪ small PFO or ASD ▪ small muscular VSD ▪ mild abnormal turbulence in branch pulmonary artery.	▪ Isolated patent arterial duct (PDA) ▪ Trisomy 13 ▪ Trisomy 18

Diagnoses prior to the newborn screening opportunity

Some infants will become symptomatic before newborn screening and present clinically. The number of infants will vary due to the timing of newborn screening. Based on data from the Northern region relating to timing of diagnosis (based on symptomatic clinical presentation) of CHDs, it has been estimated that of 530 CHDs present per 100,000 live births (term and preterm), 86 infants with CHDs will be excluded from screening at birth (19 antenatal diagnoses and 67 associated conditions), an additional 21 will become symptomatic by 24 hours of age, and a further 102 infants will have become symptomatic by 48 hours of age. The antenatal detection rate and timing of newborn screening will have a significant impact on newborn screening detection rates for CHDs.[2]

Summary: Criterion 2

The epidemiology (birth prevalence) of CHDs is well-documented for all CHDs and for specific defects. Some non-cardiac conditions, which are often identifiable at birth, are known to be associated with specific CHD diagnoses. Associated conditions that indicate the need for specialist referral and investigation included trisomy and certain congenital anomalies, such as gastroschisis and exomphalos. Around 195 infants per 100,000 live births, including 67 with CHDs, might be excluded from newborn screening at birth for these indications.

The natural history of CHDs after birth is well-understood and CHDs can be grouped according to the timing of clinical presentation, symptoms and signs at presentation and likelihood of collapse. This classification provides an indication of the specific defects which may benefit from targeting at newborn screening and the type of test that is most likely to detect each condition. The natural history of CHDs during fetal development is less well-defined and it is possible that some defects develop or become more severe later in pregnancy, after the second trimester screening opportunity, while other defects are normal in fetal life and only become abnormal if they persist after birth.

There is a latent or preclinical phase for CHDs, which will allow early detection before clinical deterioration. This is related in part to the change from fetal to newborn circulation that begins at birth and may take a few days to complete. During pregnancy, the fetal circulation may support structural cardiac abnormalities such that these only become symptomatic after birth. After birth, 'duct-dependent' CHDs manifest clinically when the ductus arteriosus closes; other defects may take longer to present clinically, for example CHDs leading to high pulmonary flow may manifest with poor feeding and breathlessness. CHDs which are likely to lead to sudden, life-threatening clinical deterioration or collapse within the first week after birth should be the primary target of newborn screening. An early screening opportunity, within the first 24 hours of life, may avoid clinical presentation of around 20% (100 per 100,000) infants with CHDs who are likely to present clinically between 24 and 48 hours after birth.

3. All the cost-effective primary prevention interventions should have been implemented as far as practicable

Not applicable. There are no primary prevention interventions available.

4. If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.

Not applicable. There are no screening tests for CHDs based on identification of a genetic mutation.

5. There should be a simple, safe, precise and validated screening test

The heterogeneity of CHDs presents particular problems for screening as potential screening tests vary widely in their capacity to detect markers of risk for life-threatening defects and no test can detect all defects equally well. The effectiveness of tests used within the context of newborn screening will be influenced by detection rates of tests in the antenatal period.

Antenatal screening

The current UK antenatal screening programme includes an assessment of fetal nuchal translucency, as part of the 'combined test' for Down's syndrome in the first trimester (between 11 weeks 0 days and 13 weeks 6 days of pregnancy) and fetal ultrasound examination for anomalies (fetal anomaly scan) in the second trimester, between 18 weeks 0 days and 20 weeks 6 days of pregnancy. The routine fetal anomaly scan is usually performed by a radiographer and includes a cardiac scan; a four-chamber view of the fetal heart and outflow tracts is recommended as part of this routine scan.[32 40] In the FASP survey 2008, 100% of obstetric units provided a routine fetal anomaly scan comprising a four chamber view of the heart to all women, and 75% also routinely performed an outlet view.[41]

First trimester screening tests

Evidence relating to the tests that have been investigated with regard to their potential use in the first trimester screening for CHDs are discussed below. All of the proposed tests involve the use of ultrasound, however this includes routine ultrasound in the first or second trimester (complete fetal anomaly scan) and more specific tests involving ultrasound, such as nuchal translucency (or nuchal fold thickness) measurement, fetal echocardiography or detection of specified additional soft markers.

Routine fetal ultrasound in the first trimester

The diagnostic value of routine fetal ultrasound in the first trimester to detect all types of fetal anomaly, including CHDs, was reviewed by the National Co-ordinating Centre for Women and Children's Health (NCC-WCH) for NICE.[32] This review concluded that there were few good quality studies[42 43] of first trimester ultrasound and, although existing studies demonstrated high specificity (99.9%) and positive likelihood ratios (624.5) for all anomalies, the sensitivity (59%) and negative likelihood ratios (0.41) were only moderate. One randomised trial[44 45] comparing fetal anomaly scan at 12 and 18 weeks gestation found the sensitivity for detecting major CHDs was not significantly different between groups (11% at 12 weeks compared with 15% at 18 weeks) provided insufficient evidence to support introduction of a 12 week anomaly scan.

The updated searches identified one systematic review of first trimester ultrasound[46] at 11-14 weeks which found that early ultrasound identified 56% (95%CI 47-65%) of CHDs identified at second trimester FAS, and had 49% specificity (95%CI 41-58%) for any isolated anomaly. The sensitivity of fetal echocardiography undertaken at this gestation was 58% (95%CI 47-69%), and not significantly different to complete ultrasound. One additional study involving a cohort of 45,191 pregnancies, found that first trimester ultrasound detected 34% of all CHDs diagnosed at second trimester scan and/or postnatal examination.

Nuchal translucency measurement in the first trimester

Nuchal translucency (NT) is measured as part of routine screening for Down's syndrome. Current guidance defining the first trimester prenatal screening and care pathway recommends karyotyping, primarily to exclude Down's syndrome. NHS FASP recommend that a raised NT (≥3.5mm) should prompt the offer of referral (for fetal anomaly ultrasound examination or echocardiography) regardless of the overall risk of Down's syndrome or completion of the combined test. If further investigations are negative, pregnant women should be offered the routine fetal anomaly scan at 18-20 weeks gestation as part of the usual pathway.

A meta-analysis[32] of data from one systematic review of nuchal translucency in low risk pregnancies [47], which included eight studies with considerable heterogeneity, as well as four additional studies, concluded that the sensitivity (around 30%) and likelihood ratios (positive=5.01, negative=0.70) for detection of CHDs using nuchal translucency varied by study and defect-type and the technique had poor diagnostic value. In the updated searches, one meta-analysis evaluated appropriate cut-offs when using first trimester nuchal translucency as a screening test for CHDs[48] and suggested that further exploration of these was warranted, while five lower quality studies supported the use of nuchal translucency as a screening test in low risk populations.[49-52]

Additional first trimester investigations

Additional tests have been proposed for screening in the first trimester. The evidence to support many of these as standalone tests for screening is limited and they are often recommended as adjuncts to NT or the fetal anomaly scan. Detection of ultrasound 'soft' markers was appraised by NICE, who concluded that there was insufficient evidence to support their use at present.[32]

The addition of Doppler to assess the value of detecting absent or reversed flow in the ductus venosus (DV) and/or tricuspid regurgitation (TR) in the fetal heart has been explored as a potential first trimester screening test. Papatheodorou et al.[53] undertook a meta-analysis to evaluate DV Doppler ultrasound in the first trimester for detecting CHDs in fetuses selected for a normal karyotype. In chromosomally normal fetuses *without* increased nuchal translucency, the sensitivity and specificity of DV Doppler alone were 19% and 96% respectively. In chromosomally normal fetuses *with* increased nuchal translucency, the sensitivity and specificity of DV Doppler were 83% and 80% respectively. As a screening test for CHDs, DV Doppler alone performs less well than NT alone; in combination, the tests have a higher detection rate but specificity is lost. Three additional studies identified in the updated search reported the use of Doppler (to image DV or TR) and identification of cystic hygroma colli as potential additional markers to enhance detection rates with NT in the first trimester; all studies selected fetuses with normal karyotype.[54-56] These studies reported sensitivity for NT>95th centile of 50-60% with false positive rates (FPR) of 6-8%[55 56] and sensitivity 25-27% with FPR 1-2% at NT>99th centile.[54] DV or TR alone was not more sensitive or specific than NT alone[55] and FPR was increased. Cystic hygroma colli was a poor marker for CHD.[56]

Second trimester screening tests

Routine fetal anomaly ultrasound in the second trimester

Findings from an HTA review[42] suggest a second-trimester scan is the most cost-effective strategy for screening for all fetal anomalies. However, existing evidence also suggests that antenatal screening technologies have variable success in recognising fetuses with serious CHDs[42] and that this is dependent on the type of defect, expertise of the person scanning[57], standard of equipment, gestation and maternal body mass index (BMI).[58 59]

A systematic review of second-trimester ultrasound[32] demonstrated overall high specificity but poor sensitivity for identifying all fetal structural anomalies. Detection rates for CHDs varied by defect-type: detection rate for hypoplastic left heart syndrome was 54%, complex cardiac malformation was 21%, atrioventricular septal defects was 13%, atrial/ventricular septal defects was 6% and isolated valve abnormalities was 23%.

No systematic reviews or meta-analyses were identified in the updated searches, however one randomized trial, four prospective observational studies and two retrospective case reviews were identified (Table 4). In a randomized trial, Westin[44] demonstrated a higher detection rate for major CHDs for fetal anomaly scan performed at 18 weeks gestation (15%) compared to a scan at 12 weeks gestation (11%); this finding was supported by two observational studies in the updated searches.[60 61] Two observational studies[62 63] demonstrated increased detection of CHDs when colour Doppler was added to routine fetal anomaly scan, however many CHDs remained undetected until birth.[62] More recently additional ultrasound views of the fetal heart, such as the 3VT[64-66] or 5-view[67] have

been advocated, however experience with these in screening low risk populations is limited and there are likely to be implications for the duration of scans and additional operator training.

Screening tests not specific to a trimester

Fetal echocardiography

Fetal echocardiography (a detailed cardiac scan by a specialist operator) is usually performed as a diagnostic test (in high-risk pregnancies or after abnormal routine cardiac scan).[68] Introduction of fetal echocardiography into routine screening would have significant resource and training implications.

Randall et al. reported a systematic review of seven studies of the diagnostic accuracy and effectiveness of fetal echocardiography performed as a routine antenatal screening test for CHDs in low risk or unselected populations; in all of these studies fetal echocardiography was undertaken in the second trimester.[69] The sensitivity of fetal echocardiography ranged widely by study and CHD subtype (from 35% to 86%), but specificity was high (99.9%).

Newborn screening tests

It is likely that some form of newborn screening for CHDs will continue for the foreseeable future as not all CHDs can be detected antenatally. The benefit of newborn screening will be reduced if antenatal detection increases significantly, however current models suggest that newborn screening will remain clinically effective and cost-effective until antenatal detection rates are above 85-90% (Annex 3).[70]

Technological developments in echocardiography and pulse oximetry mean that their application to newborns at the population level might be considered feasible adjuncts to the current clinical examination. The three possible candidate tests for newborn screening are: clinical examination alone (current practice); pulse oximetry and screening echocardiography. As the latter two tests detect different 'markers' (clinical signs) of CHDs, they do not fully 'replace' clinical examination and are therefore more likely to be considered as adjuncts to clinical examination.

Clinical examination

Clinical examination of the cardiovascular system is part of the routine clinical examination recommended for all babies in the newborn period and again at six to eight weeks of age under the Newborn and Infant Physical Examination (NIPE) programme. It is usually carried out by the health professional responsible for the routine examination of all newborn infants before discharge from the maternity unit; this may be a junior doctor or midwife. Clinical examination 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 or delayed blood flow. A presumptive positive result is defined as a finding of cyanosis or murmurs or weak pulses in the groin. NIPE standards recommend that the newborn clinical examination is performed within 72 hours of birth, and ideally within 24 hours.[71]

In practice, routine newborn clinical examination fails to detect over one half of all newborns with CHDs and detection rates vary by CHD subgroup, as defects such as coarctation and aortic stenosis are less likely to be detected before discharge.[9] Published evidence from the Northern region[72], has demonstrated that neonatal examination alone detects around 45% of *all* CHDs. Using the Northern region data in the HTA newborn screening model[2 70], it was estimated that 32% of *life-threatening* CHDs could be detected by newborn clinical examination. In Sweden, in a more recent study[37], 62.5% of *critical* CHDs were detected by clinical examination alone.

Pulse oximetry

Pulse oximetry (PO) is a simple non-invasive method of monitoring the percentage of haemoglobin which is saturated with oxygen. Light shines from a probe attached to the infant's hand or foot and

is partly absorbed by haemoglobin. The oximeter calculates the proportion of haemoglobin that is oxygenated and displays this as a percentage. The equipment required is portable and the examination can be performed by a junior doctor, midwife or other health professional.

Every baby is cyanotic until birth after which there is a rapid rise in oxygen saturation.[73] The probe location is postductal (foot) or both pre- and postductal (right hand and foot). The use of pre- (right hand) and postductal (foot) probe location (with a difference of >2-3% as abnormal) can improve detection of some CHDs. Normal values for pulse oximetry are generally assumed to be the same as those for arterial oxygen saturation in the newborn. In general levels below 95% are considered to be abnormal. Measurements should not be made when the infant is moving, crying or eating and the heart rate should be 90–160 beats per minute.[73] Although pulse oximetry may identify babies with CHDs that result in cyanosis, it will not identify defects that are only associated with murmurs or delayed or absent pulses, and is therefore best undertaken as an adjunct to clinical examination. Pulse oximetry is more likely to detect babies with obstructed pulmonary circulation (Figure 2, Groups B, C & D) than obstructed systemic circulation (Figure 2, Group A). It may also identify babies who are cyanosed for other (non-cardiac) reasons, including lung disease, and this should be considered in implementing a pathway for investigation of presumed positive screening results.

Reference lists (from the HTA and systematic reviews), and updated searches, identified 17 studies (19 papers) evaluating the diagnostic accuracy of pulse oximetry screening for CHDs, usually against echocardiography as the reference standard (Table 6). There were no randomised controlled trials (RCTs). There was considerable heterogeneity between studies, for example in relation to inclusion of antenatal diagnoses, cut-offs for defining term infants, site and timing of the test, devices and thresholds, number of repeat tests, screening pathways and length of follow-up. Two studies[37 74 75] included a control group who received a newborn clinical examination only. The age at the time of the first saturation measurement varied from 4 to > 72 hours after birth, and there was a lack of blinding in all studies. There was often differential follow-up of presumed positive and negative screen results, such that newborns with low oxygen saturation underwent echocardiography while those with normal oxygen saturation were followed up with routine physical examinations or through clinical databases (e.g. cardiology clinics, mortality or congenital anomaly registers). Despite the variability in approach, most studies performed pulse oximetry as an adjunct to clinical examination, used a cut-off level of saturation < 95% and an initial low value led to a repeat test before referral.

Thangaratinam's systematic review and meta-analysis[39] in 2012, updating a previous review from 2007,[76] included 13 studies of pulse oximetry (including over 200,000 births) performed for routine screening in low risk newborns. The authors noted evidence of publication bias and key variations in methodology, including the timing of oxygen saturation measurement (before or after 24 hours of birth), site (i.e. foot only, or foot and hand), types of CHD targeted by screening (all CHDs, critical, left-sided obstruction, cyanotic), inclusion or exclusion of antenatal diagnoses, the gold standard diagnostic reference and the duration of follow-up to ascertain false negative results. In the meta-analysis, overall sensitivity of pulse oximetry for detection of CHDs was 76.5% (95% CI 67.7-83.5%), specificity 99.9% (95% CI 99.7-99.9%) and FPR 0.14% (95% CI 0.06-0.33%). FPR was significantly higher if screening was undertaken within 24 hours of birth (0.5%) but sensitivity did not change significantly. There was no significant difference in the overall detection rate when measurement is in the foot only, although the authors suggest that specific CHDs are more likely to be missed if the pre-/postductal difference is not measured, for example coarctation or aortic stenosis (Figure 2, Group A).

The Pulse Ox Study[3 36], undertaken in Birmingham and involving 20,055 newborns was a study of test accuracy and cost-effectiveness of routine pulse oximetry as an adjunct to clinical examination. Oxygen saturation was measured in right hand and either foot, and the cut-off for an abnormal saturation was <95% in either limb or a difference of >2% between limb saturations. The primary target of screening was major CHDs (critical and serious; see Table 3). Antenatally diagnosed infants

with CHDs were included and the reference standard was echocardiography (for positive screen results) and clinical databases (for negative screen results). Of 53 babies with CHDs, 19 major (including 12 critical) CHDs were diagnosed antenatally; of 34 major CHDs (including 12 critical) not detected before birth, 10 major CHDs (including seven critical) were detected by pulse oximetry and/or clinical examination. Results are summarized in Table 4.

Table 4: Screening test accuracy reported in the PulseOx Study[3 36]

	Sensitivity	Specificity	False positive rates
Major CHDs (critical and serious CHDs): 53 cases			
Antenatal screening	35.8%	99.9%	0.1%
Pulse oximetry without clinical examination*#	28.6%	99.2%	0.8%
Critical CHDs (only): 24 cases			
Antenatal screening	50.0%	99.9%	0.1%
Pulse oximetry & clinical examination*	58.3%	99.1%	0.8%

*excluding antenatal diagnoses; # Of these 34 infants with major CHDs, 20 had normal clinical examination and normal pulse oximetry results, 5 had abnormal results on both tests, 6 had abnormal clinical examination and normal pulse oximetry results, and 3 had normal clinical examination but abnormal pulse oximetry results.

NB Infants detected through both pulse oximetry and clinical examination cannot easily be attributed to one method as abnormal pulse oximetry was followed by an expedited clinical examination (clinical examination undertaken early due to the abnormal pulse oximetry) and a routine clinical examination may have missed some of these cases.

Recently, Prudhoe et al.[31] has reported a 10-year experience with pulse oximetry in the northern region of England; oxygen saturation of <95% in any limb on two occasions led to referral for echocardiography. The study included all major CHDs (see Table 3) diagnosed up to one-year after birth; of 77 major CHDs identified, 18 (23%) were detected antenatally, 16 were excluded from newborn screening (14 due to congenital abnormalities or neonatal care admission, and two were symptomatic). Of 43 babies with CHDs who were screened, 10 (23%) were identified on pulse oximetry, 11 (26%) on clinical examination, one (2%) became symptomatic during screening and 21 (49%) were discharged home undetected by screening (false negatives). All CHDs detected on clinical examination were serious rather than critical. The authors did not report screening test results in babies without CHDs.

Wennerholm[38] reviewed routine pulse oximetry for the Swedish health technology programme and concluded that, as a newborn screening test for critical CHDs, combined screening with pulse oximetry *and* physical examination had better diagnostic accuracy (sensitivity 83-89%, specificity 98-99%) than pulse oximetry screening alone (sensitivity 62-77%, specificity 99-100%) or physical examination alone (sensitivity 62%, specificity 98%). Based on meta-analyses involving low quality evidence from two studies, Wennerholm estimated that the risk of discharging infants with undiagnosed critical CHDs was lower when newborn screening involved pulse oximetry and clinical examination, compared with clinical examination alone (RR 0.38; 95%CI 0.20, 0.71), and the risk of severe acidosis was also reduced (RR 0.40; 95%CI 0.20, 0.40).

In the newborn screening model developed for the NHS HTA Programme[2 70], it was estimated that 68% of CHDs may be detected by combining pulse oximetry and newborn clinical examination compared with 32% detected by clinical examination alone. Interestingly, the 'baseline' detection rate using clinical examination alone was higher in the Swedish study by De Wahl Granelli (62%), than in the original UK data derived from Wren (45%). The original HTA model has been updated using new parameters for screen detection rates available from recent studies, including the PulseOx Study (Annex 2) and detection rate by specific CHD defect estimated by Prudhoe et al (see criterion 16 below).

False positive rates with pulse oximetry are important as these include non-significant CHDs and normal transitional circulation (fetal to neonatal), as well as non-cardiac conditions that lead to low oxygen saturation (Table 7). Meberg[75] and Ewer[36] report high false positive rates and provide a breakdown of the conditions detected (Table 6). Clear pathways for investigating non-cardiac causes have not been established or evaluated in studies published to date and the benefit of detecting different non-cardiac conditions is also uncertain. The higher rate of false positive results found in studies measuring oxygen saturation before 24 hours of age, may relate partly to a higher number of self-limiting causes of low saturation being identified, such as transitional circulation, however further investigation is required to fully understand the implications of these findings for clinical practice.

Screening echocardiography

An echocardiogram can visualise the four chambers of the heart, large blood vessels and the heart valves in the newborn. With Doppler technology, it can also be used to assess the direction of blood flow. In the newborn, 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, while visualisation of the main artery leaving the heart – the aorta – to rule out, for example, coarctation of the aorta - is referred to as an outlet view. The outlet view and views of the aortic arch can be technically difficult to obtain. An echocardiogram may be used as a screening test for congenital heart defects in newborn babies and is likely to be undertaken in addition to a clinical examination. *Screening* echocardiography differs from the gold standard echocardiogram performed by a paediatric cardiologist or equivalent specialist; a screening echocardiogram would be undertaken by a trained radiographer or echocardiographer and involve more limited views and a shorter screening time. Most echocardiography equipment in current use is not portable.[2]

Knowles et al. modelled the effectiveness and cost-effectiveness of echocardiography as a newborn screening test for CHDs, based on RCT data[12], and concluded that the false positive rate for screening echocardiography was unacceptably high. Importantly, screening echocardiography revealed many developmental structural abnormalities of the heart which were not considered clinically important and which may not have been recognised otherwise, as they are often not associated with murmurs or other clinical signs or symptoms.

Summary: Criterion 5

Antenatal screening

Currently, around 20-35% of CHDs are detected antenatally[6 9 17], however not all CHDs will be detected antenatally, as some may develop in later gestation and others are a feature of the normal fetal circulation and only become abnormal when they persist after birth. The fetal anomaly scan in the second trimester remains the most sensitive and specific test for screening prenatally for CHDs in a low risk population. A meta-analysis based on 12 studies concluded that nuchal translucency performed poorly as a screening test for CHDs.

Newborn screening

Newborn clinical examination currently detects less than half of all CHDs before hospital discharge. An HTA model developed based on published evidence and data from the northern region, estimated that clinical examination alone could detect 32% of life-threatening CHDs, whereas 68% of life-threatening CHDs could be detected by adding pulse oximetry to the newborn clinical examination. Subsequently, meta-analyses of routine pulse oximetry in over 200,000 newborns have estimated moderate detection rates for critical CHDs of around 60-80% for pulse oximetry, and test specificity is high.

As around 20% of all life-threatening CHDs present at birth may become clinically symptomatic between 24 and 48 hours after birth, pulse oximetry performed within 24 hours of birth will have greater potential for preclinical detection than at a later timepoint, however the false positive rate is higher with an earlier screen. Not all CHDs will be detected by newborn screening and current studies estimate that 20-30% may not be detected until after discharge home. This risk of discharge home without a diagnosis or of severe acidosis has been estimated to be reduced by around 60% with pulse oximetry.

The benefit of newborn screening will be reduced if antenatal detection increases significantly, however current models suggest that newborn screening will remain clinically effective and cost-effective for life-threatening or critical CHDs until antenatal detection rates are above 85-90%. It is unclear from current evidence, to what extent the various antenatal and newborn screening tests target the same specific cardiac defects or identify different defects across the spectrum of CHDs.

Non-cardiac conditions leading to low oxygen saturation, such as respiratory or infective illness, may be found in infants with low oxygen saturations (false positive screening results). The benefits and costs of further investigation and early diagnosis of such conditions requires further investigation before these diagnoses can be considered a benefit of screening.

6. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed

For antenatal screening, the cut-off is really only relevant to fetal nuchal translucency, while for newborn screening the distribution of test values is only relevant to pulse oximetry.

Antenatal screening: fetal nuchal translucency

NHS FASP guidelines advise referral for further investigation of pregnant women with fetal nuchal fold measurement ≥3.5 mm at the 10-13 week ultrasound scan (undertaken as part of Down's Syndrome screening) or visualized during assessment of crown-rump length. Wald's meta-analysis[48] included seven studies (five of which were also included in an earlier review and meta-analysis[47]) and evaluated the benefit of nuchal translucency (NT) for CHD detection including the cut-offs that should be used. Cut-offs were estimated as multiples of the median (MoM; observed NT divided by expected NT for crown-rump length): for FPR set at 5% (MoM = 1.7), sensitivity of NT to detect CHDs that would benefit from prenatal detection was 52% (95% CI 42-71%)while for 1% FPR (MoM = 2.5), sensitivity was 30% (95%CI 30-61%). Despite only moderate sensitivity, the authors concluded that studies of nuchal translucency for CHD screening would be timely as the detection rate was comparable with the fetal anomaly scan and nuchal translucency measurement is already part of national Down's syndrome screening. In a retrospective analysis of almost 4,000 pregnancies, Timms et al.[77] reported that a cut-off based on gestation-specific 95th percentile MoM was more effective than a cut-off based on mm.

Newborn screening: pulse oximetry

Pulse oximeters measure either functional oxygen saturation (saturated haemoglobin as a fraction of all haemoglobin capable of carrying oxygen) or fractional saturation (saturated hameoglobin as a fraction of all haemoglobin, even that not capable of carrying oxygen). Functional saturation is approximately 2% higher. The precision of oximeter readings varies with the absolute value and are generally cited as +/- 2% above 70% and +/- 4% below 70%.

Early studies of routine pulse oximetry used cut-offs lower than 95% to avoid false-positive results, but repeating the measurements if the initial oxygen saturation is between 90% and 95% limits false-positive results and higher cut-offs can be used. Cut-off levels of functional oxygen saturation of ≥95% in both pre- and postductal limbs and 2% or 3% difference in saturation between foot and right hand have been used in some studies to improve sensitivity[3 37], however Thangaratinam's

meta-analysis demonstrated no significant difference in sensitivity or false positive rate related to site of reading. Valmari has proposed that cut-offs of 95–96% may be sufficiently high to make the measurement of a preductal/ postductal difference less relevant[73], although pre- and postductal readings may detect specific CHDs that would otherwise not be detectable by pulse oximetry.[39]

The mean oxygen saturation of healthy newborns at the age of two minutes is around 73% (range 44–95%) and 67% (34–93%), respectively.[78] At one hour after birth, both measurements are usually ≥95%. As this change may occur more slowly in some newborns, the specificity of screening with pulse oximetry varies and not advisable before two hours of age.[79] Sendelbach also reported high false positive rates (>5%) applying pulse oximetry at four hours after birth.[80]

Oxygen saturation monitors have been studied in a range of populations and low peripheral perfusion (low blood flow to the skin and limbs), skin temperature, skin pigmentation, altitude and movement may all interfere with the accuracy of the measurement of arterial saturation.

Summary: Criterion 6

Antenatal screening: Fetal nuchal translucency

Appropriate cut-offs for fetal nuchal translucency used to detect CHDs in the first trimester, defined in a meta-analysis, have been proposed for use in antenatal screening for CHDs, however these require further investigation.

Newborn screening: Pulse oximetry

Studies involving routine pulse oximetry in the newborn population agree on a cut-off of <95% in either hand or foot on two consecutive occasions to define a positive screen. Some studies have also used a as an additional measure. The overall sensitivity of pulse oximetry does not vary significantly with the use of the additional cut-off of a pre-/postductal difference of 2% or 3% in oxygen saturation between right hand and either foot. It is possible that specific CHDs that are otherwise difficult to detect at newborn screening, such as coarctation of the aorta, may be detected by measuring pre- and postductal saturation, however this would need further investigation in a larger population. Pulse oximetry should be avoided in the first few hours after birth to avoid high false positive rates related to delayed transition from fetal to newborn circulation.

7. The test should be acceptable to the population

The NHS National Fetal Anomaly Screening Programme includes fetal nuchal translucency in the first trimester as a routine antenatal screening test for Down's syndrome, as well as ultrasound screening around 20 weeks of pregnancy to detect structural fetal anomalies, such as CHDs. Within the NHS Newborn and Infant Physical Examination programme, a cardiovascular examination (comprising auscultation of the heart, palpation of the femoral pulses and inspection for cyanosis) is undertaken within the newborn period and at 6-8 weeks after birth. These tests appear to be acceptable when carried out as routine screening tests antenatally and within the first year of life.

Pulse oximetry and echocardiography are not performed routinely and their acceptability in the UK as part of a routine national screening programme is not known. Focus groups undertaken for the Pulse Ox study suggested that professionals would be supportive of a newborn screening programme for CHDs using pulse oximetry and clinical examination.[3 81] Evaluation of mothers, using standardised psychological instruments, suggested that they found pulse oximetry acceptable and that false positive results did not increase anxiety significantly.

The acceptability of false positive and false negative screening results in a national screening programme in a low risk population may require further evaluation.

Summary: Criterion 7

Tests, such as the fetal anomaly scan and clinical examination of the newborn, which are included in the current NHS screening programmes appear acceptable. Nuchal translucency appears acceptable as a test in the context of Down's syndrome screening and pulse oximetry appears acceptable as a test in the context of research involving low risk populations. However, the acceptability of false positive screening results (requiring further investigations) and false negative screening results (involving false reassurance) screening results, when either of these tests is included in a national screening programme in a low risk population requires further evaluation.

8. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals

Antenatal screening

A measurement of increased nuchal translucency or a cardiac anomaly on fetal anomaly scan should prompt the offer of a referral to a fetal medicine specialist or an appropriate healthcare professional with a special interest in fetal medicine.

NHS FASP has developed and implemented national guidelines and standards for clinical referral, diagnostic investigation and management of the pregnancy following screening detection of a

1. fetal nuchal translucency measurement of ≥3.5mm at 11^{+0} – 13^{+6} weeks gestation, undertaken as part of the combined test for Down's syndrome screening or visualised during assessment of crown-rump length in the absence of biochemistry, or
2. structural cardiac anomaly on a fetal anomaly ultrasound scan at 18^{+0} – 20^{+6} weeks gestation.

It would also be advisable to review experience with the current cut-offs used for nuchal translucency in Down's syndrome screening and the effectiveness of the current referral pathway from the perspective of screening for CHDs.

Newborn screening

A presumed positive result at newborn clinical examination should prompt referral for an expert cardiological opinion, and further investigations such as detailed echocardiography, to confirm or exclude a CHD diagnosis. Auditable standards and guidelines for cardiological referral after an abnormal clinical examination have been developed and implemented by NIPE.

A presumed positive result on pulse oximetry screening should prompt referral for an expert cardiological opinion, and further investigations such as detailed echocardiography, to confirm or exclude a CHD diagnosis. However, pulse oximetry used as a screening test for CHD may incidentally detect other conditions, for example respiratory conditions that cause low oxygen saturation. Further assessment after pulse oximetry should determine whether the underlying cause of hypoxaemia is likely to be cardiac or non-cardiac in origin and should include adequate follow-up to determine the cause if this is considered not to be cardiac in origin. The Pulse Ox study included echocardiography as the reference standard investigation after all positive screens.[3] American Academy of Pediatrics[82] guidance is for specialist paediatric assessment to exclude non-cardiac causes of hypoxemia prior to echocardiography. In practice, this may be applied to reduce the requirement for echocardiography to fewer than one-third of screen positive cases[83], however the risk of missing cases of CHD cannot currently be quantified as there has been limited evaluation of referral pathways.

A policy for investigation after a positive screen result on pulse oximetry has not clearly been established and evaluated in practice. Essential considerations prior to implementation of pulse oximetry in a national screening programme would be:

- An agreed policy of investigation for cardiac and non-cardiac causes

- The availability of services and trained operators for diagnostic investigation for cardiac and non-cardiac causes
- The development of appropriate information for parents.

Summary: Criterion 8

Antenatal screening

Referral to a specialist for investigation after an abnormal result on measurement of increased nuchal translucency (in Down's syndrome screening) or fetal anomaly scan is established as part of the current screening and care pathway. Subsequent diagnostic investigations are dependent on clinical judgment. Consideration would need to be given to whether the referral policy after nuchal translucency remains appropriate if a cut-off appropriate to screen specifically for CHDs is introduced.

Newborn screening

The pathway for investigation after an abnormal clinical examination has been implemented by NIPE. A pathway for clinical investigation after a positive screen result on pulse oximetry has not been clearly established or evaluated in practice. Essential considerations prior to implementation of pulse oximetry in a national screening programme would therefore be to agree a policy for investigation to identify cardiac and non-cardiac causes of low oxygen saturation, including consideration of the resource implications and acceptability to parents.

9. If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out

Not applicable. No screening tests for CHD involve identification of a genetic mutation.

10. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment

Almost without exception, the definitive surgical intervention for specific congenital heart defects remains the same whether the diagnosis has been made after a positive screening test or clinical presentation. Nevertheless early detection through antenatal or newborn screening permits anticipatory care at delivery or soon after birth and can prevent death, or the morbidity due to cardiovascular collapse, before definitive management can be initiated. Children with duct-dependent CHDs are at particular risk of sudden clinical deterioration during the first few days of life and poor clinical status at the time of intervention increases interventional mortality and has an adverse effect on neurodevelopmental outcomes.

Earlier detection of CHDs would avoid a significant proportion of the complications and mortality associated with cardiovascular collapse subsequent to delayed diagnosis and treatment of CHD. In the Baltimore Washington Infant study, 10% of infants with CHDs who died were only diagnosed after death and the most significant risk factor was early discharge from hospital after birth.[84] Abu-Harb also reported that almost one-third of CHDs were only diagnosed after death in the northern region of England. In Pfammatter's study cohort, 10% of infants with CHDs experienced significant delay in diagnosis and, of these, over one-fifth had clinical complications associated with this delay. Although there are no studies which have looked directly at the impact on preoperative clinical deterioration or postoperative survival from newborn screening, a study by Brown provides evidence that the prevention of cardiovascular collapse before surgical or catheter intervention

improves both short-term surgical outcomes, including mortality, and decreases the length of stay in hospital.[1]

Prenatal diagnosis can allow a choice of birth place in order to optimise postnatal management. In utero transport to a specialist cardiac centre for delivery has been shown to improve survival of infants with left ventricular outflow tract obstruction.[85] There is also evidence from several studies of prenatal diagnosis to suggest outcomes may be improved for some children whose CHDs were detected before birth, allowing anticipatory care at delivery. In a French population-based cohort of children with transposition of the great arteries (TGA), infants with a prenatal diagnosis experienced reduced mortality and improved neurocognitive outcomes in the longer-term compared with those diagnosed after birth.[5 35] Kumar[86] has demonstrated better preoperative clinical status and Copel[87] has shown better survival to hospital discharge for infants with a prenatal diagnosis of CHD compared with those with a postnatal diagnosis, however other authors have failed to find a significant benefit from prenatal diagnosis.[88 89] Studies of prenatal diagnosis do not therefore provide definitive evidence for a benefit from prenatal screening and an important confounding factor is that the patient groups in whom CHDs are detected pre- and postnatally may differ significantly. Although antenatal diagnosis permits termination of severely affected pregnancies, parents who continue with the pregnancy are more likely to choose surgery for their child after birth however severe the CHD.

Although studies directly comparing outcomes in screened and unscreened populations are lacking, existing evidence appears to suggest that there is a benefit to survival and longer-term postoperative outcomes from early detection of CHD and prevention of cardiovascular collapse prior to surgical or catheter intervention.

Summary: Criterion 10

Surgery and catheter intervention provide effective treatment for CHDs. Early detection through antenatal screening facilitates anticipatory care at delivery to prevent clinical deterioration, or offers parents the choice of termination of pregnancy. Early detection of life-threatening CHDs in asymptomatic newborns allows management aimed at preventing cardiovascular collapse before intervention, a particular risk for duct-dependent cardiac defects, and there is some evidence that this can lead to improved short and long-term outcomes after surgery.

11. There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered

Current practice is for babies with CHDs detected on the fetal anomaly scan to be referred to a fetal medicine consultant or clinician with a specialist interest in fetal medicine.

Children with CHDs detected after birth should be referred to a paediatric cardiologist in one of the specialist paediatric cardiac centres throughout the UK for specialist investigation and management. Within these specialties, there exist agreed evidence-based guidelines for treatment of CHDs. National outcomes audit is undertaken through NICOR Congenital (formerly Central Cardiac Audit Database [CCAD]).

Summary: Criterion 11

Management of a positive antenatal screen result includes referral to a fetal medicine specialist for further investigation.

Evidence-based policies exist for the management of CHDs within specialist paediatric cardiology services.

12. Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme

Clinical management of diagnostic investigation and referral for treatment is undertaken within a limited number of specialist centres. The configuration of specialist provision has recently undergone review under the Safe and Sustainable Review by the NHS National Specialised Commissioning Group (NSCG) and a smaller number of centres has been recommended.[90] The NSCG has established an expert working group to establish standards of care for paediatric cardiac surgery. Regular national audit of outcomes after paediatric cardiac surgery and catheter interventions by NHS providers is undertaken through NICOR Congenital. Mortality outcomes at 30-days and 1 year post-procedure are comprehensively collected and validated through data linkage to death registrations.

Summary: Criterion 12

Specialist paediatric cardiac services have recently undergone review to optimise provision. Regular national audit of paediatric cardiac surgery outcomes facilitates ongoing monitoring of existing services.

13. There should be evidence from high quality Randomised Controlled Trials (RCT) that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (eg. Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.

One randomised trial compared first and second trimester fetal anomaly ultrasound scanning.[44] One RCT compared screening echocardiography with routine clinical examination.[12]

Summary: Criterion 13

With the exception of two RCTs of fetal anomaly ultrasound and screening echocardiography in newborns, evidence is from observational studies.

14. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public

Antenatal ultrasound is attractive to pregnant women and their partners as it provides early confirmation of pregnancy and reassurance about fetal wellbeing, however these positive expectations of the scan may also increase feelings of anxiety, shock and disappointment when it shows a problem.[42] No trials comparing ultrasound with no ultrasound have looked at its social and psychological impact on parents and babies. Fetal ultrasound screening can also lead to findings of uncertain clinical importance, with important psychological consequences.

Focus groups undertaken for the Pulse Ox study [3 81] suggested that parents and professionals found PO and clinical examination acceptable tests in the context of newborn screening for CHDs. Parental anxiety may increase in relation to false negative results as this implies a false reassurance from newborn screening. In the recent large population studies[31 36 37 74 91 92] of pulse oximetry screening involving 20,000 to 50,000 infants, the proportion of all cases resulting in a false negative result ranged from 12% to 34%. There may have been an underestimate of false negative results due to incomplete ascertainment of cases as the duration and completeness of follow-up varied between

studies and appeared limited in some populations. False positive results are also of concern to parents and may raise anxiety. Overall false positive rates for pulse oximetry appear to be around 1-1.5%[36 39], however higher false positive rates were reported in some studies.[39]

There is a high rate of false positive screening results associated with screening echocardiography and public and professional attitudes to this would require further exploration.

Summary: Criterion 14

Antenatal ultrasound, newborn clinical examination and pulse oximetry appear acceptable as screening tests. However the acceptability of high false positive rates (which may raise anxiety) and false negative rates (leading to false reassurance) requires further exploration for all screening modalities.

15. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment)

This varies between screening tests.

Current evidence reviews suggest that visual confirmation of fetal wellbeing is the primary reason why women seek ultrasound during pregnancy, and that the benefits of fetal anomaly scanning outweigh the harms. NICE concluded that detection of surgically treatable congenital anomalies on antenatal ultrasound led to increased anxiety levels in the parents but counselling by specialist staff helped to alleviate these. The benefits and harms arising from the identification of 'soft markers' at fetal anomaly ultrasound have not been fully defined.

Existing evidence suggests that the benefits of screening outweigh the harms for newborn screening using clinical examination with or without pulse oximetry as the screening test.[3]

The benefits may not be considered to outweigh harms for screening echocardiography due to the higher false positive rate.[2]

Summary: Criterion 15

Existing evidence suggests that the benefits outweigh the harms for newborn screening, when the screening test is clinical examination with or without pulse oximetry, and for antenatal screening, when the screening test is antenatal ultrasound.

16. The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (ie. value for money). Assessment against this criteria should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource

Antenatal screening

In the NICE clinical guideline on diabetes in pregnancy[32], a cost-effectiveness model compared a four chamber cardiac ultrasound scan with the four chamber plus outflow tracts scanning view to screen antenatally for CHDs. The baseline analysis suggested that the four chamber plus outflow tracts view had an incremental cost-effective ratio (ICER) of £24,000 relative to the four chamber view alone; this is within the cost-effectiveness range of £20,000 to £30,000 per QALY used by NICE.

Newborn screening: clinical examination (CE), pulse oximetry (+CE), echocardiography (+CE)

Estimates for the cost effectiveness of three different newborn screening strategies (clinical examination, pulse oximetry and clinical examination, and screening echocardiography and clinical examination) were obtained from a decision analysis model produced for the HTA in 2005, which used population-based data on CHD prevalence and survival from the northern region, screening parameters retrieved from a systematic literature review and primary cost data.[2 70] _ENREF_70 This model suggested that the ICER for pulse oximetry as an adjunct to clinical examination was acceptable but that total programme costs and ICER for screening echocardiography (in relation to timely diagnoses of life threatening CHDs) was unlikely to be. A subsequent cost-effectiveness analysis undertaken for the HTA using PulseOx Study data[27] estimated that the cost of adding pulse oximetry to newborn clinical examination was £24,900 per additional timely diagnosis (detection before death or collapse).

When the parameters for the 2005 decision analysis model were updated with screening parameters from the Pulse Ox Study and to 2010/11 costs, pulse oximetry as an adjunct to clinical remained cost-effective (Annex 2) although the costs varied with different scenarios tested:

- The cost per additional timely diagnosis of *critical or major CHD* (defined in the Pulse Ox study) using pulse oximetry was £24,000
- If only *life-threatening CHDs* (defined in the original decision analysis model) were considered to benefit from screening detection, fewer cases were considered to benefit from screening detection and the estimated cost per additional timely diagnosis was £35,000
- When the antenatal detection rate was reduced from 52 per 100,000 (in the Pulse Ox study) to the lower Northern region rate (10 per 100,000 as applied in the original decision analysis model), then the number detected by newborn screening increased and the cost per timely diagnosis of *life-threatening CHD* was reduced to £20,000.

Even with conservative assumptions, such as a high antenatal detection rate and lower number of CHDs benefitting from earlier diagnosis, pulse oximetry as an adjunct to CE detected 19-37 additional diagnoses and the cost per additional diagnosis varied between £15,000 and £35,000. The results of the most recent review of pulse oximetry[31] have also been incorporated into the model, with a cost per timely diagnosis of £20,166.

Roberts et al.[27] suggests that each additional timely diagnosis would result in at least 5 additional quality-adjust life-years (QALYs). As NICE has a willingness to pay threshold of £20,000-£30,000 per QALY, the potential willingness to pay for each additional diagnosis is potentially greater than £100,000. The updated decision analysis model incorporating the more accurate pulse oximetry data from the Pulse Ox study, therefore suggests that even with the most conservative assumptions, there is a 92% chance that pulse oximetry with clinical examination is cost-effective if a decision-maker is willing to pay £100,000 per additional timely diagnosis.

Previous models have not estimated the life-time QALYs associated with earlier identification of CHD as a result of pulse oximetry screening or the costs of the repair and life-time monitoring. An estimation of cost per QALY gained over the life-time of the patients has been made possible by the development of the life-time model of Tetralogy of Fallot.[29] Although it is recognised that Fallot's tetralogy is not a major or critical CHD so the estimate remains modest, this is the best estimate available to date. Using the best available information, a preliminary conservative estimate of the cost per QALY gained with pulse oximetry with clinical examination compared to clinical examination alone is £5,659 per QALY gained, well within the NICE threshold for cost-effectiveness. Further work is required to determine the life-time QALYs and costs of major or critical CHDs if a more precise estimate is to be obtained, although this is likely better information will reduce the cost per QALY gained given the shorter life expectancy of critical CHDs not detected at birth than that assumed in the model.

Pulse oximetry at birth compared to after 24 hours

The most recent cohort data on the effectiveness of pulse oximetry screening by Prudhoe et al. [31] contains a summary of all cohort data published from 1998-2009 broken down by specific congenital heart anomalies and with information on timing of the screen. Incorporating this information into the model allows for a cost a direct comparison of screening infants at birth compared to at 24 hours. The false positive rate for different timings was taken from the systematic review by Thangaratinam et al.[39]

More cases of *critical or major CHD* (defined in the Pulse Ox study) are identified by pulse oximetry if screening occurs at birth (88 cases per 100,000 live births) compared to at 24 hours (65 cases per 100,000 live births) at an additional cost per case detected of £3,409. This is mainly due to infants who are identified through clinical presentation as having a major CHD before the screening test, as the test itself does not appear to function significantly differently at the two time points (although there is a significantly higher false positive rate at birth). Screening within 24 hours of birth appears to result in more QALYs, as more cases of major or critical CHDs overall are identified, although for a higher cost (at a cost per QALY gained of £3,229).

Summary: Criterion 16

The existing evidence strongly suggests that pulse oximetry in conjunction with clinical examination is more cost-effective than clinical examination alone. Further evidence, including estimation of QALYs, continues to support this. More cases of *critical or major CHD* (defined in the Pulse Ox study) are identified by pulse oximetry if screening occurs at birth (88 cases per 100,000 live births) compared to at 24 hours (65 cases per 100,000 live births) at an additional cost per case detected of £3,409, however the false positive rate is also higher at birth. The cost-effectiveness of screening at different time points is also dependent on the outcome used (cost per timely diagnosis versus cost per QALY gained).

17. All other options for managing the condition should have been considered (eg. improving treatment, providing other services), to ensure that no more cost effective intervention could be introduced or current interventions increased within the resources available

Services for children with CHDs were included within the Safe and Sustainable review of specialist services and recommendations made for reconfiguring and improving these to optimise their clinical benefit and cost-effective use of resources.[90]

Although specific risk groups are likely to be excluded from newborn screening (e.g. children with Down's syndrome or non-cardiac anomalies), modelling of screening outcomes using parameters from the Northern region and Pulse Ox study (Annex 2) would suggest that newborn screening is still effective and cost-effective after exclusion of these groups.

Summary: Criterion 17

It is unlikely that further increasing the clinical and cost-effectiveness of alternative interventions would have sufficient impact to remove the need for improved screening. Newborn screening remains cost-effective even after exclusion of specific high-risk groups, such as infants recognised at birth to have trisomy or gastroschisis.

18. There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards

The FASP and NIPE screening programmes are monitored against an agreed set of quality assurance standards. If further screening tests were added, such as pulse oximetry, these would need to be reviewed to include quality assurance for the additional tests. For pulse oximetry, this would include

clearly defining the investigation of positive screening results, in particular 'false positive' results in which a low oxygen saturation was due to a non-cardiac cause.

Summary: Criterion 18

Monitoring systems for antenatal and newborn screening programmes already exist and these could be developed to include quality assurance and monitoring of screening for CHDs.

19. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme

Adequate staffing and facilities are already provided for antenatal and the newborn screening clinical examination.

Additional facilities would need to be considered for investigation and diagnosis after a presumed positive screen result on pulse oximetry. This may include referral for respiratory and neurological investigation if initial investigations did not identify a cardiac cause for the abnormal oxygen saturation.

Adequate staffing for a screening echocardiography service would need to be considered.

Summary: Criterion 19

Adequate staffing and facilities are already provided for current antenatal and newborn screening programmes. Additional facilities would be required for investigation and diagnosis after a presumed positive screen result on pulse oximetry, particularly if initial investigations did not identify a cardiac cause for low oxygen saturation.

20. Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice

This is currently provided for tests undertaken within the FASP and NIPE screening programmes.

Information has been developed and used in a research context to describe pulse oximetry screening; this would provide a basis for developing appropriate information for participants.[81] Such information should include discussion of false negative and false positive results, as well as any further investigations that may be required to exclude other cause of low oxygen saturation when cardiac causes are not identified.

Evidence-based information for participants is lacking for screening echocardiography

Summary: Criterion 20

Evidence-based information for participants in antenatal and newborn screening exists but is lacking for pulse oximetry as a screening test and would need to be established.

21. Public pressure for widening the eligibility criteria, for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public

All low risk pregnancies and most newborns (except those excluded with associated conditions) would be eligible for screening. There is unlikely to be pressure to broaden the population eligible for screening.

There may be pressure to change the timing of pulse oximetry, as evidence suggests that false positive rates are higher if the test is undertaken within 24 hours of birth.[39] However a later screen may lead to a higher number of infants collapsing before screening. Some issues may be addressed through provision of appropriate education to parents and implementation of clear policies for investigation, but these may also have resource implications.

Summary: Criterion 21

Public pressure for changing the screening process have been considered and should be addressed through the and provision of appropriate information to parents, the development of clear clinical protocols for investigation and management and regular audit of the screening programme.

22. If screening is for a mutation the programme should be acceptable to people identified as carriers and to other family members

Not applicable.

Conclusions

CHDs are one of the most common congenital anomalies, affecting between four and 10 per 1,000 live births. They are responsible for up to 40% of deaths due to congenital malformations, however it is estimated that around 80% of babies born with CHDs now survive to 16 years of age. In the longer-term, children with CHDs have a higher risk of cognitive and motor deficits, emotional and behavioural problems, which can have a significant negative impact on their educational outcomes and quality of life. Most infants born with CHDs in the UK are diagnosed before one year of age, although around 25%-30% of infants born with CHDs are not diagnosed until after discharge from hospital and up to 15% of CHDs may remain undiagnosed at death.

CHDs comprise a wide range of different structural cardiac malformations with very variable clinical presentation and prognosis. Children with CHDs classified as *life-threatening* or *critical* are likely to experience cardiovascular collapse, and poor clinical status at the time of a surgical or catheter procedure increases interventional mortality. *Critical* defects should be the primary target of screening as early detection in the fetal or newborn period allows anticipatory care, at delivery or soone after birth, and may prevent death or the morbidity consequent on cardiovascular collapse. A secondary target of screening are *serious* or *significant* CHDs that convey low risk of collapse, but where early knowledge of the diagnosis can support planned interventions and care. Finally some defects are not functionally significant or may even spontaneously resolve in early childhood (e.g. small muscular ventricular septal defects), thus do not benefit from screening detection.

The current UK screening programme for CHDs involves a fetal anomaly scan, including four chamber and outlet tract views of the heart, at 18-20 weeks gestation and a newborn physical examination (including auscultation for murmurs, palpation of the femoral pulses and observation for cyanosis) in the first 72 hours of life and at 6-8 weeks of age. Due to the natural history of their development and the variable clinical presentation of CHDs, no screening test will detect all defects equally well. Antenatal screening appears to detect around 30-50% 0f CHDs, while newborn clinical examination may detect 30-60% of CHDs. If antenatal detection of CHDs, which offers parents a choice of pregnancy termination, continues to increase, then there is likely to be an impact on the prevalence and spectrum of cardiac defects amenable to newborn screening, however it has been estimated that antenatal detection would need to rise to over 85% before newborn screening ceases to be cost-effective. For the foreseeable future, an integrated system of antenatal and newborn screening is likely to be required.

Several additional tests for CHDs have been proposed and evaluated in recent years, of which the most prominent are first trimester fetal nuchal translucency measurement, and routine pulse oximetry as an adjunct to clinical examination in newborns. Fetal nuchal translucency is already undertaken in the UK as part of Down's syndrome screening and infants with abnormal findings are referred for further investigation. As evidence regarding the performance of fetal nuchal translucency measurements *as a screening test targeting CHDs* is limited, further evaluation of the current screening pathway and thresholds for referral as currently implemented would be advisable before considering further its application to early detection of cardiac defects.

Routine pulse oximetry is probably the most promising additional newborn screening modality, particularly for duct-dependent defects obstructing the pulmonary circulation. Recent evidence reviews demonstrate that pulse oximetry and clinical examination used in combination have high specificity (>99%), moderate sensitivity (60-80%) and an acceptable false positive rate (<2%) for newborn screening for critical CHDs. The addition of pulse oximetry as a newborn screening test is likely to reduce the number of infants with CHDs who experience severe acidosis before intervention and the number of infants discharged from hospital before CHD is recognised. However, there are no randomised controlled trials of pulse oximetry and many studies are of moderate or low quality; very few have involved a direct comparison with clinical examination or included blinding of operators to previous antenatal or newborn findings. Moreover, there is considerable heterogeneity

between studies, for example in the site and thresholds for measuring oxygen saturation, timing of screening, number of repeated measures, population coverage and exclusion criteria. It is very likely that false negative results were underascertained in many studies due to differential follow-up of positive and negative test arms. There remains therefore some uncertainty about the true costs and benefits of pulse oximetry if it were to be integrated into the existing antenatal and postnatal screening pathway and used routinely in a low-risk population rather than within the context of a clinical or test accuracy study. Furthermore, as detection rates vary between CHDs, it is also possible that the relative prevalence of these at birth (due also in part to variability in the antenatal detection rate between defects) could influence overall screening performance to a greater extent than has been recognised in smaller studies which focus on overall detection rates for critical CHDs.

While a non-invasive oxygen saturation measurement appears acceptable to parents and healthcare staff in a research context, but there is limited evidence about the psychological impact on parents of receiving false positive or false negative screening results. Some elements of the screening pathway are not well-described in the current literature or vary significantly between studies, such as the exclusion of certain groups of infants from newborn screening (e.g. preterm infants, infants with Down's syndrome or recognised congenital malformations diagnosed at birth, and those admitted to specialist neonatal care units). In view of the high proportion of non-cardiac causes of a low oxygen saturation, the establishment of formal pathways for investigation of cardiac and non-cardiac causes of a positive pulse oximetry screen result would require careful agreement, implementation and appraisal.

The management of CHDs is concentrated within specialist paediatric cardiac centres. Recent re-evaluation of this specialist service configuration has been performed resulting in clear goals for the optimisation of future provision. Evidence-based guidelines support current interventions and regular monitoring of short-term outcomes is achieved through comprehensive national cardiac audit. Monitoring of long-term outcomes and quality of life for children surviving beyond infancy is less comprehensive but high quality studies exist, mainly from north America and Europe.

Implications for policy

This review confirms that antenatal and newborn screening for CHDs meets NSC criteria. However, the current policy of a fetal anomaly scan and newborn physical examination to screen for CHDs (in the current NHS FASP and NIPE screening programmes) has limited effectiveness and is estimated to detect 50% or fewer CHDs (at each of these screening opportunities). Overall 25-30% of babies born with serious CHDs may remain undiagnosed at hospital discharge. The current programmes are cost-effective and highly acceptable to a low-risk population and no evidence was identified during the review to support their cessation.

It would additionally be of value to establish the detection rates for specific CHDs through the current programmes as a baseline for future change. Recording outcomes by specific cardiac defect would facilitate better understanding of whether some antenatal and postnatal screening tests add value (i.e. effectively target specific CHDs that other tests do not detect) or do not add value (i.e. duplicate efforts by targeting the same defects, or target CHDs that are not functionally significant).

It is also essential that in appraising the acceptability of CHD screening, the 'cumulative' false positive rates and total burden of referrals for additional investigations are considered, rather than tests in isolation, as this better reflects the experience of a systematic and integrated screening pathway for women, their partners and babies.

Fetal nuchal translucency

As evidence regarding the performance of fetal nuchal translucency measurements *as a screening test targeting CHDs* is limited and does not support its introduction as an additional first trimester

screening test for CHD at present. Further evaluation of the current antenatal screening pathway as currently implemented and, in particular, the thresholds and pathways for referral after fetal nuchal translucency measurement, would help inform future consideration of the benefits of first trimester screening for CHDs.

Routine pulse oximetry for newborn screening

There is now considerable research evidence to demonstrate that pulse oximetry, as an adjunct to clinical examination, increases the detection rate of critical or life-threatening CHDs at the newborn screening opportunity. Importantly, there have been no randomised controlled trials and many studies are small and only of moderate or low quality. Although evidence presented in this review demonstrates that pulse oximetry is a clinically effective and cost-effective screening modality for detecting *critical or life-threatening* CHDs, thus meriting implementation as part of the newborn screening programme, there remains sufficient uncertainty about its use in a routine screening context to support a pilot or staged introduction (such as carried out in the initial implementation of the MCADD screening programme by the NSC). A staged introduction could address important uncertainties relating to optimisation of the screening and referral pathways, investigation of false positive screen results and implementing monitoring and audit to ascertain false negative results and screening performance. Key issues to be addressed in a pilot would include:

- determining screening coverage (i.e. infants to be excluded from newborn screening),
- appraising the impact of antenatal diagnoses on pregnancy terminations and CHD prevalence at live birth (by specific defect where possible)
- defining optimal test procedures for oxygen saturation measurement and newborn clinical examination (including timing, pre- and postductal siting, number of repetitions and the temporal relationship between pulse oximetry and clinical examination),
- clarifying and testing pathways for referral for further investigations after a screen positive result (including cardiac and non-cardiac causes)
- the development of information for parents and health professionals across the antenatal and newborn continuum
- instituting a training curriculum for midwives and others involved in newborn screening using pulse oximetry
- establishing routine data systems (and/or routine data linkage, e.g. between screening programmes) for audit, quality assurance and monitoring of longer term outcomes.

Implications for research

This evidence review highlighted several areas where further research would be of benefit:

Oxygen saturation measurement: Evidence would suggest that routine oxygen saturation measurement should not be performed before 4 hours of age, and that false positives are more likely within the first 24 hours. However, delaying measurement beyond 24 hours must be balanced against the number of affected infants who will become clinically symptomatic between 24 and 48 hours of age and therefore will not benefit from screening detection. The site of testing (postductal only, or pre- and postductal) does not appear to have a significant impact on overall detection rates but there is uncertainty about the detection rate for individual defects that warrants further investigation. Finally testing pathways, including the number of repeated saturation measurements and the timing of clinical examination, varies between studies and different options should be compared.

Referral pathways: Further evaluation of 'diagnostic' tests to investigate presumed positive screening results and, in particular, to differentiate between cardiac and non-cardiac causes of low oxygen saturation could inform the implementation of diagnostic pathways that minimize the

burden of investigation for mothers and babies, whilst ensuring that the maximum benefit is achieved from screening.

Impact of antenatal screening: It is important to determine the proportion of specific CHD defects that are prenatally detected, in order to determine their birth prevalence and understand the impact on newborn screening. Evaluation of the antenatal and newborn screening as an integrated screening pathway for CHDs would help identify current gaps in provision.

Data linkage to evaluate screening outcomes: There exist several routine data sources that record screening results, diagnoses and short-term interventional outcomes for CHDs (e.g. including congenital anomaly registers, Eurocat, regional databases, mortality registers, cardiology clinics and cardiac surgical audit), although the majority of these do not have national coverage. Data linkage could be explored to improve ascertainment of screening outcomes, such as detection of false negatives, short-term mortality or interventional outcomes.

QALYs: Although some studies have estimated the life-time QALYs attributable to different CHDs, the assumptions may not be applicable across all defects. More recent studies have begun to refine these models but further work in this area would provide better information about the cost-effectiveness of early detection and intervention for different defects.

Review Methodology

Three searches were undertaken by Paula Coles, Information Scientist in September 2012 to:

(1) provide a summary of current knowledge relating to the use of fetal nuchal translucency as an antenatal screening test for cardiac defects
(2) provide a summary of current knowledge relating to screening for heart defects at 18-20 weeks gestation and their detection rates
(3) updating from the 2005 HTA literature review, the evidence relating to pulse oximetry as a screening test for congenital heart defects.

For searches (1) and (2), the sources searched were: Medline (OvidSP), Embase, Cochrane Library.

And the dates of the search were: January 2003-September 2012.

For search (3), the sources searched were: Medline (OvidSP), Embase, PsychINFO, Cochrane Library.

The dates of the search were: January 2003-August 2012.

Inclusion and Exclusion Criteria

The review included:

- Cohort studies
- National series
- Systematic reviews and cohorts related to epidemiology
- Systematic reviews and randomised controlled trials related to screening, diagnostics or treatment

The review excluded:

- Foreign language studies
- Conference reports
- Non-systematic reviews
- Non-national case series reporting on the outcomes of a series of infants diagnosed and treated at a single centre

- Case series comparing different diagnostic or therapeutic approach
- National cohorts updated by more recent publication from the same country/authors
- Cohorts related to longer term developmental, psychological or quality of life outcomes among infants with CHDs and not involving screening
- Studies in selected populations and not involving low risk pregnancies.
- Where the NICE Antenatal Care guidelines addressed the performance of an antenatal screening test, only studies published since this evidence review (i.e. from June 2007 on – see http://www.nice.org.uk/nicemedia/live/11947/40148/40148.pdf) were included.

Quality criteria

A hierarchy based on methodological quality was applied to the papers reviewed according to the following list, and those higher in the table were considered to be of higher methodological quality:

- Systematic review/meta-analysis
- Randomised controlled trial/randomised trial
- Other trial
- Prospective/retrospective cohort study
- Case series
- Other studies – non-systematic literature review, case series, etc.

Search strategy

Search 1: First trimester screening and nuchal translucency

SEARCH STRATEGY (Medline OvidSP)
1. exp Heart Defects, Congenital/ (112002)
2. ((heart or cardiac) adj (defect$ or anomal$ or malformation$ or abnormalit$)).tw. (17649)
3. coarct$.tw. (7433)
4. (double outlet right ventricle or DORV).tw. (1244)
5. (double outlet adj2 ventricle).tw. (1290)
6. endocardial cushion defect.tw. (295)
7. ((left ventric$ outflow adj2 obstruct$) or LVOT$).tw. (2001)
8. ((interrupt$ adj3 aort$ heart) or IAA).tw. (3596)
9. (hypoplastic left heart or HLH$).tw. (3722)
10. ((mitral or aorti$) adj (atresia or stenosis)).tw. (16644)
11. PVOD.tw. (114)
12. Eisenmenger$ syndrome.tw. (658)
13. ((transposition adj3 great arter$) or TGA).tw. (7561)
14. (univentric$ heart or UVH).tw. (487)
15. single ventric$.tw. (2182)
16. (anomalous pulmonary adj2 drainage).tw. (639)
17. (anomalous pulmonary venous adj (return or connection)).tw. (1441)
18. (TAPVD or TAPVR or TAPVC or PAPVD or PAPVR).tw. (362)
19. (ventricular septal defect or VSD).tw. (9037)
20. (((atrioventricular or ventricular) adj septal defect) or VSD or AVSD).tw. (9683)
21. (pulmonary adj2 (atresia or stenosis)).tw. (6682)
22. (tricuspid adj2 stenosis).tw. (573)
23. tetralogy of fallot.tw. (5823(
24. patent ductus arteriosus.tw. (5625)

25. atrial septal defect.tw. (5933)
26. patent foramen ovale.tw. (2989)
27. ventricular septal defect.tw. (7873)
28. branch pulmonary artery.tw. (192)
29. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
or 22 or 23 or 24 or 25 or 26 or 27 or 28 (155329)
30. exp Prenatal Diagnosis/ (56233)
31. 29 and 30 (3608)
32. (screen$3 or detect$3 or test or tests or testing).tw. (2735789)
33. Mass Screening/ (75474)
34. 32 or 33 (2752939)
35. (pregnan$ or antenatal$ or prenatal$).tw. (386332)
36. exp Pregnancy/ (672396)
37. 35 or 36 (760234)
38. 31 or 38 (4457)
39. Nuchal Translucency Measurement/ (752)
40. nuchal translucency.tw. (1553)
41. 40 or 41 (1706)
42. 39 and 42 (263)
43. limit 42 to yr="2003 -Current" (194)

Search 2: Second trimester ultrasound screening

SEARCH STRATEGY (Medline OvidSP)
1. exp Heart Defects, Congenital/ (112448)
2. ((heart or cardiac) adj (defect$ or anomal$ or malformation$ or abnormalit$)).tw. (17738)
3. coarct$.tw. (7460)
4. (double outlet right ventricle or DORV).tw. (1250)
5. (double outlet adj2 ventricle).tw. (1296)
6. endocardial cushion defect.tw. (295)
7. ((left ventric$ outflow adj2 obstruct$) or LVOT$).tw. (2017)
8. ((interrupt$ adj3 aort$ heart) or IAA).tw. (3612)
9. (hypoplastic left heart or HLH$).tw. (3738)
10. ((mitral or aorti$) adj (atresia or stenosis)).tw. (16729)
11. PVOD.tw. (117)
12. Eisenmenger$ syndrome.tw. (663)
13. ((transposition adj3 great arter$) or TGA).tw. (7623)
14. (univentric$ heart or UVH).tw. (494)
15. single ventric$.tw. (2202)
16. (anomalous pulmonary adj2 drainage).tw. (639)
17. (anomalous pulmonary venous adj (return or connection)).tw. (1445)
18. (TAPVD or TAPVR or TAPVC or PAPVD or PAPVR).tw. (367)
19. (ventricular septal defect or VSD).tw. (9072)
20. (((atrioventricular or ventricular) adj septal defect) or VSD or AVSD).tw. (9720)
21. (pulmonary adj2 (atresia or stenosis)).tw. (6708)
22. (tricuspid adj2 stenosis).tw. (576)
23. tetralogy of fallot.tw. (5858)
24. patent ductus arteriosus.tw. (5667)
25. atrial septal defect.tw. (5952)
26. patent foramen ovale.tw. (3023)

27. ventricular septal defect.tw. (7900)
28. branch pulmonary artery.tw. (193)
29. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or
22 or 23 or 24 or 25 or 26 or 27 or 28 (156046)
30. exp Prenatal Diagnosis/ (56396)
31. 29 and 30 (3626)
32. (screen$3 or detect$3 or test or tests or testing).tw. (2754727)
33. Mass Screening/ (75851)
34. 32 or 33 (2771937)
35. (midtrimester or 2nd trimester or second trimester).tw. (10883)
36. Pregnancy Trimester, Second/ (11734)
37. 35 or 36 (17994)
38. 29 and 34 and 37 (266)
39. Ultrasonography, Prenatal/ (22568)
40. (ultrasonogra$ or ultrasound or scan).tw. (279634)
41. 39 or 40 (290210)
42. 38 and 41 (225)
43. limit 42 to yr="2003 -Current" (131)

Search 3: Newborn screening using pulse oximetry

SEARCH STRATEGY (Medline OvidSP)
1. exp Heart Defects, Congenital/ (112002)
2. (congenital adj (heart or cardiac) adj (defect$ or anomal$ or malformation$ or abnormalit$)).tw. (7462)
3. coarct$.tw. (7433)
4. (double outlet right ventricle or DORV).tw. (1244)
5. (double outlet adj2 ventricle).tw. (1290)
6. endocardial cushion defect.tw. (295)
7. ((left ventric$ outflow adj2 obstruct$) or LVOT$).tw. (2001)
8. ((interrupt$ adj3 aort$ heart) or IAA).tw. (3596)
9. (hypoplastic left heart or HLH$).tw. (3722)
10. ((mitral or aorti$) adj (atresia or stenosis)).tw. (16643)
11. PVOD.tw. (114)
12. Eisenmenger$ syndrome.tw. (658)
13. ((transposition adj3 great arter$) or TGA).tw. (7559)
14. (univentric$ heart or UVH).tw. (487)
15. single ventric$.tw. (2182)
16. (anomalous pulmonary adj2 drainage).tw. (639)
17. (anomalous pulmonary venous adj (return or connection)).tw. (1441)
18. (TAPVD or TAPVR or TAPVC or PAPVD or PAPVR).tw. (362)
19. (ventricular septal defect or VSD).tw. (9037)
20. (((atrioventricular or ventricular) adj septal defect) or VSD or AVSD).tw. (9683)
21. (pulmonary adj2 (atresia or stenosis)).tw. (6682)
22. (tricuspid adj2 stenosis).tw. (573)
23. tetralogy of fallot.tw. (5823)
24. patent ductus arteriosus.tw. (5625)
25. atrial septal defect.tw. (5933)
26. patent foramen ovale.tw. (2988)
27. ventricular septal defect.tw. (7873)

28. branch pulmonary artery.tw. (192)
29. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
or 22 or 23 or 24 or 25 or 26 or 27 or 28 (150251)
2
30. exp Infant, Newborn/ (468430)
31. (neonat$ or infan$ or newborn$).tw. (491017)
32. 30 or 31 (735382)
33. Neonatal Screening/ (6368)
34. screen$3.tw. (402180)
35. 33 or 34 (403882)
36. pulse oximet$.tw. (5392)
37. Oximetry/ (9042)
38. neonatal echo$.tw. (90)
39. Echocardiography/ (61483)
40. 36 or 37 or 38 or 39 (72646)
41. 29 and 32 and 35 and 40 (164)
42. Prevalence/ (164071)
43. Incidence/ (155981)
44. (prevalen$ or inciden$).tw. (869199)
45. 42 or 43 or 44 (973794)
46. 2 and 32 and 45 (471)
47. (expectation$ or satisfaction$ or acceptab$ or belief$ or attitude$ or emotion$ or stress$ or anxi$ or
behavio$ or wellbeing or psycho$ or social or counsel$ or awareness or knowledge).tw. (2146154)
48. exp Communication/ (342447)
49. false negative reactions/ or false positive reactions/ (32074)
50. Anxiety/ (47029)
51. exp Family Relations/px [Psychology] (6692)
52. nurse-patient relations/ or physician-patient relations/ (84318)
53. exp Parent-Child Relations/ (42411)
54. 47 or 48 or 49 or 50 or 51 or 52 or 53 (2503335)
55. exp Parents/px [Psychology] (28120)
56. (parent$ or mother$ or father$).tw. (386131)
57. 55 or 56 (392482)
58. 40 and 54 and 57 (153)
59. natural history.tw. (32866)
60. (mortality or morbidity).tw. (492875)
61. surviv$.tw. (638117)
62. quality of life.tw. (122129)
63. death.tw. (411527)
64. (long term or follow up).tw. (903372)
65. 59 or 60 or 61 or 62 or 63 or 64 (2090324)
66. 29 and 32 and 40 and 65 (841)
67. 1 and 2 and 65 (1360)
68. 41 or 46 or 58 or 66 or 67 (2678)
69. limit 68 to yr="2003 -Current" (1306)

Search results

Search 1: First trimester screening and nuchal translucency

The search strategies retrieved 410 references in total (194 Medline, 212 Embase, 4 Cochrane Library). After removal of duplicates, a total of 293 potentially relevant references were left. The title and abstracts of the 293 citations were scanned for relevance to nuchal translucency as an antenatal screening test for CHDs (initially by PC and subsequently by RK). In the updated searches, 27 studies were identified which reported nuchal translucency measurement to detect CHDs in the first trimester of pregnancy. Eight non-systematic literature reviews were of lower quality and excluded[93-100] as were studies investigating nuchal translucency in selected pregnancies. Fourteen papers were relevant for inclusion; these abstracts are presented in Table 5.

Search 2: Second trimester ultrasound screening

The search strategies retrieved 285 references in total (131 Medline, 150 Embase, 4 Cochrane Library). After removal of duplicates, a total of 201 potentially relevant references were left. The title and abstracts of the 285 citations were scanned for relevance to routine midtrimester ultrasound as an antenatal screening test for CHDs (initially by PC and subsequently by RK). The following inclusion and exclusion criteria were applied:

Included:

- second trimester ultrasound screening for heart defects in low risk populations

Excluded:

- ultrasound screening in the first trimester (unless compared with first trimester)
- echocardiography (unless applied to low risk pregnancies for second trimester screening)
- high risk pregnancies or selected population groups.

The updated search retrieved seven studies of fetal echocardiography.[101-107] As fetal echo was only performed as a diagnostic investigation in a high risk or selected population, these studies were excluded from the review.

The updated searches identified one systematic review[46], one randomized trial[44], one prospective cohort study[108] and two case series[109 110] reporting findings with first trimester ultrasound screening for CHDs and/or fetal anomalies. Two case series did not provide data in a low risk population and were excluded.

Abstracts included in the review are presented in Table 6.

Search 3: Newborn screening using pulse oximetry

Search strategies retrieved 4453 papers relating to pulse oximetry, and to the epidemiology and long-term outcomes from CHDs. After exclusion of abstracts (initially by PC and subsequently by RK) which did not include pulse oximetry, there were 24 systematic reviews, meta-analyses, guidelines, recommendations and technology assessments, as well as 46 additional papers, that were relevant to routine pulse oximetry in asymptomatic newborns. These 46 papers covered test accuracy, screening, cost-effectiveness, and acceptability of pulse oximetry. After removal of duplicates, there were 21 papers retrieved for review. The studies included in the systematic reviews by Thangaratinam and Wennerholm were also included in the review, as well as one additional paper by Prudhoe published electronically in 2013 (see Table 7 for references and details). Abstracts included in the review are presented in Table 7.

Table 5: Studies of nuchal translucency and first trimester scans in low risk populations (included)

First Author	Year	Number	Gestation	Study Design	Screening Test	Study Aim	Summary of Findings
Systematic reviews and meta-analyses							
Wald[48]	2008	29,935 fetuses	10-14 weeks	Systematic review and meta-analysis.	Nuchal translucency	To assess the performance of NT for screening for CHDs which would benefit from prenatal detection (i.e. CHD would lead to serious disability and pregnancy termination might be chosen; intra-uterine treatment may decrease morbidity; prenatal diagnosis would lead to altered postnatal management/outcome).	CHDs were categorised by potential to benefit from prenatal detection and detection rates (sens) were estimated for these using different false positive rates (FPR) by varying NT cut-offs. Cut-offs were calculated as multiples of the median (MoM; observed NT divided by expected NT for crown-rump length). For MoM=1.7 and 5% FPR, sens= 52%(42-71%); for MoM=2.5 and 1% FPR, sens=30%(30-61%). Evaluation of NT for CHD screening would be timely as it is already part of Down's screening.
Makrydimas [47]	2003	58,492 fetuses	10-14 weeks	Systematic review and meta-analysis.	Nuchal translucency	To evaluate the performance of NT for prenatal screening detection of CHDs.	Did not select studies based on CHD outcomes; included 5 studies subsequently included in Wald's meta-analysis. Significant heterogeneity between studies in CHD prevalence, cut-offs and exclusions. NT above 99th centile: sens=31%, spec=98.7%. Higher detection of HLH, COA, AS and multiple anomalies. Estimated costs.
Rossi[46]	2011	20,962 fetuses	11-14 weeks	Systematic review and meta-analysis.	Fetal anomaly ultrasound in first trimester	To review efficacy of early ultrasound (US) to identify fetal structural anomalies (including CHDs).	Outcome: confirmation of anomaly on ultrasound at 18-22 weeks gestation. For all CHD, sens=56%(95% CI:47-65%); fetal echo was not more sensitive than complete ultrasound. For any isolated anomaly, spec=49%(41-58%). Some anomalies will never be detected early due to natural history of development.

Table 5: Studies of nuchal translucency and first trimester scans in low risk populations (included)

First Author	Year	Number	Gestation	Study Design	Screening Test	Study Aim	Summary of Findings
Papatheodo-rou[53]	2011	100,872 fetuses	1st trimester	Systematic review and meta-analysis.	Ductus venosus (DV) doppler ultrasound	To evaluate diagnostic accuracy of first trimester DV doppler for detection of CHD in chromosomally normal fetuses.	In chromosomally normal fetuses with no increased nuchal translucency (NT): sensitivity(sens)=19%, specificity(spec)=96%. In chromosomally normal fetuses with increased nuchal translucency (NT): sens=83%, spec=80%. DV needs further evaluation before considering as a potential screening test for CHD.
Detection of CHDs using nuchal translucency (NT) in a low risk population							
Caliskan[49]	2009	956 pregnancies	11-14 weeks	Prospective case series	Nuchal translucency	To assess the value of NT to detect Down's syndrome and CHD.	DS risk calculated from maternal and gestational age, NT and serum biochemical markers. If high risk for DS, karyotyping was performed; if NT increased, fetal echo was performed. Increased NT>99th centile, had 29% sensitivity, 82% sensitivity.
Muller[50]	2007	6,132 pregnant women	1st trimester	Screening pilot study	Nuchal translucency	To assess performance of NT screening in 1st trimester as marker for major CHDs.	Screening uptake was 83%; 4876 NT measurements were taken. 13 cases of major CHD were diagnosed; 2 were in fetuses with increased NT. NT>99th: sens=8% for all CHD, sens=15% for major CHD. Association too weak to justify NT as single screening strategy.
Bruns[51]	2006	3,664 pregnancies	11-13 weeks	Multi-centre retrospective study	Nuchal translucency	To assess the accuracy of first trimester NT for detection of CHDs.	Median NT in fetuses with CHD was 1.70mm and 1.60mm in fetuses without NT. Sens range 15-20%, FPR range 86.4-97.9% depending on cut-off. Despite low sens of test, increased NT is an important risk factor for referral.
Hafner[52]	2003	12,978 fetuses	1st trimester	Retrospective analysis	Nuchal translucency	To assess the accuracy of first trimester NT>=95th centile for	All pregnant women underwent NT which was analysed retrospectively in

Table 5: Studies of nuchal translucency and first trimester scans in low risk populations (included)

First Author	Year	Number	Gestation	Study Design	Screening Test	Study Aim	Summary of Findings
						detection of CHDs.	fetuses/newborns with CHD and normal chromosomes. 26% of 27 CHD cases had increased NT but this included associated anomalies. Relative risk of CHD was 6.6 times higher in fetuses with increased NT.
Detection of CHDs using first trimester ultrasound scans (with/without nuchal translucency)							
Grande[109]	2012	13,723 fetuses	11-14 weeks	Retrospective case review	1st trimester ultrasound (US)*/Nuchal translucency (NT)/DV Doppler/nasal bone*	To evaluate diagnostic accuracy of first trimester US *and soft markers for detection of fetal anomaly in chromosomally normal fetuses.*	439 anomalies: 194 major, 245 minor. 49% of anomalies detected at early US (EUS)- ranging from 25% (e.g. TGA) to 100% (e.g. hypoplastic left heart [HLH]). Skeletal and cardiac anomalies had highest detection rates - *these were also the anomalies with most associated NT/DV abnormalities. Nasal bone not associated with anomalies. NT/DV are useful markers at EUS.*
Syngelaki[108]	2011	45,191 pregnancies	11-13 weeks	Prospective cohort	1st trimester US	To assess performance of 1st trimester US for fetal anomaly screening.	Comparison of 1st and 2nd trimester scan. 332 chromosomal abnormalities excluded. Fetal abnormalities in 488, of which 213 detected at 11-13 weeks (detection rate varied by body system; 34% major CHDs detected). Only 34% of CHDs had raised NT>95th centile.
Abu-Rustum[110]	2010	1370 fetuses	11-14 weeks	Retrospective case review	Nuchal translucency (NT) + 4 chamber ultrasound	To evaluate sensitivity of first trimester cardiac ultrasound and NT for detection of CHD.	8 CHD cases (diagnosed by paediatrician/cardiologist at birth). NT>95th in 6/8 fetuses; cardiac US abnormal in 6/8. 1st trimester US detected 75% and 2nd trimester 25%. No FPR reported.

Table 5: Studies of nuchal translucency and first trimester scans in low risk populations (included)

First Author	Year	Number	Gestation	Study Design	Screening Test	Study Aim	Summary of Findings
Detection of CHDs using nuchal translucency with additional tests or soft markers							
Pereira[55]	2011	40,990 fetuses	11-13 weeks	Prospective cohort	Nuchal translucency (NT) + tricuspid regurgitation (TR) + DV Doppler	To assess added value of TR+DV Doppler with NT for detecting CHDs in fetuses with normal karyotype.	85 CHD cases. Sens=58%(95%CI 47-68%) for NT>95th, reversed DV or TR, with 8% FPR. Improves screening efficacy.
Sananes[56]	2010	12,910 fetuses	1st trimester	Retrospective case review	Nuchal translucency + cystic hygroma colli	To assess value of cystic hygroma colli for detecting CHDs in fetuses with normal karyotype.	Use of NT as well as ultrasound to detect cystic hygroma colli (CHC) reviewed. 44 cases of CHD. Sens of NT>95th=54.5%, FPR=8% (at >3.5mm cut-offs sens=27%, FPR 2%; at 1.5MoM sens=50%, FPR=8.9%). CHC associated weakly with CHD.
Bas-Budecka [54]	2010	4,720 fetuses	11-14 weeks	Prospective study	Nuchal translucency (NT) + DV Doppler	To evaluate diagnostic accuracy of first trimester DV doppler and NT for detection of CHD in chromosomally normal fetuses.	13 cases of CHD. NT>=99.8th centile: sens=45%, spec=92%, PPV=1.5%. NT>=99th centile: sens=25%, spec=98.5%, PPV=3.2%. Abnormal DV flow in 61.5% CHD affected fetuses. Abnormal NT/DV indicates need for fetal echo.

Table 6: Studies of second trimester routine ultrasound scan (included)

First Author	Year	Number	Gestation	Study Design	Screening Test	Study Aim	Summary of Findings
Detection of CHDs on routine fetal anomaly scan							
Eggebo[62]	2012	6,781 fetuses	2nd trimester	Prospective observational study	Routine ultrasound scan with colour flow Doppler	To investigate the detection rate for CHDs in a low risk population of second trimester ultrasound scan and colour flow Doppler.	Outcome: diagnosis of major CHDs prenatally or in the neonatal period. Scan included a grey-scale 4 chamber and outlet view, followed by 3 colour Doppler cross-sectional views. Of 39 CHDs in 6,781 fetuses examined, 26 (67%) were detected prenatally; 9/26 were detected mainly due to colour Doppler. Colour Doppler improved detection but not all CHDs were detected prenatally.
Nadel[63]	2010	1,766 fetuses	2nd trimester	Retrospective case series	Routine ultrasound scan with colour flow Doppler	To investigate the detection rate for CHDs in a low risk population of second trimester ultrasound scan and colour flow Doppler.	Outcome: diagnosis of major CHDs at second trimester scan. Scan included grey-scale, followed by colour Doppler views. Of 17 CHDs identified in 1,766 fetuses examined, 4 were detected on colour Doppler only. Of these, all were pulmonary valve abnormalities and only 3 required treatment neonatally.
Hildebrand [61]	2010	21,189 pregnancies	2nd trimester	Prospective observational study	Routine ultrasound scan	To investigate the detection rate for all fetal and chromosomal anomalies in a low risk population, comparing first trimester (with NT>=3mm) with second trimester fetal anomaly scan.	Outcome: All prenatally and neonatally detected fetal and chromosomal anomalies (some CHD specific data). One centre performed first trimester scan and 4 did second trimester scans. 13% of all anomalies (88% lethal anomalies) were detected in 1st trimester scan group compared with 29% of all anomalies (92% lethal anomalies) in 2nd trimester group. More chromosomal anomalies detected in 1st (71%) than in 2nd trimester (42%). Later

Table 6: Studies of second trimester routine ultrasound scan (included)

First Author	Year	Number	Gestation	Study Design	Screening Test	Study Aim	Summary of Findings
							scans have higher sensitivity for CHDs.
Westin[44]	2006	39,572 pregnancies	1st and 2nd trimester	Randomised trial	Nuchal translucency/18 week fetal anomaly scan	To compare prenatal diagnosis using two fetal anomaly scan screening policies, with additional NT in 12 week group.	Outcome: prenatal or neonatal diagnosis of CHDs. 11% of CHD detected prenatally in 12 week scan group compared with 15% in the 18 week scan group. Prenatal detection was low but the 18 week scan was better.
Nakling[111]	2005	18,181 pregancies	2nd trimester	Prospective observational study	Routine ultrasound scan	To describe provision and outcomes of routine fetal anomaly scans in clinical practice in a national population.	Outcome: prenatal or neonatal diagnosis of CHDs. Clinical practice outside tertiary centres. 267 congenital anomalies identified prenatally or neonatally. Second trimester detection rate was 39% (103/267); specificity was 99.9% (17903/18067) and PPV was 90% (103/124); false positive rate was 9% (11/124). Detection rates varied by anomaly type.
Factors influencing accuracy of routine fetal anomaly scan							
Aagaard-Tillery[58]	2010	8,555 pregnant women	2nd trimester	Prospective observational study	Routine ultrasound scan	To evaluate screening performance related to BMI.	Maternal obesity (BMI>30) resulted in lower sensitivity and higher false positive rate (FPR) compared with women with BMI<25: sens=8%, FPR=92% versus, sens=22%, FPR=78% respectively.
Hendler[59]	2005	372 women having repeat scans	2nd trimester	Retrospective review of selected cases	Repeat scan after routine ultrasound scan	To investigate whether a repeat ultrasound improves visualisation of the fetal heart in obese and non-obese women.	Obese: BMI>=30. Median gestation at first scan 19 weeks, and at second scan 21 weeks. At repeat scan 11% of fetal hearts were suboptimally visualised and this varied by BMI: BMI<30, 1.5%; BMI 30 to <35, 12%; BMI 35 to <=40, 17%; BMI>=40, 20%. CHD found on 1 scan.
Tegnander[57]	2006	29,035	2nd trimester	Prospective	Routine ultrasound	To evaluate screening performance	Ultrasonographers with experience of

Table 6: Studies of second trimester routine ultrasound scan (included)

First Author	Year	Number	Gestation	Study Design	Screening Test	Study Aim	Summary of Findings
		fetuses		observational study	scan	related to operator experience.	>=2000 scans were compared with those with experience of 200-2000 scans.35/82 (43%) CHDs were prenatally detected. 4-chamber and outlet view were achieved in 75% scans by more experienced, and 36% by less experienced operators. Detection rates for major CHDs were 52% and 32% respectively.
Del Bianco[64]	2006	2,847 fetuses	2nd trimester	Prospective interventional study	Fetal cardiac ultrasound scan	To evaluate 3 vessel and trachea view (3VT) alone and with colour Doppler (3VTC) for detecting CHDs in low risk population.	Sensitivity of 3VT/3VTC was 88%. The scan was feasible and promising but further evaluation is needed.

Table 7: Studies of routine pulse oximetry in asymptomatic newborns

First Author	Year	Number	Study Design	Study Aim	Summary of Findings
Health Technology Assessment (HTA) reports, systematic reviews and meta-analyses					
Thangaratinam [39]	2012	229,421 newborns	Systematic review and meta-analysis (13 studies)	To evaluate the performance of pulse oximetry (PO) as a newborn screening test for CHDs in asymptomatic infants. Update of previous review.	Systematic review of publications between 1951 and 2011; selection of studies assessing accuracy of routine PO for detecting critical CHDs in newborns. Overall sensitivity 76.5%(95% CI 67.7-83.5%), specificity 99.9% (99.7-99.9%), false positive rate (FPR) 0.14% (0.06-0.33%). PO<95% has high specificity and moderate sensitivity as a newborn screening test for critical CHDs.
Thangaratinam [76]	2007	35,960	Systematic review and meta-analysis (8 studies)	To evaluate the performance of pulse oximetry as a newborn screening test for CHDs in asymptomatic infants.	Systematic review of publications between 1951 and 2006, involving routine PO for detecting CHDs in newborns. Overall sensitivity 63%(95% CI 39-83%), specificity 99.8% (99-100%), false positive rate (FPR) 0.2% (0-1%). PO<95% has high specificity and low FPR for newborn screening.
Ewer[3 36]	2012	20,055	HTA report	To evaluate the performance of pulse oximetry (<95% or pre-/postductal difference >2%) as a newborn screening test for CHDs in asymptomatic infants. Cost-effectiveness and acceptability to parents and healthcare staff also assessed.	Prospective test accuracy study assessing PO prior to discharge for detecting major CHDs (critical-*death or intervention within 28 days of birth*-and serious-*death or intervention from 1 month to 1 year*) against composite reference standard (clinical follow-up, echocardiography, regional registers) for added value over routine antenatal ultrasound. 53 (24 critical, 29 serious) CHDs. For 35 major CHDs (excl. antenatal diagnoses): sensitivity 28.6%(95%CI 14.6-46.3%), specificity 99.2%(99.0-99.3%), FPR 0.8%. 40 babies with low oxygen saturation had respiratory and/or infective illness. Cost was twice clinical examination alone.
Wennerholm [38]	2011	N/A	HTA report (review of 8 studies)	To evaluate the diagnostic accuracy of pulse oximetry in screening asymptomatic newborns before discharge and assess whether PO alone or in addition to physical examination, leads to increased detection of critical CHD and reduced mortality and morbidity.	Primary outcome: Sensitivity/specificity in detecting CCHD (echocardiography as reference standard). Secondary outcomes: Undetected CHD at discharge. Mortality and/or morbidity in newborns with CHD. PO screening demonstrated good diagnostic accuracy to detect CHD in asymptomatic newborns, but there were insufficient data to evaluate mortality and morbidity. The costs associated with PO were higher than examination alone due to additional

Table 7: Studies of routine pulse oximetry in asymptomatic newborns

First Author	Year	Number	Study Design	Study Aim	Summary of Findings
					time required.
Mahle[82 112]	2009	N/A	Systematic review and position statement	To address the state of the evidence on the routine use of pulse oximetry in newborns to detect critical congenital heart disease (CCHD).	The American Heart Association and the American Academy of Pediatrics reviewed the literature (1966-2008) on detection of CCHD, missed or delayed diagnoses and clinical studies of pulse oximetry (PO) in asymptomatic newborns. In a pooled analysis of PO performed *after 24 hours of life*, sensitivity was 69.6%, and positive predictive value was 47.0%. FPR was 0.035%. Routine PO performed after 24 hours has low cost and low FPR. Future large studies are needed to determine whether PO is appropriate for routine assessment of the newborn.
Updated searches identified a further 18 reviews which were excluded as they did not provide data on newborn screening in a low risk population(17) or were policy statements (1).					
Other studies of pulse oximetry accuracy					
Hines [113]	2012		Prospective observational study	Evaluation of an algorithm for nurse-led PO screening in asymptomatic newborns.	
Ruegger[114]	2010	251 newborns	Prospective observational study	Assessing whether pulse oximetry on the left hand provides a pre- or postductal reading.	In first 4 hours of life, oxygen saturation was measured in both hands and one foot. No significant difference between the saturation in the hands was observed and both can be considered preductal.
Aamir[115]	2007	670,245 births	Retrospective case notes review	To identify delayed diagnoses of CCHDs potentially detectable through PO screening.	Confirmed delayed diagnoses of CHDs in 47 infants. Coarctation was the most common diagnosis. Age at diagnosis was 3 days to 7 months.
De Wahl Granelli[116]	2005	266 newborns		To evaluate the feasibility of detecting duct-dependent CHDs using two oximeters.	66 newborns with CHDs and 200 with normal hearts on echocardiography. Pulse oximetry performed. Median postductal saturation was 99% in normal hearts and 90% in CHDs using the new generation oximeter. The older model oximeter gave more readings <95% in normal hearts than did the new generation.

Table 7: Studies of routine pulse oximetry in asymptomatic newborns

First Author	Year	Number	Study Design	Study Aim	Summary of Findings
Reich (2 publications)[117] [118]	2008	7,962 newborns	Prospective observational study	To assess whether a single pulse oximetry reading reliably contributes to detection of CHDs	Three hospitals undertook routine pulse oximetry on newborns; readings were downloaded for later evaluation of reliability. No postnatal diagnoses were made through PO. Human factors influencing readings were oximetry training, probe placement and nursing experience. Training and quality assurance are required to ensure reliability.
Excluded: 2 conference abstracts, 7 duplicate publications.					

Individual studies included in systematic reviews							
Studies reviewed by Knowles et al.(2005)							
First author	***Date***	***No. newborns***	***No. with CHD***	***Study design***	***CHD outcome***	***Test***	***Findings:*** *TP=true positive; FP=false positive; FN=false negative; TN=true negative; DR=detection rate; sp=specificity; FPR=false positive rate; R/b=reviewed by*
Hoke[119]	2002	2,908 term (≥34 wks gestation)	36	Case-control (healthy term newborn controls); arbitrary recruitment; ambi-spective; not blind	Critical CHD: duct-dependent or left heart obstructive	<24 hrs; Foot **AND** right hand; <95% foot or 7% difference	TP=4;FP=53;FN=0;TN=2819; DR=100%; sp=98.2%; FPR=1.8% Low quality study, with selection bias and multiple tests. (R/b Knowles, 2005 & Thangaratinam, 2007/2012)
Richmond[7]	2002	5,626	40	Cross-sectional; prospective; consecutive; Not blind; asymptomatic newborns	Any CHD	<24 hrs; Foot; <95%	TP=8;FP=56;FN=1;TN=5561; DR=88.9%; sp=99.0%; FPR=1.0% (R/b Knowles, 2005; Thangaratinam, 2007/2012; Prudhoe 2013)
Reich[120]	2003	2,114	3	Cross-sectional; prospective; consecutive; Not blind; asymptomatic newborns	Cyanotic CHD	>24 hrs; Foot **OR** hand; <95%	TP=0;FP=4;FN=0;TN=2110; sp=99.8%; FPR=0.2% Low quality as sample size insufficient. Excluded babies who had a fetal echocardiogram, admitted to NICU admission, or birth weight≥1.5kg. (R/b Knowles, 2005; Thangaratinam, 2007/2012; Prudhoe 2013)
Koppel[121]	2003	11,281	5	Cross-sectional; prospective;	Critical cardiovascular	>24 hrs; Foot;	TP=1;FP=1;FN=2;TN=11275; DR=60.0%; sp=100%; FPR=0% Test not described. Excluded babies with prenatal

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				consecutive; Not blind; asymptomatic newborns	malformation (likely to need surgery in first month of life)	≤95%	diagnosis. Follow-up through congenital anomaly registers. Low quality evidence. (R/b Knowles 2005; Thangaratinam 2007/2012; Wennerholm 2011; Prudhoe 2013)
Studies since 2005 – reviewed by Prudhoe et al. (2013), Thangaratinam et al. (2007/2012) & Wennerholm et al. (2011)							
Bakr[122]	2005	5,211	13	Cross-sectional; prospective; consecutive; Not blind; asymptomatic newborns	All CHD	<24 hrs; Foot **AND** right hand; <95% (any limb)	TP=3;FP=2;FN=0;TN=5206; DR=100%; sp=100%; FPR=0% Excluded NICU admission. Multiple tests. Low quality.
Arlettaz[123]	2006	3,262	15	Cross-sectional; prospective; consecutive; Not blind; asymptomatic newborns	CHD of functional consequence	<24 hrs; Foot; <95%	TP=12;FP=12;FN=0;TN=3238; DR=100%; sp=99.6%; FPR=0.4% Antenatal diagnosis included. Outcome not critical or life-threatening CHD but provided defect-specific rates. Small sample size.
Rosati[124]	2005	5,292	3	Cross-sectional; prospective; consecutive; Not blind; asymptomatic newborns (term)	Critical cardiovascular malformation (likely to need surgery in first month of life)	>24 hrs; Foot; <96%	TP=2;FP=1;FN=1;TN=5288; DR=66.7%; sp=100%; FPR=0% Targeted outcome comparable with Koppel. Follow-up through echo referrals. Small sample size. Low quality.
De Wahl Granelli[37]	2009	39,821	60 in cohort; 100 in control group	Prospective observational cohort study; consecutive; not blind	Critical CHD (duct-dependent)	>24 hrs; Foot **AND** right hand; <95% or difference>3%	TP=19;FP=68;FN=10;;TN=39724; DR=65.5%; sp=99.8%; FPR=0.2% 4 clinics within 1 region. Multiple repeat tests if 90-94%. Excluded antenatal diagnoses. Control population of babies not born in screening hospitals. Follow-up by echo, cardiology clinics and mortality register. Moderate/high quality.
Kawalec[91]	2006	27,200	7	Prospective; consecutive; not blind; term newborns.	Critical CHD (requiring intervention in first month of life)	>24 hrs; Foot; <96%	TP=7;FP=13;FN=1;TN=27179; DR=87.5%; sp=100%; FPR=0% Excluded antenatal diagnoses. Conference report only.

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Studies since 2005 (continued)							
Sendelbach [80]	2008	15,299 (15,233 screened)	4	Prospective observational study; consecutive; blind at 4hrs but not at discharge.	Critical CHD (duct-dependent or cyanotic)	<24 hrs (4 hrs); Foot; <96%	TP=1; FP=24;FN=0;TN=15208; DR=cannot be estimated; sp=99.8%; FPR=0.2% One clinic population. Excluded NICU admissions, preterm <35 wks gestation and birth weight<2100g. Reference standard: echo. Moderate quality but small sample size.
Meberg[74 75]	2008	57,959 (50,008 screened)	35	Prospective observational study; consecutive; not blind	Critical CHD (duct-dependent or cyanotic)	<24 hrs; Foot; <95%	TP=27;FP=297;FN=8;TN=49676; DR=77.1%; sp=99.4%; FPR=0.6% Compared two regions (14 clinics): one with neonatal exam only and one adding pulse oximetry. Excluded NICU admissions and prenatal diagnoses. Different devices used. Reference standard: echo & CHDs registered on population databases at 6 months after final study birth. FP included 55 pneumonia/septicaemia, 54 transient tachypnea, 6 persistent pulmonary hypertension, 6 pneumothorax, 5 amniotic fluid aspiration, 8 miscelleaneous, 147 healthy with transitional circulation. Moderate quality.
Riede[92]	2010	48,348 (41,455 screened)	18	Prospective observational study; Consecutive; Not blind; Asymptomatic newborns	Critical CHD (duct-dependent or cyanotic)	>24 hrs; Foot; <96%	TP=14;FP=40;FN=4;TN=41384; DR=77.8%; sp=99.9%; FPR=0.1% Based in 34 clinics. Excluded preterm <37 wks gestation or if abnormal newborn clinical exam. Different devices used. Reference standard: echo & referrals for follow-up. 3 protocol violations. 40 FP included 15 persistent pulmonary hypertension, 13 sepsis, 12 healthy. Moderate quality.
Tautz[125]	2010	3,695 (3,364 screened)	11	Prospective observational study; Consecutive; Not blind; Term newborns	Critical CHD (definition unclear)	<24 hrs and >24 hrs; Foot; <95%	TP=9;FP=9;FN=2;TN=3,344; DR=81.8%; sp=99.7%; FPR=0.27% Based in 3 clinics. Excluded preterm <35 wks gestation and ventilated newborns. Multiple tests allowed. Reference standard: echo. Low quality.

Table 7: Studies of routine pulse oximetry in asymptomatic newborns

Studies since 2005 (continued)							
Ewer[3 36]	2012, 2011	20,055	53 major CHD (of which 24 critical)	Prospective observational study; Consecutive; Not blind; Asymptomatic newborns	Critical CHD; also reported 'major' CHD=critical + serious CHD	<24 hrs and >24 hrs; Right hand **AND** foot; <95% or difference >2%	*Including antenatal diagnoses* For critical CHDs: TP=18;FP=177;FN=6;TN=19854; DR=75.0%; sp=99.1% For major CHDs: TP=26;FP=169;FN=27;TN=19833; DR=49.1%; sp=99.1% *Excluding antenatal diagnoses* For critical CHDs: TP=7;FP=170;FN=5;TN=19850; DR=58.3%; sp=99.1% For major CHDs: TP=10;FP=167;FN=25;TN=19830; DR=28.6%; sp=99.1% Excluded preterm <34 wks gestation or NICU admissions; included antenatal diagnoses. Test accuracy study. 169 FP: including 6 significant CHDs, 40 respiratory/infective illnesses. Sensitivity analyses and cost-effectiveness analyses performed. Test acceptable to staff & parents.
Additional studies published 2011-2013							
Prudhoe[31]	2013	29,925 incl Richmond[7]	27 critical; 50 serious	Retrospective review of consecutive CHD diagnoses and routine pulse oximetry findings.	Critical CHD (also reported 'serious' CHD)	<24 hrs and >24 hrs; Foot; <95%	For critical CHD: TP=5; FN=22;FP/TN=not known; For serious CHD: TP=5; FN=45;FP/TN=not known; Insufficient data to estimate screening performance. Routine use of pulse oximetry reviewed in population of 31,946 babies (29,925 screened) over 10 years. Specific defects reviewed. Ascertainment of CHDs diagnosed up to 1 year of age using population registers, cardiology databases and congenital anomaly registers. Some duct-dependent CHDs likely to be missed by pulse oximetry.
Turska-Kmiec[126]	2012	52,993 (51,698 screened)	15	Prospective observational cohort study; consecutive; not blind; asymptomatic newborns.	Critical CHD (requiring intervention in first month of life)	<24 hrs; Foot; <95%	Screening with PO alone: TP=15;FP=14;FN=4;TN=51665; DR=78.9%; sp=99.9%; FPR=0% Involved 51 neonatal units in one region. Excluded antenatal diagnoses. Reference standard: paediatric cardiologist. Follow-up of false negatives through hospital admissions and public health data. FP: 2 infections, 1 non-significant CHD, 3 pneumonia, 8 transitional circulation.

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Additional studies published 2011-2013							
Vaidyanathan [127]	2011	5,487 newborns	425 CHDs (17 major CHDs)	Prospective observational study; consecutive; not blind; asymptomatic newborns	All (major) CHDs	>24 hrs; Foot; <94%	For major CHDs: TP=15; FN=2; DR=20%; sp=88%. Included antenatal diagnoses. Reference standard: echo. Follow-up all newborns at 6 weeks.
Audit of screening with pulse oximetry							
Walsh[128]	2011	14,564 newborns	Audit of screening program	To audit screening with pulse oximetry in a state program (Tennessee).			Screening between 24hrs and discharge, using saturation threshold <95%. Antenatal diagnosis of CHDs was 66%; antenatal diagnosis and clinical examination identified 43/44 infants with CHDs. 1 true positive case. 112 false positive cases; cost of investigation of 1 false positive case was high.
Cost-effectiveness of screening with pulse oximetry							
Roberts[27]	2012		Cost-effectiveness analysis; Health Technology Assessment	To compare pulse oximetry (PO) as an adjunct to clinical examination with clinical examination (CE) alone for detection of CHDs in newborns.			PO with CE is twice as costly as CE alone but provides more timely diagnoses. The incremental cost-effectiveness ratio for PO+CE compared with CE alone is approximately £24,000 per timely diagnosis 9in a population with antenatal screening). The probability of PO being cost-effective is >90% at a willingness-to-pay threshold of £100,000 and assuming a gain of 5 QALYs.
Wennerholm [38]	2011		Health Technology Assessment	Costing of new screening policy taking additional time for PO screening test into account.			The costs associated with an introduction of PO at Sahlgrenska University Hospital were estimated to be around 800.000 SEK during the first year, and lower thereafter. The costs estimated were higher than for CE due to the additional time required for screening. Costs may be balanced by reduced intensive care use.
Griebsch[2 70]	2007		Decision analysis model; Health Technology Assessment	To compare pulse oximetry (PO) as an adjunct to clinical examination, screening echocardiography (SE) as an adjunct to clinical examination, and clinical examination alone for detection of CHDs in newborns.			Additional cost per timely diagnosis (before cardiovascular collapse or death) was £4,894 for PO and £4,496,666 for SE. Adding PO to clinical examination is likely to be cost-effective, while SE is unlikely to be cost-effective as a newborn screening strategy.

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Acceptability of screening with pulse oximetry					
Powell[81]	2012	813 mothers of screened infants	Questionnaire survey	To assess acceptability to mothers of pulse oximetry screening for CHDs and to assess factors influencing participation.	Mothers recruited into Pulse Ox Study: 119 mothers with false positive (FP) results, 15 with true positive (TP) results, 679 with true negative (TN) results. Anxiety was not significantly higher for FP results than TN. Most were satisfied with screening; higher participation & satisfaction for White British ethnicity.
UK surveys of newborn screening practice for CHDs					
Shastri[129]	2012		Telephone survey (2010).	Survey of all level 2 and 3 neonatal units in the UK to assess use of pulse oximetry (PO); specifically whether it was a routine part of the newborn examination and if so, if the method used and personnel involved.	All 155 units responded. 20 units (13%) routinely practised PO. PO was usually performed within 24 hrs of birth, by a trained nurse or junior doctor. Single postductal oxygen saturation (foot) <95%, or preductal (right hand) and postductal with cut-off <95% in any limb or a difference >3% used in different units. PO result <90% initiated urgent echo; 90-95% led to repeat PO and referral if still abnormal.
Kang[130]	2011	224 hospital maternity units	Telephone interview survey	To survey the use of pulse oximetry screening in the UK.	209/224 (93%) of units did not routinely use pulse oximetry (PO). Of 15 using PO, 5 measured pre- and postductal saturation, 9 measured postductal only and 1 preductal only. Thresholds varied from <94 to <96% and/or difference of >2-3%. 13 units performed echocardiography locally, 2 performed a chest X-ray and 2 an ECG. PO was not used widely and practice was inconsistent.

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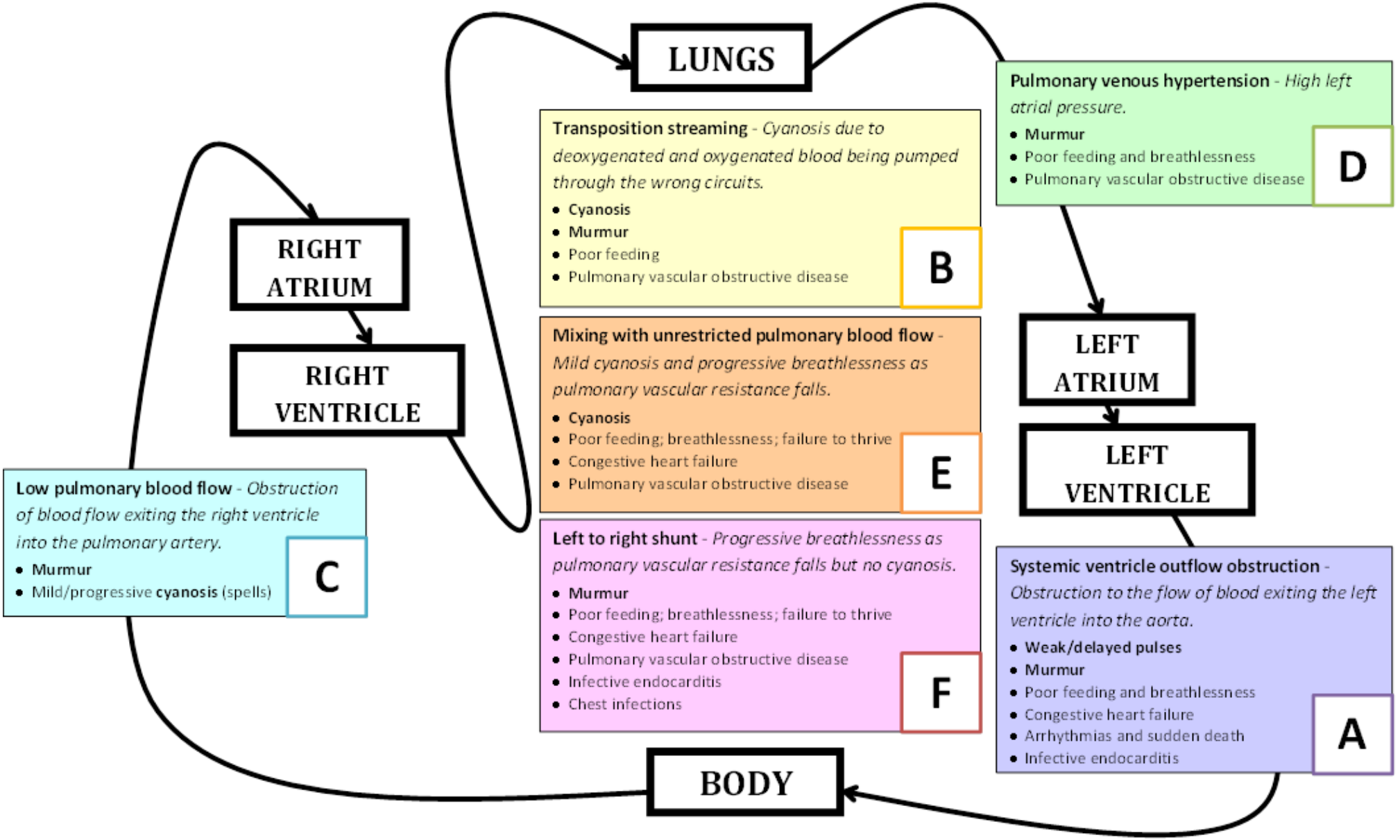
Annex 1: CHD Classification for Newborn Screening



Annex 1: CHD Classification for Newborn Screening

	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**
SHORT PRE-SYMPTOMATIC INTERVALS	Hypoplastic left heart syndrome Critical aortic stenosis Interrupted aortic arch Tight coarctation of the aorta	Transposition of the great arteries (duct-dependent) Transposition of the great arteries + small atrial septal defect Transposition of the great arteries + ventricular septal defect Double outlet right ventricle (transposition type)	Pulmonary atresia + intact ventricular septum Pulmonary atresia + ventricular septal defect Critical pulmonary stenosis Severe tetralogy of Fallot DORV + pulmonary stenosis Univentricular heart + tricuspid atresia + pulmonary atresia Severe Ebstein's anomaly Congenitally corrected transposition of the great arteries + pulmonary stenosis/atresia + ventricular septal defect	Obstructed total anomalous pulmonary venous connection Critical mitral stenosis Severe cor triatriatum	*Unlikely to present during this period*	*Unlikely to present during this period*
MODERATE PRE-SYMPTOMATIC INTERVALS	Coarctation of the aorta Moderate aortic stenosis	Transposition of the great arteries with large ventricular septal defect; Double outlet right ventricle (Taussig-Bing type)	Tetralogy of Fallot Severe pulmonary stenosis Pulmonary infundibular stenosis+ ventricular septal defect Absent pulmonary valve Ebstein's anomaly Congenitally corrected transposition of the great arteries + ventricular septal defect + pulmonary stenosis	Mild/moderate mitral stenosis Mitral regurgitation Cor triatriatum	Unobstructed total anomalous pulmonary venous connection Univentricular heart with unrestricted pulmonary flow Truncus arteriosus	Large ventricular septal defect Double outlet right ventricle with subaortic ventricular septal defect Atrioventricular septal defect or common atrium Aortopulmonary window Large patent ductus arteriosus Congenitally corrected transposition of the great arteries + tricuspid regurgitation + ventricular septal defect
OFTEN REMAIN ASYMPTOMATIC THROUGHOUT CHILDHOOD	Moderate or mild aortic stenosis Subvalvular aortic stenosis Supravalvular aortic stenosis Bicuspid aortic valve Moderate or mild coarctation of the aorta	Unlikely to present during this period	Moderate pulmonary stenosis Pulmonary valve insufficiency Congenitally corrected transposition of the great arteries	Mitral valve disease	Unlikely to present during this period	Atrial septal defect Small ventricular septal defect Small patent ductus arteriosus Patent foramen ovale Partial anomalous pulmonary venous connection

Cost-Effectiveness of Alternative Screening Strategies for Congenital Heart Disease

Updating Knowles et al (2005) with values from the 2012 PulseOx study

Background

In 2005 the HTA published a systematic review by Knowles et al(2005) that investigated the relative effectiveness of different screening strategies to identify congenital heart defects (CHDs) in newborn babies. Using the information from the systematic review and expert opinion, a decision analytical model was developed to assess the relative costs and outcomes of clinical examination (CE) alone compared to CE plus Pulse Oximetry (CE + PO) and CE plus screening with echocardiography (CE + SE). The model found that, per population of 100,000 infants, CE + PO would detect 82 (68%) of 121 undiagnosed, life threatening CHD cases at screening, CE + SE would detect 83 (69%) cases and CE alone would detect 39 (32%) cases. Overall, CE+PO and CE+SE resulted in 37 additional timely diagnoses of life threatening CHD compared to CE alone, at an additional cost per timely diagnosis of £4,900 for CE + PO compared to CE alone and £4.5 million per case for CE+SE compared to CE+PO. The model though had significant uncertainty associated with some of the values. In particular, the sensitivity of PO was based on expert opinion alone, yet was a key determinant of cost-effectiveness in the model. As a result, the study concluded more information on the test performance of PO was required.

Since 2005 additional studies have been published on the sensitivity and specificity of PO including a systematic review and cost-effectiveness analysis:

- Ewer et al (2012) published the PulseOx study – 20,055 asymptomatic new born babies across six UK maternity units were screened with PO before discharge and followed up for 12 months. The study compared the accuracy of PO screening in detecting major CHDs , which were subdivided into critical (causing death or requiring invasive intervention before 28 days) and serious (causing death or requiring invasive intervention between 1 and 12 months of age). 53 infants had major CHD, 24 critical. The sensitivity of PO for detecting critical cases was 75% with a specificity of 99.12%. For all major cases the sensitivity was 49.06% with a specificity of 99.16%.
- As part of the PulseOx study, Roberts et al (2012) published a cost-effectiveness analysis comparing CE to CE + PO. CE + PO identified 30 additional cases of CHD per 100,000 live births at a cost of £24,000 per additional case detected. There is a 90% probability that CE + PO is cost-effective compared to CE at a willingness to pay of £100,000 per additional case detected. The study also included a time-and-motion study to better estimate the time taken to screen each new born with CE or PO. The model relied heavily on published information from Knowles et al (2005) and hence was not as detailed as the 2005 model.
- Thangaratinam et al (2012)conducted a systematic review to assess the performance of PO in identifying CHD. They identified 13 studies with data for 229,241 newborns. The combined sensitivity of PO across the 13 studies was 76.5% (95% CI 67.7-83.5) with a specificity of 99.9% (95% CI 99.7-99.9).

Aim

The aim of this work is to update the 2005 Knowles et al HTA decision analytical model with the results of the PulseOx study and to update costs to 2010/2011 values.

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Table 1 provides a summary of the values updated in the model. The sensitivity and specificity of PO were updated to reflect the results of the PulseOx study for critical and major CHD cases; major CHDs were subdivided into critical (causing death or requiring invasive intervention before 28 days) and serious (causing death or requiring invasive intervention between 1 and 12 months of age). In a separate analysis the sensitivity of PO has been broken down by different CHDs as identified in Knowles et al (2005). This was based on previous work mapping cases from PulseOx to the 2005 HTA report completed by Knowles (2011) (Newborn Screening Strategies for CHD). Antenatal detection rates of CHDs were also updated from the PulseOx study and Knowles 2011. The time taken per infant to screen for CHDs using PO and CE was updated from the time-and-motion study conducted as part of the PulseOx cost-effectiveness analysis (Roberts et al, 2012).

As the main comparison is CE alone compared to CE + PO, the sensitivity used in the model for separate CHDs is calculated from the number of newborn cases of CHD detected by PO *and* CE divided by the number of cases of CHD. If PO failed to identify any cases for a particular CHD then the sensitivity of CE from Wren et al (1999) is used. All other values are the same as Knowles et al (2005).

Table A1: Values updated in Knowles et al model

Variable	Original Value (HTA 2005)	New Value	Source of New Value
Sensitivity and Specificity of PO+CE (cases detected/number cases)			
Sensitivity PO – TGA	0.950	0.857 (6/7)	PulseOx
Sensitivity PO – AS	0.596	0 for PO (0/2) CE 0.544	Wren
Sensitivity PO – TAPVC	0.950	1 (1/1)	PulseOx
Sensitivity PO – HLH/MA	0.950	1 (5/5)	PulseOx
Sensitivity PO – COA/IAA	0.600	0.5 (4/8)	PulseOx
Sensitivity PO – PA	0.940	1 (3/3)	PulseOx
Sensitivity PO – VSD	0.714	0 for PO (0/6) CE 0.493	Wren
Sensitivity PO - Non targeted CHD	0.667	0.390 (16/41)	PulseOx
Sensitivity PO – all critical		0.75 (18/24)	PulseOx
Sensitivity PO – all major		0.4906 (26/53)	PulseOx
Specificity PO	0.990	0.991 (19,819/19,986)	PulseOx
Antenatal detection rates per 100,000 live births minus exclusions (% of total cases)			
TGA	0.7 (2.4%)	7.8 (28.6%)	PulseOx
AS	1.6 (0.8%)	0 (0%)	PulseOx
TAPVC	0 (0%)	0 (0%)	PulseOx
HLH/MA	3 (21%)	14.3 (100%)	PulseOx
COA/IAA	2.7 (6%)	5.4 (12.5%)	PulseOx
PA	1.7 (7%)	24 (100%)	PulseOx
VSD	3.3 (1.8%)	0 (0%)	PulseOx
Non targeted CHD	6 (4.6%)	4.8 (3.7%)	PulseOx
Time taken to screen			
Pulse Oximetry	2 minutes	6.9 minutes	PulseOx
Clinical examination	2 minutes	8.57 minutes	PulseOx
Updated costs and throughput			
Cost per clinical	£1.17	£10.53	PulseOx

examination			PSSRU (Curtis 2012)
Cost per PO – machine costs	£0.31	£1.14	PulseOx HES (2011) (maternity ward throughput)
Cost per PO – staff costs	£0.56	£5.75	PulseOx PSSRU (Curtis 2012)
Cost per Echo – screening machine costs	£13.85	£14.54	PSSRU (Curtis 2012)
Cost per Echo – screening staff costs	£6.53	£6.17	PSSRU (Curtis 2012)
Cost per Echo – diagnostic staff costs	£60.20	£81	PSSRU (Curtis 2012)
Cost per treatment of collapse	£3,215	£4,128	PSSRU (Curtis 2012) Roberts (1998)
Post Mortem	£866	£1,209	PSSRU (Curtis 2012) Roberts (1998)
Ambulance costs	£218	£233	Reference Costs (2011)

Abbreviations: TGA – transposition of the great arteries; **AS** – aortic stenosis; **TAPVC** – total anomalous pulmonary venous connection; **HLH** – hypoplastic left heart; **MA** – mitral (valve) atresia; **COA** – coarctation (of the aorta); **IAA** – interrupted aortic arch; **PA** – pulmonary atresia; **VSD** – ventricular septal defect

Method

The methodology used is the same as that used in the Knowles et al (2005) HTA report. Figure 1 provides a flow chart of movement of live newborns through the model (from basic model structure in excel model).

Assumptions:

- Other congenital conditions (extracardiac abnormality, lethal trisomy and Down syndrome) are excluded from the total number of targeted CHD diagnoses.
- Newborns that had a positive identification of CHD at neonatal screen are excluded from the total number of targeted CHD diagnoses.
- Of those not excluded, 93% are screened for CHD in the CE alone and CE+PO arms. 91% are screened in the CE+SE arm.
- All newborns screened receive a CE including those in the CE+PO and CE+SE groups.
- All infants that screen positive on CE, PO or SE receive a diagnostic echocardiography. Infants positive on a PO receive 2 PO tests.
- Time of screening is at 24 hours after birth.

Different analyses

1) This analysis is based on the original model from Knowles et al (2005) HTA report using Northern Region data on the prevalence of CHD and the proportion identified and excluded at antenatal screen due to positive identification of CHD or other congenital conditions. All the original assumptions of the model hold, but costs are updated to 2010/2011 values and the assumptions about time taken to screen are updated from the PulseOx cost-effectiveness analysis.
2) Fully updated model using new values in Table A1, with specific sensitivity for each CHD classification. Antenatal screen detection rates are from the PulseOx study.

3) As in analysis (2), but the sensitivity and specificity of PO is divided into critical and major only.
4) As in analysis (2), but the percentage of cases of CHD identified as part of antenatal screening is from the Northern Region rates, as used in Knowles et al (2005).
5) As in (2) but screening is at birth instead of at 24 hours.
6) As in (1) but the sensitivity and specificity of PO are from the Thangaratinam et al (2012) systematic review.

Results

Table A2 summarises the results of analysis (1) and (2).

Analysis 1: Increasing the costs to 2010/2011 values and the time taken to conduct CE and PO increased the costs of all three screening strategies. The cost per timely diagnosis for CE+PO compared to CE increased significantly from £4,900 per timely diagnosis to £17,633. This was due mostly to an increase in the estimate of the time taken per PO and increased machine costs per test. The cost of SE did not increase as much though and hence the cost per timely diagnosis has decreased from £4.5 million per case to £2.4 million per case comparing CE+PO to CE+SE.

Analysis 2: When the values in the model are updated for the sensitivity and specificity of PO and antenatal detection rates from PulseOx, the cost of the programme is similar to analysis (1), but the detection rate for CE+PO is lower than in the original model (55% compared to 69%). The sensitivity of PO is higher in PulseOx than Knowles et al (2005) for AS, TAPV, HLH/MA and PA (see Table A1 and Table A3), but functions worse in the other targeted CHDs. Part of the reduction in detection rate is because more cases are detected antenatally per 100,000 live births in the PulseOx results (52 for PulseOx compared to 10 in Knowles et al). As all cases of PA and HLH are detected antenatally, the improved performance of PO does not factor for these two CHDs. CE+PO has 19 more timely diagnoses of targeted CHD per 100,000 live births than CE alone and costs an additional £664,411, which is an additional cost per timely diagnosis of £35,371.

Analysis 3: The PulseOx study was not powered to calculate the sensitivity of PO for specific CHDs and the estimates used in the model for the sensitivity and antenatal screening rates are based on very small numbers, ranging from a maximum of 8 newborns for COA to a minimum of 1 newborn for TAPVC. TableA 4, analysis (3) provides a summary of the results for if the effectiveness of antenatal screening from the PulseOx study is used but the sensitivity of PO is based on the combined results for all major CHDs. PO+CE results in an additional 30 cases of CHD receiving a timely diagnosis per 100,000 live births compared to CE alone and costs an additional £666,056. This translates to a cost of £22,083 per additional timely diagnosis. The results are very similar to the results of Roberts et al (2012) who calculated that PO+CE would result in 30 additional timely diagnoses compared to CE alone at an additional cost per timely diagnosis of £24,000. CE+PO dominates CE+SE in that it results in more timely diagnoses for a lower cost.

Analysis 4: If the sensitivity of PO is kept CHD specific based on the PulseOx study, but the antenatal detection rate from the North of England study is used, CE+PO has 32 more timely diagnoses of targeted CHDs than CE alone for an additional cost of £19,731 per timely diagnosis (see Table A4, analysis (4)).

Analysis 5: 77% of PO screens in PulseOx were conducted within 24 hours of birth. Knowles et al (2005) also found a different incremental cost per timely diagnosis closer to birth. If the PulseOx values for the sensitivity of PO for different CHD diagnoses and the antenatal detection rate are used but PO is carried out close to birth, CE+PO has an additional 25 timely diagnoses of targeted CHD per

100,000 births at an additional cost per timely diagnosis of £26,260 compared to CE alone (see Table A5 analysis (5)).

Analysis 6: The recently published meta-analysis by Thangaratinam et al (2012) combines the results of 13 studies of the sensitivity and specificity of PO across 229,421 live births. The combined sensitivity of PO is 76.5% (95% CI 67.7-83.5) with a specificity of 99.9% (95% CI 99.7-99.9). If this value is used in the original Knowles et al (2005) model using North of England rates of antenatal detection of targeted CHD, CE+PO results in an additional 40 timely diagnoses of targeted CHD per 100,000 live births at an additional cost per timely diagnosis of £14,970 compared to CE alone (see Table A5 analysis (6)).

Table A2: Results of analysis (1) and (2) per 100,000 live births

	Analysis (1) Original 2010/2011 prices			**Analysis (2) All updated to PulseOx**		
Screening Strategy	**CE**	**CE+PO**	**CE+SE**	**CE**	**CE+PO**	**CE+SE**
Expected number targeted CHD	121			89		
True Positives (detection rate)	39 (23%)	82 (68%)	83 (69%)	27 (31%)	49 (55%)	57 (64%)
Number of timely diagnosed cases	33.8	70.7	71.3	23.8	42.5	49.5
Total programme cost	£1.1m	£1.8m	£3.1m	£1.1m	£1.8m	£3.1m
Cost per timely diagnosis (compared to CE)		£17,633	£52,646		£35,371	£77,624
Cost per timely diagnosis (compared to CE+PO)			£2.4m			£191,463
Expected cases targeted CHD at birth	166.63			166.63		
Number diagnosed antenatally	10			52		
Total number diagnosed and excluded before screen	46			78		
False Negatives	73	30	27	55	34	24
False Positives	443	1144	4778	445	913	4782

Table A3: Results of analysis (1) and (2) by CHD per 100,000 live births

	Analysis (1) Original 2010/2011 prices			Analysis (2) All updated to PulseOx		
Screening Strategy	**CE**	**CE+PO**	**CE+SE**	**CE**	**CE+PO**	**CE+SE**
Prevalence TGA	28			28		
Diagnosed Antenatally	0.7			7.8		
Expected cases to be screened	14.7			7.5		
Number with timely diagnosis	4.6	11.3	10.5	2.7	6	6.2
Prevalence AS	33.7			33.7		
Diagnosed Antenatally	1.6			0		
Expected cases to be screened	27.7			29.4		
Number with timely diagnosis	12.6	13.8	18.7	14.9	14.9	22
Prevalence TAPVC	9.5			9.5		
Diagnosed Antenatally	0			0		
Expected cases to be screened	7.5			7.5		
Number with timely diagnosis	0.2	6.7	4.1	0.2	6.9	4.1
Prevalence HLH/MA	15.8			15.8		
Diagnosed Antenatally	3			14.3		
Expected cases to be screened	9.1			0.8		
Number with timely diagnosis	2.1	5.2	5.3	0.2	0.5	0.5
Prevalence COA/IAA	54.6			54.6		
Diagnosed Antenataly	2.7			5.4		
Expected cases to be screened	46.3			43.5		
Number with timely diagnosis	8.1	21.9	21.5	7.6	17.2	20.2
Prevalence PA	25			25		
Diagnosed Antenatally	1.7			24		
Expected cases to be screened	15.3			0		
Number with timely diagnosis	6.2	12.4	11.6	0	0	0

Table A4: Results of analysis (3) and (4) per 100,000 live births

	Analysis (3) PulseOx sensitivity non CHD specific - all critical cases equal			Analysis (4) North England antenatal detection rate. CHD specific sensitivity		
Screening Strategy	**CE**	**CE+PO**	**CE+SE**	**CE**	**CE+PO**	**CE+SE**
Expected number targeted CHD	89			121		
True Positives (detection rate)	27 (31%)	62 (70%)	57 (63.9%)	39 (32%)	77 (64%)	83 (70%)
Number of timely diagnosed cases	23.8	53.9	49.6	33.8	66	71.3
Total programme cost	£1.1m	£1.8m	£3.1m	£1.1m	£1.8m	£3.1m
Cost per timely diagnosis (compared to CE)		£22,083	£77,624		£19,731	£52,646
Cost per timely diagnosis (compared to CE+PO)			dominated			£255,519
Expected cases targeted CHD at birth	166.63			166.63		
Number diagnosed antenatally	52			10		
Total number diagnosed and excluded before screen	78			46		
False Negatives	55	21	24	73	35	27
False Positives	445	997	4782	443	911	4778

Table A5: Results of analysis (5) and (6) per 100,000 live births

	Analysis (5) All updated to PulseOx. Screen at birth			Analysis (6) Sensitivity and specificity of PO from meta-analysis. North England antenatal detection		
Screening Strategy	**CE**	**CE+PO**	**CE+SE**	**CE**	**CE+PO**	**CE+SE**
Expected number targeted CHD	111			121		
True Positives (detection rate)	34 (31%)	64 (57%)	73 (66%)	39 (32%)	86 (71%)	83 (69%)
Number of timely diagnosed cases	30.3	55.5	63.6	33.8	74.1	71.3
Total programme cost	£1.1m	£1.8m	£3.1m	£1.1m	£1.8m	£3.1m
Cost per timely diagnosis (compared to CE)		£26,260	£60,151		£14,970	£52,646
Cost per timely diagnosis (compared to CE+PO)			£166,122			dominated
Expected cases targeted CHD at birth	166.63			166.63		
Number diagnosed antenatally	52			10		
Total number diagnosed and excluded before screen	122			46		
Expected number targeted CHD	111			121		
False Negatives	69	39	28	73	26	27
False Positives	479	942	4893	443	578	4778

Probabilistic Sensitivity analysis:

All of the values in the model were varied for a probable range and distribution for analysis (2). This was done for 10,000 repetitions of the model. The results of the simulations were compared across the three screening programmes to calculate the net monetary benefit for a given willingness to pay for a timely diagnosis. This is calculated by multiplying the number of timely diagnoses per 100,000 births for a screening programme by a willingness to pay for a timely diagnosis, minus the total cost of the screening programme. The net monetary benefit for each repetition of the model is then used to create cost-effectiveness acceptability curves, which represent the proportion of times each option has the highest net monetary benefit for a given willingness to pay for a timely diagnosis (see Figure A2). At a willingness to pay of £70,000 per timely diagnosis, CE+PO has a 67% probability that it is cost-effective compared to CE alone and CE+SE. Comparing CE+PO to CE alone, there is a 92% chance that CE+PO is cost-effective compared to CE alone for a willingness to pay of an additional £100,000 per timely diagnosis (see Figure A3).

Figure A2: Probability of each screening programme being cost-effective for a range of values of willingness to pay for a timely diagnosis

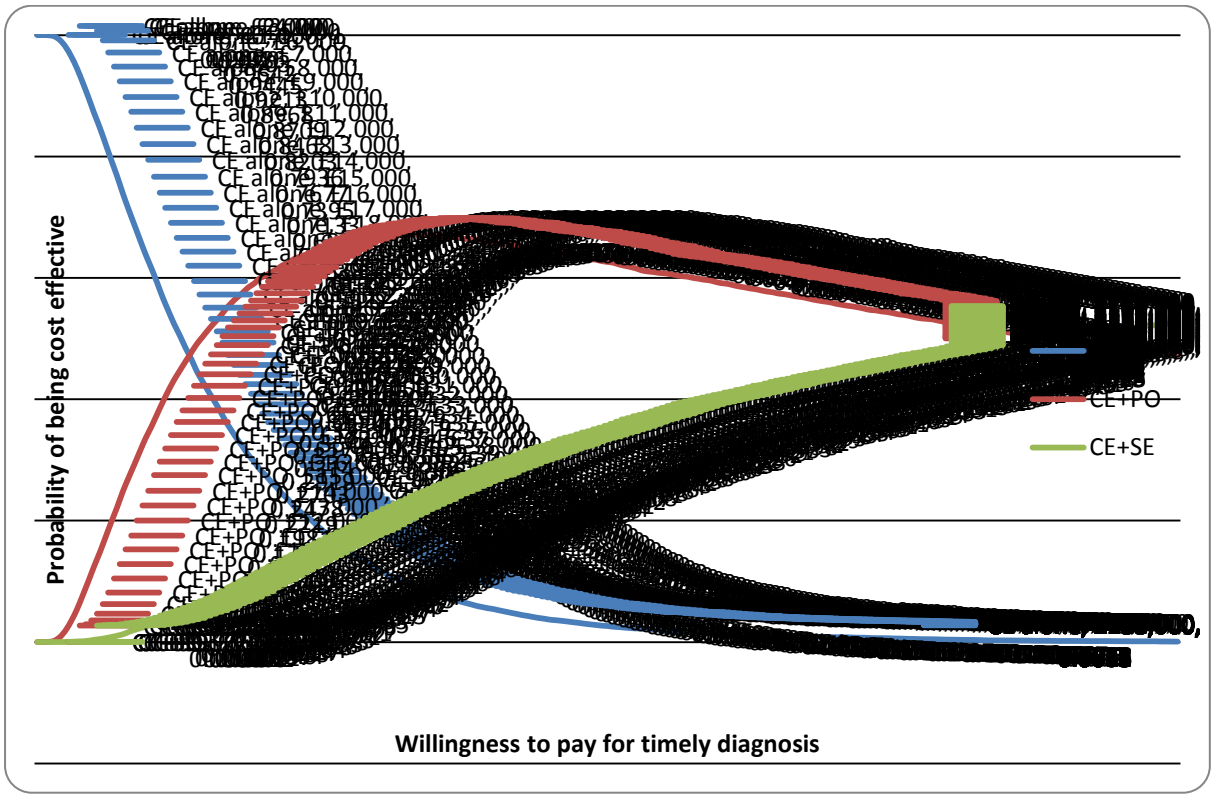
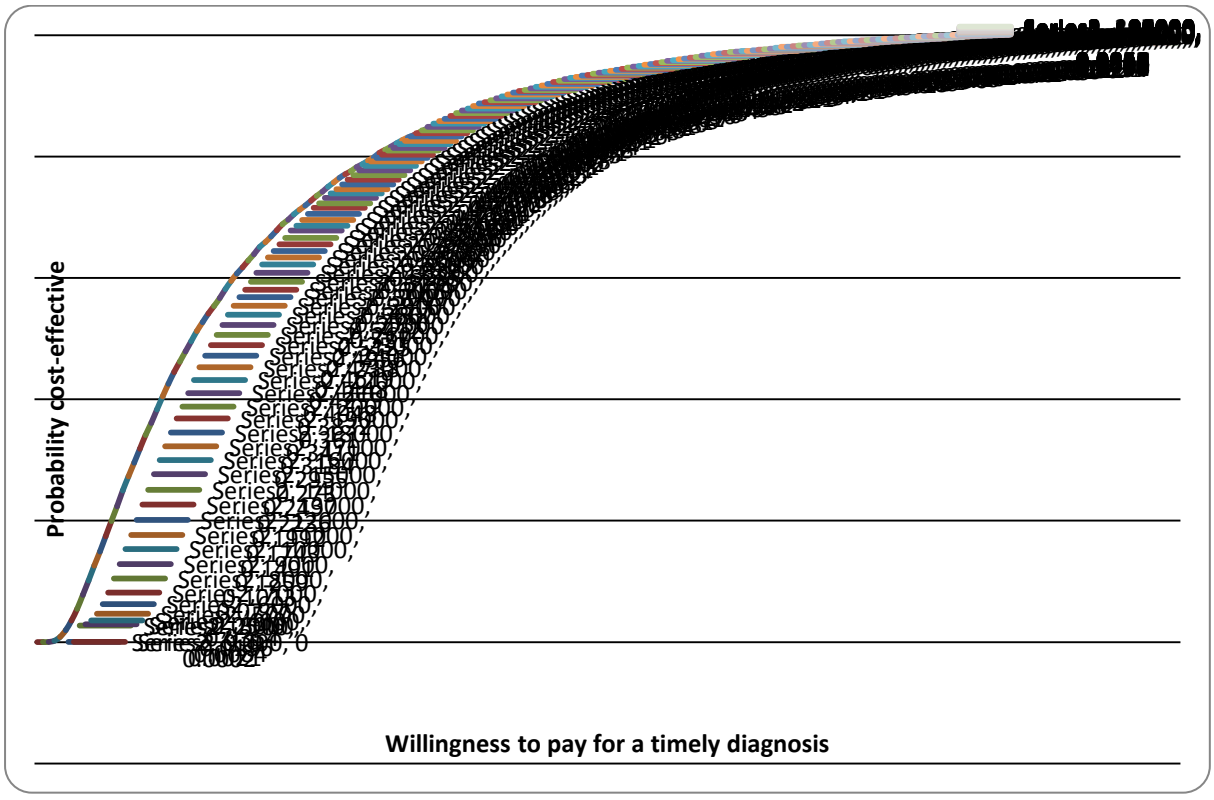


Figure A3: Probability that CE+PO is cost-effective compared to CE for a range of values of willingness to pay for a timely diagnosis



Discussion

More cases of life threatening CHD receive a timely diagnosis when Pulse Oximetry (PO) testing is included in addition to a clinical examination (CE) for newborn screening. The decision analytical model developed in Knowles et al (2005) found that PO in addition to CE results in 37 additional cases of life threatening CHD receiving a timely diagnoses of per 100,000 live births, compared to CE alone. When the model is updated with results from the 2011 PulseOx study, the number of additional cases reduces to 19 additional timely diagnoses per 100,000 live births. The costs for all three screening programmes were higher in the updated model than in the 2005 model, particularly for PO, but similar across the six analyses run. PO plus CE is likely to cost £35,371 per additional case detected compared to CE alone if the values from the PulseOx study are used. If the assumptions of the model are modified or values from other studies are used, the cost per additional case timely diagnosis of life threatening CHD varies from £14,970 if the results of a recent meta-analysis are used to £35,371. In all analyses PO consistently identifies more CHD cases than CE at an additional programme cost of approximately £650,000-£700,000 per 100,000 live births. Given that based on the latest ONS figures there are approximately 720,000 births per year, implementing PO screening for all newborns at 24 hours of age, except those identified antenatally as having a CHD, would be at an additional cost of £4.7million per year to the NHS to achieve an a*dditional* 137-350 timely diagnoses of life threatening CHD per year.

One of the weaknesses of the model is that it is unclear what a decision maker would be willing to pay for an additional timely diagnosis. Given that for the targeted CHD conditions, timely diagnosis is associated with better outcomes and increase the chance that newborns survive into teenage years with reasonable quality of life, Robert's et al (2012) makes the statement that it would be reasonable to assume that each additional case given a timely diagnosis could result in at least 5 additional quality adjusted life years (QALYs). QALYs are a measure used by the National Institute for Health and Clinical Excellence (NICE) to allow comparisons of quality of life gained across different disease areas, where 1 QALY is equal to 1 year of life in perfect health and 0 is equivalent to death. Given that NICE has a willingness to pay threshold of £20,000-£30,000 per QALY gained, the potential willingness to pay for an additional case diagnosed could be greater than £100,000. Using the new PulseOx values and even taken the extreme uncertainty in the model into account there is a 92% chance that CE+PO is cost-effective compared to CE alone at a willingness to pay of £100,000 per additional case of targeted CHD identified.

Conclusions

Further studies on the clinical and cost-effectiveness of using PO to screen for CHD have continued to identify it as a viable and cost-effective option for making timely diagnoses of life threatening CHD compared to CE alone. Incorporating the values from further research into the Knowles et al (2005) model the findings are consistent with previous studies. Additional information on how many QALYs are gained from a timely diagnosis of life threatening CHD would provide greater clarity on the cost-effectiveness of the different screening options.

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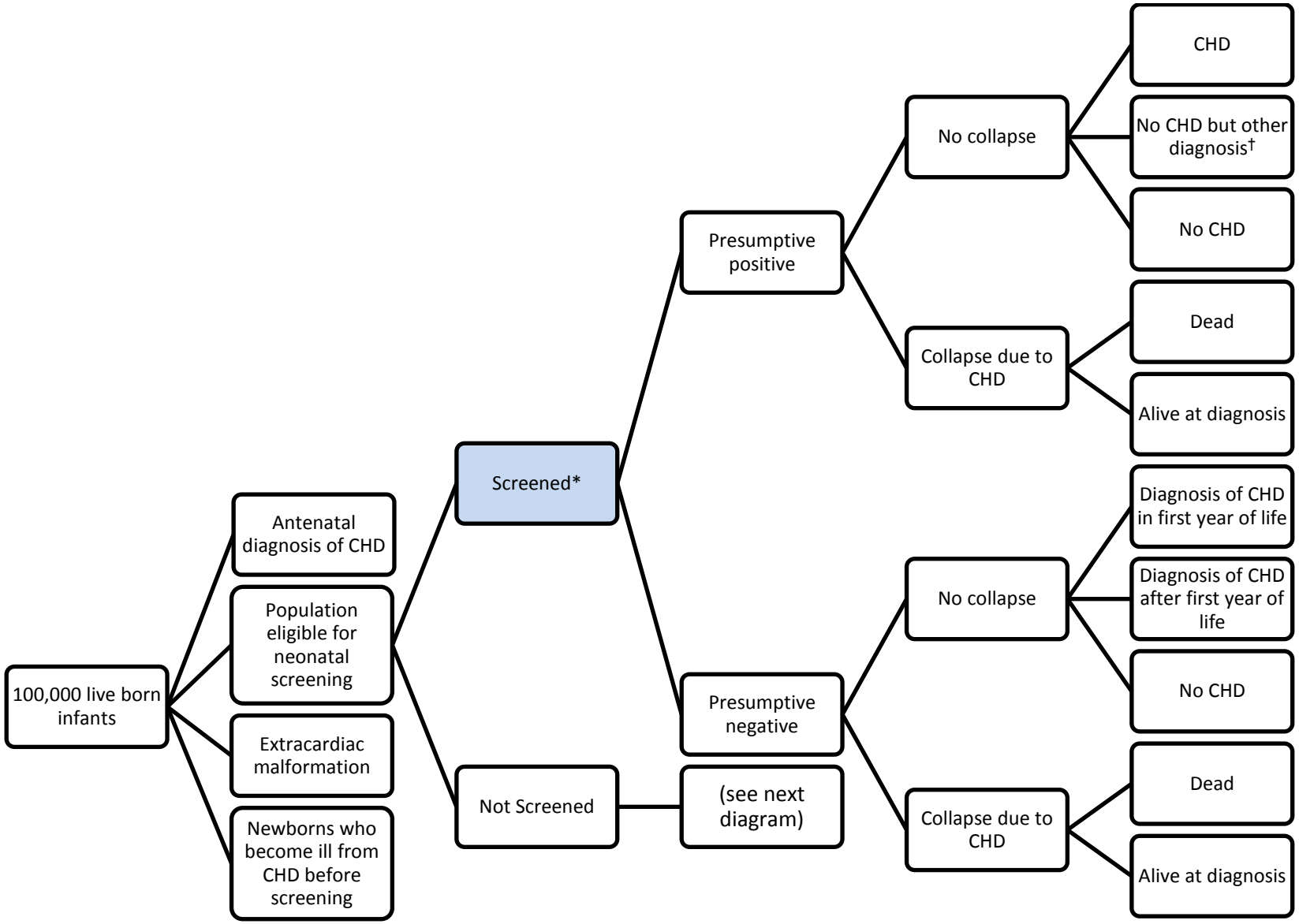
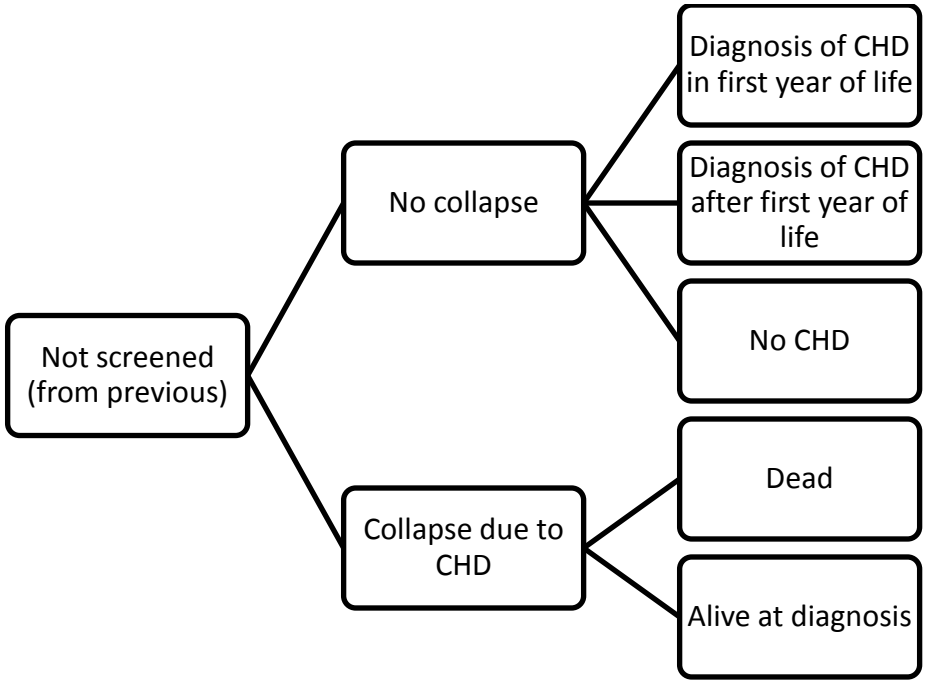
Annex 2: Cost-effectiveness summary

Figure A1: Basic Model Structure (adapted from original Excel model)





*Screened using one of the three strategies: CE, CE+PO or CE+SE

†Some false positives may have a diagnosis other than CHD (see Table A6). This is likely to be around 207 cases per 100,000 live births assuming PO screening takes place within 24 hours and based on combined figures of current best evidence. Assuming approximately 1000 false positives per 100,000 live births, this represents 20% of all false positive cases. The diagnoses for the non CHD false positives can be broken down into:

- 97 infections (pneumonia or septicaemia) per 100,000 live births
- 61 cases of Transient Tachypnea of the Newborn (TTN) per 100,000 live births
- 25 cases of Persistent Pulmonary Hypertension of the Newborn (PPHN) per 100,000 live births
- 12 other respiratory conditions per 100,000 live births
- 12 other cases (not infections or respiratory) per 100,000 live births

Annex 2: Cost-effectiveness summary

Table A6: Sources of data for non-CHD causes of a positive screening test result with PO

First Author, Publication year	Live births (n)	Causes of non-CHD screen positive result
Richmond, 2002 (ref. 7)	6,166	**13 non-CHD cases:** ***respiratory*** 7 TTN 2 PPHN 1 spontaneous pneumothorax ***other*** 1 septo-optic dysplasia 1 arachnoid cyst haemorrhage 1 PDA, multicystic kidney/renal failure *(NB 447 direct to NNU)*
Meberg, 2008 (ref. 74)	57,959	**134 non-CHD cases:** ***infection*** 55 pneumonia/septicaemia ***respiratory*** 54 TTN 6 PPHN 5 amniotic fluid aspiration 3 other respiratory ***other*** 3 hypoglycaemia 1 polycythaemia 1 cardiomyopathy
De Wahl-Granelli, 2008 (ref. 37)	31,946	**23 non-CHD cases:** ***infection*** 10 infection ***respiratory*** 6 PPHN 7 other respiratory
Riede, 2010 (ref. 92)	41,445	**28 non-CHD cases:** ***infection*** 13 sepsis ***respiratory*** 15 PPHN
Ewer, 2013 (personal communication) *(from 2010-2013 audit of Pulse oximetry screening programme, Birmingham Women's Hospital)*	23,146	**135 non-CHD cases:** ***infection*** 49 pneumonia 29 sepsis ***respiratory*** 37 TTN 11 PPHN 3 meconium aspiration 1 pneumothorax ***other*** 1 hyperinsulinaemia 1 skull fracture 1 jaundice

An additional sensitivity analysis concerning the effect of differing rates of antenatal detection on newborn screening.

From: Newborn screening for congenital heart defects: a systematic review and cost effectiveness analysis. (Reported in Griebsch et al.[70])

Summary of findings

Background

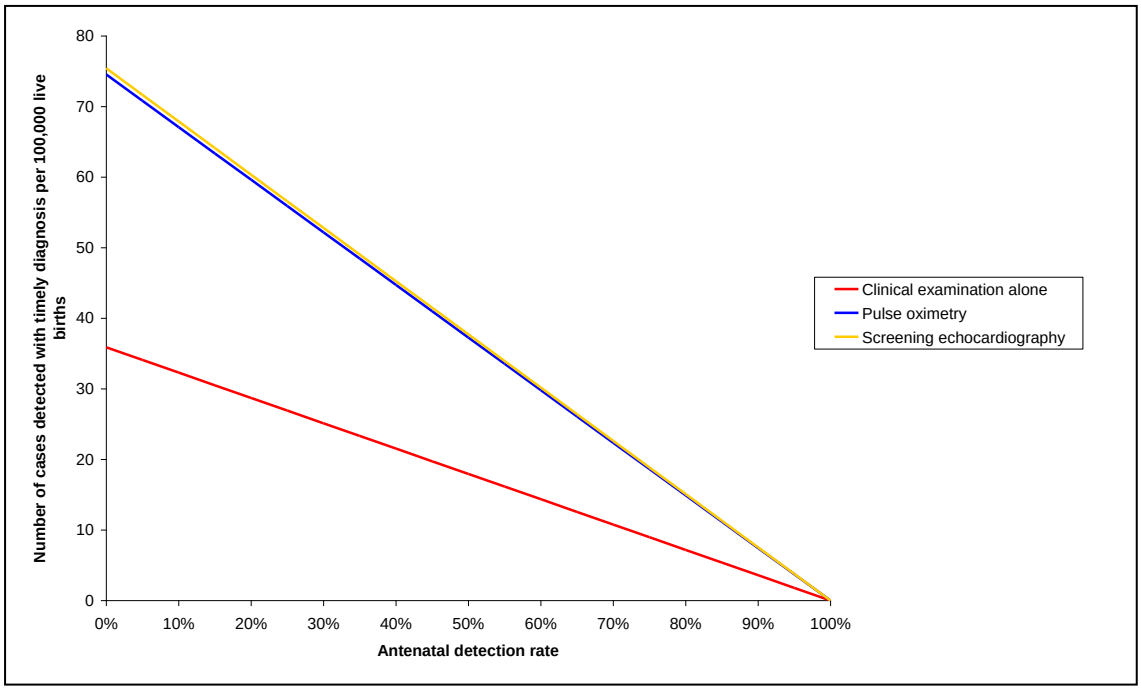
The screening model presented to the child health sub-group of the National Screening Committee at a workshop on 23rd January 2004, took account of average antenatal detection rates for congenital heart defects in the UK, around 10% in the Northern Region and 25% in a national study, and also doubled this to determine the effect of a hypothetically more effective antenatal screening programme overall in the UK. Our conclusions about newborn screening are therefore 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. Following discussions at this meeting, we have undertaken a further analysis and calculated the outcomes, costs and incremental cost-effectiveness rations 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 is assumed to take place at 24 hours of age. This paper summarises our findings.

Results

Figure A compares the number of cases detected by each newborn screening strategy, for a population of 100,000 live births, as the antenatal detection rate increases for the primary outcome of the model: timely diagnosis of life threatening congenital heart defects. Clinical examination detects only about half of the cases that pulse oximetry and screening echocardiography can detect and the latter two strategies are therefore discussed here in more detail. As the proportion of congenital heart defects detected antenatally increases, the number of cases remaining to be detected by newborn screening falls. 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) are predicted to be detected through the use of pulse oximetry undertaken in addition to clinical examination.

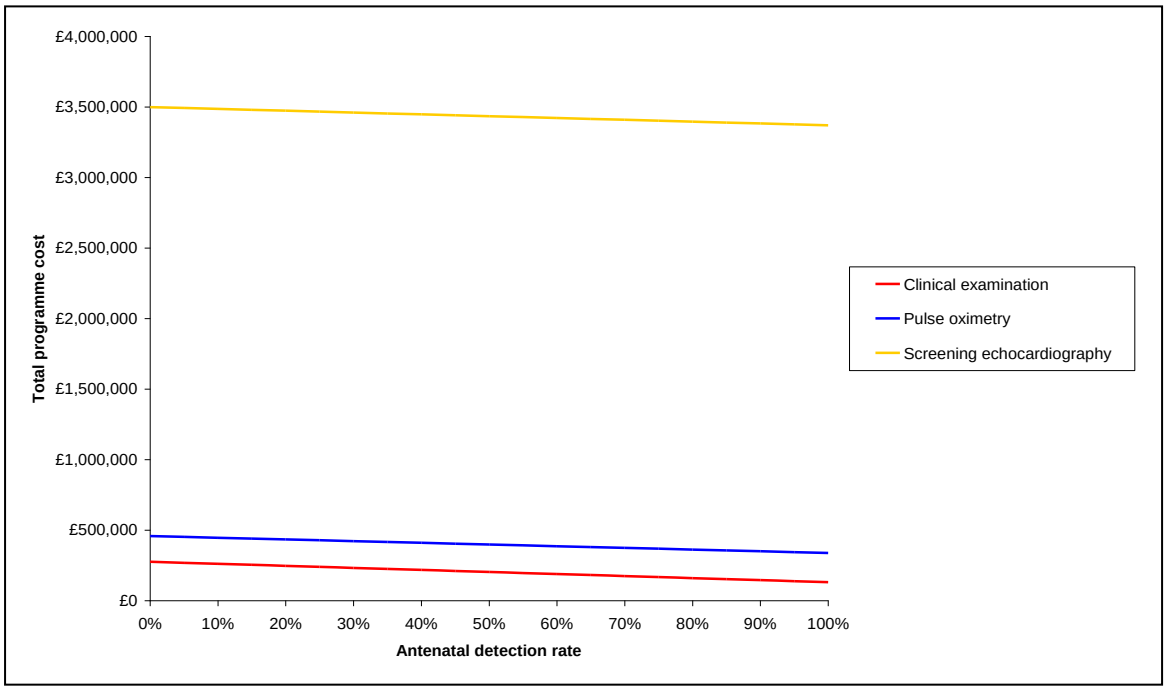
Annex 2: Cost-effectiveness summary

Figure A: Number of cases detected with timely diagnosis and antenatal detection rate (per 100 000 live births)



The overall costs of the newborn screening programme are only marginally reduced by an increased antenatal detection rate because the numbers of cases detected are so small (see Figure B).

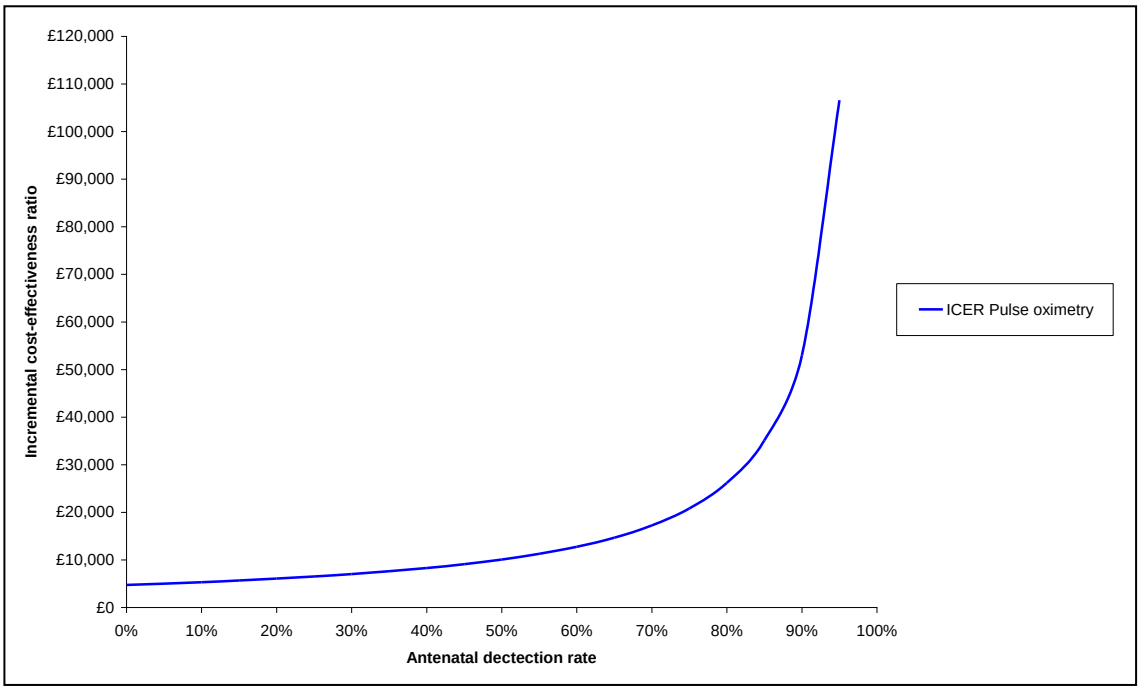
Figure B: Total programme costs and antenatal detection rate (per 100 000 live births)



However, the additional cost per additional timely diagnosis made through newborn screening does increase as the antenatal detection rate rises and this can be shown by calculating the incremental cost-effectiveness ratio (ICER).

Figure C shows that the incremental cost-effectiveness ratio for pulse oximetry, compared to the baseline newborn screening strategy of clinical examination alone, rises sharply if more than 70% of cases are detected antenatally. The ICER for each additional case detected by pulse oximetry, once an antenatal detection rate of 80% is reached, is about £30,000.

Figure C: Incremental cost-effectiveness ratio for pulse oximetry (pulse oximetry relative to clinical examination alone) and antenatal detection rate



The costs of detecting additional cases through newborn screening rises more steeply once the antenatal detection rate increases above 80%. 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.

Interpretation

If the antenatal detection rate is 10%, then newborn screening with pulse oximetry or screening echocardiography would detect around 70 cases of congenital heart defects. If 80% of cases are detected antenatally, then the number of cases detected by newborn screening decreases to around 15 per 100,000 live births. However, even if antenatal detection succeeds in identifying 90% of cases before birth, between 5-10 further cases of life threatening congenital heart defects would be detected by newborn screening. This would suggest that until the percentage of cases detected antenatally is above 90%, there are still a significant number of additional cases of life threatening congenital heart defects that could be detected through newborn screening. Clearly, approaches to early detection of congenital heart defects, through screening, requires an integrated approach across antenatal and newborn screening programmes.